

the Division of Trading and Markets and the Chief Economist and Director of the Division of Economic Analysis. So as to avoid any confusion of the public, and to ensure its inclusion in this year's edition of the Code of Federal Regulations, this correction sets out the language relating to agency procedure that was not included with the original amendments. Consequently, the Commission is not seeking public comment. Similarly, the Commission finds good cause to make this correction clarifying the omissions effective immediately.

In final rule, FR Doc. 97-9399, published on April 11, 1997 (62 FR 17702) make the following corrections:

#### **PART 11—[CORRECTED]**

1. On page 17702, in the second column, § 11.1 is corrected to read as follows:

##### **§ 11.1 Scope and applicability of rules.**

The rules of this part apply to investigatory proceedings conducted by the Commission or its staff pursuant to Sections 6(c) and 8 and 12(f) of the Commodity Exchange Act, as amended, 7 U.S.C. 9 and 15 and 12 and 16(f) (Supp. IV, 1974), to determine whether there have been violations of that Act, or the rules, regulations or orders adopted thereunder, or, in accordance with the provisions of Section 12(f) of the Act, whether there have been violations of the laws, rules or regulations relating to futures or options matters administered or enforced by a foreign futures authority, or whether an application for designation or registration under the Act should be denied. Except as otherwise specified herein, the rules will apply to the conduct of investigation whether or not the Commission has authorized the use of subpoenas in the particular matter to compel the production of evidence.

2. On page 17702, in the third column, § 11.2, paragraph (a) is corrected to read as follows:

##### **§ 11.2 Authority to conduct investigations.**

(a) The Director of the Division of Enforcement and members of the Commission staff acting pursuant to his authority and under his direction may conduct such investigations as he deems appropriate to determine whether any persons have violated, are violating, or are about to violate the provisions of the Commodity Exchange Act, as amended, or the rules, regulations or orders adopted by the Commission pursuant to that Act, or, in accordance with the provisions of Section 12(f) of the Act, whether any persons have violated, are

violating or are about to violate the laws, rules or regulations relating to futures or options matters administered or enforced by a foreign futures authority, or whether an applicant for registration or designation meets the requisite statutory criteria. For this purpose, the Director may obtain evidence through voluntary statements and submissions, through exercise of inspection powers over boards of trade, reporting traders, and persons required by law to register with the Commission, or when authorized by order of the Commission, through the issuance of subpoenas. The Director shall report to the Commission the results of his investigations and recommend to the Commission such enforcement action as he deems appropriate. In particular matters the Director of the Division of Trading and Markets and the Chief Economist and Director of the Division of Economic Analysis, and members of their staffs acting within the scope of their respective responsibilities, are also authorized to investigate, report and recommend to the Commission in accordance with these rules.

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Issued in Washington, DC on January 27, 1998, by the Commission.

**Jean A. Webb,**

*Secretary of the Commission.*

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## **DEPARTMENT OF HEALTH AND HUMAN SERVICES**

### **Food and Drug Administration**

**21 CFR Parts 54, 312, 314, 320, 330, 601, 807, 812, 814, and 860**

[Docket No. 93N-0445]

#### **Financial Disclosure by Clinical Investigators**

**AGENCY:** Food and Drug Administration, HHS.

**ACTION:** Final rule.

**SUMMARY:** The Food and Drug Administration (FDA) is issuing regulations requiring the sponsor of any drug, including a biological product, or device marketing application (applicant), to submit certain information concerning the compensation to, and financial interests of, any clinical investigator conducting certain clinical studies. This requirement will apply to any covered clinical study of a drug or device submitted in a marketing application that the applicant or FDA relies on to

establish that the product is effective, including studies that show equivalence to an effective product, or that make 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 and/or disclose those financial interests, as required, when covered clinical studies are submitted to FDA in support of product marketing. This regulation is intended to ensure that financial interests and arrangements of clinical investigators that could affect reliability of data submitted to FDA in support of product marketing are identified and disclosed by the sponsor of any drug, biological product, or device marketing application. If the applicant does not include certification or disclosure, or both, if required, or does not certify that it was not possible to obtain the information, the agency may refuse to file the application. FDA intends to propose to extend these requirements to submissions for marketing approval related to human foods, animal foods, and animal drugs in a subsequent issue of the **Federal Register**.

**DATES:** This regulation becomes effective on February 2, 1999. Submit written comments on the information collection requirements by April 3, 1998.

**ADDRESSES:** Submit written comments on the information collection requirements to the Dockets Management Branch (HFA-305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1-23, Rockville, MD 20857.

**FOR FURTHER INFORMATION CONTACT:** Mary C. Gross, Office of External Affairs, Food and Drug Administration (HF-60), 5600 Fishers Lane, Rockville, MD 20857, 301-827-3440, FAX 301-594-0113.

#### **SUPPLEMENTARY INFORMATION:**

##### **I. Background**

In the **Federal Register** of September 22, 1994 (59 FR 48708), FDA published a proposed regulation to help ensure that financial interests and arrangements of clinical investigators that could affect reliability of data submitted to FDA in support of product marketing are identified and disclosed by the sponsor of any drug, biological product or device marketing application (applicant). In this document, FDA proposed to require disclosure by applicants of the following types of financial interests and arrangements: Compensation made to the clinical investigator in which the value of the compensation could be affected by the

study outcome; a proprietary interest by the investigator in the tested product, such as a patent; a significant equity interest in the sponsor of the covered study; or significant payments by the sponsor of the covered study of other sorts, such as a grant to fund ongoing research, compensation in the form of equipment, or retainers for ongoing consultation or honoraria. If, to the best of the applicant's knowledge, a clinical investigator did not have any of these financial interests or arrangements, FDA proposed that an applicant might provide a statement of certification to FDA.

In the course of developing this rule, FDA met with many outside groups with an interest in the issues involved, including regulated industry, consumer groups, health professionals and clinical investigators. These issues were also discussed at a meeting with FDA's Science Board in September 1993, and, at that meeting, there was general support for the concept of disclosure of potentially biasing financial interests and arrangements of clinical investigators to FDA, not only from Science Board members but also from the pharmaceutical, device and biotechnology industries.

FDA received 58 written comments on the proposed rule. Many of these comments supported the proposed rule, some raised substantive concerns and challenges to the rule, and one comment, from the Pharmaceutical Research and Manufacturer's Association urged FDA to hold a public hearing on the provisions of the proposed rule. In response, FDA convened a public meeting on July 20, 1995, to provide interested parties with an opportunity to present further public comment to FDA on the proposed rule. Representatives of seven organizations presented testimony to FDA during the public meeting; copies of the testimony and related comments have been filed with the Dockets Management Branch (address above) and are available for public review. FDA also convened a second meeting on March 29, 1996, with the agency's Science Board. At this meeting, issues relating to the proposed rule were discussed by a panel that included representatives from the: Pharmaceutical Research and Manufacturers Association, Health Industry Manufacturer's Association, Public Citizen Health Research Group, American Medical Association, Association of American Medical Colleges, and the Biotechnology Industry Organization. According to representatives of drug and device manufacturers, the financial arrangements in the proposed rule

required to be disclosed are uncommon, and the proposed rule as written would not impose an extreme burden on industry. The groups represented and the Science Board members agreed unanimously that applicants should disclose to FDA any financial arrangement with a clinical investigator and any clinical investigator interest, whereby the compensation to the clinical investigator or interest could be affected by study outcome (e.g., payments in the form of stock options or royalties, possession of a patent, etc.), and Science Board members recommended that FDA finalize the proposed rule with only slight modifications. Transcripts, meeting minutes, and executive summaries from these open meetings may be examined at FDA's Dockets Management Branch (address above).

## II. Summary of Comments

1. Several comments stated that section 704 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 374) (the act) expressly prohibits FDA from inspecting financial data of companies and that FDA cannot obtain access to this information by having the request come from a reviewing division at headquarters rather than a field investigator. One comment said that there is nothing in section 505(d) of the act (21 U.S.C. 355(d)) that might be construed as authorizing FDA to require submission of financial data in order to evaluate the approvability of a new drug application (NDA). The same comment said that section 505(b) of the act specifically lists the information that must be submitted with an NDA, and it does not include submission of financial data.

In the preamble to the proposal (59 FR 48708 at 48712 to 48713), FDA discussed in detail the legal authority for this regulation. The agency cited sections 505, 510(k), 513, 515, 519, 520(g), 522, and 701(a) of the act (21 U.S.C. 360(k), 360c, 360e, 360i, 360j(g), 360l, 371(a) and section 351 of the Public Health Service Act (PHS Act) (42 U.S.C. 262)) as authority for the regulation and noted that the Supreme Court has upheld FDA's authority to issue regulations to ensure the reliability of clinical study results, including requirements to minimize bias. (See *Weinberger v. Hynson, Westcott & Dunning, Inc.*, 412 U.S. 606 (1973).) After reviewing the comments, FDA continues to believe, for the reasons stated in the preamble to the proposal that it has authority to require applicants to submit information concerning certain financial interests of clinical investigators conducting

clinical studies. To conclude otherwise would unduly restrict FDA's ability to perform the role assigned to it by Congress to assess data submitted in product marketing applications and to determine whether the products meet the criteria for approval set for in the act.

Although the authority provided in section 704 of the act does not extend to financial data, other provisions of the act provide the agency with the authority to obtain the information it needs to adequately assess the safety and effectiveness of drugs and devices. For example, section 505(d) of the act includes the requirement that efficacy of drugs be demonstrated by adequate and well controlled investigations. The language in section 505(d) of the act is intended to help ensure that consumers are not exposed to products for which efficacy has not been demonstrated. A critical factor in determining whether a study is well controlled is the extent to which potential bias on the part of the investigator has been minimized (see 21 CFR 314.126(b)(5)). FDA believes that a clinical investigator's financial interests could introduce bias into a study and affect the reliability of data submitted to FDA in support of a marketing application. Information about such interests is critical to the agency's role of determining efficacy of products based on valid, reliable, and unbiased data.

Section 505(k) of the act also provides authority for the issuance of these regulations. Under section 505(k) of the act, the agency may issue regulations requiring the applicant to make and keep records and reports of data relating to clinical study experience and other data and information that are necessary to determine whether grounds exist to withdraw approval of an NDA or an abbreviated new drug application (ANDA). Section 505(k) of the act also provides the agency with the authority to access such records and to copy and verify them. The additional authorities relied on by FDA to issue these regulations are discussed in the preamble to the proposal.

FDA believes this rule is consistent with the agency's general rulemaking authority set forth in section 701(a) of the act, which authorizes the agency to issue regulations for the efficient enforcement of the act. The agency continues to rely on the statutory authorities discussed here and in the preamble to the proposal as authority for this regulation.

2. Some comments said that FDA has not demonstrated an adequate need for the rule, that there is no factual justification for the rule and that FDA

has never shown that if FDA does not receive financial disclosure information, public health or safety would be threatened. One comment said that there is no evidence to demonstrate that studies by clinical investigators with particular financial interests are more likely to be biased than studies performed by other clinical investigators, and that there are many other potential sources of bias that FDA does not take into account.

FDA disagrees with these comments and believes there is factual justification to require collection of this information. Over the past several years, FDA has received information on potentially problematic payment schemes through numerous sources, including: Published newspaper articles, congressional reports, a Government Accounting Office report, congressional inquiries and public testimony and comments. Although FDA learned through these sources that problematic financial interests and arrangements do exist, FDA has had no formal mechanism to collect this information from applicants. FDA acknowledges that other sources of potential bias exist and could influence a clinical investigator's judgment or behavior, such as a quest for prestige within the scientific community, a preference for confirming a personal hypothesis or the desire for future contracts with the sponsor of a study. Such potential biases are difficult to assess and minimize, but the reliability to assess and minimize all bias does not argue against addressing some potential sources of bias. Certain kinds of payment arrangements for clinical trials would result in a higher payment or financial gain from a particular outcome (that is, from a "successful" study rather than one that did not show the therapy's effectiveness) and gives the investigator a potential "stake" in that outcome. Payments that are greater for one outcome than another or that are in the form of stock options or royalties are examples of such payment arrangements and clearly have the potential to bias the outcome of clinical trials, adversely affecting the integrity of the data submitted to FDA.

In June 1991, the Inspector General of the Department of Health and Human Services submitted a management advisory report to FDA asserting that FDA's failure to have a mechanism for collecting information on "financial conflicts of interest" among clinical investigators who study products undergoing FDA review could constitute a "material weakness" under the Federal Managers' Financial Integrity Act. Although FDA determined that a material weakness did not exist,

FDA has concluded there is a need to address this issue through rulemaking. In the preamble to the proposed rule, the agency explained that the existence of unbiased clinical research and reliable data are essential to FDA's assessment of the safety and effectiveness of new human drugs, biological products, and medical devices. Although payment arrangements required to be disclosed in this final rule have been described by industry sponsors as uncommon, small businesses in certain medical device and biologic industries appear to enter into certain arrangements more frequently, because of a lack of readily available capital or as a natural byproduct of the "inventor/investigator" relationship (see comment 3 of section I of this document). For these reasons, FDA believes the rule is needed and justified.

3. One comment, although not opposed to the concept of disclosure, said the requirement as proposed was not an effective way to ferret out the corruption of studies by financial arrangements. Another comment said that disclosure is warranted, but that disclosure alone is not enough, that clinical investigators should be banned from owning an equity interest that exceeds \$25,000 in the sponsor of a covered study and should be banned from receiving significant payments of other sorts from the sponsor of a covered study that exceed \$5,000 per year.

FDA's intention, by finalizing the rule, is to make the agency aware of payments and financial arrangements by sponsors of covered studies that could lead to the introduction of bias into the clinical trial process, so that this can be taken into account in the review process and to discourage such practices, not to "ferret out corruption of studies." FDA is encouraging applicants to work with FDA and clinical investigators to minimize the occurrence of such financial arrangements or to ensure that covered clinical studies are sufficiently well designed and managed to eliminate the possibility that bias due to potentially problematic financial arrangements will influence the outcome of the study.

FDA does not agree that it should ban certain financial arrangements. FDA recognizes that therapeutically beneficial products have been developed through clinical investigations that were conducted by the product-patent holder, or for which clinical investigators were compensated with equity in the sponsor's firm, and is therefore not prohibiting any arrangement, nor ruling out the

possibility of relying on studies conducted under these circumstances as a basis for product approval. Rather FDA intends to give such studies particularly close scrutiny and evaluation.

4. Several comments said the rule will affect acceptance of data from studies conducted outside the United States by investigators who are foreign nationals. One comment suggested that an exemption for foreign investigators may be necessary. Some comments stated that the disclosure requirements may be in conflict with foreign privacy regulations, and that different cultural standards may prevent compliance with the rule by foreign investigators. A few comments also said the final rule should be applied prospectively to avoid penalizing applicants and clinical investigators whose clinical investigations are already in progress.

In response to these comments, FDA notes that the comments relating to acceptance of data from studies conducted outside the United States did not specifically identify information pertinent to this rule that could not be supplied by a foreign investigator. Most of the information sought, even for studies conducted outside the United States, is known to the applicant and needs no clinical investigator disclosure. Only the question of ownership of equity in the sponsor of the covered study requires disclosure by the clinical investigator. With regard to comments about applying the rule retrospectively, FDA believes it is important to know about the financial arrangements and payments considered in this rule that are problematic in a timely manner and does not believe implementation should be long deferred. In order to give applicants time to comply with the final rule and to avoid delayed submissions, however, FDA will require applicants to comply with the rule 1 year after the publication date of the final rule. FDA recognizes that there may be times where, despite the applicant's diligent efforts to obtain the needed information to make appropriate certification or disclosure, the applicant may be unable to obtain the information. Thus, FDA is amending the final rule to permit an applicant, who can show conclusively why this information cannot be obtained, to certify that the applicant acted diligently to obtain the information but was unable to do so and to include the reason why such information could not be obtained.

5. Several comments said the proposed rule is unnecessary because adequate controls exist to ensure data integrity. For example, the comments

said that FDA has adequate mechanisms in place in its review and inspection processes to detect and deal with investigator bias. Another comment said that FDA already has substantial oversight to assess whether clinical studies are well controlled and designed with scientific rigor. Others said that the primary methods for managing potential bias based on financial interests are quality study design (e.g. multiple investigators, multiple investigational sites, segregation or pooling of data for comparative analyses and objective tests to evaluate key safety and effectiveness parameters), study monitoring, and statistical analysis. One comment said that for double-blinded studies, it was theoretically impossible for any type of bias to affect the conduct of the study, irrespective of any separate financial relationship.

FDA agrees that excellence in study designs, careful monitoring and analysis of trials by sponsors, the ability of FDA to inspect study sites, and FDA's detailed review of studies are critical elements in assessing data integrity. No single component is entirely adequate to ensure study integrity, however, and as explained in the proposed rule, the independence and lack of bias of clinical investigators is also critical. FDA believes that in addition to other steps, a mechanism is needed for collecting information concerning specific financial interests of clinical investigators that could affect data integrity.

6. Some comments objected to the lack of objective criteria for use by FDA reviewers to evaluate financial interest disclosure statements. These comments said that FDA reviewers should not be given unfettered discretion in making this determination, but that FDA should develop specific criteria based on factual need. One comment said that lack of resources would prevent FDA from carrying out this function adequately and that specific criteria should be developed to help alleviate this concern. This comment also suggested that certain interests should be prohibited to provide a more clear-cut and less labor intensive evaluative approach. Other comments supported FDA's plan to evaluate the information on a case-by-case basis, stating that FDA should exercise flexibility and not state specific criteria for this purpose.

As noted in the preamble to the proposed rule, FDA believes that the specific financial arrangements and the steps taken to minimize bias (e.g., through study design) must be considered on a case-by-case basis. Many factors could affect the believability of data derived from

clinical studies, such as the endpoint used, number of investigators, the methods of blinding and the method of evaluation. For example, if a covered study had randomized assignment of patients to treatment, an easily determined endpoint or an endpoint assessed by a blinded observer other than the investigator, and multiple study sites, FDA could determine that an otherwise problematic financial interest of a clinical investigator would not have affected the covered study. In other cases, there might be sufficient replication of critical results to render the questionable data less important, or it might be possible to carry out further analyses or observations that would provide assurance as to the reliability of the data. If FDA were to determine that the financial interests of any clinical investigator raised a serious question about the integrity of the data, FDA could choose from a range of remedial actions. Depending on the seriousness of the questions raised, the agency could initiate agency audits of the data derived from the clinical investigator in question; request that the applicant submit further analyses of the data (e.g., to evaluate the effect of investigator's data on study results); or request that the applicant conduct additional independent studies to confirm the results of the covered study; or refuse to treat the covered clinical study as pivotal or primary data upon which an agency action can be taken. Any attempt to write rigid evaluation criteria would inhibit the flexibility needed to interpret submissions in a fair and reasonable way.

7. Three comments suggested that applicants should know in advance what FDA considers to be problematic arrangements so as not to delay product review. One comment stated that FDA should include in the regulation a timeframe for the agency to inform an applicant of a remedial action that FDA might deem appropriate to take under new § 54.5(c). The comment added that, once FDA has received all required financial disclosure information, the agency should be required to inform the applicant within a reasonable period of time, not to exceed 60 days, if the financial interests of a clinical investigator raised a sufficiently serious question about the integrity of the study data to warrant any of the steps included in new § 54.5 (c), i.e., initiate agency audits of data derived from the clinical investigator in question; request that the applicant submit further analyses of data to evaluate the effect of the investigator's data; request that the applicant conduct additional

independent studies to confirm the results of the covered study; or refuse to treat the covered clinical study as pivotal or primary data upon which an agency action could be based.

FDA disagrees with the comments requesting that FDA be required to inform the applicant about potentially problematic financial arrangements within a specified time period because the determination of such remedies is inseparable from the review of the application and depends on such factors as the study design, and availability of other data, etc. Concerns arising from financial disclosure will be treated like any other concerns arising from the review of a marketing application and will be communicated along similar timeframes. As was stated in the proposed rule, however, FDA strongly encourages early consultation with the agency in cases where the sponsor of the clinical study is concerned that he may be entering into problematic financial arrangements with a clinical investigator.

8. In the proposed rule, FDA asked for comment on its proposed definition of a significant equity interest as "any ownership interest, stock option, or other financial interest whose value cannot be readily determined through reference to public prices, or any equity interest in a publicly traded corporation that exceeds 5 percent of total equity." The responses covered a wide range. One comment requested that FDA clarify whether 5 percent of total equity refers to 5 percent of the investigator's equity or 5 percent of the equity of the corporation and said that holding 5 percent of equity of publicly traded companies is only relevant if it represents a significant portion of the investigator's net worth. A second comment said that a "significant interest" (determined by reference to a dollar amount) in the equity or other securities of the sponsor should be of relevance regardless of whether that interest exceeds 5 percent and that the reference point of 5 percent is not sufficient in and of itself in light of the wide range of capitalization of corporations in the industry. Another comment said that FDA's rule should be made consistent as far as setting dollar or equity thresholds with the Public Health Service (PHS) final rule and the National Science Foundation (NSF) statement of policy on objectivity in research published on July 11, 1995. One comment recommended the threshold for disclosure of an equity interest be \$10,000 or 2.5 percent ownership interest in the sponsor.

FDA has carefully considered whether equity interests should be disclosed to

FDA and what threshold level should trigger disclosure. There are varied thresholds applied within academia, such as threshold levels at some institutions for disclosure of \$5,000 cash and \$20,000 equity interest in a publicly traded company. In addition, the PHS final rule and the NSF statement of policy have defined a significant financial interest to be "anything of monetary value, including but not limited to, salary or other payments for services (e.g., consulting fees or honoraria); equity interests (e.g., stocks, stock options or other ownership interests); and intellectual property rights (e.g., patents copyrights and royalties from such rights). The term does not include \* \* \* :

any equity interest that, when aggregated for the Investigator and the Investigator's spouse and children, meets both the following tests: does not exceed \$10,000 in value as determined through reference to public prices or other reasonable measures of fair market value, and does not represent more than a 5 percent ownership interest in any single entity; or salary, royalties or other payments that when aggregated for the Investigator and the Investigator's spouse and dependent children over the next 12 months are not expected to exceed \$10,000.

In response to the comments submitted to the proposed rule, as well as the comments and recommendations made by FDA's Science Board at the meeting held on March 29, 1996, FDA has eliminated the 5 percent equity holding provision from the final rule. The agency recognizes that for many corporations, this would represent an unrealistically large threshold interest. Instead, in this final rule, FDA defines "significant equity interest in the sponsor of the covered study" to mean any ownership interest, stock option, or other financial interest whose value cannot be readily determined through reference to public prices or any equity interest in a publicly traded company that exceeds \$50,000 that is held by the clinical investigator during the time the clinical investigator is carrying out the study and for 1 year following the completion of the study. FDA, thus, agrees with the comments stating that a 5 percent equity interest in a publicly held company could vary enormously and believes that a \$50,000 disclosure threshold strikes the appropriate balance between the agency's need to be aware of and help minimize the potential for bias in clinical data and the need to avoid unreasonably burdening clinical investigators and applicants.

9. A few comments said that the definition of significant payments of other sorts in new § 54.2(f) should apply only to research grants, retainers and honoraria that are related to the study.

A few comments said that the \$5,000 threshold limit for such payments was too low and that the applicable timeframe should be clarified. Some comments suggested that FDA only require disclosure of payments made directly to the clinical investigator and not to an institution, such as a university that employs the investigator. Some comments suggested that FDA delete the requirement for disclosure of significant payments of other sorts entirely.

Retention of this provision, as proposed, was discussed at the FDA Science Board meeting on March 29, 1996. Most Science Board members and many panelists agreed that information on "significant payments of other sorts" made by the sponsor of the covered study (such as a grant to fund ongoing research, compensation in the form of equipment, a retainer for ongoing consultation, or honoraria), even if not directly related to the conduct of the study, should be disclosed because these types of financial arrangements exist and have the potential to give the clinical investigator an "interest" in the company. In response to the comments that described the \$5,000 disclosure threshold for these payments as too low and taking into account the discussion with Science Board members, FDA has raised the threshold dollar amount that would trigger disclosure to FDA from \$5,000 to any amount exceeding \$25,000 made by the sponsor of the covered study directly to the clinical investigator or to the institution for support of activities of the investigator, exclusive of costs associated with the conduct of the trial or of any other clinical trial. FDA believes this approach strikes a reasonable balance between the agency's need to be aware of and help minimize the potential for bias in clinical data and the need to avoid unreasonably burdening applicants. FDA is also clarifying that the period for which this disclosure must be made includes the period during the conduct of the study and for 1 year following completion of the study.

10. One comment said that applicants should not be responsible for veracity of the investigators' disclosure statements to the companies.

FDA recognizes that clinical investigators could provide incorrect financial information to applicants. FDA does not expect to prosecute any applicant who takes appropriate steps to obtain accurate information and through no fault of its own unknowingly submits to FDA erroneous financial information that was provided to the applicant by the clinical investigator.

11. In the proposed rule, FDA requested comment on whether certification and disclosure statements should be generally disclosable to the public. FDA received many comments on this issue, the majority opposing the public release of this information. Those who argued in favor of releasing this information said that public disclosure of financial information in some useful form is critical because shrinking Government resources make it impossible for FDA to monitor these arrangements properly, and the public should be able to play some effective oversight role in this area. These comments said that public disclosure of this information is necessary in order to discourage the occurrence of substantive financial abuses at the outset of the clinical trial process. Comments opposing this view argued that the public would not be in a position to interpret this information properly, that public release of this information is an unwarranted intrusion into the private affairs of clinical investigators, and that disclosure of this information could discourage highly qualified investigators from participating in research. One comment said that there may be some instances where public disclosure should be required, and that disclosure to an advisory committee should be kept confidential and limited to the circumstances where the investigator's interests surpass a specific threshold.

FDA agrees with those comments that stated that certain types of financial information requested under the rule, notably equity interests, should be surrounded by a reasonable expectation of privacy. Therefore, such information would be protected from public disclosure unless circumstances clearly outweigh the identified privacy interest.

FDA does believe, however, that there may be legitimate public interest in the information that warrants its disclosure. Certain requested information such as a patent ownership, already may be public information and would, therefore, be releasable. In other cases, a financial arrangement may so affect the reliability of the study that it may become necessary for the information to be disclosed publicly during the evaluation of the study (e.g., during an advisory committee meeting).

Because the full range and impact of such arrangements cannot be predicted, and because of the variability of both clinical trials and their financing mechanisms, it is impossible to establish a comprehensive rule regarding public disclosure of reported information. FDA, intends, therefore, to proceed on a case-by-case basis in determining whether the circumstances

outweigh the privacy interest of the clinical investigator(s). FDA will determine for each instance of disclosure when to make the information public and by what means.

In any consideration of disclosure issues, it is useful to keep in mind FDA's expectation that these issues will not affect the great majority of clinical investigators who participate in studies of FDA-regulated products. FDA expects that only a small minority of clinical investigators will have financial interests of any kind that are disclosable to FDA; and of that number, FDA expects that only a small subset would be involved in situations in which the investigator's privacy interest would be outweighed by the public interest. FDA strongly encourages any firm that is required to disclose interests and arrangements of one or more clinical investigators to meet with FDA early on for guidance on management of the affected clinical study to help ensure that the potential impact of the disclosed financial situation on the integrity of the study does not rise to this level of concern.

12. Some comments said that compliance with PHS disclosure requirements should be deemed sufficient to satisfy FDA's requirements. One comment said that an investigator who receives PHS funds should be required only to provide the company with a copy of his PHS disclosure statement. A third comment said that FDA should reexamine timing of the disclosure to be consistent with the PHS rule. Another comment said that FDA should not rely on PHS disclosure because the two agencies are separate and that research institutions should not have to rely on disclosures submitted directly to institutions as substitutes for compliance procedures imposed on companies.

This issue was raised for comment in the September 1994 proposed rule. After considering the comments, FDA concludes PHS and FDA disclosures should not be interchangeable. Although the PHS rule and the comparable NSF policy have some objectives similar to those of FDA's rule, the PHS rule and the NSF policy have a different focus. They deal with policies of Federal grant making agencies and the credibility of the scientific enterprise, including such issues as: Potential personal profit from federally funded research, undue secrecy or refusal to share scientific data from publicly funded research, and the potential detrimental effect upon academic programs by inappropriate use

of graduate students or "conflicts of commitment." Although FDA acknowledges the validity of such concerns, FDA's responsibilities are directed at helping to ensure data integrity for the purposes of product review. Thus, this rule is focused on payment arrangements and other financial interests of clinical investigators that have the potential for introducing bias into studies intended to support marketing applications. It is important that FDA be aware of such interests and arrangements as part of its evaluation of marketing applications. Because much of the information reported under the PHS rule is not related to the product review process, but is more relevant to issues of basic research, FDA has determined that it is appropriate for FDA to have different reporting requirements.

13. Several comments argued that FDA underestimated the paperwork burden on applicants and clinical investigators of the procedures for financial disclosure specified in the proposed rule. One comment from a pharmaceutical firm maintained that, while not overly onerous for investigators, the accumulated paperwork would probably cost pharmaceutical companies in excess of \$1 to 1.5 million annually. Another firm said that the rule would increase study costs by 5 percent. A trade association described the disclosure procedures as amounting to a "severe paperwork burden," and another comment alleged that FDA conducted a cursory examination of the additional number of hours required to comply with these procedures.

The agency took a careful and thorough approach in assessing the number of hours that would be spent by applicants because of a continuing concern that the rulemaking should not impose undue burdens on industry. FDA believes that the comments have overestimated the costs and difficulties of complying with this regulation. In an effort to provide a clearer understanding of the paperwork burden involved, FDA has reassessed the potential paperwork costs for applicants, using current data and more conservative assumptions than those used at the time the proposed rule was drafted. To facilitate reporting, the agency has developed forms for certification and disclosure and has added language to the final rule to allow an applicant to attach to one certification statement a list of all investigators for whom the applicant is certifying. In this way, preparation and submission of multiple statements is

avoided, and the process is streamlined for applicants.

FDA believes that the collection of information required by this regulation and the preparation and submission of a certification statement would not be onerous. Firms who contracted for covered studies would already have on hand all information pertaining to financial arrangements with clinical investigators and significant payments of other sorts; proprietary interests (e.g., patents) of clinical investigators; and equity interests of investigators in nonpublicly traded enterprises. Applicants who were the sponsors of covered studies would need only to obtain from investigators information on the clinical investigators' equity interests in the applicant, a step that would be necessary only if the applicant is publicly traded. Applicants who did not contract for covered studies must obtain the required information from the sponsor of the covered studies and the investigators or demonstrate conclusively that it was not possible to do so. In either case, a large amount of time would not be required. Clinical investigators, for their part, can reasonably be expected to have easily accessible records on their personal equity interests for tax purposes. They should not have difficulty providing this information to sponsors of the covered studies.

As noted, FDA believes that preparation and submission of the certification statement and the list of investigators to whom the statement applies represents a modest effort. In the estimate presented in section V of this document, the agency has used the figure of 1 hour of preparation time for these materials, which it believes to be more than adequate to cover the actual work involved. FDA believes that preparation of a disclosure statement and the accompanying explanation of steps taken to minimize the potential for bias of the covered study is appreciably more time-consuming and has assigned 4 hours to this activity.

The agency assumes that every applicant will submit a certification statement for at least one clinical investigator. The agency further assumes, based on current data, that 1,000 sponsors will submit marketing applications for drugs, biologics, or devices each year, with this number broken down for different types of applications as follows:

TABLE 1.—ANNUAL ESTIMATED NUMBER OF MARKETING APPLICATIONS FOR DRUGS, BIOLOGICS, AND DEVICES

Type of Application	No. of Sponsors
<i>Drugs</i>	
New drug application (NDA)	135
NDA supplement	100
Abbreviated new drug application (ANDA)	240
ANDA supplement	120
Rx to over-the-counter switch	10
<i>Biologics</i>	
Product license application (PLA)	25
PLA supplement	10
<i>Devices</i>	
Premarket approval (PMA)	50
PMA supplement	10
Reclassification petitions	4
510(k)	300

There is no firm basis for estimating the frequency of disclosure by applicants. FDA assumes that from 1 to 10 percent of applicants would need to submit disclosure for one or more clinical investigators. In estimating the total burden hours for this activity, FDA has assumed a 10 percent rate, which is the maximum number of applicants that might be estimated to disclose annually. The agency believes this figure will in all likelihood be smaller, perhaps markedly so.

The conforming amendments to drug, biologics, and medical device regulations that accompany this rule provide for sponsors of the covered studies to obtain the necessary financial information (e.g., equity interests) from investigators at the time the investigator is retained by the sponsor of the covered study, along with other required information. FDA concludes that it is reasonable to assume that a sponsor could incorporate financial disclosure information into the sponsor's existing system for maintaining investigator information, and the addition of this information would represent a negligible expenditure of time. It is estimated that 15 minutes will be required to add this information to an application record.

The agency estimates that to comply with information collection activities under this final rule, applicants will spend a total of 1,000 hours annually for certification activities (1,000 applicants multiplied by 1 hour) and 400 hours for disclosure (100 applicants multiplied by

4 hours). The total time estimated to be spent by clinical investigators is 4,600 hours (46,000 clinical investigators multiplied by 6 minutes). The total estimated annual burden is 6,000 hours for the drug, biologics, and device industries and all clinical investigators. Once again, FDA has reached this total after carefully analyzing the activities involved, and using high-end assumptions for both the amount of time that would be required for each activity and the number of applicants who would disclose. As noted in section V of this document, FDA invites comments on these estimates.

14. Several comments alleged that FDA has failed to comply with the requirements of the Regulatory Flexibility Act. These comments stated that FDA should conduct a Regulatory Flexibility Analysis under the Regulatory Flexibility Act, because "the impact of the rule will fall disproportionately on small firms, since they may not be able to pay clinical investigators on a fee-for-service basis." These comments said the rule would significantly affect small firms because of such factors as "the thousands of investigators who would need to provide information to sponsors," the composition of the medical device industry, 98 percent of which is made of small businesses, and the "severe paperwork burden."

Included in this final rule is a Regulatory Flexibility Analysis to assess the impact of the regulation on the industries subject to this rule. In this analysis, which is included in section IV of this document, the agency concludes that this final rule does not have a significant impact on a substantial number of small businesses.

15. Several comments recommended that FDA limit the scope of the rule with respect to covered studies. One comment said that Phase 1 safety studies should be exempted because they are "preliminary in nature and not as pivotal as state 2 or 3 trials." Another comment said that the rule should cover only those studies that the applicant considers to be "adequate and well controlled investigations intended to provide substantial evidence of effectiveness for new drugs." A third comment urged that the rule exempt bioavailability/pharmacokinetic studies, which, the comment said, generally result in objective, quantitative results based on tangible data. This comment recommended limiting the studies covered by the regulation to studies of a non-pharmacokinetic nature, studies with subjective endpoints, and single-investigator studies. A comment from a pharmaceutical firm said that the regulation should target specific types of

investigations, such as unblinded device studies. Another comment stated that, based on the definition in new § 54.2(e), the rule would appear to encompass large-scale open-label studies, such as studies involving some cardiovascular therapies, compassionate use studies, and parallel track studies, all of which might be submitted in support of an NDA. The comment noted that investigators in such studies could number in the thousands and said that it would be an unwarranted administrative burden to require an applicant to obtain financial information from each clinical investigator.

The definition of covered clinical study in the rule refers to studies on which the sponsor relies to support efficacy and studies where a single investigator makes a significant contribution to safety. That generally would not include Phase 1 tolerance studies or pharmacokinetic studies (except for bioequivalence studies) and would include clinical pharmacology studies only when they are critical to an efficacy determination. In general, large open studies, treatment protocols and other studies with large numbers of investigators would not be covered. In these studies, the large number of investigators generally means that no single investigator has a major responsibility for the data. In addition, important adverse events will generally be apparent because they lead to cessation of therapy and submission of the case report form. Although it is not impossible that a financial interest could be important in these studies, it is relatively unlikely and the agency has concluded that the effort needed to obtain financial information for the investigators in these studies should not be undertaken.

16. Some comments maintained that the regulation would deter investigators from participating in clinical research and would be a hindrance to clinical research. One comment stated, "while investigators will initially see no issue, as soon as FDA takes the first action to set a precedent, some investigators will become reluctant to participate in clinical studies."

FDA does not agree. The agency estimates that the majority of clinical investigators will have no financial arrangements or interests subject to disclosure under the terms of the regulation. For those investigators who have such interests, FDA is not prohibiting or requiring divestiture of any financial interests, nor does FDA believe an investigator should be penalized in any way for holding such

interests. It is, therefore, difficult to see why investigators would be deterred by this regulation from participating in clinical research. As for those comments suggesting that the regulation would hinder clinical research, FDA does not believe the final regulation will impose a significant burden and certainly not a burden sufficient to hinder clinical research.

17. In the preamble to the proposed rule, FDA requested comment on whether the agency should require disclosure of interests held by a clinical investigator in a firm considered to be a competitor of the sponsor of the covered study. Comment received was almost equally divided with respect to such disclosure. One comment in support of disclosure of competing interests stated that competing interests are just as likely to result in bias; others said that if the purpose of financial disclosure is to detect bias, it shouldn't matter whether the bias is positive or negative. Comments opposed to disclosure of such interests said that such a requirement might not be realistic inasmuch as it is often not possible to identify every company that is in competition with the sponsor of the covered study. A comment from one trade association stated that such interests should not concern FDA, and a comment from another trade association said that, in this regard, it should be sufficient to FDA for a sponsor of a covered study to be willing to use an investigator.

FDA agrees with the arguments presented by the comments opposing a requirement for disclosure of competing interests, and such a requirement is not included in this final rule.

18. In the preamble to the proposed rule, FDA asked for comment on whether the definition of a clinical investigator should include business partners of the investigator, who might share in profits from the investigator's arrangements or financial interests. The majority of comments on this issue opposed the inclusion of business partners, but these and other comments addressed other aspects of the definition. One comment concurred with the definition. Several comments found the definition to be too broad and stated that, as proposed, the definition would involve all study personnel and, thus, pose an enormous administrative burden. Two comments recommended limiting the scope of the definition to the principal investigator only, and one comment recommended that the definition include the principal investigator and the principal investigator's immediate family. Other comments argued that the definition

should not include the investigator's immediate family. Some comments suggested that the definition of clinical investigator for the purposes of this rule should be consistent with the definitions of clinical investigator in various agency regulations, including regulations governing investigational drugs and devices, as well as 21 CFR part 50, Protection of Human Subjects, and 21 CFR part 56, Institutional Review Boards, or consistent with the definition in the PHS rule.

FDA agrees with the comments opposing the inclusion of business partners as unnecessary and potentially burdensome. With regard to making the definition of clinical investigator consistent with the PHS regulation on objectivity in research and various other agency regulations, FDA believes that those definitions are broader than needed to achieve the goals of this regulation. For example, the definition of investigator in the PHS final rule on objectivity in research means the principal investigator and any other persons responsible for the design, conduct, or reporting of research funded by PHS, or proposed for such funding. FDA agrees with those comments supporting a more narrow definition of clinical investigator and defines clinical investigator for the purpose of this rulemaking to be any listed or identified investigator or subinvestigator who is directly involved in the evaluation of research subjects. As in the PHS rule, FDA's definition of clinical investigator, in new § 54.2(d), also includes the investigator's spouse and dependent children.

19. FDA did not propose to require disclosure of financial interests in, and arrangements with, the sponsor of the covered study by full-time employees of the sponsor of the covered study, explaining that the agency gives an appropriate level of scrutiny to the submitted data in such instances on the assumption that such employees have a clear financial as well as other interests in the outcome of the research. The majority of comments agreed that the rule should not cover such full-time employees. Some comments, however, did not support a blanket exemption for such employees. One comment argued that employee incentives such as promotion or termination could depend on product approval. Another comment said that full-time employees should be subject to disclosure requirements if they meet the equity threshold. A third comment stated that if all employees are treated with maximum scrutiny, further disclosure "may not be necessary." One comment said that employees who are

part-time employees of the applicant should also be exempt.

The agency treats data from clinical investigators who are the employees of sponsors with maximum scrutiny and will continue to do so because such employees can be assumed to have significant financial interests in the outcome of studies, often including stock options and significant equity interest in their employers. Because part-time employees also may receive such incentives, FDA would apply similar scrutiny to them. Thus, FDA has changed the language in new § 54.4 with respect to identifying clinical investigators who are full-time employees of the sponsor to read "full- or part-time employees of the sponsor of a covered study," clarifying that the agency will not require certification or disclosure for part-time employees.

20. Several comments argued that refusal to file a marketing application is an overly harsh response to an investigator's financial interests. One comment noted that applications may contain reports of studies not conducted by the sponsor and asked whether such studies would be excluded from the refusal-to-file provision. Another questioned whether the agency would refuse to file an application if one disclosure statement should be missing in the face of hundreds being provided.

In new § 54.2(e) FDA has defined a covered clinical study as one the applicant or FDA relies on to establish that the product is effective or that make a significant contribution to the demonstration of safety. This generally would not include studies reported only briefly or in the form of a publication, unless the latter were intended to be the critical supportive study. The rule emphasizes that an applicant may consult with FDA as to which clinical studies constitute "covered clinical studies." Although most marketing studies that meet this definition will have been conducted by the applicant, some critical studies may have been conducted by an academic or governmental organization (e.g., by the National Institutes of Health or Veteran's Administration) or by another firm. In these cases, the relevant financial interests are those that are sponsor-independent (patent ownership) or that relate to the sponsor of the study (e.g., payment in options or significant payments of other sorts). The applicant should be aware of all interests that investigators might have (e.g., patent rights) but the applicant may not be aware of prior arrangements with the study sponsor such as an expectation of a royalty payment, significant payments of other sorts, or of

an ownership interest in a nonpublicly traded study sponsor. It is possible that some of this information cannot be obtained.

The conforming amendments to parts 312 and 812 (21 CFR parts 312 and 812) require clinical investigators to provide sponsors the information needed to allow an applicant to submit certification and disclosure statements. FDA has given further consideration to the application of the refusal-to-file provision, however, and concludes that where circumstances make it impossible for an applicant of an application to obtain the information needed for certification or disclosure for one or more clinical investigators, and the applicant explains these circumstances adequately, the agency will not refuse to file an application. The refusal to file provision is not based on the investigator's financial interest but on failure of the applicant to disclose them.

21. Two comments suggested that, before the final rule becomes effective, FDA conduct a series of educational fora on these new requirements to ensure that they are understood by the industry that must comply with them.

FDA welcomes the suggestion. Just as the agency has opened the development of the regulation to public participation in a number of ways, it will now seek opportunities to describe the provisions of the final rule to all segments of the public. FDA will take these steps in addition to working with applicants, as the agency has indicated consistently it will do, to help ensure that their clinical research is carefully managed with respect to protection from potential bias.

### III. Conforming Amendments

At the time the regulations in new part 54 were proposed, FDA proposed conforming amendments to certain regulations for drugs, biologics, and devices. The final amendments to these regulations have been modified as necessary to ensure continuing conformity with the final regulations and will take effect at the time those regulations become effective. The amendments are described in detail in the following sections.

#### A. Amendments to Regulations for Human Drug Products

In its regulations governing investigational new drug applications, FDA is amending § 312.53(c), which applies to the selection of investigators, to require sponsors to obtain financial information from clinical investigators. As noted in the preamble to the proposed rule, this amendment provides for sponsors to acquire financial information from clinical investigators

before starting clinical investigations. This will enable the sponsor, and any future potential applicant, to discover potential bias on the part of the clinical investigator before the investigation begins and permit the sponsor to consult with FDA on management of the situation. As noted previously, the sponsor of a clinical study and the applicant for a marketing application would be the same entity in the majority of cases. However, in some cases, an applicant would have obtained the product and related studies from the study sponsor, including the relevant information as to financial interests of clinical investigators.

Section 312.57 is amended to require sponsors to maintain records on financial interests and arrangements of investigators and investigators' immediate families as required in new part 54.

The agency is amending §§ 314.50 and 314.60 (21 CFR 314.50 and 314.60) to require that all NDA's, amendments to applications, and supplements that contain new data from a previously unreported study include certification and disclosure statements as required in new part 54. FDA is amending § 314.94 (21 CFR 314.94) to require certification or disclosure statements in ANDA's. The agency originally proposed that the certification and disclosure statements be included on the application form. The agency has determined that this would be impractical, and is therefore amending §§ 314.60 and 314.94 to require that the financial certification or disclosure statement be part of the application submission, but not be included on the application form.

Under 21 CFR 314.101(d), the agency may refuse to file or receive an application that is incomplete. Failure to include a financial certification or disclosure statement, as required by amended §§ 314.50(l) and 314.94(a)(13), would give the agency grounds to refuse to file or receive the application. Similarly, amended § 314.60(a) gives the agency authority to refuse to accept any amendment to an unapproved application when that amendment contains new clinical data from an unreported study and does not include a financial certification or disclosure statement. These provisions incorporate the requirement for a financial certification or disclosure statement found in new part 54. In some situations, a certification or disclosure statement is not required under new part 54, and thus the agency would not refuse to file or receive the application, or refuse to accept the amendment for failure to include the statement. For example, new § 54.4(c) in this final rule.

FDA recognizes that it would not refuse to file an application that contains a certification from the applicant stating that it was not possible to obtain the information required for certification and disclosure and the reason, e.g., if a covered study were concluded prior to the requirement for a study sponsor to obtain this information from investigators and the investigators could not be reached or were unwilling to provide the information voluntarily.

FDA is amending 21 CFR 314.200 and 314.300 to require any person who submits clinical data as part of the hearing process for refusals to approve and for withdrawals of approvals for NDA's, abbreviated antibiotic drug applications, or ANDA's, or the hearing process for issuing, amending, and withdrawing antibiotic regulations, to submit a certification or disclosure statement.

Amendments to 21 CFR 320.36 require similar reporting and recordkeeping for certification and disclosure statements accompanying bioequivalence studies as would be required under part 312.

Amendments to 21 CFR 330.10 require certification or disclosure statements to accompany clinical data submitted as part of the over-the-counter drug monograph process.

#### B. Amendments to Regulations for Biologicals

FDA is amending the regulations at 21 CFR 601.2(a) governing the filing of applications for product licenses to require the inclusion of certification or disclosure statements, or both, as required in new part 54.

#### C. Amendments to Regulations for Medical Devices

FDA is adding a new paragraph to 21 CFR 807.87 to require the inclusion of certification or disclosure statements, or both, in a premarket notification submission. A paragraph is added to § 807.100 to allow FDA to withhold a decision on a premarket notification submission until certification or disclosure statements are submitted to FDA as required under new part 54.

FDA is amending 21 CFR 807.31 to require that certification and disclosure statements be retained at the establishment maintaining the historical file. Section 812.110 is amended to require clinical investigators to provide sponsors with sufficient accurate financial information (see 812.110) for the preparation of certification or disclosure statements.

FDA is amending § 812.43(c), which applies to the selection of monitors and investigators, to require sponsors to

obtain financial information from clinical investigators. Although not identified in the proposed rule as a conforming amendment to the device regulations, this revision is consistent with the requirement in § 812.110(d) that investigators provide financial information to sponsors to obtain the information. This amendment provides for sponsors to acquire financial information from clinical investigators before starting clinical investigations. This will enable the sponsor (and any future applicant) to discover potential bias on the part of the investigator before the investigation begins and permit the sponsor to consult with FDA on management of the situation. This conforming amendment parallels the drug conforming amendment in § 312.53(c).

FDA is amending § 812.140(b)(3) to require sponsors to maintain records on financial interests and arrangements of investigators and investigators' immediate families as required in new part 54. This conforming amendment is consistent with the recordkeeping requirements in new part 54.

FDA is amending 21 CFR 814.20 to require the inclusion of certification or disclosure statements in premarket approval applications. The agency is also amending 21 CFR 814.42 to provide that the agency may refuse to file an application or amendments that contain clinical data unless certifications or disclosure statements are included as required by new part 54.

FDA is amending 21 CFR 814.112 to require applicants of humanitarian device exemption (HDE) applications to submit certification or disclosure statements. The regulation on HDE's was issued after publication of the financial disclosure proposal. This amendment is consistent with the other conforming amendments requiring financial disclosure information for premarket approval applications.

Because supporting data are needed in a reclassification petition to satisfy the requirements of a determination of safety and effectiveness of a device, FDA is amending 21 CFR 860.123 to require any sponsor who submits clinical data as part of a reclassification petition to include certification or disclosure statements, or both, as required by new part 54.

#### IV. Summary of Changes

FDA has made the following changes in the final rule in response to comments received on the proposed rule as discussed previously in this preamble and to clarify the intent of the regulation:

1. Recognizing that the firm submitting a marketing application might not have sponsored the covered studies, FDA has changed the term defined in new § 54.2(b) from "Significant equity interest in the applicant" to "Significant equity interest in the sponsor of a covered study" and has revised new § 54.2(f) ("Significant payments of other sorts") to contain similar clarifying language. FDA has defined "applicant" and sponsor of the covered study at new § 54.2(g) and (h) and has added language to the purpose statement in 21 CFR 51.1 to distinguish a sponsor of a covered study from a sponsor of a marketing application (i.e., applicant). The agency has also added language to the scope of the regulation in new § 54.3, to make it clear that the requirements of the regulation apply to applicants whether or not the applicant was the sponsor of the studies submitted. The applicant is responsible for obtaining the information required by the regulation or for demonstrating conclusively why it is not possible to do so. The agency has added similar clarifying language to appropriate sections of the disclosure requirements in new § 54.4 and requirements for recordkeeping and record retention in new § 54.6.

2. FDA has made one further change in the definition of a significant equity interest in new § 54.2(b). In the proposed rule, a disclosable equity interest in a publicly traded corporation was defined as "any equity interest in a publicly traded corporation that exceeds 5 percent of total equity, and no applicable time period was stated. In the final rule, FDA has defined an equity interest in a publicly traded corporation as one that exceeds \$50,000 during the time the clinical investigator is carrying out the study and for 1 year following completion of the study." FDA has eliminated the 5 percent equity holding provision and has replaced it with the \$50,000 threshold because FDA recognizes that for many corporations, a 5 percent equity interest represents an unrealistically large threshold interest. FDA has clarified the time period whereby applicants are required to disclose information to FDA for 1 year following completion of the study (i.e., after enrollment of all the subjects and followup subjects in accordance with the clinical protocol) to further reduce the possibility that clinical investigators could exert undue influence during final data analysis.

3. In response to comments that the definition of "clinical investigator" in new § 54.2 (d) of FDA's proposed rule was too broad, FDA has revised this definition to clarify that it includes only

principal and subinvestigators who are directly involved in the treatment and evaluation of research subjects and their spouses and dependent children.

4. In the final rule, FDA has shortened and clarified the definition of covered clinical study in new § 54.2(e).

5. In new § 54.2(f) of the proposed rule, FDA defined "significant payments of other sorts" as "payments that exceed \$5,000 (e.g., grants to fund ongoing research compensation in the form of equipment or retainers for ongoing consultation or honoraria) or that exceed 5 percent of the total equity in a publicly held and widely traded company." In the final rule, FDA has set the threshold for disclosure of such payments at a value of more than \$25,000 and has further revised and clarified this definition so that it reads as follows:

Significant payments of other sorts means payments made by the sponsor of a covered study to the investigator or the institution to support activities of the investigator that have a monetary value of more than \$25,000, 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.

6. The opening paragraph of proposed § 54.4 required the applicant to "completely and accurately disclose or certify information concerning the financial interests of a clinical investigator who is not a full-time employee of the sponsor \* \* \*". In response to a comment, FDA is changing this phrase to read "not a full-time or part-time employee of the sponsor for each covered clinical study."

7. Section 54.4(a) of the proposed rule stated that an applicant shall submit for each covered clinical study either a certification or disclosure statement. FDA has revised this statement to make it clear that the applicant must submit a certification or disclosure statement for each investigator who participated in a covered clinical study, as opposed to each covered clinical study. FDA recognizes that, in some instances, an applicant might need to submit both certification and disclosure statements to cover the interests of all clinical investigators who participated in one covered study. The agency has also changed this statement to make it clear that the applicant may submit one certification statement to cover all investigators for whom certification is made.

8. FDA has also made provision in new § 54.4 of the final rule for an

applicant who can demonstrate that it was not possible to obtain the information required for certification and disclosure to certify that the applicant, acted with due diligence, to obtain the information needed to certify or disclose but was unable to do so. For example, if the laws of a foreign country preclude the applicant from obtaining the financial information, a statement submitted to FDA referencing such laws would be appropriate.

9. FDA has deleted the statement in new § 54.6 of the proposed rule that if the application is not approved, a sponsor shall retain covered records "for 2 years after the product, for which the application was submitted, was shipped and delivered to clinical investigators for testing." FDA has deleted this statement because it is inconsistent with other recordkeeping requirements.

10. Also in new § 54.6(a)(1) and (a)(2), FDA has deleted the requirement from the proposed rule that sponsors must show all compensation paid to clinical investigators and has replaced it with a statement requiring applicants to complete records showing any financial arrangement as described in new § 54.4(a)(3)(i) and (a)(3)(ii). FDA has made the change in order to ease recordkeeping requirements and require applicants to maintain records that may raise potential problematic financial arrangements. Similarly, FDA has revised the conforming amendments in § 312.57 to ease recordkeeping requirements and has added § 812.43(c)(5) to identify the device sponsors' requirements.

## V. Analysis of Impacts

FDA has examined the impacts of the final rule under Executive Order 12866 and the Regulatory Flexibility Act (5 U.S.C. 601-612). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; and distributive impacts and equity). The agency believes that this final rule is consistent with the regulatory philosophy and principles identified in the Executive Order. The agency concludes that the rule is a significant regulatory action as defined by the Executive Order. The following discussion summarizes the agency's economic assessment, and where possible, presents quantitative estimates of the impact of the regulation on the industries subject to this rule.

### A. Regulatory Flexibility Analysis

The Regulatory Flexibility Act requires agencies to prepare a Regulatory Flexibility Analysis for each rule unless the agency certifies that the rule would not have a significant economic impact on a substantial number of entities. As explained in section IV.B of this document, the agency believes that this final rule will not have a significant economic impact on a substantial number of small entities. Nevertheless, the rule may impose significant costs on a few small businesses. Because FDA cannot adequately quantify all of this impact, it has prepared a Regulatory Flexibility Analysis as part of its economic assessment. This analysis, which is summarized in section IV.B of this document, is available for review at the Dockets Management Branch (address above).

FDA finds that it is important to the public health to ensure, as much as possible, that the safety and efficacy data submitted to the agency in support of marketing applications are free of the effects of any bias that may result from the financial interests of investigators. The information received through the reporting requirements in the final rule will help the agency to determine the reliability of data submitted in marketing applications. In addition, the reporting requirements will help to ensure that sponsors of covered studies consider potentially problematic financial arrangements and interests in the early stages of product development and, if necessary, consider how best to minimize such potential sources of bias in their clinical studies.

The final rule will affect firms that sponsor marketing applications containing clinical data in the human drug, biologic, and medical device industries. Although FDA receives about 1,000 marketing applications and supplements per year that will be subject to this rule, the agency believes that only a few of these applications will be more than minimally affected. Public comments in response to the proposed rule indicate that potentially problematic financial arrangements occur only occasionally, although perhaps more often within the small biotechnology and medical device firms that choose to utilize, for example, the inventor of a product as a clinical investigator, or to make payments to the clinical investigator in the form of equity interests such as stock options. While FDA cannot determine the precise number of such arrangements, representatives from the drug and device industries (Science Board

Meeting, March 29, 1996) report that sponsors only rarely reimbursed clinical investigators by those means described as problematic in the final rule.

The rule will create costs in three areas: Reporting, recordkeeping, and research. Reporting and recordkeeping are discussed in section V of this document. The agency estimates that total reporting costs of sponsors and investigators will be less than \$450,000 annually and estimates no additional costs for recordkeeping. However, these costs are offset by the significant public health benefits of FDA's being able to adequately assess the reliability of clinical trial data and thus ensure the safety and efficacy of regulated products. As described previously, financial interests especially if combined with unblinded study designs, studies with subjective endpoints, and single investigator studies may increase the risk that purposeful or inadvertent bias could influence the outcome of the study.

Research costs can be incurred either before the product application has been submitted to the agency or after the agency begins its review. Costs may be incurred before an application is submitted when a clinical investigator has a disclosable interest and the sponsor modifies a trial protocol or alters procedures to minimize the potential for investigator bias. However, even where the investigator has a disclosable interest or arrangement, many clinical protocols will not need to be modified because they already are designed to minimize potential for investigator bias. (Sponsors are encouraged to meet with FDA to discuss protocol design and this is common practice with sponsors of covered clinical studies of human drugs and biologics). Although a few protocols may require some adjustment to the design, such as having a blinded observer carry out critical observations, most changes would be minor and not costly. In some cases, sponsors might choose a different investigator. Where a protocol is altered, however, sponsors would incur costs for modifying the protocol, preparing additional analyses, or hiring additional investigators. This would occur, however, only where there was a potentially important problem to resolve.

Costs could also occur after a marketing application is submitted if FDA determined that the financial interests of an investigator raise serious questions about the integrity of the data. In such a case, the agency may audit the data derived from the investigator, request that the applicant submit further analyses of the data, request that the

applicant conduct additional independent studies to confirm the results of the questioned study, or refuse to accept the result of the covered clinical study. The likelihood that this rule would require additional research will decline rapidly, however, as applicants adjust to the new requirements by designing studies that minimize the potential bias.

Because relevant clinical trials for most new drug and biological products are blinded and involve multiple sites and multiple investigators, the agency does not anticipate significant modifications to protocols for most of these products. Clinical trials for medical devices, however, tend to be smaller, involving fewer sites and fewer investigators. In addition, there is a higher possibility of "inventor/investigator" relationships in this industry and, therefore, the sponsors of medical device marketing applications may be more likely than sponsors of applications in other industries to

require protocol modifications that could lead to higher costs.

Unfortunately, until the agency collects the financial disclosure information that could be used to determine the frequency and type of future research protocol adjustments, it cannot project the likely magnitude of these research costs. That is, because FDA does not know which clinical protocols may have unacceptable potential biases, the agency has no means of quantifying the number of the research protocols that might be modified or the associated costs of such modifications. FDA notes, however, that such costs would occur only in the presence of potentially biased clinical trial data that would otherwise be used to support new product approval decisions and would therefore be worthwhile. Because such occurrences would be quite uncommon, FDA concludes that, in aggregate, these costs would be small.

### B. Small Business Impact

The Small Business Administration (SBA) uses employment size criteria to identify small businesses in the industries affected by this rule. SBA defines a drug company (Standard Industrial Code (SIC) 2834) as small if there are fewer than 750 employees; whereas biologic (SIC's 2835 and 2836) and medical device companies (SIC's 3841, 3842, 3843, 3844, 3845, and 3851) are considered small if employment is less than 500. Table 2 displays the distribution of companies by employment size. Even if the employment size category of 500+, which is the largest category reported by SBA, were considered as the small business threshold, approximately 87 percent of drug companies, 85 percent of biologic companies and 94 percent of device companies would be considered small. On this basis, most of the firms affected by this rule are small businesses.

TABLE 2.—NUMBER OF FIRMS BY EMPLOYMENT SIZE FOR 1993<sup>1</sup>

Industry	Employment Size				
	<20	20 to 99	100 to 499	1	Total
Drug	332	155	80	85	652
Biologic	208	92	50	65	415
Medical device	2,936	835	381	273	4,425

<sup>1</sup> Source: Special Census Tabulation prepared by U.S. Bureau of Census for U.S. Small Business Administration, Tab 3 - United States.

One industry comment expressed concern that the "impact of the rule will fall disproportionately on small firms, since they may not be able to pay clinical investigators on a fee-for-service basis." The writer was particularly concerned about the adverse effect this rule will have on the medical device industry and the "thousands of investigators who would need to provide information to sponsors."

FDA agrees that the smallest firms will exhibit the highest incidence of potentially problematic financial arrangements. Medical device and biotechnology sponsors that have few resources, especially new start-up companies, are more likely to engage in unconventional compensation arrangements than other companies. These smaller firms would also be more likely than the larger firms to have "inventor/investigator" relationships.

Even among the smallest firms, however, very few will incur significant costs. In fact, the majority of companies counted in Table 2 will not be affected by this rule. For example, only about 5 percent of the approximately 6,000 medical device companies will produce

any devices affected by the rule. For those relatively few firms that sponsor or conduct clinical trials, FDA has been told by industry representatives that only a small subset will have disclosable arrangements.

And even a smaller subset of firms may incur increased research costs, because only in rare cases would sponsors of the covered study need to modify original protocols, particularly because sponsors of the covered studies are encouraged to consult with the agency whenever a questionable financial arrangement or interest emerges. These consultations are particularly important, because the cost to modify a clinical trial design before a clinical trial is conducted is far lower than the cost to address a problem after the trial is completed. For these few instances where a sponsor of a covered study may need to take additional steps to minimize the potential for bias, FDA believes that the benefits of correcting potentially biased results will more than offset the costs of any needed research modifications.

### C. Analysis of Alternatives

FDA has considered various alternatives to publishing this final rule including not requiring submission of this information to the agency. After meeting with numerous groups including regulated industry and others, it was decided that it was necessary for FDA to require submission of this information in order for FDA to be adequately aware of influences that could affect data reliability. FDA also considered the need to prohibit certain financial interests where the original investigator was compensated in ways that have the potential to influence the outcome of the study. FDA decided against that option, however, because FDA recognizes that therapeutic products that benefit the public health have been developed by these means. Instead, FDA intends to give these types of financial arrangements close scrutiny.

Changes to the September 1994 proposed rule have been made to clarify the intent of the regulation and as a result of public comment, including meetings with industry, consumer groups, health professionals, and clinical investigators. Table 3 lists

changes made in the final rule that will reduce the economic impact on small businesses:

TABLE 3.—COMPARISON OF THE IMPACT OF THE PROPOSED RULE AND FINAL RULE ON FINANCIAL DISCLOSURE BY CLINICAL INVESTIGATIONS IN REDUCING THE ECONOMIC IMPACT ON SMALL BUSINESSES

Proposed Rule	Final Rule
(a) Definition of significant equity interest "any ownership interest stock option, or other financial interest whose value cannot be readily determined through reference to public prices, or any equity interest in a publicly traded corporation that exceeds 5 percent of total equity".	(a) Significant equity defined as exceeding \$50,000 during the time the trial is carried out for 1 year following completion of the study.
(b) \$5,000 disclosure threshold for significant payments of other sorts from the sponsor.	(b) Increased disclosure threshold to amounts exceeding \$25,000.
(c) Broader definition of clinical investigator and asked for comment on the inclusion of business partners.	(c) Narrowed definition to principal and subinvestigators and their immediate families.

## VI. Paperwork Reduction Act of 1995

This final rule contains information collection requirements that are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501–3520). The title, description, and respondent description of the information collection requirements are shown below with an estimate of the annual reporting and recordkeeping burden. Included in the estimate is the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing each collection of information.

### *Title:* Financial Disclosure by Clinical Investigators

*Description:* This final rule requires the sponsor of any drug (including a biological product), or device marketing application to certify to the absence of certain financial interests of clinical investigators and/or disclose those financial interests as required, when covered clinical studies are submitted to FDA in support of product marketing.

*Description of Respondents:* Respondents are sponsors of marketing applications containing clinical data from studies covered by the regulation. These sponsors represents

pharmaceutical, biologic and medical device firms. Many of these firms are small entities especially in the areas of medical devices and biologics/biotechnology. Respondents are also clinical investigators who provide financial information to sponsors of marketing applications.

FDA received a number of comments on the information collection estimates in the proposed rule (see comment no. 13 of section II of this document for a summary and response to these comments). The agency has added language to the final rule to allow one certification statement to cover all investigators for which the applicant is certifying in an application. FDA has also recalculated its estimate of the total number of hours that will be necessary to complete the information collection requirements associated with this final rule.

The applicant will incur reporting costs in order to comply with the final rule. Applicants will be required to submit, for example, a complete list of clinical investigators for each covered study, a list that is already required 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.

The clinical investigator will have to supply information pertaining to significant stock ownership in that company (e.g., whether the clinical investigator, his spouse or dependent child owns \$50,000 or more stock in that company).

Because the sponsor would be aware of any payments to investigators, patents or licenses held by investigators, and any other significant financial arrangements with investigators, most of the information that is necessary to certify or disclose is already available to the sponsor of the study. Similarly, sponsors that are nonpublicly traded corporations can easily identify their stockholders. The only information that the sponsor will need to obtain from the investigator would be the investigator's stock holdings in the sponsor, if the sponsor is publicly traded.

FDA expects that almost all applicants will submit a certification statement in § 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 (80 percent clerical time, 20 percent managerial).

BILLING CODE 4160-01-F

DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service Food and Drug Administration  <b>CERTIFICATION: FINANCIAL INTERESTS AND                  ARRANGEMENTS OF CLINICAL INVESTIGATORS</b>	Form Approved: OMB No. xxx-xxxx Expiration Date: xx/xx/xx
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**TO BE COMPLETED BY APPLICANT**

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

- (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators		

- (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).
- (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
FIRM / ORGANIZATION	
SIGNATURE	DATE

**Public reporting burden for this collection of information** is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

DHHS Reports Clearance Officer  
 Paperwork Reduction Project (0910-xxxx)  
 Humphrey Building, Room 531-H  
 200 Independence Ave., SW  
 Washington, DC 20201

*An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.*

Please DO NOT RETURN this application to this address.

TABLE 4.—ESTIMATED NUMBER OF APPLICATIONS, CLINICAL TRIALS, AND INVESTIGATORS SUBJECT TO THE PROPOSED RULE BY TYPE OF APPLICATION<sup>1</sup>

Application Type	Total Number Applications	Number of Applications Affected	Number of Trials	Number of Investigators
<i>Drugs</i>				
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	2,500	120	1	2
Rx switch	20	10	2	4
<i>Biologics</i>				
Product license application (PLA)	25	25	3 to 10	3 to 100
PLA efficacy supplement	10	10	1 to 3	3 to 100
<i>Medical Devices</i>				
Premarket approval (PMA)	50	50	1	10 to 20
PMA supplement	400	10	1	3 to 10
Reclassification petitions	8	4	1	3 to 10
510(k)	6,000	300	1	20

<sup>1</sup> Source: Agency estimates.

When certification is not possible and disclosure is made using the following 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 steps taken, describing them will be straightforward. The agency estimates

that it will take about 4 hours to prepare this narrative, 90 percent management time and 10 percent clerical.

BILLING CODE 4160-01-F

DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service Food and Drug Administration  <b>DISCLOSURE: FINANCIAL INTERESTS AND          ARRANGEMENTS OF CLINICAL INVESTIGATORS</b>	<b>Form Approved: OMB No. xxx-xxxx</b> <b>Expiration Date: xx/xx/xx</b>						
<b>TO BE COMPLETED BY APPLICANT</b>							
<p>The following information concerning _____, who participated as a clinical investigator in the submitted study _____, is submitted in accordance with 21 CFR part 54. The named individual has participated in financial arrangements or holds financial interests that are required to be disclosed as follows:</p> <p style="text-align: center; border: 1px solid black; padding: 2px;"><i>Please mark the applicable checkboxes.</i></p> <ul style="list-style-type: none"> <li><input type="checkbox"/> any financial arrangement entered into between the sponsor of the covered study and the clinical investigator involved in the conduct of the covered study, whereby the value of the compensation to the clinical investigator for conducting the study could be influenced by the outcome of the study;</li> <li><input type="checkbox"/> any significant payments of other sorts from the sponsor of the covered study such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria;</li> <li><input type="checkbox"/> any proprietary interest in the product tested in the covered study held by the clinical investigator;</li> <li><input type="checkbox"/> any significant equity interest in the sponsor of the covered study held by the clinical investigator as defined in 21 CFR 54.2(b).</li> </ul> <p>Details of the individual's disclosable financial arrangements and interests are attached, along with a description of steps taken to minimize the potential bias of clinical study results by any of the disclosed arrangements or interests.</p> <table border="1" style="width: 100%; border-collapse: collapse; margin-top: 10px;"> <tr> <td style="width: 50%; padding: 5px;">NAME</td> <td style="width: 50%; padding: 5px;">TITLE</td> </tr> <tr> <td colspan="2" style="padding: 5px;">FIRM / ORGANIZATION</td> </tr> <tr> <td style="width: 60%; padding: 5px;">SIGNATURE</td> <td style="width: 40%; padding: 5px;">DATE</td> </tr> </table>		NAME	TITLE	FIRM / ORGANIZATION		SIGNATURE	DATE
NAME	TITLE						
FIRM / ORGANIZATION							
SIGNATURE	DATE						
<p><b>Public reporting burden for this collection of information is estimated to average 4 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:</b></p> <p>DHHS Reports Clearance Officer          Paperwork Reduction Project (0910-xxxx)          Humphrey Building, Room 531-H          200 Independence Ave., SW          Washington, DC 20201</p> <p style="text-align: right;"><i>An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.</i></p> <p style="text-align: center;">Please DO NOT RETURN this application to this address.</p>							

FORM FDA 3455 (7/97)

EF  
Created by Electronic Document Services/USDHHS: (301) 443-2454

Until the agency begins to collect information on the financial arrangements between investigators and applicants, it cannot know the actual number of disclosable arrangements. Therefore, it is not possible to predict the total cost to industry of preparing these explanatory statements with any certainty, although the agency was told by industry representatives that few would be needed because the financial arrangements described in this rule are uncommon. FDA estimates that from 1 percent to 10 percent of the applications would need disclosure statements, and

has used the extremely conservative estimate of 10 percent in Table 5 below. 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 (greater than \$50,000) in the sponsor of

the covered study during the time of the clinical study and for 1 year after, or (2) disclose such interest. 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. The time required for this task may range from 5 to 15 minutes. Assuming a physician's hourly cost of \$87.69,<sup>1</sup> a \$336,695 estimated cost to investigators was calculated. Clinical investigators are accustomed to supplying such information in even greater detail when applying for research grants.

TABLE 5.—ESTIMATED ANNUAL REPORTING BURDEN

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)	1,000	1	1	1	1,000
54.4(a)(3)	100	1	1	4	400
54.4 (Clinical investigators)	46,000	1	1	.10	4,600
Total					6,000

The sponsors of covered studies will be required to maintain complete records of compensation agreements with any compensation paid to nonemployee clinical 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 application. This time is consistent with the current recordkeeping requirements for other information related to

marketing applications for human drugs, biologics, and medical devices. FDA judged the incremental costs associated with this new activity to be negligible because firms already maintain records of compensation as standard business practice and the required records pertaining to the financial interests of the investigators will typically consist of only one additional piece of paper per investigator. Currently, sponsors of

covered studies must maintain many records with regard to clinical investigators, including protocol agreements and investigator resumes or curriculum vitae and the inclusion of information required by this rulemaking would add little to this recordkeeping burden. FDA estimates that an average 15 minutes will be required for each recordkeeper to add this record to clinical investigators' files.

TABLE 6.—ESTIMATED ANNUAL RECORDKEEPING BURDEN

21 CFR Section	No. of Recordkeepers	Annual Frequency per Recordkeeping	Total Annual Records	Hours per Recordkeeper	Total Hours
54.6	1,000	1	1,000	.25	250

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

Although the September 22, 1994 (59 FR 48708), proposed rule provided a 90-day comment period under the Paperwork Reduction Act of 1980, and this final rule responds to the comments received, FDA is providing an additional opportunity for public comment under the Paperwork Reduction Act of 1995 that became effective after the expiration of the comment period and applies to this final rule. Therefore, FDA now invites comments on: (1) Whether the proposed collection of information is necessary for the proper performance of FDA's

functions, including whether the information will have practical utility; (2) the accuracy of FDA's estimate of the burden of the proposed collection of information, including the validity of the methodology and assumptions used; (3) ways to enhance the quality, utility, and clarity of the information to be collected; and (4) ways to minimize the burden of the collection of information on respondents, including through the use of automated collection techniques, when appropriate, and other forms of information technology.

Branch (address above). Comments should be identified with the docket number found in brackets in the heading of this document.

At the close of the 60-day comment period, FDA will review the comments received, revise the information collection provisions as necessary, and submit these provisions to OMB for review. FDA will publish a notice in the **Federal Register** when the information collection provisions are submitted to OMB, and an opportunity for public comment to OMB will be provided at that time. Prior to the effective date of this final rule, FDA will publish a notice in the **Federal Register** of OMB's

<sup>1</sup> Physician mean net income (after expenses, before taxes) for all specialties is \$182,395.20. Source: American Medical Association. Wage rate assumes 2,080 hours worked per year.

Individuals and organizations may submit comments on the information collection provisions of this final rule by April 3, 1998. Comments should be directed to the Dockets Management

decision to approve, modify, or disapprove the information collection provisions. An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

#### List of Subjects

##### 21 CFR Part 54

Biologics, Drugs, Medical devices, Reporting and recordkeeping requirements.

##### 21 CFR Part 312

Drugs, Exports, Imports, Investigations, Labeling, Medical research, Reporting and recordkeeping requirements, Safety.

##### 21 CFR Part 314

Administrative practice and procedure, Confidential business information, Drugs, Reporting and recordkeeping requirements.

##### 21 CFR Part 320

Drugs, Reporting and recordkeeping requirements.

##### 21 CFR Part 330

Over-the-counter drugs.

##### 21 CFR Part 601

Administrative practice and procedure, Biologics, Confidential business information.

##### 21 CFR Part 807

Confidential business information, Imports, Medical devices, Reporting and recordkeeping requirements.

##### 21 CFR Part 812

Health records, Medical devices, Medical research, Reporting and recordkeeping requirements.

##### 21 CFR Part 814

Administrative practice and procedure, Confidential business information, Medical devices, Medical research, Reporting and recordkeeping requirements.

##### 21 CFR Part 860

Administrative practice and procedure, Medical devices.

Therefore, under the Federal Food, Drug, and Cosmetic Act, and under authority delegated to the Commissioner of Food and Drugs, 21 CFR chapter I is amended as follows:

1. Part 54 is added to read as follows:

## PART 54—FINANCIAL DISCLOSURE BY CLINICAL INVESTIGATORS

### Sec.

- 54.1 Purpose.
- 54.2 Definitions.
- 54.3 Scope.
- 54.4 Certification and disclosure requirements.
- 54.5 Agency evaluation of financial interests.
- 54.6 Recordkeeping and record retention.

**Authority:** 21 U.S.C. 321, 331, 351, 352, 353, 355, 356, 357, 360, 360c–360j, 371, 372, 373, 374, 375, 376, 379; 42 U.S.C. 262.

### § 54.1 Purpose.

(a) The Food and Drug Administration (FDA) evaluates clinical studies submitted in marketing applications, required by law, for new human drugs and biological products and marketing applications and reclassification petitions for medical devices.

(b) The agency reviews data generated in these clinical studies to determine whether the applications are approvable under the statutory requirements. FDA may consider clinical studies inadequate and the data inadequate if, among other things, appropriate steps have not been taken in the design, conduct, reporting, and analysis of the studies to minimize bias. One potential source of bias in clinical studies is a financial interest of the clinical investigator in the outcome of the study because of the way payment is arranged (e.g., a royalty) or because the investigator has a proprietary interest in the product (e.g., a patent) or because the investigator has an equity interest in the sponsor of the covered study. This section and conforming regulations require an applicant whose submission relies in part on clinical data to disclose certain financial arrangements between sponsor(s) of the covered studies and the clinical investigators and certain interests of the clinical investigators in the product under study or in the sponsor of the covered studies. FDA will use this information, in conjunction with information about the design and purpose of the study, as well as information obtained through on-site inspections, in the agency's assessment of the reliability of the data.

### § 54.2 Definitions.

For the purposes of this part:

(a) *Compensation affected by the outcome of clinical studies* means compensation that could be higher for a favorable outcome than for an unfavorable outcome, such as compensation that is explicitly greater for a favorable result or compensation to the investigator in the form of an equity interest in the sponsor of a covered

study or in the form of compensation tied to sales of the product, such as a royalty interest.

(b) *Significant equity interest in the sponsor of a covered study* means any ownership interest, stock options, or other financial interest whose value cannot be readily determined through reference to public prices (generally, interests in a nonpublicly traded corporation), or any equity interest in a publicly traded corporation that exceeds \$50,000 during the time the clinical investigator is carrying out the study and for 1 year following completion of the study.

(c) *Proprietary interest in the tested product* means property or other financial interest in the product including, but not limited to, a patent, trademark, copyright or licensing agreement.

(d) *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.

(e) *Covered clinical study* means any study of a drug or device in humans submitted in a marketing application or reclassification petition subject to this part that the applicant or FDA relies on to establish that the product is effective (including studies that show equivalence to an effective product) or that make a significant contribution to the demonstration of safety. An applicant may consult with FDA as to which clinical studies constitute "covered clinical studies" for purposes of complying with financial disclosure requirements.

(f) *Significant payments of other sorts* means payments made by the sponsor of a covered study to the investigator or the institution to support activities of the investigator that have a monetary value of more than \$25,000, 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 the completion of the study.

(g) *Applicant* means the party who submits a marketing application to FDA for approval of a drug, device, or biologic product. The applicant is responsible for submitting the appropriate certification and disclosure statements required in this part.

(h) *Sponsor of the covered clinical study* means the party supporting a

particular study at the time it was carried out.

#### § 54.3 Scope.

The requirements in this part apply to any applicant who submits a marketing application for a human drug, biological product, or device and who submits covered clinical studies. The applicant is responsible for making the appropriate certification or disclosure statement where the applicant either contracted with one or more clinical investigators to conduct the studies or submitted studies conducted by others not under contract to the applicant.

#### § 54.4 Certification and disclosure requirements.

For purposes of this part, an applicant must submit a list of all clinical investigators who conducted covered clinical studies to determine whether the applicant's product meets FDA's marketing requirements, identifying those clinical investigators who are full-time or part-time employees of the sponsor of each covered study. The applicant must also completely and accurately disclose or certify information concerning the financial interests of a clinical investigator who is not a full-time or part-time employee of the sponsor for each covered clinical study. Clinical investigators subject to investigational new drug or investigational device exemption regulations must provide the sponsor of the study with sufficient accurate information needed to allow subsequent disclosure or certification. The applicant is required to submit for each clinical investigator who participates in a covered study, either a certification that none of the financial arrangements described in § 54.2 exist, or disclose the nature of those arrangements to the agency. Where the applicant acts with due diligence to obtain the information required in this section but is unable to do so, the applicant shall certify that despite the applicant's due diligence in attempting to obtain the information, the applicant was unable to obtain the information and shall include the reason.

(a) The applicant (of an application submitted under sections 505, 506, 507, 519(k), 513, or 515 of the Federal Food, Drug, and Cosmetic Act, or section 351 of the Public Health Service Act) that relies in whole or in part on clinical studies shall submit, for each clinical investigator who participated in a covered clinical study, either a certification described in paragraph (a)(1) of this section or a disclosure statement described in paragraph (a)(3) of this section.

(1) Certification: 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 interests and arrangements described in paragraph (a)(3) of this section. The form shall be dated and signed by the chief financial officer or other responsible corporate official or representative.

(2) If the certification covers less than all covered clinical data in the application, the applicant shall include in the certification a list of the studies covered by this certification.

(3) Disclosure Statement: 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:

(i) Any financial arrangement entered into between the sponsor of the covered study and the clinical investigator involved in the conduct of a covered clinical trial, whereby the value of the compensation to the clinical investigator for conducting the study could be influenced by the outcome of the study;

(ii) Any significant payments of other sorts from the sponsor of the covered study, such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria;

(iii) Any proprietary interest in the tested product held by any clinical investigator involved in a study;

(iv) Any significant equity interest in the sponsor of the covered study held by any clinical investigator involved in any clinical study; and

(v) Any steps taken to minimize the potential for bias resulting from any of the disclosed arrangements, interests, or payments.

(b) The clinical investigator shall provide to the sponsor of the covered study sufficient accurate financial information to allow the sponsor to submit complete and accurate certification or disclosure statements as required in paragraph (a) of this section. The investigator shall promptly update this information if any relevant changes occur in the course of the investigation or for 1 year following completion of the study.

(c) Refusal to file application. FDA may refuse to file any marketing application described in paragraph (a) of this section that does not contain the information required by this section or a certification by the applicant that the

applicant has acted with due diligence to obtain the information but was unable to do so and stating the reason.

#### § 54.5 Agency evaluation of financial interests.

(a) *Evaluation of disclosure statement.* FDA will evaluate the information disclosed under § 54.4(a)(2) about each covered clinical study in an application to determine the impact of any disclosed financial interests on the reliability of the study. FDA may consider both the size and nature of a disclosed financial interest (including the potential increase in the value of the interest if the product is approved) and steps that have been taken to minimize the potential for bias.

(b) *Effect of study design.* In assessing the potential of an investigator's financial interests to bias a study, FDA will take into account the design and purpose of the study. Study designs that utilize such approaches as multiple investigators (most of whom do not have a disclosable interest), blinding, objective endpoints, or measurement of endpoints by someone other than the investigator may adequately protect against any bias created by a disclosable financial interest.

(c) *Agency actions to ensure reliability of data.* 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:

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

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

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

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

#### § 54.6 Recordkeeping and record retention.

(a) *Financial records of clinical investigators to be retained.* An applicant who has submitted a marketing application containing covered clinical studies shall keep on file certain information pertaining to the financial interests of clinical investigators who conducted studies on which the application relies and who are not full or part-time employees of the applicant, as follows:

(1) Complete records showing any financial interest or arrangement as described in § 54.4(a)(3)(i) paid to such clinical investigators by the sponsor of the covered study.

(2) Complete records showing significant payments of other sorts, as described in § 54.4(a)(3)(ii), made by the sponsor of the covered clinical study to the clinical investigator.

(3) Complete records showing any financial interests held by clinical investigators as set forth in § 54.4(a)(3)(iii) and (a)(3)(iv).

(b) *Requirements for maintenance of clinical investigators' financial records.*

(1) For any application submitted for a covered product, an applicant shall retain records as described in paragraph (a) of this section for 2 years after the date of approval of the application.

(2) The person maintaining these records shall, upon request from any properly authorized officer or employee of FDA, at reasonable times, permit such officer or employee to have access to and copy and verify these records.

**PART 312—INVESTIGATIONAL NEW DRUG APPLICATION**

2. The authority citation for 21 CFR part 312 continues to read as follows:

**Authority:** 21 U.S.C. 321, 331, 351, 352, 353, 355, 356, 357, 371; 42 U.S.C. 262.

3. Section 312.53 is amended by adding new paragraph (c)(4) to read as follows:

**§ 312.53 Selecting investigators and monitors.**

\* \* \* \* \*

(c) \* \* \*

(4) *Financial disclosure information.* Sufficient accurate financial information to allow the sponsor to submit complete and accurate certification or disclosure statements required under part 54 of this chapter. The sponsor shall obtain a commitment from the clinical investigator to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following the completion of the study.

\* \* \* \* \*

4. Section 312.57 is amended by redesignating paragraphs (b) and (c) as paragraphs (c) and (d) and by adding new paragraph (b) to read as follows:

**§ 312.57 Recordkeeping and record retention.**

\* \* \* \* \*

(b) A sponsor shall maintain complete and accurate records showing any financial interest in § 54.4(a)(3)(i), (a)(3)(ii), (a)(3)(iii), and (a)(3)(iv) of this

chapter paid to clinical investigators by the sponsor of the covered study. A sponsor shall also maintain complete and accurate records concerning all other financial interests of investigators subject to part 54 of this chapter.

\* \* \* \* \*

5. Section 312.64 is amended by adding new paragraph (d) to read as follows:

**§ 312.64 Investigator reports.**

\* \* \* \* \*

(d) *Financial disclosure reports.* The clinical investigator shall provide the sponsor with sufficient accurate financial information to allow an applicant to submit complete and accurate certification or disclosure statements as required under part 54 of this chapter. The clinical investigator shall promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following the completion of the study.

**PART 314—APPLICATIONS FOR FDA APPROVAL TO MARKET A NEW DRUG OR AN ANTIBIOTIC DRUG**

6. The authority citation for 21 CFR part 314 continues to read as follows:

**Authority:** 21 U.S.C. 321, 331, 351, 352, 353, 355, 356, 357, 371, 374, 379e.

7. Section 314.50 is amended by redesignating paragraph (k) as paragraph (l) and by adding new paragraph (k) to read as follows:

**§ 314.50 Content and format of an application.**

\* \* \* \* \*

(k) *Financial certification or disclosure statement.* The application shall contain a financial certification or disclosure statement or both as required by part 54 of this chapter.

\* \* \* \* \*

8. Section 314.60 is amended in paragraph (a) by adding a new sentence at the end of the paragraph to read as follows:

**§ 314.60 Amendments to an unapproved application.**

(a) \* \* \* An amendment that contains new clinical data from a previously unreported study shall contain a financial certification or disclosure statement or both as required by part 54 of this chapter, or FDA may refuse to accept any such amendment.

\* \* \* \* \*

9. Section 314.94 is amended by adding new paragraph (a)(13) to read as follows:

**§ 314.94 Content and format of an abbreviated application.**

\* \* \* \* \*

(a) \* \* \*

(13) *Financial certification or disclosure statement.* An abbreviated application shall contain a financial certification or disclosure statement as required by part 54 of this chapter.

\* \* \* \* \*

10. Section 314.200 is amended in paragraph (d)(3) by adding a new sentence after the first sentence to read as follows:

**§ 314.200 Notice of opportunity for hearing; notice of participation and request for hearing; grant or denial of hearing.**

\* \* \* \* \*

(d) \* \* \*

(3) \* \* \* A financial certification or disclosure statement or both as required by part 54 of this chapter must accompany all clinical data submitted.

\* \* \*

\* \* \* \* \*

11. Section 314.300 is amended in the introductory text of paragraph (b)(6) by adding a new sentence after the first sentence to read as follows:

**§ 314.300 Procedure for the issuance, amendment, or repeal of regulations.**

\* \* \* \* \*

(b) \* \* \*

(6) \* \* \* A financial certification or disclosure statement or both as required by part 54 of this chapter must accompany all clinical data submitted with the request for hearing. \* \* \*

\* \* \* \* \*

**PART 320—BIOAVAILABILITY AND BIOEQUIVALENCE REQUIREMENTS**

12. The authority citation for 21 CFR part 320 continues to read as follows:

**Authority:** 21 U.S.C. 321, 351, 352, 355, 357, 371.

13. Section 320.36 is amended by designating the existing text as paragraph (a) and by adding new paragraph (b) to read as follows:

**§ 320.36 Requirements for maintenance of records of bioequivalence testing.**

\* \* \* \* \*

(b) Any person who contracts with another party to conduct a bioequivalence study from which the data are intended to be submitted to FDA as part of an application submitted under part 314 of this chapter shall obtain from the person conducting the study sufficient accurate financial information to allow the submission of complete and accurate financial certifications or disclosure statements

required under part 54 of this chapter and shall maintain that information and all records relating to the compensation given for that study and all other financial interest information required under part 54 of this chapter for 2 years after the date of approval of the application. The person maintaining these records shall, upon request for any properly authorized officer or employee of the Food and Drug Administration, at reasonable time, permit such officer or employee to have access to and copy and verify these records.

**PART 330—OVER-THE-COUNTER (OTC) HUMAN DRUGS WHICH ARE GENERALLY RECOGNIZED AS SAFE AND EFFECTIVE AND NOT MISBRANDED**

14. The authority citation for 21 CFR part 330 continues to read as follows:

**Authority:** 21 U.S.C. 321, 351, 352, 353, 355, 360, 371.

15. Section 330.10 is amended by adding new paragraph (f) to read as follows:

**§ 330.10 Procedures for classifying OTC drugs generally recognized as safe and effective and not misbranded, and for establishing monographs.**

(f) *Financial certification or disclosure statement.* Any clinical data submitted under this section must be accompanied by financial certifications or disclosure statements or both as required by part 54 of this chapter.

**PART 601—LICENSING**

16. The authority citation for 21 CFR part 601 continues to read as follows:

**Authority:** 21 U.S.C. 321, 351, 352, 353, 355, 360, 360c–360f, 360h–360j, 371, 374, 379e, 381; 42 U.S.C. 216, 241, 262, 263; 15 U.S.C. 1451–1461.

17. The introductory test of section 601.2 is amended in the introductory text of paragraph (a) by adding a sentence after the first sentence to read as follows:

**§ 601.2 Applications for establishment and product licenses; procedures for filing.**

(a) \* \* \* The applicant shall also include a financial certification or disclosure statement(s) or both for clinical investigators as required by part 54 of this chapter. \* \* \*

**PART 807—ESTABLISHMENT REGISTRATION AND DEVICE LISTING FOR MANUFACTURERS AND DISTRIBUTORS OF DEVICES**

18. The authority citation for 21 CFR part 807 continues to read as follows:

**Authority:** 21 U.S.C. 331, 351, 352, 360, 360c, 360e, 360i, 360j, 371, 374.

19. Section 807.31 is amended by adding new paragraph (d)(3) to read as follows:

**§ 807.31 Additional listing information.**

(d) \* \* \*  
(3) A copy of the certification and disclosure statements as required by part 54 of this chapter shall be retained and physically located at the establishment maintaining the historical file.

20. Section 807.87 is amended by redesignating paragraphs (i) through (k) as paragraphs (j) through (l), respectively, and by adding a new paragraph (i) to read as follows:

**§ 807.87 Information required in a premarket notification submission.**

(i) A financial certification or disclosure statement or both, as required by part 54 of this chapter.

21. Section 807.100 is amended by redesignating paragraph (a)(4) as paragraph (a)(5) and by adding new paragraph (a)(4) to read as follows:

**§ 807.100 FDA action on a premarket notification.**

(a) \* \* \*  
(4) Withhold the decision until a certification or disclosure statement is submitted to FDA under part 54 of this chapter.

**PART 812—INVESTIGATIONAL DEVICE EXEMPTIONS**

22. The authority citation for 21 CFR part 812 continues to read as follows:

**Authority:** 21 U.S.C. 331, 351, 352, 353, 355, 356, 357, 360, 360c–360f, 360h–360j, 371, 372, 374, 379e, 381, 382, 383; 42 U.S.C. 216, 241, 262, 263b–263n.

23. Section 812.43 is amended by adding new paragraph (c)(5) to read as follows:

**§ 812.43 Selecting investigators and monitors.**

(c) \* \* \*  
(5) Sufficient accurate financial disclosure information to allow the sponsor to submit a complete and accurate certification or disclosure statement as required under part 54 of this chapter. The sponsor shall obtain a commitment from the clinical investigator to promptly update this information if any relevant changes

occur during the course of the investigation and for 1 year following completion of the study. This information shall not be submitted in an investigational device exemption application, but shall be submitted in any marketing application involving the device.

24. Section 812.110 is amended by redesignating paragraph (d) as paragraph (e) and adding new paragraph (d) to read as follows:

**§ 812.110 Specific responsibilities of investigators.**

(d) *Financial disclosure.* A clinical investigator shall disclose to the sponsor sufficient accurate financial information to allow the applicant to submit complete and accurate certification or disclosure statements required under part 54 of this chapter. The investigator shall promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following completion of the study.

25. Section 812.140 is amended by revising paragraph (b)(3) to read as follows:

**§ 812.140 Records.**

(b) \* \* \*  
(3) Signed investigator agreements including the financial disclosure information required to be collected under § 812.43(c)(5) in accordance with part 54 of this chapter.

**PART 814—PREMARKET APPROVAL OF MEDICAL DEVICES**

26. The authority citation for 21 CFR part 814 continues to read as follows:

**Authority:** 21 U.S.C. 351, 352, 353, 360, 360c–360j, 371, 372, 373, 374, 375, 379, 379e, 381.

27. Section 814.20 is amended by redesignating paragraph (b)(12) as paragraph (b)(13) and adding new paragraph (b)(12) to read as follows:

**§ 814.20 Application.**

(b) \* \* \*  
(12) A financial certification or disclosure statement or both as required by part 54 of this chapter.

28. Section 814.42 is amended by adding new paragraph (e)(5) to read as follows:

**§ 814.42 Filing a PMA.**

\* \* \* \* \*

(e) \* \* \*

(5) The PMA is not accompanied by a statement of either certification or disclosure as required by part 54 of this chapter.

29. Section 814.112 is amended by adding new paragraph (a)(4) to read as follows:

**§ 814.112 Filing an HDE.**

(a) \* \* \*

(4) The HDE is not accompanied by a statement of either certification or disclosure, or both, as required by part 54 of this chapter.

\* \* \* \* \*

**PART 860—MEDICAL DEVICE CLASSIFICATION PROCEDURES**

30. The authority citation for 21 CFR part 860 continues to read as follows:

**Authority:** 21 U.S.C. 360c, 360d, 360e, 360i, 360j, 371, 374.

31. Section 860.123 is amended by adding new paragraph (a)(10) to read as follows:

**§ 860.123 Reclassification petition: Content and form.**

(a) \* \* \*

(10) A financial certification or disclosure statement or both as required by part 54 of this chapter.

\* \* \* \* \*

Dated: October 15, 1997.

**Michael A. Friedman,**

*Lead Deputy Commissioner for the Food and Drug Administration.*

**Donna E. Shalala,**

*Secretary of Health and Human Services.*

[FR Doc. 98-2407 Filed 1-30-98; 8:45 am]

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**DEPARTMENT OF HEALTH AND HUMAN SERVICES**

**Food and Drug Administration**

**21 CFR Parts 510, 520, 524, and 558**

[Docket No. 97N-0508]

**Animal Drugs, Feeds, and Related Products**

**AGENCY:** Food and Drug Administration, HHS.

**ACTION:** Final rule.

**SUMMARY:** The Food and Drug Administration (FDA) is amending the animal drug regulations to remove those portions reflecting approval of eight new animal drug applications (NADA's) for which the sponsors have requested withdrawal of approval. The NADA's provide for use of products which are no longer made or marketed. In a notice published elsewhere in this issue of the **Federal Register**, FDA is withdrawing approval of the NADA's.

**EFFECTIVE DATE:** February 12, 1998.

**FOR FURTHER INFORMATION CONTACT:** Mohammad I. Sharar, Center for Veterinary Medicine (HFV-216), Food and Drug Administration, 7500 Standish Pl., Rockville, MD 20855, 301-594-1722.

**SUPPLEMENTARY INFORMATION:** In a notice published elsewhere in this issue of the **Federal Register**, FDA has withdrawn approval of the following NADA's:

NADA No.	Drug name	Sponsor name and address
38-247	Hygromycin B Type A medicated article	Mountaire Feeds, Inc., 124 East Fifth, P.O. Box 5391, North Little Rock, AR 72119, formerly Mountaire Vitamins, Inc., 400 North Poplar St., P.O. Box 9210, North Little Rock, AR 72119
44-013	Tylosin Type A medicated article	do.
65-273	Chloramphenicol capsules, USP	Zenith Goldline Pharmaceuticals, Inc., 140 Legrand Ave., Northvale, NJ 07647, formerly Zenith Laboratories, Inc., 50 Williams Dr., Ramsey, NJ 07446
65-456	Tetracycline HCl capsules, USP	do.
95-736	Hygromycin B Type A medicated article	Mountaire Feeds, Inc.
98-895	Starbar GX-118 Topical (phosmet)(prolate)	Wellmark International, 1000 Tower Lane, Bensenville, IL 60106, formerly Sandoz Agro, Inc., 1300 East Touhy Ave., Des Plaines, IL 60018
137-138	Pyrantel tartrate Type A medicated article	Mountaire Feeds, Inc.
139-239	Banminth (pyrantel tartrate) Type A medicated article	Growmark, Inc., 950 North Meridian St., Indianapolis, IN 46204-3909, formerly at 1701 Towanda Ave., Bloomington, IL 61701

The sponsors requested withdrawal of approval of the NADA's under 21 CFR 514.115(d) because the products are no longer made or marketed.

The regulations are amended in 21 CFR 520.390b(b)(1), 520.2345a(b)(4), 524.1742(b), 558.274(a)(6) and (c)(1)(i), 558.485(a)(21) and (a)(25), and 558.625(b)(84) to remove those portions which reflect approval of these NADA's.

Also, with withdrawal of approval of these NADA's, these firms are no longer sponsors of approved NADA's. Therefore, 21 CFR 510.600(c)(1) and (c)(2) are amended to remove entries for the firms.

**List of Subjects**

*21 CFR Part 510*

Administrative practice and procedure, Animal drugs, Labeling, Reporting and recordkeeping requirements.

*21 CFR Parts 520 and 524*

Animal drugs.

*21 CFR Part 558*

Animal drugs, Animal feeds.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under the authority delegated to the Commissioner

of Food and Drugs and redelegated to the Center for Veterinary Medicine, 21 CFR parts 510, 520, 524, and 558 are amended as follows:

**PART 510—NEW ANIMAL DRUGS**

1. The authority citation for 21 CFR part 510 continues to read as follows:

**Authority:** 21 U.S.C. 321, 331, 351, 352, 353, 360b, 371, 379e.

**§ 510.600 [Amended]**

2. Section 510.600 *Names, addresses, and drug labeler codes of sponsors of approved applications* is amended in the table in paragraph (c)(1) by