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OFFICE OF INSPECTOR GENERAL

THE FOOD AND DRUG ADMINISTRATION'S OVERSIGHT OF CLINICAL TRIALS

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EXECUTIVE SUMMARY

OBJECTIVE

1. To determine the extent to which the Food and Drug Administration (FDA) conducted inspections of clinical trials from fiscal year (FY) 2000 to FY 2005.
2. To assess FDA's processes for inspecting clinical trials.

BACKGROUND

The Federal Food, Drug, and Cosmetic Act generally requires all new drugs and medical devices (hereinafter referred to as investigational products) to undergo clinical trials on human subjects to demonstrate the safety and efficacy of these products before they are approved for sale in the United States. The sponsors, clinical investigators, and institutional review boards (IRBs) that conduct and oversee these trials must comply with FDA regulations designed to protect the human subjects participating in them. The Office of Inspector General (OIG) received a congressional request to review FDA oversight of clinical trials after a series of news articles highlighted vulnerabilities.

Three FDA centers regulate medical investigational products for human use: the Center for Drug Evaluation and Research, the Center for Biologics Evaluation and Research, and the Center for Devices and Radiological Health. FDA's Office of Regulatory Affairs (ORA) conducts onsite bioresearch monitoring (BiMo) inspections of sponsors, clinical investigators, and IRBs as assigned by the centers.

BiMo inspections are not required by Federal regulations; the centers decide when to assign them. Inspections can result in one of three classifications: no action indicated (NAI), voluntary action indicated (VAI), or official action indicated (OAI). After the inspection, BiMo investigators recommend a classification for the inspection, and the assigning center reviews the inspection report and assigns a final classification. Although FDA takes no additional action for inspections classified as NAI, it may take additional action for VAI and OAI inspections.

We used seven data sources for this study: BiMo inspections data; file reviews of all inspections that BiMo investigators or a center classified as OAI; an e-mail survey of BiMo investigators; interviews with FDA officials; observations of BiMo inspections; analysis of the National

Institutes of Health (NIH) clinical trial registry; and reviews of FDA policies, procedures, and guidance documents.

FINDINGS

Data limitations inhibit FDA's ability to effectively manage the BiMo program. Because FDA does not maintain a clinical trial registry, it is unable to identify all ongoing clinical trials and their associated trial sites. Further, because FDA does not maintain an IRB registry, it is unable to identify all IRBs. Even though FDA maintains six databases to track BiMo inspections, none includes complete information needed to track all such inspections. For example, ORA's database does not include complete information for inspection events that occur after it completes its inspection. The center databases do not consistently track inspection information.

Other factors hinder FDA's ability to effectively manage the BiMo program. Centers and ORA inconsistently classify OAI and NAI inspections. FDA relies on voluntary compliance to correct violations of regulatory significance. Uncertainty of timing and lack of coordination impede FDA's ability to conduct BiMo inspections. In addition, FDA guidance and regulations do not reflect current clinical trials practices.

We estimate that FDA inspected 1 percent of clinical trial sites during the fiscal year 2000–2005 period. FDA conducted 2,856 BiMo inspections that required a clinical trial site visit during the FY 2000–2005 period. Because FDA cannot identify the total number of clinical trial sites, we used the NIH clinical trial registry to estimate the proportion of clinical trial sites the BiMo inspections reached. The centers conduct more inspections that verify clinical trial data than inspections that focus on human subject protections. Seventy-five percent of the BiMo inspections during the FY 2000–2005 period were surveillance inspections, which generally target previously completed trials and often focus on verifying the quality of clinical trial data. Also, FDA inspected few IRBs, which offer considerable oversight of human subject protections.

RECOMMENDATIONS

To improve the BiMo information systems and processes, FDA should take the following actions:

Improve information systems and processes.

Develop a clinical trial database that includes all clinical trials. FDA should develop a comprehensive internal database of clinical trials to more effectively identify and target ongoing clinical trials for inspection.

Create an IRB registry. This registry would give FDA basic information about IRBs that it now lacks. By identifying all IRBs overseeing clinical trials, FDA could target IRBs more effectively for inspection.

Create a cross-center database that allows complete tracking of BiMo inspections. A database that includes timely and complete information about all BiMo inspections would help FDA better coordinate and track inspections.

Establish a mechanism to provide feedback to BiMo investigators on their inspection reports and findings. Improved feedback between the centers and BiMo investigators could lead to a common understanding of the regulations and guidelines that govern BiMo inspections.

Seek legal authority to provide oversight that reflects current clinical trial practices. FDA should consider seeking additional authority that covers all of the stakeholders in the management and conduct of clinical trials. In particular, FDA could seek to expand its authority to include the colleagues and subordinates of a clinical investigator if they participate in the conduct of a clinical trial.

AGENCY COMMENTS AND OFFICE OF INSPECTOR GENERAL RESPONSE

FDA concurred with four of our five recommendations listed above. FDA did not address our recommendation to establish a mechanism to provide feedback to BiMo investigators on their inspection reports and findings.

FDA pointed out that BiMo inspections make up only one part of its efforts to ensure human subject protections, noting that it views its protocol review before a clinical trial commences as the most important step in protecting human subjects. We recognize the important role that FDA's protocol review plays in protecting human subjects. We note, however, that this report addresses another important part of the system for protecting human subjects: oversight of the trials once they are actually underway.

The agency also highlighted the efforts of its Human Subject Protection/Bioresearch Monitoring Council and emphasized the importance of risk-based approaches to BiMo inspections.

Where appropriate, we made changes to the report based on FDA's technical comments.

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BACKGROUND

The Federal Food, Drug, and Cosmetic Act generally requires all new drugs and medical devices (hereinafter referred to as investigational products) to undergo clinical trials on human subjects to demonstrate the safety and efficacy of these products before they are approved for sale in the United States.[1] [2] FDA has promulgated regulations to protect the rights, safety, and well-being of the human subjects who participate in these trials. These regulations apply to the sponsors, clinical investigators, and institutional review boards (IRBs) that conduct or oversee clinical trials for investigational products. FDA inspects clinical trials to determine whether each of these groups complies with the relevant regulations.

The Office of Inspector General (OIG) received a congressional request to review FDA's oversight of clinical trials after a series of news articles highlighted vulnerabilities.[3] The series identified problems with FDA's oversight of clinical trials, including insufficient informed consent procedures, inadequate training and certification requirements for IRBs, limited Federal regulations, and FDA's failure to enforce existing regulations.

Clinical Trials

Sponsors. The person or entity responsible for developing and testing an investigational product is the product's sponsor. Sponsors of drug and biological products must file an investigational new drug (IND) application with FDA before they can begin clinical trials; device

[1] In some instances devices do not go through a formal approval process but go to market through a premarket notification and determination of substantial equivalence by FDA. In these instances, clinical trials may not be necessary. See Federal Food, Drug, and Cosmetic Act of 1938, P. L. No. 75-717, 52 Stat.1040 (1938) (amended 2004).
21 U.S.C. § 360(o).

[2] 21 U.S.C. §§ 355(i), 360(j).

[3] David Evans, Mike Smith, Liz Willen, "Drug Industry Human Testing Masks Death, Injury, Compliant FDA," Bloomberg News, November 2, 2005.

sponsors submit investigational device exemptions (IDE).[4] INDs and IDEs provide FDA with information on the study protocol, the qualifications of trial personnel, and assurances that trials will protect human subjects' welfare, among other details.[5] A sponsor may begin its clinical trial 30 days after FDA receives an IND or IDE, provided that the agency does not place the study on clinical hold.[6]

FDA regulations require sponsors to select qualified clinical investigators to conduct the trials needed to bring an investigational product to the market.[7] A clinical trial generally involves many clinical investigators working in multiple trial sites, including sites outside the United States.

Sponsors must also ensure that proper monitoring occurs throughout the clinical trial.[8] In part, this means that sponsors must ensure that clinical investigators comply with the relevant FDA regulations. Key FDA regulations pertaining to clinical trials address informed consent procedures, data management practices, and clinical trial oversight processes.[9]

If the clinical trials demonstrate the investigational product to be safe and effective, sponsors that wish to market a product in the United States must submit a new product application to FDA.[10] [11] Provisions within the Prescription Drug User Fee Act of 1992 (PDUFA) and the Medical Device User Fee and Modernization Act of 2002 (MDUFMA) require FDA to expedite the process for the review of product applications.[12] FDA reviews the clinical trial data and may choose to inspect facilities as part of the application review process.[13] If FDA

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[4] 21 CFR § 312.20 (drugs and biologics); 21 CFR § 812.20 (medical devices).

[5] 21 CFR § 312.23.

[6] 21 CFR § 312.40 (drugs and biologics); 21 CFR § 812.30 (medical devices).

[7] 21 CFR § 312.50 (drugs and biologics); 21 CFR § 812.40 (medical devices).

[8] Ibid.

[9] Ibid. See also FDA, "Compliance Program Guidance," Chapter 48: Sponsors, Contract Research Organizations and Monitors Part 1—Background (February 2001). Available online at http://www.fda.gov/ora/compliance_ref/bimo/7348_810/default.htm. Last accessed on January 16, 2006.

[10] The drug development and approval process may take several years. For more information, see Congressional Research Service, "The U.S. Drug Approval Process: A Primer," June 2001.

[11] 21 CFR § 314.50 (drugs); 21 CFR § 601 (biologics); 21 CFR § 814.20 (devices).

[12] 21 U.S.C. §§ 301, 379f(j).

[13] 21 CFR § 314 (drugs); 21 CFR § 600.21 (biologics); 21 CFR § 814.44 (devices).

approves a new product, sponsors can market and sell it in the United States.

Clinical investigators. Clinical investigators' responsibilities include recruiting subjects, supervising clinical studies of the investigational product, and reporting study results to the sponsor.[14] Before they begin drug and biological clinical trials, clinical investigators must sign an FDA Form-1572 (Statement of Investigator).[15] By signing this form, investigators agree to follow a research protocol that the sponsor provides to FDA, report any unexpected adverse outcomes to sponsors and IRBs, obtain informed consent from all subjects participating in the research, and comply with all relevant FDA regulations.[16]

Institutional Review Boards. IRBs are committees that an institution designates to oversee clinical investigators and their research.[17] IRBs are often affiliated with hospitals and academic medical centers, but they also exist in managed care organizations and Government agencies and as for-profit entities that are independent of the institution in which the research takes place. IRBs generally oversee many and varied clinical trials.[18]

IRBs are intended to ensure that clinical investigators take appropriate steps to protect the rights and welfare of human subjects. All clinical trial research involving human subjects must be approved by an IRB.[19] Once an IRB approves a clinical trial, Federal regulations require it to reevaluate the trial at least once a year.[20]

Food and Drug Administration Oversight of Clinical Trials

Three centers within FDA individually regulate different types of medical investigational products for human use. These centers are the Center for Drug Evaluation and Research (CDER), the Center for Biologics Evaluation and Research (CBER), and the Center for Devices

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[14] 21 CFR § 312.60 (drugs and biologics); 21 CFR § 812.100 (devices).

[15] Although the Center for Devices and Radiological Health does not require a Form FDA 1572, it does require an investigator agreement. See 21 CFR § 812.43(c) (devices); 21 CFR § 312.53 (drugs and biologics).

[16] 21 CFR § 50.312.

[17] 21 CFR § 56.102.

[18] Larger IRBs may oversee more than 500 trials in a given year. See Institutional Review Boards Registration Requirements, 69 Fed. Reg. 40,556 (July 6, 2004).

[19] 21 CFR § 56.109(a).

[20] 21 CFR § 56.109(f).

and Radiological Health (CDRH).[21] CDER and CBER share regulations for the development of investigational products; CDRH has its own regulations.[22]

The centers use onsite inspections to ensure that clinical investigators, sponsors, and IRBs comply with FDA regulations while developing investigational products. In 1977, FDA established the Bioresearch Monitoring Program (BiMo) to develop cross-center guidelines for these inspections of clinical investigators, sponsors, and IRBs (hereinafter referred to as BiMo inspections).[23] BiMo's objective, as it relates to clinical trials, is to "assure the quality and integrity of data submitted to FDA to demonstrate the safety and efficacy of regulated products, and to determine that human rights and the welfare of human and animal research subjects are adequately protected."[24] The "Compliance Program Guidance Manual" contains the current guidelines for BiMo inspections.

FDA's Office of Regulatory Affairs (ORA) conducts all onsite inspection activities for the agency. ORA employs about 1,300 investigators who conduct a total of 22,000 inspections annually. About 200 investigators (hereinafter referred to as BiMo investigators) have received specialized training to conduct BiMo inspections and have conducted these inspections in recent years.[25] BiMo investigators work out of all 19 of ORA's district offices.

Types of Bioresearch Monitoring inspections. The centers assign two general types of BiMo inspections: surveillance inspections and directed inspections. Most surveillance inspections target concluded clinical trials and retrospectively review compliance with FDA regulations. Many directed inspections target trials that are still treating human subjects (ongoing trials). The centers can assign surveillance and directed inspections to ORA at any point during the development of an

[21] FDA's Center for Veterinary Medicine and Center for Food Safety and Applied Nutrition oversee investigational products as well, but are outside the scope of our evaluation.

[22] 21 CFR § 312 (drugs and biologics); 21 CFR § 812 (devices).

[23] 21 U.S.C. §§ 355, 360(i).

[24] FDA, "Bioresearch Monitoring Program Coordination Background." Available online at: http://www.fda.gov/ora/compliance_ref/bimo/background.html. Last accessed on February 5, 2007.

[25] Although some investigators conduct BiMo inspections exclusively, most investigators also conduct other types of inspections for FDA.

investigational product. Although FDA has the authority to conduct surveillance and directed BiMo inspections, it is not required to do so.

Surveillance inspections are generally routine inspections that the centers assign to ORA to verify that a clinical investigator, a sponsor, or an IRB complied with FDA regulations during clinical trials for an investigational product. Data verification inspections are a principal type of surveillance inspection. Data verification inspections usually occur 2 to 3 years after the clinical trials for an investigational product conclude and focus on verifying the clinical trial data that a sponsor submitted to support a new product application.

The centers assign directed inspections to ORA for a variety of reasons, including complaints about the conduct of a clinical trial from an interested party, problems noted during previous inspections, or problems identified at similar sites. Other factors may also lead the centers to assign a directed inspection of a clinical trial, such as an unusually high number of subjects enrolled at one site under one clinical investigator or a treatment that may be considered higher risk. Directed inspections that target ongoing clinical trials allow the centers and BiMo investigators to review the conduct of a clinical trial and advise where corrective action may be needed while the trial is still ongoing, thereby offering further human subject protections.

Bioresearch Monitoring inspection process. ORA's BiMo investigators conduct BiMo inspections according to the "Compliance Program Guidance Manual." Also, staff at the center that assigned a BiMo inspection may issue additional instructions for the BiMo investigator. The manual's instructions vary based on the type of inspection (i.e., clinical investigator, sponsor, or IRB).[26] If a BiMo investigator identifies violations of FDA regulations, he/she records them on a Form FDA-483 (Inspectional Observations Report). After the inspection, the BiMo investigator sends the assigning center a copy of the FDA-483 and an Establishment Inspection Report (EIR), which includes background

[26] FDA, "Compliance Program Guidance Manual," Chapter 48.809: Institutional Review Board (September 1997); Chapter 48.810: Bioresearch Monitoring—Sponsors, Contract Research Organizations, and Monitors (February 2001); Chapter 48.111: Clinical Investigators (September 2000).

information and copies of all inspection documents. In the EIR, the BiMo investigator recommends a classification for the inspection.[27]

Inspection classifications and actions taken. Staff at the assigning center classify each inspection based on the EIR and other information they have about the investigational product. BiMo inspections can result in one of three classifications: no action indicated (NAI), voluntary action indicated (VAI), or official action indicated (OAI). An NAI classification signifies few or no violations of FDA regulations. Generally, FDA takes no action in these cases. An inspection receives a VAI classification and an untitled letter when the violations are serious enough to record, but the center does not believe the violations cross "the threshold of regulatory significance."[28] FDA does not require the clinical investigators, sponsors, or IRBs that receive VAI classifications to address the violations found during the inspection.

Centers classify inspections as OAI and issue warning letters to the inspected entity when investigators find violations of "regulatory significance."[29] FDA considers warning letters an important tool in ensuring voluntary compliance. If the inspection subject does not take corrective action to address violations cited in the warning letter, FDA may take enforcement actions, such as disqualifying data or barring a clinical investigator from conducting research. Warning letters and enforcement actions are publicly available on FDA's Web site.

FDA requests that the inspected entity respond to the violations listed in a warning letter by sending a justification or a corrective action plan to the assigning center. FDA's "Regulatory Procedure Manual" states, "If necessary to ensure that corrections have been implemented, follow-up inspections should be conducted promptly after the agreed upon date of completion of the promised corrections."[30]

Recent Food and Drug Administration Initiatives

Recently, FDA has taken steps to improve its BiMo inspection processes. In 2004, it created the BiMo Steering Committee to review

[27] Although most recommended classifications made by BiMo investigators are classified as no action indicated, voluntary action indicated, or official action indicated, BiMo investigators may also choose not to recommend a classification.

[28] Ibid., p. 4-27.

[29] The centers are required to get the concurrence of FDA's Office of Chief Counsel for all warning and untitled letters. See FDA, "Regulatory Procedures Manual," Chapter 4: Advisory Actions, p. 4-26, March 2007.

[30] Ibid., p. 4-11.

BiMo processes and make recommendations for improving them. During the course of our study, FDA renamed that committee the Human Subject Protection/Bioresearch Monitoring Council. In 2006, the committee issued new guidance on clinical trial conduct and policy.[31]

Prior Office of Inspector General Reports

Previous OIG reports documented weaknesses in the oversight that FDA and IRBs provide for clinical trials. In 1998, a series of reports concluded that IRBs lacked the time and the expertise to sufficiently monitor the research taking place under their jurisdiction.[32] The reports found that IRBs often conducted minimal review of studies after the initial approval of the research. Additionally, IRBs provided little training for investigators and board members.

A 2000 report documented weaknesses in clinical trial oversight. The report found that data integrity concerns, more than human subject protection, drove FDA's oversight of clinical investigators and that the BiMo program lacked clear and specific guidelines.[33]

METHODOLOGY

Scope

Our study focused on BiMo inspections of sponsors, clinical investigators, and IRBs in clinical trials from FY 2000 through FY 2005. We included all of the BiMo inspections conducted for CBER, CDER, and CDRH that are listed in FDA's inspections databases for this 6-year period.

Data Sources and Analysis

We used seven data sources for this study. See Appendix A for a detailed methodology.

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[31] In 2006, FDA issued the following new guidance: Draft Guidance: Process for Handling Referrals to FDA Under 21 CFR § 50.54; Additional Safeguards for Children in Clinical Investigations, May 2006; Guidance for Industry: Using a Centralized IRB Process in Multicenter Clinical Trials, March 2006; Guidance for Clinical Trial Sponsors: Establishment and Operation of Clinical Trial Data Monitoring Committees, March 2006; Information Sheet Guidances for IRBs, Clinical Investigators, and Sponsors, January 2006.

[32] Department of Health and Human Services, OIG, "Institutional Review Boards: A Time for Reform," OEI-01-97-00193, June 1998; OIG, "Low-Volume Institutional Review Boards," OEI-01-97-00194, October 1998; "Institutional Review Boards: Their Role in Reviewing Approved Research," OEI-01-97-00190, June 1998.

[33] Department of Health and Human Services, OIG, "FDA Oversight of Clinical Investigators," OEI-05-99-00350, June 2000.

Food and Drug Administration's Bioresearch Monitoring inspections data. We analyzed FDA's BiMo inspections data to evaluate how FDA tracks and manages BiMo inspections. We also calculated the number and type of inspections FDA conducts. We used data from six FDA databases for BiMo inspections. The three centers maintain separate databases to track BiMo inspections: two databases each for CBER and CDER and one for CDRH. ORA maintains the Field Accomplishment and Compliance Tracking System (FACTS).

From each database, we analyzed the records for BiMo inspections of sponsors, clinical investigators, and IRBs that BiMo investigators conducted for the three centers during the FY 2000–2005 period. We excluded laboratory and bioequivalence inspections from our analysis.

File review. Using the FDA databases, we identified and reviewed all BiMo inspections for which the BiMo investigator recommended OAI or a center classified as OAI in FY 2000–2005. We reviewed 668 files, including 99 CBER inspection files, 248 CDER inspection files, and 321 CDRH inspection files.

E-mail survey of Bioresearch Monitoring investigators. We surveyed BiMo investigators about their experiences with FDA guidance, classification recommendations, inspection followup with the assigning centers, and challenges conducting BiMo inspections. We received completed surveys from 76 percent of the BiMo investigators (170 out of 223).

Interviews with Food and Drug Administration officials. We conducted telephone interviews with all 19 ORA district directors and supervisors of investigation branches (hereinafter referred to as supervisors). The interviews focused on the supervisors' experiences with the supervisory role, interactions with the BiMo investigators they supervise, interactions with the assigning centers, classification recommendations, and challenges in supervising BiMo inspections. We also interviewed senior FDA officials in the agency's headquarters and at each center.

Observation of Bioresearch Monitoring inspections. We observed the process that BiMo investigators followed, as well as the interactions between the investigator(s) and the inspection subject(s). We observed two clinical investigator inspections and one IRB inspection.

Clinical trials registry site estimate. From the population of trials on the National Institutes of Health's (NIH) clinical trials registry as of February 2007, we selected a stratified random sample of 150 trials. Because the registry is separated by phase of the trial, the three strata

used for the sample were Phase I, Phase II, and Phase III of the clinical trial. We excluded 43 of the sampled trials and the final sample size to estimate that the number of trial sites was 107. (See Appendix A, Table 7, for our sample design.)

Review of Food and Drug Administration regulations, guidance, policies, and procedures documents. We obtained and reviewed all relevant FDA regulations, guidance, policies, and procedures documents for conducting BiMo inspections.

Standards

We conducted this review 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.

Data limitations inhibit FDA's ability to effectively manage the BiMo program

FDA relies on BiMo inspections as a principal mechanism for overseeing clinical trials after it reviews the protocol. BiMo inspections help to ensure the quality and integrity of clinical trial data, and to determine whether sponsors, clinical investigators, and IRBs are complying with regulations that protect human subjects while they are enrolled in clinical trials.

FDA lacks a complete clinical trial registry

Because FDA does not maintain a clinical trial registry, it is unable to indentify all ongoing clinical trials and their associated trial sites. Limited clinical trials that are regulated by FDA can be found on a clinical trial registry run by NIH.[34] Included within this data bank is information on FDA-regulated studies to treat serious or life-threatening diseases and conditions. Sponsors are not required to submit information on any other type of clinical trials that FDA regulates.

FDA lacks an IRB registry

Because FDA does not maintain an IRB registry, it is unable to identify all IRBs. IRBs are important because their primary purpose is to ensure that clinical investigators take appropriate steps to protect the rights and welfare of human subjects. BiMo inspections of IRBs offer the centers considerable oversight of human subject protections. Because IRBs usually oversee many and varied clinical trials, the centers can review numerous trials across the centers with each BiMo inspection of IRBs.

The Office of Human Research Protections (OHRP) oversees all federally sponsored research that includes human subjects.[35] OHRP maintains a database consisting of all IRBs that oversee this research. Although the OHRP database likely contains many IRBs that oversee some FDA-regulated clinical trials, it does not contain IRBs that oversee clinical trials regulated exclusively by FDA.

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[34] Section 113 of the 1997 Food and Drug Administration Modernization Act directs the Secretary of the Department of Health and Human Services to act through NIH to establish and operate a databank of information on clinical trials for drugs to treat serious or life-threatening diseases or conditions. 42 U.S.C. § 282(j)(3)(A).

[35] OHRP oversees research that is conducted or supported by HHS. See 45 CFR Part 46.

FDA has acknowledged the importance of creating an IRB registry and published a proposed rule in July 2004 for the creation of one.[36] According to FDA, the benefits of such a registry would include being able to identify IRBs that review clinical trials regulated by FDA, having a complete list of IRBs for educational and outreach purposes, and being able to easily identify IRBs for inspection.[37]

No FDA database includes complete information for all BiMo inspections, hindering FDA's ability to track BiMo inspections

FDA maintains six databases to track BiMo inspections. Although ORA's database, FACTS, includes information on all BiMo inspections, it does not consistently include information about inspection-related events that occur after an investigator submits an inspection report to the centers. For example, 48 percent of BiMo inspection records in FACTS (2,557 out of 5,312 records during the FY 2000–2005 period) lack the centers' final classifications. Because of these omissions, FDA cannot use FACTS to track inspections from assignment through a center's final action.

Tracking BiMo inspections using data from the centers is challenging because of the number of databases involved and their inconsistencies. The three centers used five separate databases to track BiMo inspection data in the FY 2000–2005 period.[38]

The center databases do not uniformly track inspections. First, each database contains different information about BiMo inspections. Second, when the centers track similar information, they do not do so in the same way. For example, each database uses different categories to identify the reason a center initiated an inspection.[39] (See Table 1 on the next page.) These categories are difficult to translate across databases. For example, FACTS and one of CBER's databases indicate whether an inspection was based on a complaint. However, the other databases combine complaint-based inspections with other types of inspections, which means that FDA cannot identify which inspections were prompted by complaints for all centers. Also, the databases define different types of inspections as surveillance and as directed. FDA

[36] Institutional Review Boards Registration Requirements, 69 FR 40,556 (July 6, 2004).

[37] Ibid., 40,557.

[38] CBER and CDER maintain two databases each to track inspections.

[39] None of the databases indicates whether an inspected trial was completed or ongoing.

cannot use these databases to track inspections across centers unless it controls for all of these discrepancies.

Table 1: Categories Center and ORA Databases Use To Track Reason for Inspection

Database	Inspections Included	Category
ORA FACTS	All BiMo inspections ORA conducts	• Complaint (for cause, based on a complaint) • Compliance (followup to previous violations) • Surveillance (routine inspections that are not based on preexisting information about a firm; includes data integrity inspections)[2]
CBER IRB	CBER's IRB inspections	• Text field (most entries in this field do not indicate reason for inspection)
CBER CISM[1]	CBER's clinical investigator and sponsor inspections	• Complaint • Surveillance (site selected because of high risk; includes blood, cell, gene, vaccine, and other)[2]
CDER COMIS[3]	Completed inspections of trials for drug products	• Data audit (most are based on new product application) • For cause (based on prior problems complaint)
CDER DSI[4]	CDER inspections starting in FY 2004 or later	• For cause (based on previous problems or complaint)[4] • Routine data audit (based on a new product application) • Information gathering • Surveillance[2]
CDRH database	All CDRH BiMo inspections of IRBs, clinical investigators, and sponsors	• Routine • For cause • Directed • Vulnerable population • Probability sampling • Field initiated • Center initiated • Expedited review • Surveillance[2] • Followup inspection after OAI inspection

[1]CISM is clinical investigator, sponsor, and monitor.
[2]The databases define surveillance differently.
[3]COMIS is the Center Office Management Information System.
[4]DSI is the Division of Scientific Investigations. In the CDER DSI database, inspections can be more than one type.

Source: OIG analysis of ORA, CBER, CDER, and CDRH data, 2006.

The five center databases do not uniformly track other important inspection-related data, such as (1) whether the inspection targets an ongoing or completed clinical trial, (2) ORA's recommended classification, and (3) follow-up inspection information.

Other factors hinder FDA's ability to effectively manage the BiMo program

Centers and ORA inconsistently classify OAI and NAI inspections

According to FY 2000–2005 CDER and CDRH data, these centers often disagreed when ORA recommended an OAI classification, the most serious classification category.[40] (See Table 2.) During this 6-year period, CDER revised 68 percent of ORA's OAI recommendations and CDRH revised 23 percent of ORA's OAI recommendations. The centers reclassified most of these inspections to VAI, a classification that neither requires the inspected entity to formally address violations the center identified nor makes the classification publicly available.

The centers do not systematically track their reasons for revising ORA's recommended classifications. However, our review of 668 FDA inspection files identified two key reasons for changing OAI classifications to VAI. The most common reasons were that the center, in conjunction with an Office of Chief Counsel review, determined that the violations were not serious enough to warrant a warning letter and therefore an OAI classification, and that the inspection subject promised corrective actions.

Table 2: CDER and CDRH Agreement With ORA Recommended Classifications, FY 2000–2005

Center	Percentage of All Recommendations Center Revised	Percentage of OAI Recommendations Center Revised	Percentage of VAI Recommendations Center Revised	Percentage of NAI Recommendations Center Revised
CDER	14% (303 of 2,090)	68% (133 of 195)	2% (25 of 1,328)	26% (145 of 567)
CDRH	13% (193 of 1,506)	23% (62 of 271)	7% (47 of 688)	15% (84 of 547)

Source: OIG analysis of CDER and CDRH data, 2006.

CDER and CDRH also revised some of ORA's NAI recommendations. In other words, center reviewers sometimes identified violations when a BiMo investigator found no significant violations at the inspection site. CDER reclassified 26 percent of the inspections that ORA identified as

[40] We could not conduct this analysis for CBER because it does not record ORA's recommended classification.

NAI. CDRH reclassified 15 percent of the inspections that ORA identified as NAI.

These reclassifications suggest that ORA and the centers sometimes interpret the regulations and guidance for BiMo inspection classifications differently. Although the centers ultimately classify inspections, they rely on BiMo investigators to identify violations at the inspection site and collect evidence to support inspection classifications. If BiMo investigators interpret the regulations and guidelines differently than center reviewers do, they may miss evidence to support an OAI classification when one would be appropriate. Conversely, BiMo investigators may spend time gathering evidence to support an OAI classification that the center does not support.

BiMo supervisors and investigators reported that a lack of feedback from the centers and inadequate training may contribute to the differences in interpreting inspection classifications. Eighteen of nineteen BiMo supervisors we spoke with stated that the centers rarely or never provide feedback on the inspection reports that the districts submit to the centers. Further, 19 percent of the BiMo investigators we surveyed (32 of 170) responded that they would like more information on the centers' final classifications or feedback on their inspection-related performance.

FDA relies on voluntary compliance to correct violations of regulatory significance

The centers send warning letters for 70 percent of inspections classified as OAI. The centers can respond to OAI inspections by issuing an untitled letter, issuing a warning letter, disqualifying a clinical investigator, or disqualifying data gathered in the clinical trial. Our analysis of center data shows that the centers chose to respond to 70 percent of inspections they classified as OAI during the FY 2000–2005 period by issuing warning letters. (See Table 3 on the next page.) The centers' next most common response to OAIs was untitled letters, which they sent for 16 percent of OAI inspections. Less frequently, the centers took more formal actions, including initiating disqualification of inspection subjects or disqualifying data from clinical trials.

Warning letters and untitled letters rely on voluntary compliance, so FDA must reinspect individuals who receive these letters to ensure that they do not repeat violations in future clinical research. If the centers do not track the response to warning letters and untitled letters, they

cannot ensure that voluntary compliance occurs. According to FDA's "Regulatory Procedures Manual," "Warning Letters are issued only for violations of regulatory significance. Significant violations are those violations that may lead to enforcement action if not promptly and adequately corrected. A Warning Letter is the agency's principal means of achieving prompt voluntary compliance with the Federal Food, Drug, and Cosmetic Act."[41]

Table 3: Centers' Official Actions for BiMo Inspections Classified as OAI

Center	Percentage of OAIs That Resulted in a Warning Letter	Percentage of OAIs That Resulted in an Untitled Letter	Percentage of OAIs That Resulted in a Disqualification Letter	Percentage of OAIs That Resulted in Disqualified Data	Unknown Action
CBER	82% (55 of 67)	6% (4 of 67)	12% (8 of 67)	0% (0 of 67)	0% (0 of 67)
CDER	57% (38 of 67)	16% (11 of 67)	18% (12 of 67)	2% (1 of 67)	8% (5 of 67)
CDRH	71% (151 of 214)	20% (42 of 214)	3% (6 of 214)	1% (1 of 214)	7% (14 of 214)
Total	**70% (244 of 348)**	**16% (57 of 348)**	**8% (26 of 348)**	**1% (2 of 348)**	**6% (19 of 348)**

Source: OIG analysis of CDER, CDRH, and CBER inspection files, 2006.

Although CBER and CDER fail to track inspection followup, CDRH data show that that center conducts few follow-up inspections. Center databases fail to track whether the center conducted a followup to an inspection classified as VAI or OAI. CDRH's database indicates whether an inspection was initiated as a followup to a prior violative inspection. However, the database does not link the followup inspection to the violative inspection. Nor does it indicate in the record for the violative inspection that followup occurred. CDRH data show that the center conducted 3 follow-up inspections for every 100 inspections classified as OAI or VAI in the FY 2000–2005 period (36 follow-up inspections for 1,048 inspections classified as OAI and VAI).

[41] FDA, "Regulatory Procedures Manual," Warning Letter Procedures, p. 4-1-1, March 2007. Available online at http://www.fda.gov/ora/compliance_ref/rpm. Last accessed April 9, 2007.

Uncertainty and lack of coordination impede FDA's ability to conduct BiMo inspections

In interviews, center and ORA staff reported that inspections triggered by new product applications affect the conduct and timing of other inspections. The centers cannot predict how many new product applications they will receive each year and therefore cannot plan for the inspections that these applications trigger. At the beginning of each fiscal year, the centers plan and budget for BiMo inspections. During the year, the centers also receive new product applications, which generate BiMo inspection assignments with short due dates because of the overall performance goals of PDUFA and MDUFMA.[42] Assignments based on new product applications are usually retrospective reviews that focus on verifying clinical trial data used in the application. These assignments generally take priority over all other BiMo inspections. Because each center has a set budget for all inspections, an unexpected rise in new product applications may mean that the ORA districts have more inspections overall and more inspections with short due dates than they originally planned.

Because of the uncertainties of timing and prioritization involved with BiMo inspections, districts sometimes must delay some of the other inspections that ORA conducts, particularly those with later due dates. In fact, 11 of 19 district supervisors we interviewed stated that assignments for inspections related to marketing applications create challenges for managing resources. Staff in five district offices reported asking the centers for additional time to complete BiMo inspections; two offices estimated that they request extensions for about 20 percent of BiMo assignments. Staff in four other districts reported that they have to cancel other inspections when they have too many unexpected BiMo assignments.

Additionally, the centers generally fail to coordinate assignments with one another or the districts. When asked if they faced any challenges conducting BiMo inspections, staff from 7 of the 19 district offices reported that lack of planning and coordination by the centers created challenges for the district. For example, staff in a district that oversees

[42] PDUFA requires pharmaceutical companies to pay fees to FDA when submitting Preapproval Marketing Applications and New Drug Applications. These fees are dedicated to expediting the review of product applications for CDER and CBER. MDUFMA has the same requirement for device applications. The BiMo inspection serves as one step of the evaluation process. 21 U.S.C. §§ 379g(4), 379j.

a large geographic area reported that inspection assignments for distant sites would be more manageable if they could combine multiple inspections in a single trip. However, this is not feasible without coordinating across the assigning centers.

Failure to coordinate BiMo assignments across centers may also impede BiMo Steering Committee goals. In interviews, BiMo Steering Committee members reported that they want to increase the number of inspections of ongoing trials and inspections that focus on high-risk sites. One committee member we interviewed told us that the current system, in which each center independently issues assignments and tracks data, does not allow for the timely coordination necessary to target high-risk and ongoing inspections across centers.

FDA guidance and regulations do not reflect current clinical trial practices

According to interviews with center officials and ORA supervisors, FDA's guidance and regulations for clinical trials have fallen behind industry practices. FDA officials reported that when the agency developed clinical trial regulations, a single investigator at a single site ran each clinical trial. Since then, clinical trials have grown increasingly complex. Trials are larger and involve multiple sites within and outside the United States.[43]

FDA officials told us that clinical investigators frequently delegate tasks that include direct care to human subjects to colleagues or subordinates. Current FDA regulations do not address colleagues or subordinates. When FDA conducts an inspection and finds significant deficiencies related to individuals other than the clinical investigator, the agency may only take action against the clinical investigator.

Finally, although sponsors increasingly conduct clinical trials outside the United States, FDA authority over foreign trials remains limited. For example, one center official estimated that 20 to 25 percent of the trials for products that FDA oversees occur outside the United States. According to the official, centers are often unaware that foreign trials

[43] Regarding the increasingly complex management structures of clinical trials, see Department of Health and Human Services, OIG, "The Globalization of Clinical Trials: A Growing Challenge in Protecting Human Subjects," OEI-01-00-00190, September 2001. See also Iain M. Cockburn, "The Changing Structure of the Pharmaceutical Industry," Health Affairs, 23(1) pp. 10–22, 2004; and R. A. Rettig, "The Industrialization of Clinical Research," Health Affairs, 19(2), pp. 129–146, 2000. Regarding the growing size and complexity of clinical trials, see Institute of Medicine, "The Future of Drug Safety: Promoting and Protecting the Health of the Public," Chapters 1 and 2, 2006.

have taken place because FDA's investigational product regulations generally do not apply outside the United States. When ORA does inspect foreign clinical trials and finds violations, the centers can only disqualify data from consideration in a new product application.

We estimate that FDA inspected 1 percent of clinical trial sites during the fiscal year 2000-2005 period

As previously noted, FDA lacks a complete database that includes information on all BiMo inspections. However, FDA also lacks registries that contain complete clinical trial and IRB information. Failure to track all clinical trials and IRBs limits the centers' ability to oversee trials through BiMo inspections. First, the centers cannot assign BiMo inspections of trials and IRBs that they cannot identify. Second, the centers cannot identify the percentage of trials and IRBs that BiMo inspections reach. To identify the percentage of trials and IRBs that BiMo inspections reached during the FY 2000–2005 period, we used estimates of clinical trial and IRB populations from Government sources outside FDA.

The centers reported 2,856 BiMo inspections that required a clinical trial site visit for the FY 2000–2005 period.[44] (See Table 4 on the next page.) However, the centers do not have data to identify the percentage of trial sites that these inspections reached. Therefore, we used the number of INDs and IDEs the centers received as well as estimates from the clinical trial registry that NIH maintains to estimate the percentage of trial sites that the BiMo inspections reached.[45]

[44] We excluded IRB and sponsor inspections from this analysis because they generally do not take place at a clinical trial site.

[45] Section 113 of the 1997 FDAMA directs the Secretary of the Department of Health and Human Services to act through NIH to establish and operate a databank of information on clinical trials for drugs to treat serious or life-threatening diseases or conditions. Included within this databank is information on studies to treat serious or life-threatening diseases and conditions conducted under FDA IND regulations. Although the NIH registry does not include all the clinical trials FDA oversees, it provides the best available estimate of the average number of trial sites associated with clinical trials. The registry is available at www.clinicaltrials.gov.

Table 4: Centers' BiMo Inspections With Site Visits by Fiscal Year

Fiscal Year	CDER	CDRH	CBER	Total
2000	296	91	143	530
2001	186	113	79	378
2002	194	153	109	456
2003	226	167	103	496
2004	219	189	75	483
2005	221	183	108	512
Total	**1,342**	**896**	**617**	**2,855**

Source: OIG Analysis of CDER, CDRH, and CBER data, 2006.

We included only clinical investigator, contract research organization, and sponsor monitor inspections.

Although FDA cannot identify the total number of clinical trial sites operating during the FY 2000–2005 period, the centers did track the 15,268 INDs and IDEs that they received during this period. However, each IND or IDE may involve many trial sites, so the number of INDs and IDEs cannot substitute for the total number of trial sites. Therefore, to estimate the total number of trial sites, we calculated the average number of clinical trial sites associated with a random sample of clinical trials listed on the NIH clinical trials registry. We found that clinical trials listed on that registry had an average of 23 sites per trial.[46] Based on these figures, we estimate that the 15,268 INDs and IDEs the centers received included about 350,000 trial sites.

Using the estimate of 350,000 trial sites, we estimate that FDA's 2,855 inspections reached just under 1 percent of the trial sites associated with the INDs and IDEs the centers received.

[46] A 95-percent confidence interval for our sample is +/- 8 trial sites, or between 15 and 31 sites per trial. Using this range, we calculate that FDA's 2,855 inspections reached at most just over 1 percent of trial sites associated with the 15,268 applications received by the centers.

Centers assign more surveillance inspections than directed inspections

For the FY 2000–2005 period, 75 percent of BiMo inspections were surveillance inspections. Surveillance inspections generally focus on verifying the clinical trial data that sponsors submitted with their new product applications. Further, most surveillance inspections target completed trials. Data verification inspections serve an important purpose in enabling FDA to assess the quality of the data used to support new product applications. However, because these inspections take place after trials conclude, they cannot ensure that sponsors, clinical investigators, and IRBs are taking the necessary actions to protect human subjects during the trials.

Some of the directed inspections that the centers assigned during the FY 2000–2005 period likely focused on ongoing trials. For example, CBER annually targets a high-risk category of clinical trials for inspection, which may include ongoing clinical trials.[47] CDRH implemented a program in the past year to increase the number of inspections that focus on higher-risk clinical trials that may be ongoing. However, the three centers do not track whether inspections target ongoing trials, so we could not estimate the proportion of BiMo inspections that reached ongoing trials. Several senior FDA officials reported to us that they recognize the need to inspect more ongoing clinical trials to protect human subjects.

Centers inspect few IRBs

Our analysis of center data shows that in the FY 2000–2005 period, FDA conducted an average of 214 IRB inspections each year. The number of IRB inspections has decreased annually since 2002. (See Table 5 on the next page.) IRB inspections offer the centers considerable oversight of human subject protections. Because IRBs usually oversee a variety of clinical trials, the centers can review numerous trials across the centers with each IRB inspection.

At most, we estimate that during the FY 2000–2005 period, the centers inspected an average of about 6 percent of IRBs each year, or less than 40 percent of all IRBs in the 6-year period we evaluated. Because the centers do not track the total population of IRBs, we used the IRB database maintained by OHRP to estimate the population of IRBs. OHRP oversees all research that the Federal Government sponsors.

[47] Past examples include studies focusing on pediatric populations and gene therapy studies.

The OHRP database includes all IRBs that oversee research sponsored by the Government, so it likely underestimates the population of IRBs overseeing all clinical trial research. In February 2007, OHRP reported 3,579 IRBs in its IRB database.[48]

Table 5: IRB Inspections as a Percentage of Total BiMo Inspections

Fiscal Year	Number of IRB Inspections	Total BiMo Inspections	Percentage of Inspections That Are IRB inspections
2000	198	795	25%
2001	187	633	30%
2002	278	812	34%
2003	251	854	29%
2004	207	779	27%
2005	163	769	21%
Total	**1,284**	**4,642**	**28%**

Source: OIG Analysis of CDER, CDRH, and CBER data, 2006.

IRB inspections assigned to ORA are allowed longer timeframes than inspections of clinical investigators or sponsors. A center's inspection assignment includes a due date. In many cases, the centers allow ORA up to 1 year to complete IRB inspections. By comparison, ORA generally has 30 to 90 days to complete inspections of clinical investigators.[49]

Center data show that despite these longer timeframes, ORA frequently failed to meet the requested due dates for IRB inspections. ORA failed to meet CDRH's deadlines for 60 percent of IRB inspections (214 out of 359); 24 percent (85 of 359) were more than 60 days late. Similarly, ORA failed to meet CBER's deadline for 38 percent of that center's IRB inspections (24 of 63).[50]

[48] OHRP oversees research that is conducted or supported by the U.S. Department of Health and Human Services. See 45 CFR Part 46.

[49] In some cases, IRB inspections are directed because of a past OAI or some other concern. In these instances, the timeframes are shorter than the timeframes presented here.

[50] We could not determine the timeliness of CDER inspections because CDER does not include the inspection due date in its database.

FDA conducts BiMo inspections to ensure the quality and integrity of clinical trial data and to determine whether sponsors, clinical investigators, and IRBs are complying with regulations that protect human subjects enrolled in clinical trials. Our evaluation identified a lack of comprehensive reporting and tracking systems, a lack of coordination among the centers and ORA, and regulations that do not fully reflect current clinical trial practices.

No Federal requirements prescribe the number or type of BiMo inspections FDA must conduct. However, FDA relies on BiMo inspections as a principal mechanism for overseeing clinical trials after it reviews the protocol. We recognize that resource limitations may be a factor in determining the extent of FDA's oversight of clinical trials using BiMo inspections. However, to ensure its effectiveness in meeting BiMo objectives, the inspection program needs comprehensive management and reporting systems.

FDA has taken steps to improve the BiMo inspection program. For example, in 2004 it created the BiMo Steering Committee to identify and address weaknesses in the BiMo program. We identified additional steps that FDA can take to improve oversight of clinical trials. These changes will help FDA plan and conduct BiMo inspections more effectively. These changes will also help FDA meet the BiMo objective of "determining that human rights and the welfare of human research subjects are adequately protected."

FDA should:

Improve Information Systems and Processes

FDA's BiMo inspections are a principal mechanism to ensure the quality and integrity of clinical trial data and to determine that human subjects are protected. However, the weaknesses we identified in the BiMo information systems and management processes inhibit FDA's ability to effectively oversee and manage BiMo inspections across centers. To improve the effectiveness of the BiMo program, FDA should take the following actions:

Develop a clinical trial database that includes all clinical trials. FDA should develop a comprehensive database to use as an internal management tool to more effectively identify ongoing clinical trials for inspection. Although NIH currently maintains a clinical trial registry, that registry was not intended to be a comprehensive listing of clinical trials. It was created to

inform the public regarding potentially new life-saving treatments. Because the registry contains clinical studies to treat serious or life-threatening diseases and conditions conducted under FDA's IND regulations, it excludes most other clinical trials subject to FDA regulation, such as medical device studies.

Create an Institutional Review Board registry. By identifying all IRBs overseeing clinical trials, FDA could target IRBs more effectively for inspection. FDA has acknowledged the importance of creating an IRB registry and published a proposed rule in July 2004. Recently, the agency set a timetable of March 2008 for issuance of a final rule.[51]

OHRP currently maintains an IRB registry for studies under its auspices.[52] FDA could build upon OHRP's existing IRB registry to create a larger and more inclusive database while minimizing the administrative burden for IRBs.

Create a cross-center database that allows complete tracking of Bioresearch Monitoring inspections. FDA cannot efficiently manage BiMo inspections across centers without a database that includes timely and complete information about all BiMo inspections. A single, consistent database would require the centers to agree about which fields are essential and how they should be defined. At a minimum, the database should include: (1) specific information on the reason for an inspection, (2) whether the inspection targets an ongoing or a completed clinical trial, (3) ORA's recommended classification, and (4) follow-up inspection information.

Establish a mechanism to provide feedback to Bioresearch Monitoring investigators on their inspection reports and findings. Improved feedback between the centers and BiMo investigators could lead to a common understanding of the regulations and guidelines. This would minimize the likelihood that an investigator would miss evidence to support an OAI classification when one would be appropriate or spend time gathering evidence to support an OAI classification that the center does not corroborate.

Seek legal authority to provide oversight that reflects current clinical trial practices. FDA should consider seeking additional authority that covers all of the stakeholders in the management and conduct of clinical trials.

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[51] 72 FR 22,520 (April 30, 2007).

[52] OHRP oversees research that is conducted or supported by the U.S. Department of Health and Human Services. See 45 CFR § 46.

In particular, FDA should consider seeking authority to include the colleagues and subordinates of a clinical investigator if they participate in the conduct of a clinical trial.

AGENCY COMMENTS AND OFFICE OF INSPECTOR GENERAL RESPONSE

FDA concurred with four of our five recommendations. These recommendations aimed to improve information systems and processes related to the BiMo program. FDA did not address our recommendation to establish a mechanism to provide feedback to BiMo investigators on their inspection reports and findings.

Specifically, FDA concurred with our recommendations to develop a clinical trial database that includes all clinical trials, to create an IRB registry, to create a cross-center database that allows complete tracking of BiMo inspections, and to seek legal authority to provide oversight that reflects current clinical trial practices.

FDA pointed out that BiMo inspections make up only one part of its efforts to ensure human subject protections, noting that it views its protocol review before a clinical trial commences as the most important step in protecting human subjects. We recognize the important role that FDA's protocol review plays in protecting human subjects and made several changes to our report to reflect this point. We do note, however, that this report addresses another important part of the system for protecting human subjects: oversight of the trials once they are actually underway.

The agency highlighted the efforts of its Human Subject Protection/Bioresearch Monitoring Council in identifying key issues that needed to be addressed, such as coordination, tracking mechanisms, regulations, and guidance. FDA also emphasized the importance of risk-based approaches to BiMo inspections rather than committing to inspecting a specified percentage of clinical trials.

Where appropriate, we made changes to the report based on FDA's technical comments.

See Appendix B for complete agency comments.

APPENDIX A

METHODOLOGY

Scope

Our study focused on Bioresearch Monitoring (BiMo) inspections of sponsors, clinical investigators, and Institutional Review Boards (IRBs) in clinical trials from fiscal year (FY) 2000 to FY 2005. We reviewed all of the inspections that BiMo investigators conducted for the Center for Drug Evaluation and Research (CDER), the Center for Biologics Evaluation and Research (CBER), and the Center for Devices and Radiological Health (CDRH) that are listed in Food and Drug Administration's (FDA) inspections databases for this 6-year period. We excluded BiMo inspections that focused on the bioequivalence and laboratory compliance programs.[53]

Data Sources and Analysis

We used seven data sources for this study.

Food and Drug Administration's Bioresearch Monitoring inspections data. We analyzed FDA inspections data to evaluate how FDA tracks and manages BiMo inspections. We also calculated the number and type of inspections FDA conducts.

We analyzed data from six FDA databases for BiMo inspections. Each center we evaluated and the Office of Regulatory Affairs (ORA) maintain separate databases to track BiMo inspections. CDRH and ORA each maintain a single database. CBER and CDER each maintain two databases.

From each database, we analyzed the records for BiMo inspections of clinical investigators, sponsors, and IRBs for CBER, CDER, and CDRH during the FY 2000 to 2005 period.

We analyzed fields in the databases that indicate the type of inspections that the centers conducted in the FY 2000 to 2005 period. (See Table 6.) Each center tracks inspections differently, so we could not gather information on every variable for all centers.

[53] We excluded laboratory BiMo inspections because they were not clinical in nature. We excluded bioequivalence BiMo inspections because they do not necessarily follow the same investigational product processes described in the Background on p. 2.

Using the fields listed in Table 6, we evaluated the number and types of inspections that FDA conducted from FY 2000 to 2005. We conducted all database analysis in SAS®.

The following is a description of each of the databases:

- *Field Accomplishment and Compliance Tracking System* (FACTS): We received FACTS data from ORA in July 2006. The FACTS data included 5,850 records. We removed 472 records that either duplicated other records or targeted subjects outside our scope (for example, manufacturers). We excluded 66 records that ORA coded as "Cancelled" or "Returned" or that the Center for Veterinary Medicine requested. Our analysis includes 5,312 FACTS records.

- *CBER data:* We received data from CBER's two databases in July 2006. CBER dedicates one database to clinical investigator and sponsor inspections. This database originally contained 714 records. We removed records that did not fall within the scope of this study, including five manufacturing inspections, four inspections classified as "no inspection," three inspections classified as "out of business," and eight inspections classified as "washout." We also removed 11 inspections that did not include inspection start dates. Our analysis includes 683 inspection records from this database.

  CBER uses a second database to track IRB inspections. This database included 73 records. We used all of these inspection records in our analysis.

- *CDER data:* We received data from one CDER database, the Center Office Management Information System (COMIS), in October 2006. CDER uses COMIS to track closed inspections of CDER drug products trials that started before FY 2004. The COMIS data originally included 4,237 inspection records. However, many of these records were duplicates. After we removed the duplicate records, COMIS included 1,196 inspection records.

  We received data from a second CDER database, the Division of Scientific Investigations database (DSI), in December 2006. CDER uses the DSI database to track all inspections starting in FY 2004 or later. The DSI database originally included 1,137 inspection records. We removed records that did not fit within the scope of our study, including inspections that started after FY 2005 ended. Our analysis included 1,107 inspection records from the DSI database.

- *CDRH data:* We received data from CDRH in November 2006. CDRH's database originally included 2,762 inspection records. We excluded 1,168 inspection records, including records that ORA classified as "no inspection made" and records that CDRH classified as "washout," "out of business," or "cancelled." Our analysis included 1,594 CDRH records.

Table 6: Variables Used To Analyze FDA BiMo Inspections Data

Variable	CBER	CDRH	CDER
Inspection Subject	Yes	Yes	Yes
Reason for Inspection	Not available	Yes	Yes
ORA Recommended Classification	Not available	Yes	Yes
Center Final Classification	Yes	Yes	Yes
Official Actions	Yes	Yes	Database 1: Not available Database 2: Yes
Assignment Date	Yes	Yes	Yes
Inspection Start Date	Yes	Not available	Yes
Inspection End Date	Yes	Yes	Not available
Trial Status: Ongoing or Closed	Not available	Not available	Not available

Source: OIG analysis of CDER, CDRH, and CBER data, 2006.

File review. We used FDA's databases to identify all inspections that either ORA or a center classified as OAI. We reviewed 248 CDER inspection files, 99 CBER inspection files, and 321 CDRH inspection files, for a total of 668 files.

We reviewed the files using a Microsoft Access® protocol. Our protocol included inspection assignment, classification, official actions, and correspondence between the center and the inspection subject. We analyzed data from the file reviews using SAS®.

E-mail survey of Bioresearch Monitoring investigators. ORA headquarters provided us with a list of the 231 ORA field investigators who had spent 100 or more hours conducting BiMo inspections in the previous 5 years. We removed eight investigators from the original sample because they

no longer conduct inspections or had not conducted an onsite inspection in several years or we could not obtain contact information for them.

Our survey solicited respondents' experiences with FDA guidance, inspection and classification recommendations, inspection followup with the assigning centers, and challenges in conducting BiMo inspections. Before sending the survey, we solicited comments from ORA officials and a BiMo investigator about the survey's content and clarity. We incorporated their feedback into the final survey.

We e-mailed each investigator an introductory letter explaining the survey and the study in August 2006. Later in the month, we e-mailed the survey. In September 2006, we e-mailed a second copy of the survey to those who had not responded. At the end of September, we called the investigators who had not yet replied. We received responses from 170 BiMo investigators for a 76-percent response rate.

Interviews with Food and Drug Administration officials. We conducted telephone interviews with all 19 ORA directors of investigation (DIB) who oversee BiMo investigators. Several DIBs invited supervisors in their districts to participate in the interviews.

The interviews focused on the DIBs' experiences with the supervisory role, interactions with BiMo investigators, interactions with the assigning centers, classification recommendations, and their challenges in supervising BiMo inspections. Before the interviews, we solicited comments from ORA officials and a DIB about the interview guide's content and clarity. We incorporated their feedback into the final interview guide. We conducted the interviews in October and November 2006. At least two OIG staff participated in each interview.

We also interviewed senior FDA officials at FDA headquarters, ORA, CBER, CDER, and CDRH.

Observation of Bioresearch Monitoring inspections. We observed three BiMo inspections: two clinical investigator inspections and one IRB inspection. FDA initiated the two clinical investigator inspections because of new product applications. The IRB inspection was a directed inspection.

We based our observations on a protocol that focused on the process that the BiMo investigator followed as well as the interactions between the investigator(s) and the inspection subject(s). At least two OIG staff participated in each inspection visit.

Clinical trial registry site estimate. To compute an estimate of the average number of clinical trial sites associated with a clinical trial, we used data from the clinical trials listed on the National Institutes of Health's clinical trials registry as of February 2007. We selected a stratified random sample of 150 trials. Because the registry is separated by trial phase, the three strata used for the sample were Phase I, Phase II, and Phase III of the clinical trial. (See Table 7 for our sample design.)

Table 7: Clinical Trial Registry Site Estimate Sample Design

Stratum	Population Size	Sample
Phase I	1,866	40
Phase II	4,566	50
Phase III	4,863	60

Source: Office of Inspector General analysis of the National Institutes of Health's Clinical Trial Registry.

We first counted the total number of clinical trial sites for each of the three clinical trial phases. This served as our population size. Using the OIG Office of Audit Service's RAT-STATS software, we chose random numbers to select the clinical trial. Because each trial in the registry was assigned a number, we were able to use the random numbers to identify the sampled trial. After sampling the trials, we counted the number of sites associated with each sampled trial.

We excluded 43 of the 150 clinical trials sampled. There were three situations in which the sampled trials were unusable and therefore had to be excluded. First, some of the trials appeared in the population multiple times because they were named Phase I/Phase II or Phase II/Phase III. If a trial was listed as Phase I/Phase II, it was counted as Phase II. Similarly, if a trial was listed as Phase II/Phase III, it was counted as a Phase III. Eighteen occurrences of a Phase I/Phase II trial in the Phase I population were excluded, as were seven occurrences of a Phase II/Phase III trial in the Phase II population. In addition, no sites were listed for 16 trials. Finally, terminated trials occurred twice in the sample. We used the remaining sample of 107 trials to compute the average number of sites per trial. The sample was weighted using standard statistical formulas for a stratified sample. Based on these formulas, the estimated average number of sites for a clinical trial is 23. This estimate can vary by +/-8 trials at the 95-percent confidence level.

Review of Food and Drug Administration policies, procedures, and guidance documents. We obtained and reviewed all relevant policies, procedures, and guidance documents issued by FDA for conducting BiMo inspections. We used these documents to better understand the process for conducting inspections of clinical trials.

APPENDIX B

Agency Comments

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

DATE: JUL 3 0 2007

TO: Inspector General

FROM: Deputy Commissioner for Operations

SUBJECT: Food and Drug Administration Response to Office of Inspector General Draft Report on the "Food and Drug Administration's Oversight of Clinical Trials" (OEI-01-06-00160)

The Food and Drug Administration (FDA) has completed its review of the Office of Inspector General Draft Report on "Food and Drug Administration's Oversight of Clinical Trials" (OEI-01-06-00160). FDA's comments are in the attachment.

If you need any additional information, please have one of your staff members contact Regina Ledesma at (301) 827-1223.

Janet Woodcock, M.D.

Attachment

Food and Drug Administration (FDA) Response to Office of Inspector General (OIG) Draft Report on FDA's Oversight of Clinical Trials (OEI-01-06-00160)

We are pleased to note that the Office of Inspector General's primary recommendations, summarized on page iii of the Executive Summary, are concordant with, and are captured by, our on-going Human Subject Protection (HSP)/Bioresearch Monitoring (BIMO) modernization initiative. Outlined below are several more global, contextual comments on the report followed by Appendix A which outlines factual errors and Appendix B which provides specific technical comments, respectively.

- The report focuses only on one component of human subject protection and bioresearch monitoring, namely inspections. We believe it would provide clarity if the report specifically recognized this fact. Protecting human subjects is a broad mandate and the programs are numerous. Inspections are but one narrow part. In fact, FDA believes the most important component of the BIMO program in protecting human subjects is the protocol review. In order to ensure the highest degree of human subject protection FDA carefully scrutinizes all protocols submitted to the agency and will require sponsors to revise protocols as necessary, thus ensuring the greatest protection of human subjects before a clinical investigation even begins. Therefore, we devote particular attention to assessing data quality in the studies that will lead to regulatory decisions and look more closely at sites that appear to have significant problems. While clinical investigator and sponsor inspections frequently focus on completed trials, they also help ensure that sponsors and clinical investigators have appropriate systems in place for ensuring human subject protection and data integrity for all research ongoing at the site, as well as any future studies. Although we are not able to visit more than a tiny fraction of sites, and therefore human subject protection must exist in the absence of FDA's presence during the clinical trial, we believe that the possibility of an inspection helps keep all parties aware of their responsibilities.

- FDA recognized that clinical trials had evolved significantly since the agency's first BIMO program was initially instituted. In 2004 FDA formed a multidisciplinary group that included representatives from each of the centers and offices within FDA to carefully scrutinize the current programs and develop consensus policy about what should be the scope and direction of a modern program. FDA formally announced the HSP/BIMO initiative and formation of the HSP/BIMO steering committee in June 2006 and has subsequently transformed the steering committee into a permanent council responsible for central coordination and human subject protection. This steering committee conducted an in-depth inventory of the HSP/BIMO program and identified key issues that need to be addressed, which included coordination, training, tracking mechanisms, and guidance/ regulation revisions.

- FDA recognizes that the lack of central coordination of inspections has created some challenges for the centers and districts. One of the more immediate goals of the BIMO modernization initiative is to develop better communication and coordination between headquarters, the Centers and the field. However, this is not to spare resources so that we

can inspect a particular percentage of sites, but rather to enhance the efficiency and impact of the inspections that we do chose to perform. FDA believes that a risk-based approach is necessary in order to capitalize on our limited resources and will target inspections accordingly. FDA does not believe there is an ideal percentage of inspections that should be conducted annually and assigning an arbitrary number is not a good metric for ensuring the protection of human subjects.

- FDA would like to share some additional thoughts on the recommendations in the OIG report.

  1. Develop a clinical trial registry that includes all clinical trials: It should be made clear that this recommendation is to develop an internal, non-public listing of all trials, as noted during the June 13, 2007 exit conference the OIG held with FDA. FDA agrees with the recommendation to develop an internal, non-public listing of all trials, and has begun this process as part of our efforts to create an electronic platform for managing all of FDA's regulated product information.

  2. Create an IRB registry: FDA agrees that an IRB registry is important and issued a proposed rule, in conjunction with OHRP, in 2004. The agency is working diligently with OHRP to finalize this rule. In addition, as part of our determination to build BIMO into a quality system, we believe that we should take a risk-based approach to IRB inspections, ensuring that we leverage our efforts in different areas and avoid duplicative work and consolidate current efforts that overlap.

  3. Create a cross-center database that allows complete tracking of BIMO inspections: FDA agrees that a cross-center database would provide a more complete tracking mechanism for BIMO inspections.

  4. Seek legal authority to provide oversight that reflects current clinical trial practices: FDA concurs that our current regulations do not reflect the state of the modern clinical trial enterprise. In particular, we believe there are entities that often have responsibility for direct subject care that are not recognized by our regulations. Therefore, FDA recently promulgated draft guidance to begin to address these gaps (Protecting the Rights, Safety, and Welfare of Study Subjects – Supervisory Responsibilities of Investigators) and has already begun consideration of rulemaking. Similarly, FDA is continuing to draft new, as well as revise, guidances and regulations in several other areas. During the early fact-finding phase of the HSP/BIMO initiative FDA identified a number of areas that should be addressed. Over the past couple of years FDA has held several public meetings and issued a number of guidances related to clinical trials; more recently FDA published the following guidances: (1) Adverse Event Reporting to IRBs (April 2007), (2) Computerized Systems Used in Clinical Investigations (May 2007), (3) Using a Centralized IRB Review Process (March 2006), (4) Five Information Sheet Guidances for Clinical Investigators, IRBs, and Sponsors (February 2006).

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