

Department of Health and Human Services

**OFFICE OF
INSPECTOR GENERAL**

**THE FOOD AND DRUG
ADMINISTRATION'S OVERSIGHT
OF CLINICAL INVESTIGATORS'
FINANCIAL INFORMATION**



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OBJECTIVE

1. To describe the extent and nature of clinical investigators' disclosed financial interests reported to the Food and Drug Administration (FDA) for marketing applications approved in fiscal year (FY) 2007.
2. To assess FDA's oversight of clinical investigators' financial information.

BACKGROUND

Most new drugs, biological products, and medical devices undergo clinical trials on human subjects before they are marketed in the United States. Sponsors, generally pharmaceutical or device companies, oversee clinical trials conducted by clinical investigators. Before clinical trials begin, sponsors submit a pretrial application to FDA outlining their study design. After clinical trials are completed, sponsors wishing to market their product submit a marketing application to FDA.

Sponsors must collect financial information from clinical investigators before clinical trials. However, sponsors submit financial information to FDA only when they submit their marketing application after clinical trials end. For each clinical investigator, sponsors submit a financial form either certifying that the investigator does not have a financial interest or disclosing the financial interest. Federal regulations also allow sponsors to indicate that they acted with due diligence but were unable to obtain financial information from a clinical investigator. For each disclosed financial interest, sponsors must attach details of the financial interest and a record of their actions to minimize potential bias toward clinical trial results.

FDA assigns marketing applications to a multidisciplinary team for review. Reviewers evaluate financial information as well as sponsors' actions to minimize any potential bias related to clinical investigators' disclosed financial interests. Reviewers provide written notes that are used to determine whether a marketing application should be approved by FDA. If reviewers suspect that disclosed financial interests compromised data integrity, they are required to take action to ensure the reliability of the data.

We reviewed financial forms, attachments, and accompanying FDA review notes for all 118 marketing applications approved by FDA in FY 2007. We also reviewed FDA regulations and guidance, conducted

structured interviews with FDA officials, and sent an electronic survey to FDA reviewers.

FINDINGS

One percent of clinical investigators disclosed a financial interest.

Among clinical investigators listed in financial forms, 1 percent disclosed at least one financial interest. This represents 206 of the 29,691 clinical investigators listed in financial interest forms. Of these 206 clinical investigators, almost all disclosed only one financial interest, with a few disclosing two or three financial interests.

FDA cannot determine whether sponsors have submitted financial information for all clinical investigators. FDA cannot determine whether sponsors have submitted complete financial information for all clinical investigators because it does not have a complete list of clinical investigators. In addition, FDA does not use onsite inspections to confirm that submitted financial information is complete.

Forty-two percent of FDA-approved marketing applications were missing financial information. Twenty-three percent of approved marketing applications were missing a certification or disclosure form or required attachments. In 28 percent of marketing applications, sponsors used the due diligence exemption to indicate that they were unable to provide complete financial information. Although allowed by regulation, sponsors' use of the diligence exemption results in no financial information for FDA reviewers. Some marketing applications had both missing attachments and the due diligence exemption was marked.

FDA did not document a review of any financial information for 31 percent of marketing applications. When FDA reviewers used a review template, they were more likely to document a review of financial information.

Neither FDA nor sponsors took action for 20 percent of marketing applications with disclosed financial interests. In 20 percent of marketing applications, FDA reviewers did not take action and sponsors did not indicate that they minimized potential bias during the clinical trials. For over half of these marketing applications, reviewers did not document a review of financial information. In addition, when FDA did take action, their actions were inconsistent.

RECOMMENDATIONS

FDA should ensure that sponsors submit complete financial information for all clinical investigators.

- FDA should use a complete list of clinical investigators to check that sponsors have submitted financial information for all clinical investigators.
- FDA should check that sponsors have submitted all required attachments to financial forms.
- FDA should update guidance to sponsors regarding the due diligence exemption.
- FDA should add a review of financial information to the onsite inspection protocol.

FDA should ensure that reviewers consistently review financial information and take action in response to disclosed financial interests.

- FDA should require that all centers consistently use a template that includes a prompt to document a review of financial information.
- FDA should provide additional guidance and training to reviewers.

FDA should require that sponsors submit financial information for clinical investigators as part of the pretrial application process.

AGENCY COMMENTS AND OFFICE OF INSPECTOR GENERAL RESPONSE

FDA expressed concerns about elements of our analysis in three of our findings. In response to FDA's concerns, we removed employees from our analysis of disclosed financial interests. For FDA's remaining concerns, we maintain that our analysis is accurate.

FDA agreed with all of our recommendations except our final recommendation that FDA require sponsors to submit financial information for clinical investigators as part of the pretrial application process. FDA emphasized that collecting financial information before a clinical trial starts is the sponsors' responsibility. However, despite this important role for sponsors, FDA has no mechanism in place to ensure

E X E C U T I V E S U M M A R Y

that sponsors are in fact collecting financial information before beginning clinical trials.

FDA also stated that it would take significant additional effort for both industry and FDA to collect and review financial information during the pretrial application process. However, pursuant to regulation, FDA already requires sponsors to collect financial information before the start of clinical trials. In addition, basic information on clinical investigators is submitted to FDA as they are added to clinical trials.

Further, FDA asserted that this additional effort would not be worthwhile because financial interests are only one form of potential bias and not all clinical trials are presented in the marketing application. Receiving financial information during the pretrial application process would allow FDA to have information on all potential sources of financial bias. FDA could then work effectively with sponsors to identify potential bias. In addition, receiving financial information related to ongoing clinical trials is in keeping with FDA's stated intention to improve its oversight of ongoing clinical trials.

We continue to recommend that FDA require sponsors to submit financial information as part of the pretrial application process. Acknowledging the burden to FDA's administrative and review staff, we encourage FDA to develop a review of financial information that best balances the additional effort with the potential benefits.

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OBJECTIVE

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BACKGROUND

Research has shown that financial relationships exist between medical companies and researchers, including researchers conducting clinical trials for the approval of new drugs, biological products, and medical devices. For example, the Journal of the American Medical Association reported that between 23 percent and 28 percent of academic researchers had financial interests in medical companies.¹

Financial relationships between researchers and medical companies may compromise the safety of human subjects and the integrity of research data. After a teenager died while undergoing experimental treatment in 1999, the President encouraged agencies to develop steps to address financial relationships. An investigation into the case found that many of the clinical investigators had financial interests in the sponsor of that clinical trial.² In another case, study results from a medical device trial may have been "cast in an overly flattering light," potentially because researchers at about half the clinical trial sites had financial interests in the device company.³

The Office of Inspector General (OIG) has worked to ensure that financial interests do not compromise clinical trials. FDA developed its 1999 regulations regarding the disclosure of clinical investigators' financial interests after OIG officials reported that FDA's failure to collect information about clinical investigators' financial interests could constitute a material weakness under the Federal Manager's Financial

¹ Justin E. Bekelman, et al., 2003. "Scope and Impact of Financial Conflicts of Interest in Biomedical Research," Journal of the American Medical Association, vol. 289(4), p. 456. Available online at <http://jama.ama-assn.org/cgi/reprint/289/4/454?ijkey=9e08192f3f85916bd89686c6af4713ad33b514ea>. Accessed on May 30, 2008.

² FDA, "Human Gene Therapy: Harsh Lessons, High Hopes." Available online at http://www.fda.gov/fdac/features/2000/500_gene.html. Accessed on May 5, 2008.

³ Abelson, Reed, "Financial Ties Cited as Issue in Spine Study." The New York Times, January 30, 2008, p. 2.

Integrity Act.⁴ Although FDA determined that a material weakness did not exist, FDA concluded that there was a need to address this issue through rulemaking.⁵

The Food and Drug Administration

Among other activities, FDA is responsible for protecting the public health by ensuring the safety, efficacy, and security of human drugs, biological products, and medical devices (hereinafter referred to as investigational products).⁶ Within FDA, the Center for Drug Evaluation and Research (CDER) regulates drugs, the Center for Biologics Evaluation and Research (CBER) regulates biological products that come from living sources (such as vaccines or gene therapies), and the Center for Devices and Radiological Health (CDRH) regulates medical devices.

Clinical Trials

The Federal Food, Drug, and Cosmetic Act generally requires that most new investigational products undergo clinical trials on human subjects to demonstrate their safety and efficacy before they are approved for sale in the United States.⁷ Sponsors, clinical investigators, and institutional review boards (IRB) play a role in clinical trials.

Sponsors. Sponsors, often pharmaceutical or device companies, are responsible for developing and testing investigational products in clinical trials.

Clinical investigators. Sponsors hire clinical investigators to conduct clinical trials. Clinical investigators may be researchers at academic institutions or practicing physicians. Typically, there are many clinical investigators working in multiple clinical trial sites, including outside the United States, for each clinical trial.

There are both primary investigators and subinvestigators. Primary investigators recruit subjects, supervise clinical studies, collect data,

⁴ 21 CFR § 54.4; FDA, “Guidance Financial Disclosure by Clinical Investigators.” Available online at <http://www.fda.gov/oc/guidance/financialdis.html>. Accessed on March 11, 2008.

⁵ 63 Fed. Reg. 5233 (Feb. 2, 1998).

⁶ FDA, “FDA’s Mission Statement.” Available online at <http://www.fda.gov/opacom/morechoices/mission.html>. Accessed on April 3, 2008.

⁷ 21 U.S.C. § 355; 21 CFR § 812.20(b)(2); FDA, “The FDA’s Drug Review Process: Ensuring Drugs Are Safe and Effective.” Available online at http://www.fda.gov/fdac/features/2002/402_drug.html. Accessed on March 11, 2008.

and report study results to the sponsor.⁸ Primary investigators must sign investigator agreements stating that they will comply with all relevant FDA regulations.⁹ Subinvestigators assist primary investigators with their responsibilities.

Institutional Review Boards. IRBs are committees that oversee clinical investigators' research to ensure that all steps are taken to protect the rights and welfare of human subjects.¹⁰ IRBs must include members from varying backgrounds and often are composed of physicians, scientists, lawyers, and ethicists.¹¹ An IRB must approve all clinical trials involving human subjects before clinical trials can begin.¹² During their reviews of clinical trials, IRBs are not required to review clinical investigators' financial information. Yet, the Department of Health and Human Services (HHS) strongly urges IRBs to look at financial information.¹³ It has been estimated that a quarter of IRBs routinely conduct such a review.¹⁴

FDA's Oversight of Clinical Trials

FDA requires that sponsors file a pretrial application before beginning clinical trials.¹⁵ ¹⁶ Pretrial applications include the study protocol, the

⁸ 21 CFR § 312.60 (drugs and biologics); 21 CFR § 812.100 (devices). FDA, "Guidance on Clinical Trials," p. 18. Available online at <http://www.fda.gov/cder/guidance/959fnl.pdf>. Accessed on May 5, 2008.

⁹ Pretrial applications submitted to CDRH include investigator agreements for subinvestigators. (21 CFR § 312.53 (drugs and biologics); 21 CFR § 812.43(c) (devices)).

¹⁰ 21 CFR § 56.

¹¹ 21 CFR § 56.107.

¹² 21 CFR § 56.101.

¹³ HHS, "Financial Relationships and Interests in Research Involving Human Subjects: Guidance for Human Subject Protection." May 12, 2004. Available online at <http://www.hhs.gov/ohrp/humansubjects/finreltn/finalguid.pdf>. Accessed on May 30, 2008.

¹⁴ National Institutes of Health (NIH), "Financial Conflicts of Interest and Research Objectivity: Issues for Investigators and Institutional Review Boards." June 5, 2000. Available online at <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-040.html>. Accessed on March 25, 2008.

¹⁵ Sponsors submit an Investigational New Drug Application to CDER or CBER per 21 CFR § 312.20. Sponsors submit an Investigational Device Exemption to CDRH per 21 CFR § 812.20.

¹⁶ FDA uses the term "sponsor" and "applicant" at different times in the regulations. FDA states that generally "the sponsor of the covered study, and the applicant company are the same party." For the purpose of this report, we refer to sponsors and applicants collectively as "sponsors." Question Seven, FDA, "Guidance Financial Disclosure by Clinical Investigators." Available online at <http://www.fda.gov/oc/guidance/financialdis.html>. Accessed on March 11, 2008.

chosen IRB(s), and assurances that human subjects will be protected.¹⁷ As part of the pretrial application to FDA, sponsors submit the names, addresses, and qualifications of all primary investigators. They must also list all subinvestigators. Pretrial applications do not include financial information about clinical investigators.

Upon successful completion of clinical trials, sponsors that wish to market a product must submit a marketing application to FDA.¹⁸ Marketing applications include clinical trial results, descriptions of the investigational products' components, proposed labeling, and financial information about clinical investigators' relationship to sponsors.

FDA assigns the marketing application to a multidisciplinary team of reviewers. Reviewers represent a variety of scientific disciplines, including medicine, pharmacology, statistics, and chemistry. Reviewers evaluate information in the marketing application relevant to their expertise.¹⁹ These reviews help determine whether FDA will approve a marketing application.

Onsite inspections. During and after clinical trials, FDA performs onsite inspections of clinical investigators, sponsors, and IRBs through the Bioresearch Monitoring Program (BiMo).²⁰ The purpose of the BiMo program is to ensure the protection of research subjects and the integrity of clinical trial data.²¹ BiMo officials work in each of the three FDA centers.

BiMo conducts both surveillance and directed inspections to determine compliance with FDA regulations. Surveillance inspections are typically routine inspections that occur after FDA receives a marketing application and target completed clinical trials. Directed inspections typically target ongoing clinical trials and occur because of specific concerns about data integrity. These concerns could include clinical investigators' financial interests.

¹⁷ 21 CFR § 312.23.

¹⁸ 21 CFR § 314.50 (drugs); 21 CFR § 601.2 (biologics); 21 CFR § 814.20 (devices).

¹⁹ FDA, "The FDA's Drug Review Process: Ensuring Drugs Are Safe and Effective." Available online at http://www.fda.gov/fdac/features/2002/402_drug.html. Accessed on March 27, 2008.

²⁰ 21 U.S.C. §§ 355 and 360i. FDA, "Compliance Program Guidance Manual," Chapter 48: Bioresearch Monitoring Background.

²¹ FDA, "Bioresearch Monitoring Program." Available online at <http://www.fda.gov/oc/gcp/compliance.html>. Accessed on October 30, 2008.

Sponsors' Financial Disclosure Requirements

Beginning in 1999, FDA required sponsors submitting marketing applications to disclose the financial interests of primary investigators and subinvestigators (hereinafter referred to as clinical investigators) who contributed data for a “covered clinical study.”²² In 2001, FDA issued guidance to sponsors providing additional details about the requirements. The guidance defines terms included in the regulations and addresses questions from the industry.²³

Pursuant to regulations, sponsors must obtain financial information from clinical investigators before clinical trials.²⁴ This is done so sponsors can consult with FDA early on regarding “any potentially problematic financial interest,” and take action to minimize any potential study bias.²⁵ Sponsors can collect financial information from clinical investigators using any format or process.

After their initial submission, clinical investigators are required to provide updates to sponsors with any changes in their financial status during clinical trials and in the year after clinical trials are complete.²⁶ Sponsors must maintain complete records detailing clinical investigators' financial information during clinical trials and for 2 years after FDA approves a marketing application.²⁷

Sponsors are required to submit financial information on clinical investigators to FDA only when they submit the marketing application after clinical trials are complete.

FDA requires that sponsors disclose the following financial interests for all clinical investigators, their spouses, and their dependent children:

- (1) any financial arrangement between the sponsor whereby the value of the compensation could be influenced by the study outcome;

²² FDA defines a “covered clinical study” as any study submitted in a marketing application relied upon to show a product is effective or any study to which a single investigator significantly contributes to the demonstration of safety. For purposes of this report, we refer to covered clinical studies as clinical trials. 21 CFR §§ 54.4 and 54.2(e).

²³ FDA, “Guidance Financial Disclosure by Clinical Investigators.” Available online at <http://www.fda.gov/oc/guidance/financialdis.html>. Accessed on March 11, 2008.

²⁴ 21 CFR § 312.53(c)(4) (drugs and biologics); 21 CFR § 812.43(c) (devices).

²⁵ 67 Fed. Reg. 6042 (Feb. 8, 2002); Question 6, FDA, “Guidance Financial Disclosure by Clinical Investigators.” Available online at <http://www.fda.gov/oc/guidance/financialdis.html>. Accessed on March 11, 2008.

²⁶ 21 CFR § 312.53 (drugs and biologics); 21 CFR § 812.43(c) (devices).

²⁷ 21 CFR § 54.6.

- (2) a sum of all significant payments exceeding \$25,000 made on or after February 2, 1999, from the sponsor. Payments include research grants, retainers for ongoing consultation, or a general honorarium. They do not include the payments, such as salaries, associated with conducting the clinical trial;
- (3) any proprietary interest in the tested product, including patents, trademarks, or licensing agreements; and
- (4) equity in the sponsor's public company exceeding \$50,000, or equity for which the value cannot be determined through public prices.²⁸

Certification: Financial Interests and Arrangements of Clinical Investigators, Form 3454. Sponsors use Form 3454 to list clinical investigators who have no financial interest with the sponsor. Sponsors can submit a single certification form for multiple clinical investigators involved with clinical trials. If sponsors cannot obtain financial information from a clinical investigator, they can indicate on the certification form that they acted with due diligence to collect the information.²⁹

FDA's 2001 guidance defines due diligence as "a measure of activity expected from a reasonable and prudent person under a particular circumstance."³⁰ In 2002, in comments to a Federal Register notice, FDA was asked to define what constitutes due diligence. In response, FDA advised sponsors to try to locate clinical investigators through at least two telephone calls, and document notes of the calls. In addition, FDA recommended that sponsors follow up in writing, sending at least two certified letters.³¹

If sponsors indicate due diligence, they are expected to describe why they were unable to obtain the financial information and document

²⁸ 21 CFR §§ 54.2 and 54.4(a)(3); FDA, "Guidance Financial Disclosure by Clinical Investigators." Available online at <http://www.fda.gov/oc/guidance/financialdis.html>. Accessed on March 11, 2008. We combined the regulations' two equity disclosures in this list because they are combined on the form that sponsors complete when disclosing a clinical investigator's financial interests.

²⁹ 21 CFR § 54.4.

³⁰ Question Three, FDA, "Guidance Financial Disclosure by Clinical Investigators." Available online at <http://www.fda.gov/oc/guidance/financialdis.html>. Accessed on March 11, 2008.

³¹ 67 Fed. Reg. 6041 (Feb. 8, 2002).

their attempts to obtain the information.³² Sponsors are required to provide the reasons why they were unable to obtain the information when they claim the due diligence exemption on the certification form. Sponsors are not required to submit documentation of their attempts to contact clinical investigators nor describe their attempts. See Appendix A for a copy of the certification form.

Disclosure: Financial Interests and Arrangements of Clinical Investigators, Form 3455. Sponsors use Form 3455 to disclose clinical investigators' financial interests. The form lists FDA's four financial disclosure categories. Sponsors must submit a separate disclosure form for each clinical investigator with financial interests.

Sponsors must include two attachments with each disclosure form. The first must provide specific details about the financial interest. The second must describe any steps taken to minimize the potential bias resulting from disclosed financial interests.³³ FDA does not specify the actions sponsors must take to minimize potential bias. See Appendix B for a copy of the disclosure form.

FDA's Oversight of Financial Information

When FDA receives a marketing application, it performs an administrative check to ensure that sponsors have included the required information, including financial forms. If sponsors neglect to submit financial forms, FDA can refuse to accept a marketing application for review.³⁴ When FDA accepts a marketing application for review, FDA reviewers evaluate the application and clinical trial data, including whether disclosed financial interests compromised the integrity of the trial data.

Marketing application review. Among other things, the marketing application review includes an evaluation of clinical investigators' disclosed financial interests to determine their potential effect on data integrity. FDA reviewers provide written notes regarding their reviews.

³² FDA, Form 3455, "Disclosure: Financial Interests and Arrangements of Clinical Investigators." Available online at <http://www.fda.gov/opacom/morechoices/fdaforms/FDA-3455.pdf>. Accessed on October 11, 2007. FDA, "Guidance Financial Disclosure by Clinical Investigators." Available online at <http://www.fda.gov/oc/guidance/financialdis.html>. Accessed on March 11, 2008.

³³ 21 CFR § 54.4(a)(3)(v).

³⁴ 21 CFR § 54.4(c).

Division directors³⁵ read these review notes to determine whether to recommend approval for a marketing application.³⁶

The process for reviewing financial information within the marketing application differs by center. CDER has a review template that reviewers are required to use to review various aspects of marketing applications, including financial information. CBER has a draft review template that reviewers may use, and that includes a review of financial information. CDRH does not have a review template.

FDA action in response to disclosed financial interests. If FDA determines that clinical investigators' disclosed financial interests raise a serious question about the integrity of the data, FDA is required to take action to ensure the reliability of the data.³⁷ For example, FDA reviewers may take action if they discover that results from clinical trial sites managed by clinical investigators with disclosed financial interests were more favorable than average.

Regulations do not stipulate specific actions, but offer examples of possible actions.³⁸ Suggested actions include requesting an onsite inspection, requesting that the sponsor submit further data analyses or conduct additional independent studies, and refusing to review clinical trial results.³⁹

Related Reports

An OIG report issued in 2000 found that FDA's overall oversight of clinical investigators was limited.⁴⁰ Additionally, a 2007 OIG report found that FDA had limited ability to effectively manage BiMo.⁴¹ The

³⁵ Centers may refer to this position under various titles, including office director and team leader. For this report, we use the term division director to indicate the FDA official who provides recommendations to the FDA Commissioner on whether to approve a marketing application.

³⁶ FDA, "The FDA's Drug Review Process: Ensuring Drugs Are Safe and Effective." Available online at http://www.fda.gov/fdac/features/2002/402_drug.html. Accessed on March 27, 2008.

³⁷ 21 CFR § 54.5(c).

³⁸ Ibid.

³⁹ Ibid.

⁴⁰ OIG, "FDA Oversight of Clinical Investigators," OEI-05-99-00350, June 2000.

⁴¹ OIG, "The Food and Drug Administration's Oversight of Clinical Trials," OEI-01-06-00160, September 2007.

evaluation estimated that FDA inspected 1 percent of clinical trial sites between 2000 and 2005.⁴²

In 2001, the Government Accountability Office (GAO) issued a report that compared financial disclosure requirements of FDA and NIH. GAO found that, unlike NIH, FDA is not notified of clinical investigators' financial information until after clinical trials are complete. GAO recommended that HHS develop specific guidance or policy concerning financial information. In response, HHS stated that to the extent specific guidance or policy was developed, it would be coordinated throughout the Department.⁴³

METHODOLOGY

Scope

To describe the extent and nature of clinical investigators' financial interests, we reviewed disclosed financial interests from marketing applications approved in FY 2007. We did not review other types of applications approved by FDA; for instance, applications for generic products. By limiting our study to marketing applications, we focused on products that have been newly released to the public.

This evaluation reviewed FDA's oversight of clinical investigators' financial interests. We did not review FDA's oversight of the financial interests of FDA employees or FDA advisory board members.

Data Collection

We collected financial forms and attachments from all 118 marketing applications approved in FY 2007. This includes 73 marketing applications approved by CDER, 32 approved by CDRH, and 13 approved by CBER. See Appendix C for financial forms submitted to each center in FY 2007.

We also conducted six structured group interviews with FDA center officials and FDA BiMo officials from each of the three centers between January and March 2008. We discussed FDA's process for overseeing financial information, guidance to sponsors and reviewers, action taken in response to disclosed financial interests, and BiMo reviews of financial information.

⁴² Ibid.

⁴³ GAO, "Biomedical Research: HHS Direction Needed to Address Financial Conflicts of Interest," GAO-02-89, p. 39, November 2001.

To assess FDA's review of financial information and actions taken in response to this review, we collected FDA reviewers' notes, completed review templates, and summary review documents (hereinafter referred to as review notes) corresponding to their evaluation of financial information in the marketing applications.

To further understand FDA's review process, we sent an electronic survey to FDA reviewers in January 2008. Survey questions pertained to reviewers' process for evaluating financial information, any instructions they received, and whether they had ever taken action in response to disclosed financial interests.

We sent the survey to 790 potential reviewers identified by FDA center officials. Of those, 337 reviewers responded and, of these, 162 indicated that they had reviewed financial information in the past 3 years. We do not project the responses to all FDA reviewers and present survey data only from the 162 reviewers as secondary evidence in our findings. See Appendix D for a breakdown of survey responses by FDA center.

Data Analysis

Describing the extent and nature of disclosed financial interests. To describe the extent of disclosed financial interests, we reviewed all financial forms in marketing applications to classify each clinical investigator as: (1) having no financial interest, (2) disclosing a financial interest, or (3) unable to provide financial information. In total, sponsors listed 29,691 clinical investigators on financial forms. We did not include clinical investigators that the sponsor identified as employees because it was ambiguous whether sponsors were disclosing a financial arrangement for these employees. Sponsors are exempt from submitting financial information for employees.⁴⁴

We also described the extent of disclosed financial interests by calculating the percentage of marketing applications with at least one disclosed financial interest.

To describe the nature of clinical investigators' disclosed financial interests, we categorized financial interests using FDA's four financial disclosure categories listed on the disclosure form. We used disclosed financial interests as the unit of analysis for this assessment because clinical investigators could disclose multiple financial interests in a marketing application.

⁴⁴ 21 CFR § 54.4.

In four marketing applications, sponsors disclosed 12 financial interests that fell below the federally defined threshold. We still categorized these as disclosed financial interests because sponsors informed FDA of financial relationships with clinical investigators.

Assessing whether marketing applications contained complete financial information. We assessed whether marketing applications had complete financial information by reviewing submitted financial forms and attachments. We categorized a marketing application as having complete financial information if it met four criteria: (1) included either a certification or disclosure form, (2) included an attachment with a description of steps taken to minimize potential bias with each disclosure form, (3) included an attachment detailing descriptions of disclosed financial interests with each disclosure form, and (4) did not claim the due diligence exemption indicating that at least one clinical investigator did not provide financial information. We categorized a marketing application as having incomplete financial information if it failed to meet any of these four criteria.

Assessing FDA's review of financial information. To assess FDA's review of financial information in FY 2007, we analyzed FDA's review notes. We calculated the percentage of marketing applications with any mention of financial information in the review notes. For this analysis, we excluded administrative checklists that are used to check for financial interests forms. Checklists help ensure that sponsors submit forms, but do not indicate whether FDA reviewers read and evaluated the forms.

We also calculated the percentage of marketing applications with disclosed financial interests that had detailed review notes. We categorized review notes as detailed if they mention any of four things: (1) the sponsors' actions to decrease potential bias, (2) aspects of the study design that may have minimized potential bias, (3) action taken to ensure data reliability, or (4) a request for additional financial information from sponsors.

Assessing sponsors' and FDA actions in response to disclosed financial interests. To assess the extent of sponsors' actions, we calculated the percentage of marketing applications on which sponsors indicated that they took action to minimize potential bias for all clinical investigators with disclosed financial interests. Regulations require that sponsors report their actions to minimize potential bias for all disclosed financial interests. Thus, we did not count two marketing applications on which

sponsors reported their steps for only some disclosed financial interests as sponsors taking actions.

To assess the extent of FDA reviewers' actions, we calculated the percentage of marketing applications with review notes indicating any action taken or requested by an FDA reviewer. To assess the nature of FDA reviewers' actions, we reviewed FDA's review notes. We categorized FDA's actions based on the examples listed in FDA regulation. Because the regulations do not provide an exhaustive list, we also considered reanalyzing clinical trial results from clinical investigators with disclosed financial interests as an action.

Limitations

The number of clinical investigators listed on financial forms from marketing applications may be slightly inflated. Sponsors often listed clinical investigators without financial interests, as an attachment to the certification form, by their clinical trial site. Because clinical investigators may work on multiple clinical trial sites, investigators may have been listed more than once. We attempted to address this by conducting electronic searches for duplicate names. As a result, we expect any potential overestimation to be minimal.

We relied solely on review notes as an indication that FDA reviewers evaluated financial information. FDA reviewers are required to evaluate financial information but are not required to provide written documentation of this review. Therefore, FDA reviewers may have evaluated financial information but failed to note their review. Nonetheless, written notes remain the most reliable evidence of an FDA review. Division directors review these written notes when determining whether to recommend that FDA approve a marketing application.⁴⁵

We also relied solely on review notes as an indication that FDA reviewers took action in response to disclosed financial interests. FDA reviewers may have taken action in response to disclosed financial interests but failed to note their action. Similar to assessing whether FDA reviewers evaluated financial information, written notes remain the most reliable evidence of FDA action.

⁴⁵ FDA, "The FDA's Drug Review Process: Ensuring Drugs Are Safe and Effective." Available online at http://www.fda.gov/fdac/features/2002/402_drug.html. Accessed on March 27, 2008.

I N T R O D U C T I O N

Standards

This study was conducted in accordance with the “Quality Standards for Inspections” issued by the President’s Council on Integrity and Efficiency and the Executive Council on Integrity and Efficiency.

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One percent of clinical investigators disclosed a financial interest

Among clinical investigators listed in financial forms, 1 percent disclosed at least one

financial interest. This represents 206 of the 29,691 clinical investigators. Of the 206 clinical investigators, almost all disclosed only one financial interest, with a few disclosing two or three financial interests. Four clinical investigators disclosed two financial interests and two clinical investigators disclosed three financial interests.

Disclosed financial interests were associated with almost half of marketing applications

Forty-two percent of marketing applications included at least one clinical investigator with a disclosed financial interest. This represents 49 of 118 marketing applications.

Although most applications had few disclosed financial interests, some applications had numerous clinical investigators with disclosed financial interests. Sixty-seven percent of the 49 marketing applications with disclosed financial interests had one or two clinical investigators with a disclosed financial interest. On the other hand, 12 percent of these 49 marketing applications included 10 or more clinical investigators with a disclosed financial interest. The application with the most disclosed financial interests had 38 clinical investigators with financial interests.

Most disclosed financial interests were payments from sponsors

Seventy-seven percent of disclosed financial interests were for payments from sponsors. Most payments were for consulting services or general honoraria. Though not required, 53 percent of payment disclosures included a specific dollar amount. The median reported payment was \$47,252, almost twice the \$25,000 minimum payment reporting threshold. The highest reported payment was a sponsors' payment of \$3.9 million to a clinical investigator's affiliated institution.

Nineteen percent of disclosed financial interests were for equity interests, primarily stock options. Though not required, 46 percent of equity disclosures included a specific dollar amount. The median reported equity interest was \$65,000. This exceeds the \$50,000 minimum equity reporting threshold by \$15,000. The highest reported equity interest was \$148,751.

Two percent of disclosed financial interests were for proprietary interests. Most of the marketing applications that included proprietary interests were for medical devices.

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Lastly, 1 percent of disclosed financial interests were “financial arrangements that could influence the study outcome.” Sponsors included additional descriptions of only one of these disclosed financial interests. This clinical investigator was a patent owner of the product. See Table 1 for a list of clinical investigators’ disclosed financial interests by FDA’s financial disclosure categories.

FDA Financial Disclosure Category	Number of Disclosed Financial Interests	Percentage of Total Disclosed Financial Interests
Payments from sponsors	165	77 percent
Equity interests	41	19 percent
Proprietary interests in tested product	5	2 percent
Financial arrangements that could influence the study outcome	3	1 percent
Total	214*	99 percent**

* Clinical investigators can disclose more than one financial interest. There were 206 clinical investigators with 214 disclosed financial interests.

** Total does not equal 100 percent because of rounding.

Source: OIG analysis of marketing applications, 2008.

FDA cannot determine whether sponsors have submitted financial information for all clinical investigators

FDA cannot determine whether sponsors have submitted financial information for all clinical investigators because it does not

have a complete list of clinical investigators. In addition, FDA does not use onsite BiMo inspections as a mechanism to confirm that submitted financial information is complete. These limitations could result in FDA being unaware of a clinical investigator’s financial interest and thus unable to gauge its potential bias on clinical trial results.

FDA does not have a complete list of clinical investigators

FDA cannot systematically check whether marketing applications have financial information for all clinical investigators because FDA does not maintain a complete list of clinical investigators. FDA was able to provide a complete list of clinical investigators for only 7 percent of marketing applications approved in FY 2007.

Although FDA maintains a database that captures demographic and inspection information on clinical investigators, it currently cannot be used to easily compile a complete list of clinical investigators per

marketing application. FDA's Bioresearch Monitoring Information System database contains information for some clinical investigators. However, the database does not list subinvestigators for two FDA centers. In addition, the database only includes clinical investigators listed in pretrial applications, and does not include any clinical investigators who might have been recruited once the clinical trials were underway.

BiMo inspections do not routinely review financial information

BiMo inspectors are not instructed to routinely review financial information as part of their inspection protocol. Currently, BiMo inspectors review financial information only when an FDA reviewer specifically requests it or when an inspector takes personal initiative. Although BiMo inspects only a small portion of all clinical trial sites, these inspections are FDA's only onsite and indepth tool for reviewing sponsors and clinical investigators.

When BiMo inspectors reviewed financial information in the recent past, they found that sponsors had submitted incomplete financial information to FDA. For instance, in 2005, an inspection found that a clinical investigator did not submit financial information for a subinvestigator. As a result, FDA issued a letter to the clinical investigator suggesting areas of improvement.

In another example, FDA reviewers, in 2006, requested an inspection of clinical investigators and a sponsor because of concerns about financial interests. BiMo inspectors found that a clinical investigator violated regulations by failing to disclose financial interests to the sponsor. BiMo inspectors also found that the sponsor failed to disclose the financial interests of an additional five clinical investigators to FDA. FDA issued the sponsor a letter suggesting areas of improvement.

Moreover, when BiMo inspectors reviewed a sponsor in 2005, they found that the sponsor collected financial information shortly before the submission of the marketing application and not before beginning the clinical trial. According to regulation, sponsors are required to collect financial information from clinical investigators before beginning clinical trials.

Forty-two percent of FDA-approved marketing applications were missing financial information

Forty-two percent of approved marketing applications did not include complete financial

information. Twenty-three percent of these marketing applications were missing required financial forms or attachments. Twenty-eight percent were missing financial information because sponsors used the due diligence exemption to indicate that they were unable to provide financial information. Although allowed by regulation, sponsors' use of the diligence exemption results in no financial information for FDA reviewers. Some marketing applications had both missing attachments and the due diligence exemption marked.

Twenty-three percent of approved marketing applications did not include required financial forms or attachments

Twenty-three percent of all 118 marketing applications approved in FY 2007 were missing financial interest forms or required attachments with disclosed financial interests. Of these, 7 percent did not include any certification or disclosure forms for any clinical investigators.

Among marketing applications with disclosed financial interests, 24 percent were missing the sponsors' actions to minimize potential bias resulting from disclosed financial interests. In addition, 18 percent of marketing applications with disclosed financial interests were missing detailed descriptions of the financial interests.

Twenty-eight percent of marketing applications indicated that sponsors were unable to provide complete financial information

Twenty-eight percent of marketing applications included certification forms on which sponsors used the due diligence exemption to claim that they were unable to obtain complete financial information. As previously stated, Federal regulations allow sponsors to indicate that they acted with due diligence but were unable to obtain financial information from a clinical investigator. In total, sponsors indicated that they were unable to provide financial information for 1,123 clinical investigators. This is more than five times the 206 clinical investigators who disclosed financial interests.

If sponsors use the due diligence exemption, regulations require them to explain why they were unable to obtain the information. In 18 percent of marketing applications indicating due diligence, sponsors did not explain why they were unable to obtain financial information from all clinical investigators, as required. When sponsors did include this

explanation, they most often reported that clinical investigators could not be located or failed to return the financial form.

FDA did not document a review of any financial information for 31 percent of marketing applications

FDA reviewers did not document a review of financial information for 31 percent of marketing applications. Over one-third of

these marketing applications included disclosed financial interests. If FDA reviewers fail to document a review, division directors may overlook disclosed financial interests and their potential impact on data integrity.

Review templates increased the likelihood of a documented review of financial information

Reviewers from CDER, the only center to consistently use a review template, documented a review of financial information for 95 percent of marketing applications. CDER reviewers used a review template 94 percent of the time when documenting a review of financial information.

Reviewers from CBER documented a review of financial information in 23 percent of marketing applications. CBER is in the process of finalizing a review template similar to CDER’s template. When CBER reviewers documented a review of financial information, they always used a template.

The CDER review template and CBER’s draft template prompt reviewers to “discuss whether the applicant adequately disclosed financial arrangements with clinical investigators and whether these arrangements raise questions about the integrity of the data.”⁴⁶ The review template assigns a specific member of the review team the responsibility of reviewing financial information.

Reviewers from CDRH documented a review of financial information in 28 percent of marketing applications. CDRH reviewers do not use a review template.

⁴⁶ FDA, “Manual of Policies and Procedures: Clinical Review Template,” July 9, 2004, p. 17. Available online at <http://www.fda.gov/cder/mapp/6010.3.pdf>. Accessed on March 28, 2008.

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See Table 2 for FDA reviewers’ documented reviews of financial information by center.

Table 2: FDA Reviewers’ Documented Reviews			
FDA Center	Marketing Applications	Percentage of Marketing Applications With Documented Reviews of Financial Information	Percentage of Documented Reviews Found in a Template
CDER	73	95 percent	94 percent
CDRH	32	28 percent	0 percent*
CDER	13	23 percent	100 percent
Total	118	69 percent	63 percent

* CDRH reviewers do not use a template.

Source: OIG analysis of FDA review notes, 2008.

Most documented reviews of marketing applications with disclosed financial interests were detailed

Seventy-three percent of marketing applications with disclosed financial interests had documented reviews. Among these documented reviews, 72 percent of review notes were detailed and the remaining 28 percent were nondetailed.

Detailed notes provided evidence of more complete analyses of how disclosed financial interests might affect clinical trial results. For example, one detailed note stated that Dr. X “received more than \$25,000 in honoraria and travel expenses for educational activities. Any bias was minimized by the independent data monitoring, by the use of multiple investigators, and by the use of double-blind placebo-controlled trials.”

Nondetailed notes indicated that a more cursory review may have been undertaken. Most commonly, nondetailed notes either mentioned that financial information was included or summarized the financial information. For example, one nondetailed note stated that “Certificates of financial disclosure were submitted in compliance with the Final Rule on Financial Disclosure by Clinical Investigators.”

Division directors reading nondetailed notes may overlook or underestimate the impact of disclosed financial interests on clinical trial results. On the other hand, division directors can use detailed notes to

determine financial interests’ potential impact on data integrity before recommending possible approval of a marketing application.

Neither FDA nor sponsors took action for 20 percent of marketing applications with disclosed financial interests

Neither FDA reviewers nor sponsors noted taking action in response to disclosed financial interests for 20 percent of

marketing applications with disclosed financial interests. FDA reviewers did not take action on 88 percent⁴⁷ of marketing applications with disclosed financial interests. However, in 67 percent of marketing applications with disclosed financial interests, sponsors indicated that they acted to minimize potential bias during the clinical trials. For example, sponsors hired independent observers to monitor clinical trial sites. Sponsors also prevented clinical investigators with financial interests from knowing whether subjects were in the experimental or the control group. When sponsors took action, FDA reviewers may have judged sponsors’ actions to be sufficient, and have seen no need for further action.

On the other hand, FDA reviewers did not take action on 20 percent of marketing applications with disclosed financial interests upon which sponsors did not indicate taking action to minimize potential bias. To protect data integrity, sponsors are required to describe their actions to minimize potential bias related to all disclosed financial interests. Although FDA reviewers may have had other reasons to believe that disclosed financial interests did not compromise data integrity, FDA reviewers did not have the assurance that sponsors acted to minimize potential bias during the clinical trials.

In addition, there was no documented FDA review of financial information in more than half of the marketing applications upon which no action was taken. Because FDA reviewers may have not reviewed financial information, they may not have had sufficient information to judge whether action to address potential bias was warranted.

See Table 3 on the next page for sponsors’ and FDA reviewers’ action in response to marketing applications with disclosed financial interests.

⁴⁷ FDA reviewers did not review 87.7 percent of marketing applications with disclosed financial interests, which we have rounded to 88 percent.

Table 3: Sponsors' and FDA Reviewers' Actions		
	Number of Marketing Applications	Percentage of Marketing Applications With Disclosed Financial Interests
No sponsor action; no FDA action	10	20 percent
No sponsor action; FDA action	3	6 percent
Sponsor action; no FDA action	33	67 percent
Sponsor action; FDA action	3	6 percent
Total	49	99 percent*

* Total does not equal 100 percent because of rounding.

Source: OIG analysis of marketing applications and FDA review notes, 2008.

FDA reviewers did not consistently take action in response to disclosed financial interests

Based on FDA reviewers' documented notes, FDA reviewers took action inconsistently. FDA reviewers took action on 12 percent of marketing applications with disclosed financial interests. However, FDA reviewers did not take action on other marketing applications with disclosed financial interests. In the cases in which FDA reviewers did not take action, they may have determined that other aspects of the marketing application mitigated the need for action, despite the disclosed financial interests. However, if this was the case, FDA reviewers did not document this assessment in their review notes. See Appendix E for a description of FDA actions taken in response to disclosed financial interests.

Marketing applications upon which FDA took action had disclosed financial interests similar to marketing applications upon which FDA reviewers took no action. In one marketing application, an FDA reviewer took action when sponsors failed to provide any financial forms. Yet FDA approved 7 percent of marketing applications without any financial forms.

In another marketing application, an FDA reviewer took action when a clinical investigator with disclosed financial interests enrolled a large number of patients. However, a different FDA reviewer took no action although two clinical investigators with disclosed financial interests enrolled a quarter of all patients.

In a third marketing application, an FDA reviewer took action because over a quarter of clinical investigators disclosed financial interests. Yet

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on two other marketing applications, over a quarter of clinical investigators disclosed financial interests, but no FDA action was taken.

Reviewer discretion may explain why action was taken in some instances and not others. FDA states that reviewers should be given the flexibility to consider financial information and steps taken to minimize bias on a case-by-case basis.⁴⁸

Despite being given such discretion, only 10 percent of surveyed FDA reviewers reported receiving instruction from FDA regarding how to review financial information. In addition, 70 percent of surveyed reviewers indicated that further instructions would be helpful.

Most FDA action can only occur after clinical trials are complete because FDA receives financial information only with the marketing application

Most FDA action to ensure that disclosed financial interests do not affect data integrity can occur only after clinical trials are complete because FDA does not receive financial information before the marketing application. FDA could take action during clinical trials, such as conducting a BiMo inspection, if it were alerted to potential issues related to financial interests. FDA encourages sponsors to engage in early consultation with FDA if they are concerned about their financial arrangements with clinical investigators.⁴⁹ However, all cases of FDA reviewers' actions in response to disclosed financial interests in FY 2007 took place after the clinical trials were complete.

When sponsors submit financial information to FDA with the marketing application, reviewers face time constraints. FDA's review of marketing applications is subject to nonbinding timelines, per Federal law.⁵⁰ Consequentially, FDA reviewers have limited time to take action to determine how disclosed financial interests may have affected data integrity. In fact, a previous OIG report found that 58 percent of CDER reviewers had concerns about time constraints for approving marketing applications.⁵¹

⁴⁸ 63 Fed. Reg. 5236 (Feb. 2, 1998).

⁴⁹ Ibid.

⁵⁰ The Prescription Drug User Fee Act, 21 U.S.C. §§ 379g-h and the Medical Device User Fee and Modernization Act, 21 U.S.C. § 379j authorize FDA to collect user fees from manufacturers in an effort to streamline and improve the timeliness of the review and approval of new drugs and medical devices.

⁵¹ OIG, "FDA's Review Process for New Drug Applications," OEI-01-01-00590, March 2003.

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Financial interests between clinical investigators and sponsors create a potential for bias that may compromise the safety of human subjects and the integrity of research data. Sponsors are required to disclose all clinical investigators' financial interests to FDA in the marketing application. In FY 2007, only 1 percent of clinical investigators disclosed a financial interest. By way of comparison, the Journal of the American Medical Association reported that between 23 percent and 28 percent of academic researchers had financial interests in medical companies.⁵² Further, we found a number of limitations in FDA's oversight, leaving FDA unable to determine whether sponsors submit financial information for all clinical investigators.

In addition, FDA approved 42 percent of marketing applications in FY 2007 that were missing financial information. FDA did not document a review of financial information for 31 percent of marketing applications.

Finally, neither FDA nor sponsors took action for 20 percent of marketing applications with disclosed financial interests. When FDA did act, it did not consistently take action in response to disclosed financial interests. These findings lead us to the following recommendations:

FDA Should Ensure That Sponsors Submit Complete Financial Information for All Clinical Investigators

To ensure that sponsors submit complete financial information for all clinical investigators, we recommend the following:

FDA should use a complete list of clinical investigators to check that sponsors have submitted financial information for all clinical investigators.

To check that sponsors have submitted financial information for all clinical investigators, FDA should create a complete list of clinical investigators for each marketing application. This could be done in a variety of ways, including:

- requiring that sponsors submit an updated list of clinical investigators with the marketing application,

⁵² Justin E. Bekelman, et al., 2003. "Scope and Impact of Financial Conflicts of Interest in Biomedical Research," Journal of the American Medical Association, vol. 289(4), p. 456. Available online at <http://jama.ama-assn.org/cgi/reprint/289/4/454?ijkey=9e08192f3f85916bd89686c6af4713ad33b514ea>. Accessed on May 30, 2008.

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- modifying the Bioresearch Monitoring Information System to identify all clinical investigators, or
- modifying other FDA databases to capture information on clinical investigators and link it to marketing applications.

FDA should check that sponsors have submitted all required attachments to financial forms. To ensure that sponsors have submitted required attachments to financial forms, FDA centers should use a checklist that includes a check for attachments to financial forms during the administrative filing of marketing applications.

FDA should update guidance to sponsors regarding the due diligence exemption. FDA should update guidance stressing that sponsors should only rarely use the due diligence exemption. Given that sponsors are required to obtain financial information from clinical investigators before starting clinical trials, sponsors should always have the information they need to submit to FDA.

In addition, FDA should update guidance to sponsors incorporating its 2002 explanation of due diligence, which is currently provided only in Federal Register comments. This would clarify that due diligence is making at least two telephone calls and sending two certified letters. This sets a higher threshold for sponsors to meet before claiming the due diligence exemption than the current threshold of “a reasonable judgment made by the sponsor.”

FDA should add a review of financial information to the onsite inspection protocol. To help identify previously unknown financial interests, FDA should add a review of financial information to sponsor and clinical investigator BiMo inspection protocols.

FDA Should Ensure That Reviewers Consistently Review Financial Information and Take Action in Response to Disclosed Financial Interests

To ensure that reviewers consistently review and take action in response to financial information, we recommend the following:

FDA should require that all centers consistently use a template that includes a prompt to document a review of financial information. To help ensure that reviews of financial information are completed and documented, CBER should finalize its draft Clinical Review Template. CDRH should develop a review template that includes a prompt to document a review of financial information.

FDA should provide additional guidance and training to reviewers. The guidance and training could address how to review financial information, how to identify bias, and how and when to take action to ensure data integrity.

FDA Should Require That Sponsors Submit Financial Information for Clinical Investigators as Part of the Pretrial Application Process

We recommend that the pretrial application process be amended to require that sponsors submit financial information for clinical investigators. As each clinical investigator begins work on a clinical trial, sponsors should be required to either certify that clinical investigators do not have a financial interest with the sponsor or disclose a financial interest. For disclosed financial interests, sponsors should describe the financial interest and sponsors' actions to minimize any potential bias these financial interests may cause.

Implementing this recommendation would require only minimal changes to FDA's current process. Sponsors are already required to collect financial information from clinical investigators prior to beginning clinical trials. Further, FDA already engages with sponsors during the clinical trials. First, FDA approves the clinical trial protocol as part of the pretrial application. Then, as clinical trials get underway, sponsors are required to submit information on each clinical investigator they hire. Financial information for each clinical investigator could be included with these submissions. However, we recognize that FDA reviewers face time and resource constraints. Thus, we recommend that FDA build this review into the pretrial application process in the best way it sees fit, perhaps focusing most attention on disclosed financial interests.

If FDA received financial information before clinical trials, FDA could ensure that sponsors are collecting financial information before trials and are taking action to ensure that disclosed financial interests do not threaten human subjects or compromise data integrity. In addition, FDA is now devoting one-third of BiMo resources to ongoing clinical trials, as opposed to focusing solely on completed trials, according to FDA officials. Having information about a clinical investigator's financial interest could help FDA target which clinical trial sites are chosen for BiMo inspections. Finally, FDA has acknowledged the importance of obtaining this information before a clinical trial. FDA asserts that receiving clinical investigators' financial information before

a trial allows sponsors the opportunity to consult with FDA and take action to minimize any potential study bias.⁵³

In addition to requiring that sponsors submit financial information during the pretrial application process, sponsors should still be required to submit financial information with the marketing application. This ensures that FDA can review updated financial information for clinical investigators. It also ensures that financial information will be submitted for any clinical investigators whose information was not submitted as part of the pretrial application process.

AGENCY COMMENTS AND OFFICE OF INSPECTOR GENERAL RESPONSE

FDA expressed concerns about elements of our analysis in three of our findings. In addition, FDA agreed with all of our recommendations except the recommendation that FDA require sponsors to submit financial information for clinical investigators as part of the pretrial application process.

With respect to the first finding that 1 percent of clinical investigators disclosed a financial interest, FDA disagreed with our decision to report 36 disclosures for employees of the sponsor. Based on FDA's concern, we removed 34 disclosures for employees from our analysis because it was ambiguous whether sponsors were disclosing a financial interest for these employees. Two employees had clearly disclosed financial interests and thus were kept in our analysis. FDA also objected to our decision to report 12 disclosures that fell below the defined threshold. We continue to include these disclosures because it was our intention to describe all disclosures in FY 2007, even those not required by regulation. We assumed that sponsors purposefully disclosed these financial interests to FDA and did not question the validity of the disclosures.

In our second finding, we state that FDA cannot determine whether sponsors have submitted financial information for all clinical investigators because it does not have a complete list of clinical investigators. FDA took exception to our statement that FDA could provide complete lists of clinical investigators for only 7 percent of marketing applications. FDA believed that we did not clearly ask for

⁵³ 67 Fed. Reg. 6042 (Feb. 8, 2002)

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this information. However, we submitted an official written request to FDA for a list of clinical investigators from approved marketing applications. From discussions with FDA, we understood that there is often no list of clinical investigators in marketing applications but that FDA would provide us these lists when found. In fact, subsequently FDA did provide us with some lists of clinical investigators, but we could not validate the accuracy or completeness of the lists provided.

Finally, FDA did not agree with our decision to consider applications indicating due diligence as incomplete. We acknowledge that regulations allow sponsors to claim the due diligence exemption, but we maintain that sponsors' failure to submit financial information for all clinical investigators, whether they indicated due diligence or not, constitutes missing financial information. In these cases, FDA reviewers have incomplete knowledge of clinical investigators' financial information.

In response to our recommendation that FDA ensure that sponsors submit complete financial information, FDA stated that it is considering revising its guidance to industry to instruct sponsors to provide a table listing all clinical investigators and indicating whether a certification form, a disclosure form, or the due diligence exemption is being provided. FDA also stated that it is reviewing its procedures to determine whether modifications are needed to ensure that all required attachments are submitted. In addition, FDA stated that it is considering providing additional advice to sponsors on the use of the due diligence exemption. Finally, FDA stated that it has updated its onsite inspection protocol to include a closer inspection of financial information.

In response to our recommendation that FDA reviewers consistently review financial information, FDA indicated that it is evaluating its review procedures and templates. In addition, FDA is considering developing additional guidance and training for reviewers on the review of financial disclosure information.

For many reasons, FDA did not agree with our final recommendation that FDA require sponsors to submit financial information for clinical investigators as part of the pretrial application process.

FDA emphasized that collecting financial information before a clinical trial starts is the sponsors' responsibility. However, FDA has no mechanism to ensure that sponsors are collecting financial information before beginning clinical trials. In fact, FDA commented that sponsors

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may find obtaining financial information difficult because there can be a significant amount of time between completion of a clinical trial and submission of the marketing application. However, if sponsors were collecting financial information for all clinical investigators before they participated in a clinical trial as required, the lag time between when the clinical trial ended and when the marketing application was submitted would be irrelevant. Receiving financial information during the pretrial application process would allow FDA to ensure that sponsors were collecting financial information before beginning clinical trials, as required.

FDA also stated that financial interests are only one potential source of bias of clinical trials, emphasizing the importance of proper study design as a means for minimizing bias. Although it is true that there are multiple sources of potential bias, FDA acknowledged that sponsors are required to collect financial information before beginning a clinical trial so that they can identify and manage all potential sources of bias to ensure that human subjects are protected and data are reliable. Similarly, FDA could use information on all potential sources of bias, including financial information, to help sponsors identify potential bias before beginning clinical trials.

FDA also believes that for industry to collect and submit financial information and for FDA to review this information during the pretrial application process would represent significant additional work. However, pursuant to regulation, FDA already requires sponsors to collect financial information from clinical investigators before starting a clinical trial. In addition, basic information on clinical investigators is submitted to FDA as they are added to clinical trials. Thus, it is unclear how submitting financial information that is already collected, as well as the other information on clinical investigators that sponsors submit to FDA, would be a significant addition of effort on sponsors' part. Further, FDA stated that it intends to improve its oversight of ongoing clinical trials. Therefore, receiving financial information about ongoing clinical trials adds to an oversight initiative that is presently underway.

FDA also pointed out that many clinical trials are ultimately not submitted in a marketing application, thus making a review of financial information in the pretrial application process a potential waste of time. However, FDA stated its intention to improve its oversight of ongoing trials. Further, even if clinical trials do not result in a marketing application, the investigational products are still being tested on human

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subjects. To protect human subjects, FDA should take a proactive approach to ensure that clinical investigators are not biased when recruiting and testing investigational products on human subjects.

We continue to recommend that FDA require sponsors to submit financial information as part of the pretrial application process. Acknowledging the added burden to FDA's administrative and review staff, we encourage FDA to develop a review of financial information that best balances the additional effort with the potential benefits.

For the full text of FDA's comments, see Appendix F. FDA's technical comments are not included, but we made changes in the report where appropriate.

CERTIFICATION OF NO FINANCIAL INTERESTS, FORM 3454

DEPARTMENT OF HEALTH AND HUMAN SERVICES Food and Drug Administration CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS	Form Approved: OMB No. 0910-0396 Expiration Date: April 30, 2009
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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

Paperwork Reduction Act Statement

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

Department of Health and Human Services
 Food and Drug Administration
 5600 Fishers Lane, Room 14C-03
 Rockville, MD 20857

DISCLOSURE OF FINANCIAL INTERESTS, FORM 3455

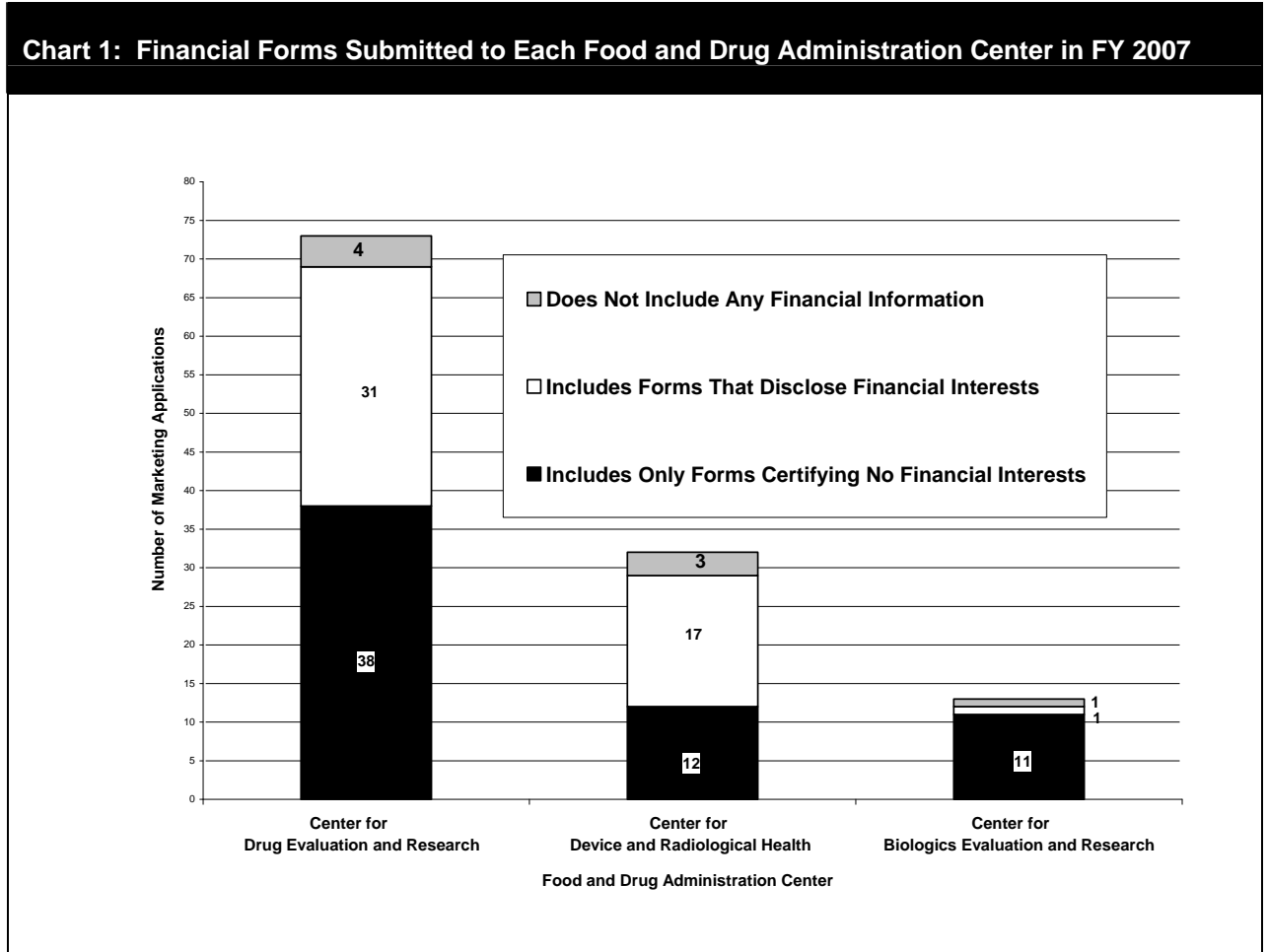
DEPARTMENT OF HEALTH AND HUMAN SERVICES Food and Drug Administration DISCLOSURE: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS	Form Approved: OMB No. 0910-0396 Expiration Date: April 30, 2009												
TO BE COMPLETED BY APPLICANT													
The following information concerning _____, who participated <div style="text-align: center; font-size: x-small;"><i>Name of clinical investigator</i></div> as a clinical investigator in the submitted study _____ <div style="text-align: right; font-size: x-small;"><i>Name of</i></div> <div style="text-align: left; font-size: x-small;"><i>clinical study</i></div> 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:													
Please mark the applicable check boxes.													
<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;													
<input type="checkbox"/> any significant payments of other sorts made on or after February 2, 1999 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;													
<input type="checkbox"/> any proprietary interest in the product tested in the covered study held by the clinical investigator;													
<input type="checkbox"/> any significant equity interest as defined in 21 CFR 54.2(b), held by the clinical investigator in the sponsor of the covered study.													
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.													
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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. Public reporting burden for this collection of information is estimated to average 4 hours per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to:													
Department of Health and Human Services Food and Drug Administration 5600 Fishers Lane, Room 14-72 Rockville, MD 20857													

FORM FDA 3455 (4/06)

FSC Graphics (201) 443-1090 EP



FINANCIAL FORMS SUBMITTED TO EACH CENTER IN FISCAL YEAR 2007



Source: Office of Inspector General analysis of marketing applications, 2008.

RESPONSE RATES FOR REVIEWER SURVEY

Our goal was to survey the Food and Drug Administration (FDA) reviewers who evaluated financial information within the past 3 years. However, not all centers could identify a specific population of reviewers that evaluate financial information. Therefore, for two centers, we sent surveys to all reviewers who reviewed a marketing application in the last 3 years. Thus, we distributed our survey to a high proportion of reviewers who did not evaluate financial information in the past 3 years. See Table 4 for survey responses by FDA center.

Center	Survey Recipients	Total Surveys Sent	Total Respondents	Respondents Who Reported Evaluating Financial Information
Center for Drug Evaluation and Research (CDER)*	Medical officers	308	109	87
Center for Devices and Radiological Health (CDRH)**	Reviewers who reviewed a marketing application in the last 3 years	305	176	61
Center for Biologics Evaluation and Research (CBER)**	Reviewers who reviewed a marketing application in the last 3 years	177	52	14
Total		790	337	162

* CDER identified medical officers as the discipline of reviewers who routinely evaluate financial information.

** CDRH and CBER could not identify a specific discipline of reviewers who routinely evaluate financial information. Therefore, the centers identified all reviewers who reviewed a marketing application in the last 3 years, regardless of whether they evaluated financial information.

Source: Office of the Inspector General analysis of electronic survey respondents, 2008.



DESCRIPTION OF FOOD AND DRUG ADMINISTRATION ACTION

When the Food and Drug Administration (FDA) reviewers took action in response to disclosed financial interests, they most often conducted their own analyses to identify potential bias. Additionally, two reviewers requested inspections from the Bioresearch Monitoring Program (BiMo) and one reviewer requested additional analysis from the sponsor. As a result of their actions, FDA reviewers determined that the disclosed financial interests did not compromise the integrity of the data. See Table 5 for details of FDA action for the six marketing applications on which FDA took action.

Table 5: Details of FDA Actions in Response to Marketing Applications With Disclosed Financial Interests

FDA Action Per Marketing Application	Reason Action Was Taken
Compared outcomes from investigators with financial interests against those without	Over a quarter of clinical investigators had disclosed financial interests
Compared outcomes from investigators with financial interests against study mean*	Some clinical investigators with disclosed financial interests had very favorable results
Compared outcomes from investigators with financial interests against study mean*	Unspecified
Requested a BiMo inspection of an investigator with a financial interest	Investigator disclosed a financial interest and had a large number of patients
Requested a BiMo inspection of the sponsor	The sponsor originally did not submit any financial forms
Requested that the sponsor submit reanalysis of study outcomes excluding clinical investigators with financial interests*	Unspecified

* Indicates marketing applications upon which sponsors also took action to decrease bias.

Source: Office of Inspector General analysis of marketing applications and FDA review notes, 2008.

AGENCY COMMENTS



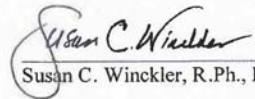
DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

To: Inspector General
From: Chief of Staff, FDA
Subject: Agency Comments to OIG Draft Report Entitled, "FDA's Oversight of Clinical Investigator's Financial Information" (OEI-05-07-00730)

FDA is providing the attached general comments to the Office of the Inspector General's Draft Report entitled, "FDA's Oversight of Clinical Investigator's Financial Information" (OEI-05-07-00730).

We appreciate the opportunity to review and comment on this draft correspondence before it is published.


Susan C. Winckler, R.Ph., Esq.

Food and Drug Administration (FDA) Response to Office of Inspector General (OIG) Draft
Report on FDA's Oversight of Clinical Investigator's Financial Information

We appreciate the Office of the Inspector General's interest in the Food and Drug Administration's oversight of clinical investigators' disclosure of financial information. Concerns about clinical investigators' financial conflicts of interest in human subjects research have led government agenciesⁱ and academic organizationsⁱⁱ to develop policies and guidance on how to identify and manage potential conflicts. Many research institutions have also developed programs to deal with these concerns.ⁱⁱⁱ

In concert with these efforts, FDA's Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires sponsors to submit, in marketing applications for drugs, biologic products and devices, certain financial information for clinical investigators who conducted studies used to support these applications. We consider this information, along with information about the design and purpose of the study and the results of bioresearch monitoring on-site inspections, in assessing the reliability of the data and determining whether the applications are approvable under the statutory requirements. We may consider clinical studies inadequate and the resulting data unreliable if, among other things, appropriate steps have not been taken in the design, conduct, reporting, and analysis of the studies to minimize bias.

FDA's oversight of clinical investigator financial disclosures is one part of our broader oversight responsibility for our clinical trials program. As previously described in our response to the OIG report on FDA's Oversight of Clinical Trials (OEI-01-06-00160), the agency launched its Human Subject Protection (HSP)/Bioresearch Monitoring (BIMO) Modernization Initiative, under which we have been carefully scrutinizing our programs and actively working to improve all aspects of our oversight activities to ensure the protection of human subjects and integrity and reliability of research data.^{iv} We are considering the OIG's recommendations in the context of this initiative. Below, we have provided some background information before we discuss the recommendations.

- Clinical investigators' financial interests could lead to purposeful or inadvertent bias that could influence the outcome of the clinical trial. As noted in the report, however, less than one percent of clinical investigators reported disclosable financial interests. There are other potential sources of bias (for example, the prestige related to new discoveries, the desire to help seriously ill patients, and the potential to publish results) that could also cause investigators to favor a particular outcome. FDA has, therefore, always emphasized the importance of proper study design as a means for minimizing bias. For example, potential bias from assigning subjects with a better prognosis to receive the test product can be minimized by using randomized assignment; similarly, potential bias in assessing therapy outcome can be minimized through blinded study designs and use of objective outcome measures.
- FDA considers the evaluation of financial information disclosed by clinical investigators to be an important aspect of assuring that clinical trials are not

compromised; that is, the data produced are reliable and human subjects are protected. However, FDA uses a variety of additional mechanisms for assuring this. These include ensuring that the study design is appropriate to the question(s) being investigated and that the potential for bias is minimized; advising sponsors on monitoring procedures to ensure that data generated in clinical trials are accurate and complete and that subjects are protected; conducting on-site bioresearch monitoring inspections of clinical investigators to verify compliance with applicable regulations;^v and relying on the replication of study results, comparing results from more than one investigator, and analyzing the data in multiple ways.

- While a number of changes have been implemented through our HSP/BIMO Modernization Initiative, we are continuing to look for additional means to improve our oversight of clinical trials. For example, alternative methods to select clinical investigator sites for inspection are being evaluated, such as risk-based approaches and using statistical evaluations to identify sites of interest. We are also shifting inspectional resources to on-going trials, improving our follow-up of violative inspections, and developing a comprehensive cross-Center database of clinical trial and bioresearch monitoring inspectional information.

I. General Comments

FDA would like to share the following comments on the recommendations in the OIG report.

1. “FDA should ensure that sponsors submit complete financial information for all clinical investigators.”
 - a. “FDA should use a complete list of clinical investigators to check that sponsors have submitted financial information for all clinical investigators.”

FDA agrees that we should have a complete list of clinical investigators in the marketing application. In fact, the Centers receive this information for new drug applications (NDAs),^{vi} biologics license applications (BLAs)^{viii} and premarket approval applications (PMAs).^{ix} In most cases, a list of clinical investigators is included in the application. If the information is missing, reviewers request it as a part of their review.

As discussed in response to recommendation 1.c. below, we are considering revising our guidance, “Guidance for Industry: Financial Disclosure by Clinical Investigators.” One change we are considering is to request that applicants provide a table listing all clinical investigators and indicating for each whether a certification, disclosure, or due diligence exemption is being provided. This would allow reviewers to check that sponsors provided complete financial disclosure information.

- b. "FDA should check that sponsors have submitted all required attachments to financial forms."

We agree that reviewers should check that all required attachments to financial forms are submitted. The Centers are evaluating their review procedures to determine if modifications may be needed to ensure the review of financial information and verify that all required information, such as the attachments to the financial forms, is submitted. The use of standardized review templates/checklists is one method by which this may be achieved.

- c. "FDA should update guidance to sponsors regarding the due diligence exemption."

We will review our guidance, "Guidance for Industry: Financial Disclosure by Clinical Investigators," to determine if additional information or clarifications are needed, including incorporation of the advice on due diligence as described in the Federal Register of February 8, 2002 (56 FR 6039).

- d. "FDA should add a review of financial information to the onsite inspection protocol."

We have updated the Compliance Program Guidance Manual (CPGM) chapter on Clinical Investigator Inspections to help ensure clinical investigators submit required financial information to sponsors. Under these revised procedures, FDA field investigators will ask clinical investigators if they have submitted the information on their financial interests to the sponsor of the covered study, and if they have updated that information (should it change during the trial or within one year of completion of the study). FDA initiated training on this new procedure in August 2008. Additionally, FDA plans to incorporate appropriate changes to the CPGM chapter on inspections of Sponsors, Monitors, and Contract Research Organizations.

- 2. "FDA should ensure that reviewers consistently review financial information and take action in response to disclosed financial information."

- a. "FDA should require that all centers consistently use a template that includes a prompt to document a review of financial interests."

FDA agrees with the importance of ensuring that reviewers conduct consistent and thorough reviews of all disclosed financial information. As indicated in response to recommendation 1.b. above, the Centers are evaluating their review procedures and templates. The Center for Drug Evaluation and Research's (CDER's) standard review template for clinical reviews includes a financial disclosure section. The standard review template is required to be filled out during the review of the NDA/BLA. In addition, CDER regularly schedules new reviewer training during which the template is discussed. The Center for

Biologics Evaluation and Research (CBER) is currently developing standard review templates that will incorporate a financial disclosure section. The Center for Devices and Radiological Health (CDRH) requires the use of PMA filing and approval checklists and is in the process of updating these checklists to include more detailed information on financial disclosure.

b. "FDA should provide additional guidance and training to reviewers."

We agree and are considering the development of additional guidance and a training program on the review of financial disclosure information for incorporation into the Centers' reviewer training programs. This guidance and/or training program may include topics, such as the regulatory requirements, appropriate documentation of the review (including the use of review templates and assuring all information and attachments are provided), and possible actions that may be taken when disclosed financial information raises concerns.

This recommendation also specifies that FDA ensure reviewers "take action" in response to disclosed financial information but does not define what is meant by this phrase. We believe there is a wide range of actions that may be taken; determining what, if any, action is appropriate is case dependent.

Part of the reviewer's consideration is the type of financial interest disclosed. Some financial interests are of greater concern than others. For example, outcome payments (that is, payment that is dependent on the outcome of the study) elicit the highest concern, but are rarely seen. Proprietary interests are also of greater concern, but are not generally seen. When there are financial interests, they are usually equity interests and/or significant payments of other sorts. Besides the type of financial interest, reviewers also consider other factors when determining if additional action is indicated. These include the total number of investigators and subjects in the study, the number and percentage of subjects enrolled by the disclosing investigator, the design of the clinical study (double-blind, single-blind, placebo-controlled, active controlled), the method of randomization, the nature of primary and secondary endpoints (objective, subjective), the method of endpoint assessment, method of evaluation, and the results of the investigator versus results of other investigators in the study.

Depending on these factors, reviewers determine which actions, if any, may be appropriate in a given situation. Actions may include a re-analysis of the data excluding the investigator's results, a clinical audit of the investigator if he/she had a large number of subjects, or a decision that the financial interests of the investigator would not have affected the outcome of the study (for example, if the investigator enrolled a small number of subjects to a randomized, blinded study with an easily assessed endpoint, such as, survival or pregnancy, and the investigator's results were similar to the results of the other investigators). In cases where the reviewer felt that the study results were unlikely to have been compromised by bias on the part of the

clinical investigator, the reviewer may decide not to include a detailed discussion in the review memo.

3. "FDA should require that sponsors submit financial information for clinical investigators as part of the **pretrial application process** (emphasis added)."

As discussed below, FDA disagrees with this recommendation and the OIG's statement that "implementing this recommendation would require only minimal changes to FDA's current process."

FDA's regulations require the collection of financial disclosure information by sponsors prior to study initiation, so that sponsors are alerted to payments and financial arrangements that could lead to bias in the clinical trial. Sponsors can then take this information into account when designing and conducting the trial. This disclosure is not intended to discourage investigators from being included in the study. Rather, disclosure allows sponsors to identify and manage potential conflicts to ensure human subjects are protected and data are reliable as they develop a regulated product. FDA receives clinical investigator financial disclosure information when a marketing application is submitted for review. In this way, agency reviewers are alerted to payments and financial arrangements that could lead to bias and can take this information into account during the review of the marketing application. FDA evaluates financial information in conjunction with the contribution of the investigator to the overall data in the application.

Because there are many potential sources of bias, only one of which is financial, bias is a concern in all trials. Sponsors of adequate and well-controlled studies [21 CFR 314.126 and 21 CFR 860.7(f)] must take steps to minimize bias, regardless of the source. Two commonly used ways to do this are randomized assignment to treatment and blinding. As explained in the preamble to the final regulation on financial disclosure (63 FR 5241, February 2, 1998), sponsors are invited to consult with FDA on the management of specific situations involving potential bias on the part of an investigator. During this consultation, FDA focuses on protecting research subjects and minimizing bias.

Most of the critical studies used to support product effectiveness have tens of investigators; some have hundreds, each with several subinvestigators. The regulations at 21 CFR 312.23(a)(6)(iii)(b) and 21 CFR 812.20(b)(4) require the submission of the name of each investigator. When the research application is first submitted to FDA, however, the majority of the clinical investigators have not yet been identified. The application is subsequently amended with the names of additional investigators on an on-going basis. Investigators continue to be added for months or even years for studies involving large numbers of subjects. Thus, the identification of investigators occurs, for the most part, well after the agency has completed its review of the study protocol.

Contrary to statements in the OIG's report that FDA receives copies of completed 1572 forms and investigator agreements, the regulations do not require that this information be submitted to FDA. Therefore, for industry to collect and submit clinical investigator financial information and for FDA to review this information on a rolling basis would represent a significant work effort. Implementation of this recommendation would require repeated review of the clinical investigators' financial disclosure information and the protocol over the duration of a clinical study. Despite this additional effort, there would be no information as to the importance of each clinical investigator's contribution to the study at that stage of the trial. An investigator who ultimately enters no subjects would not be distinguishable from an investigator with 100 subjects. In addition, investigators who participate in early phase trials may or may not participate in the pivotal trial(s) that are submitted in the marketing application. Although it is reasonable that, in some cases, discussion of financial information might avert later problems, the effort and cost of routinely doing this appear unacceptable, and the need for this activity (i.e., evidence that it would solve a recognized problem or enhance human subject protection) is not established.

It is also important to note that, of the many studies under a research application, only a few contain data critical to approval, and these are best recognized in the marketing application. Only about 50% of Phase 3 trials are ultimately submitted in a marketing application,^x and only about 20% of device studies approved by FDA are closed with the intention of submitting a PMA.^{xi}

In summary, FDA does not believe that amending its regulations^{xii} to require the submission of financial disclosure information in the pretrial application would help the agency fulfill its clinical trial oversight responsibility of protecting human subjects and ensuring the integrity and reliability of research data. Instead, it may very well have the unintended effect of adding to the complexity and cost of the clinical trial enterprise with no commensurate gain in the protection of human subjects or the quality of the data. Moreover, implementing this recommendation would add a significant burden to FDA's administrative and review staff. Given that only approximately 8% of new medicinal compounds entering Phase 1 drug testing reach the market^{xiii} and the OIG's finding that less than 1% of clinical investigators had disclosable financial information, restructuring FDA's review process to accommodate this recommendation does not seem warranted. As discussed above, through FDA's HSP/BIMO Modernization Initiative, the agency is focusing its resources on a number of projects aimed at strengthening our oversight activities, thus helping to safeguard research participants and the integrity of clinical trial data.

II. Comments on Methodology and Findings

FDA has concerns with the underlying methodology that led to several of the findings in the report. These concerns are discussed below.

1. "One Percent of Clinical Investigators Disclosed a Financial Interest" (See also Table 1: Disclosed Financial Interests)

OIG reports that "Among clinical investigators listed in financial forms, 1 percent disclosed at least one financial interest. This represents 240 of the 29,725 listed clinical investigators." FDA believes that this finding is inaccurate, and that the percentage is an overstatement of clinical investigators with disclosable interests. In performing its analysis, OIG included financial interests that do not meet the disclosure requirements under 21 CFR Part 54. Specifically, in reference to Table 1, on page 13, it is stated that "Fourteen percent of disclosed financial interests were uncategorized. Most of these were for current or former employees of the sponsor..." The regulation does not require applicants to disclose financial interests of employees of the sponsor (21 CFR 54.4), and this represented 36 of the 250 total disclosed financial interests listed in Table 1. Likewise, the 12 disclosed financial interests found in 4 marketing applications, noted on page 10, that "fell below the defined threshold" should not have been included in the analysis. Therefore, 48 of the 250 total disclosed financial interests (for the 240 listed clinical investigators) did not meet the reporting threshold of the regulation and should not have been included in the OIG's analysis.

2. "Forty-two percent of FDA-approved marketing applications were missing financial information."

As discussed on page 11 of the report, OIG considered financial disclosure information complete if four criteria were met, one of which was that a claim for the due diligence exemption was not made. By regulation, applicants are permitted to certify that they acted with due diligence to obtain the required information but were unable to do so. (21 CFR 54.4)

Use of the due diligence exemption is justifiable in a number of situations. For example, financial disclosure information may be difficult to obtain when there is a significant time lag between completion of the clinical trial and submission of the marketing application, especially if the applicant was not the sponsor of the clinical trial. For clinical trial sites outside the United States (which many marketing applications include), there is no requirement to collect financial disclosure information prospectively when the trial is not conducted under a pretrial application. Additionally, financial disclosure information is not always obtained prospectively for subinvestigators, who are often in short-term positions and frequently rotate in and out of studies. When sponsors seek financial disclosure information, the subinvestigators may have moved to another location and employers may not know or may be unwilling to provide forwarding information.

Therefore, given that applicants are permitted by regulation to claim the due diligence exemption and there are several valid and reasonable situations for its use, marketing applications in which the exemption was claimed should not have been considered to be "missing financial information."

3. "FDA does not have a complete list of clinical investigators."

On pages ii and 14, it is stated that FDA does not have a complete list of clinical investigators and that FDA was able to provide a complete list for only 7 percent of the marketing applications approved in FY 2007. As indicated in our response to recommendation 1.a. above, FDA does receive this information in marketing applications submitted for review. Based on discussions with the OIG at the December 17, 2007, entrance conference, however, FDA did not provide this information, nor was it requested of FDA in follow-up conversations.



A C K N O W L E D G E M E N T S

This report was prepared under the direction of Ann Maxwell, Regional Inspector General for Evaluation and Inspections in the Chicago regional office, and Thomas Komaniecki, Deputy Regional Inspector General.

Anne Bracken led this study and Beth McDowell served as the lead analyst. Other principal Office of Evaluation and Inspections staff from the Chicago regional office who contributed to the report include Abby Lopez; central office staff who contributed include Robert Gibbons, Ayana Everett, Matthew McMullen, and Talisha Searcy.