



NOV 28 2005

The Honorable Charles E. Grassley  
Chairman, Committee on Finance  
United States Senate  
Washington, DC 20510-6200

Dear Mr. Chairman:

Thank you for your letter of November 8, 2005, in which you addressed several issues of concern related to oversight of institutional review boards and the protection of human research subjects. Specifically, you requested that this office review the issues identified in the December 2005 issue of "Bloomberg Markets" entitled "Big Pharma's Shameful Secret" and determine appropriate issues related to the Food and Drug Administration's oversight of institutional review boards, as well as clinical trials which this office could examine. Our office has initiated this work and looks forward to meeting with your staff in early December.

In addition, you requested a comprehensive list of the recommendations that we have made over the last 10 years related to protecting human research subjects along with the status of those recommendations. The enclosed documents summarize our reports and recommendations on this topic, as well as our understanding of actions taken by the Department to date. This information was collected from our annual publication, entitled "Program and Management Improvement Recommendations," which is commonly referred to as the "Orange Book."

We appreciate your interest in our work. If you would like to discuss this response, please contact me, or have your staff call Judy Holtz, Acting Director of External Affairs at (202) 619-0260.

Sincerely,

A handwritten signature in cursive script that reads "Daniel R. Levinson".

Daniel R. Levinson  
Inspector General

Enclosures

## **OIG Reports and Recommendations Related to Clinical Trials and Institutional Review Boards**

Since 1995, the Office of Inspector General (OIG) has issued 12 reports on the Federal system for human subject protections that focus on institutional review boards (IRBs) and the Federal oversight of human subjects participating in clinical trials. Of the 12 issued reports, 10 provided recommendations. Below are summaries of these 10 reports containing recommendations.

**1. Institutional Review Boards: Their Role in Overseeing Approved Research**  
**OEI-01-97-00190**

**2. Institutional Review Boards: Promising Approaches**  
**OEI-01-97-00191**

**3. Institutional Review Boards: The Emergence of Independent Boards**  
**OEI-01-97-00192**

**4. Institutional Review Boards: A Time for Reform**  
**OEI-01-97-00193**

*(Final Reports Issued: June 1998)*

### **Summary of Four Reports:**

IRBs play a vital role in protecting human subjects who participate in research funded by HHS or carried out on products regulated by the Food and Drug Administration (FDA). In a broad-based inquiry, OIG concluded that the system of protections provided by IRBs in a rapidly changing research environment is in jeopardy. OIG determined that IRBs are reviewing too much, too quickly, with too little expertise; conducting minimal oversight of approved research; facing conflicts that threaten their independence; and providing little training for clinical investigators and board members. Moreover, neither the IRBs nor the Department devotes much attention to evaluating IRBs' effectiveness.

While OIG does not claim that there are widespread abuses of human research subjects, the system does have some significant vulnerabilities. OIG's recommendations were directed jointly to FDA and the National Institutes of Health (NIH) through the Office for Protection from Research Risks (OPRR). In the reports listed above, OIG urged FDA and NIH to grant more flexibility to IRBs while holding them more accountable for results, strengthen continuing protections for human subjects, establish requirements for educating investigators and IRB members about human subject protections, help insulate IRBs from conflicts that can compromise their mission, and address the seriousness of the workload pressures facing many IRBs. In addition, OIG proposed that FDA and NIH reexamine and reengineer their practices in overseeing IRBs. (*OIG Semiannual Report April 1, 1998 – September 30, 1998*)

## **Recommendations From This Series:**

- 1) Recast Federal IRB requirements so that they grant IRBs greater flexibility and hold them more accountable for results.
  - a) Eliminate or lessen some of the procedural requirements that Federal regulations impose on IRBs.
  - b) Require that all IRBs under the purview of NIH/OPRR and FDA undergo regular performance-focused evaluations carried out in accord with Federal guidelines.
- 2) Strengthen continuing protections for human subjects participating in research.
  - a) Require data safety monitoring boards for multisite trials that are under NIH/OPRR and FDA purview and that meet specified conditions warranting such safeguards.
  - b) Provide IRBs with regular feedback on developments concerning multisite trials.
  - c) Routinely provide IRBs with feedback on FDA action taken against investigators under their jurisdiction.
  - d) Require sponsors and investigators to notify IRBs of any prior IRB review of a research plan.
  - e) Call for increased IRB awareness of onsite research practices involving human subjects.
- 3) Enact Federal requirements that help ensure that investigators and IRB members are adequately educated about and sensitized to human-subject protections.
  - a) Require that institutions receiving funding under the Public Health Service Act for research involving human subjects have a program for educating their investigators on human-subject protections.
  - b) Require that investigators receiving funding under the Public Health Service Act for research involving human subjects attest in writing that they are familiar with and will uphold Federal policies concerning human-subject protections.
  - c) Require that each IRB under the purview of NIH/OPRR or FDA have an orientation program for new IRB members and a continuing education program for all members.
- 4) Help insulate IRBs from conflicts that can compromise their mission of protecting human subjects.
  - a) Require more extensive representation of nonscientific and noninstitutional members on IRBs.
  - b) Reinforce to IRBs and their parent institutions the importance of IRBs' maintaining sufficient independence in their mission to protect human subjects.

- c) Prohibit IRB equity owners from participating in the IRB review process.
- 5) Recognize the seriousness of the workload pressures that many IRBs face and take actions that aim to moderate them.
- a) Require that IRBs have access to sufficient resources to enable them to carry out their responsibilities as intended in Federal law.
- 6) Reengineer the Federal oversight process.
- a) Revamp the NIH/OPRR assurance process.
  - b) Revamp the FDA onsite inspection process.
  - c) Require that all IRBs register with the Federal Government and report minimal descriptive information.

## **5. Protecting Human Research Subjects: Status of Recommendations**

**OEI-01-97-00197**

*(Final Report Issued: April 2000)*

### **Summary of Report:**

OIG conducted a follow-up study to determine how fully its earlier recommendations had been implemented. While the Department has taken several promising steps to strengthen human subject protections, OIG determined that, overall, few of its recommended reforms have been enacted. There has been minimal progress in granting IRBs greater flexibility and holding them more accountable, and in strengthening continuing protections for human subjects participating in research. No educational requirements have been enacted for investigators or IRB members, and there has been no movement toward insulating IRBs from conflicts that can compromise their mission. Little has been done to moderate IRBs' workload pressures or to reengineer the Federal oversight process.

Many of OIG's recommendations call for changes in the Common Rule, a policy on human-subject protections adhered to by HHS and 16 other agencies; any changes to the rule require the concurrence of all 17 agencies. OIG acknowledges that this requirement inhibits a prompt and effective Department response and recognizes that legislative change may be necessary to achieve a timely implementation of many of its recommendations.

The problems identified by OIG's work in this area call for action on a broad front, involving not only IRBs but also other parties in the clinical research process, including sponsors and investigators. The Department has a significant new opportunity to exert Federal leadership in protecting human subjects with the move of OPRR to the Office of the Secretary and the establishment of a new advisory committee on human-subject protection issues. OIG urges that the new office, the Office of Human Research Protections (OHRP), give significant attention to OIG's earlier recommendations and those that are forthcoming from the National Bioethics Advisory

Commission. Both NIH and FDA have established a series of ongoing outreach and educational initiatives and programs. (*OIG Semiannual Report April 1, 2000 – September 30, 2000*)

**6. Recruiting Human Subjects: Pressures in Industry-Sponsored Clinical Research**  
**OEI-01-97-00195**

**7. Recruiting Human Subjects: Sample Guidelines for Practice**  
**OEI-01-97-00196**  
(*Final Reports Issued: June 2000*)

**Summary of Two Reports:**

Recent changes in the research environment are causing sponsors of clinical research to vie more aggressively to be the first to bring their products to market and are causing sites and investigators to compete more intensely for research contracts. For this review, OIG reviewed industry-sponsored clinical trials. OIG found that there is significant pressure for research investigators to recruit subjects quickly, and that some of the methods used by sponsors and investigators raise concerns about informed consent, patient confidentiality, and eligibility for enrollment that are troubling to IRBs and others involved in clinical research. Further, OIG determined that oversight of the recruitment of human subjects is minimal and largely unresponsive to emerging concerns.

OIG recommended that FDA, NIH, and OPRR provide IRBs with direction regarding oversight of recruitment practices, facilitate the development of guidelines for all parties on appropriate recruiting practices, ensure that IRBs and investigators are adequately educated about human-subject protections, and strengthen Federal oversight of IRBs. The Department has made a commitment to establish education requirements and to work with outside parties in developing consensus about appropriate recruitment practices. (*OIG Semiannual Report April 1, 2000 – September 30, 2000*)

**Recommendations:**

- 1) Provide IRBs with direction regarding oversight of recruiting practices.
  - a) Clarify that IRBs have the authority to review recruiting practices.
  - b) Provide guidance to IRBs on how to exercise this authority.
- 2) Facilitate the development of guidelines for all parties on appropriate recruiting practices.
- 3) Ensure that IRBs and investigators are adequately educated about human-subject protections.
  - a) Require education for investigators before conducting human-subject research.
  - b) Require that IRBs have a training program for board members.
  - c) Require more extensive representation of nonscientific and noninstitutional IRB members.

- 4) Strengthen Federal oversight of IRBs.
  - a) Require that all IRBs register with the Federal Government and regularly report basic descriptive information.
  - b) Revamp the FDA onsite inspection process.

## **8. FDA Oversight of Clinical Investigators**

**OEI-05-99-00350**

*(Final Report Issued: June 2000)*

### **Summary of Report:**

Companies develop new drugs, biologics, and medical devices with the assistance of clinical investigators. Sponsors, IRBs, and FDA all oversee clinical investigators' research. FDA reviews have identified serious problems with sponsors' monitoring of clinical investigators, and OIG studies have found problems with IRB oversight. In this review, OIG examined FDA's selection of clinical investigators for review and FDA's discipline of clinical investigators found in violation of FDA regulations.

FDA's bioresearch monitoring program inspects clinical investigators involved in clinical research to ensure the quality and integrity of data submitted to the agency and to protect the rights and welfare of human subjects; in most cases, these inspections occur after clinical work is completed. In fiscal year 1999, FDA inspected only 468 clinical investigators out of nearly 14,000 potentially involved in clinical trials. Although respondents indicated that program goals are ensuring data integrity and protecting human subjects, OIG found that FDA's monitoring of clinical investigators is more directly focused on verifying data, thus limiting overall oversight.

In addition, OIG concluded that the bioresearch monitoring program lacks clear and specific guidelines. While regulations state that a clinical investigator may be disqualified for repeatedly or deliberately failing to comply with regulations, at the time of this inspection there was no requirement for a review of complaints or clinical investigator inspection histories as part of the clinical investigator selection process. There is little staff training on how to select clinical investigators or how to assess what action to take when violations are found. Moreover, there are no agencywide program measures for the bioresearch monitoring program. OIG recommended that FDA define cross-center goals for the bioresearch monitoring program and develop criteria to determine whether the program is achieving those goals. Further, FDA should develop internal guidance on the thresholds that violations must meet to justify disqualifying a clinical investigator from receiving investigational products.

*(OIG Semiannual Report April 1, 2000 – September 30, 2000)*

## **Recommendations:**

- 1) Define cross-center goals for the bioresearch monitoring program and develop criteria to determine whether the program is achieving those goals.
- 2) Develop internal guidance on the thresholds that violations must meet to justify disqualifying a clinical investigator from receiving investigational products.

## **9. The Globalization of Clinical Trials: A Growing Challenge in Protecting Human Subjects**

**OEI-01-00-00190**

*(Final Report Issued: September 2001)*

## **Summary of Report:**

Inspecting the growth of foreign clinical trials for new drug applications, OIG found that clinical trials in foreign countries have increased dramatically and FDA cannot ensure the same level of protection as it can for domestic trials. An increasing number of these trials are being conducted in countries in which IRBs have limited experience in protecting human subjects. Entities familiar with international research have raised concerns about the ability of some inexperienced foreign IRBs to adequately protect human subjects.

Among other things, OIG recommended that FDA obtain more information about the foreign IRBs, encourage greater sponsor monitoring, and that OHRP encourage accreditation. FDA generally concurred with the recommendations.

*(OIG Semiannual Report April 1, 2001 – September 30, 2001)*

## **Recommendations:**

### **FDA:**

- 1) Examine ways in which FDA can obtain more information about the performance of non-U.S. IRBs' reviewing clinical trials that provide data in support of new drug applications.
- 2) Help inexperienced non-U.S. IRBs build their capacities.
- 3) Encourage sponsors to ensure that all non-U.S. investigators participating in research for new drug applications sign attestations indicating that they will uphold human-subject protections.
- 4) Encourage more rigorous monitoring of foreign research sites by sponsors.
- 5) Develop a database to track the growth and location of foreign research.

**OHRP:**

- 1) Exert leadership in developing strategies to ensure that adequate human-subject protections are afforded for non-U.S. clinical trials that are funded by the Federal Government and/or that contribute data to new drug applications.
- 2) Encourage the development of a voluntary accreditation system for human subject research programs.

**10. Clinical Trial Web Sites: A Promising Tool to Foster Informed Consent**

**OEI-01-97-00198**

*(Final Report Issued: May 2002)*

**Summary of Report:**

In assessing the use of clinical trial Web sites in fostering informed consent and the role of IRBs in overseeing the information on these Web sites, OIG found that these sites are emerging as an important recruitment strategy and show promise as a means of fostering informed consent. These Web sites, however, sometimes provide inaccurate information about the clinical trial process, exclude key information in trial listings, and fail to disclose policies that address the use of personal information collected by the Web site.

Based on these findings, OIG recommended that FDA and OHRP jointly provide guidance to IRBs regarding their responsibility for reviewing Web sites, facilitate the adoption and use of voluntary standards for clinical trial Web sites, and encourage clinical trial Web sites to undergo periodic review by independent bodies. Currently, FDA is assessing the legal feasibility of requiring attestations of good clinical practice compliance from investigators outside the United States when their data are submitted to the agency as part of an application. FDA is also more broadly reviewing its requirements for the acceptance of foreign data in support of submitted applications.  
*(OIG Semiannual Report April 1, 2002 – September 30, 2002)*

**Recommendations:**

- 1) Provide further guidance to IRBs on clinical trial Web sites.
  - a) Clarify that risk and benefit information in trial listings are subject to IRB review and approval.
  - b) Require IRB review of any prescreening used for specific trials.
- 2) Facilitate the adoption and use of voluntary standards for clinical trial Web sites.
- 3) Encourage clinical trial Web sites to undergo periodic review by independent bodies.

## List of All OEI Reports Related to Institutional Review Boards

Report Number	Report Title	Final Date	Web Link
OEI-05-94-00100	Investigational Devices: Four Case Studies	April 1995	<a href="http://oig.hhs.gov/oei/reports/oei-05-94-00100.pdf">http://oig.hhs.gov/oei/reports/oei-05-94-00100.pdf</a>
OEI-01-97-00190	Institutional Review Boards: Their Role in Overseeing Approved Research	June 1998	<a href="http://oig.hhs.gov/oei/reports/oei-01-97-00190.pdf">http://oig.hhs.gov/oei/reports/oei-01-97-00190.pdf</a>
OEI-01-97-00191	Institutional Review Boards: Promising Approaches	June 1998	<a href="http://oig.hhs.gov/oei/reports/oei-01-97-00191.pdf">http://oig.hhs.gov/oei/reports/oei-01-97-00191.pdf</a>
OEI-01-97-00192	Institutional Review Boards: The Emergence of Independent Boards	June 1998	<a href="http://oig.hhs.gov/oei/reports/oei-01-97-00192.pdf">http://oig.hhs.gov/oei/reports/oei-01-97-00192.pdf</a>
OEI-01-97-00193	Institutional Review Boards: A Time for Reform	June 1998	<a href="http://oig.hhs.gov/oei/reports/oei-01-97-00193.pdf">http://oig.hhs.gov/oei/reports/oei-01-97-00193.pdf</a>
OEI-01-97-00194	Low-Volume Institutional Review Boards	Oct. 1998	<a href="http://oig.hhs.gov/oei/reports/oei-01-97-00194.pdf">http://oig.hhs.gov/oei/reports/oei-01-97-00194.pdf</a>
OEI-01-97-00195	Recruiting Human Subjects: Pressures in Industry-Sponsored Clinical Research	June 2000	<a href="http://oig.hhs.gov/oei/reports/oei-01-97-00195.pdf">http://oig.hhs.gov/oei/reports/oei-01-97-00195.pdf</a>
OEI-01-97-00196	Recruiting Human Subjects: Sample Guidelines for Practice	June 2000	<a href="http://oig.hhs.gov/oei/reports/oei-01-97-00196.pdf">http://oig.hhs.gov/oei/reports/oei-01-97-00196.pdf</a>
OEI-01-97-00197	Protecting Human Research Subjects: Status of Recommendations	April 2000	<a href="http://oig.hhs.gov/oei/reports/oei-01-97-00197.pdf">http://oig.hhs.gov/oei/reports/oei-01-97-00197.pdf</a>
OEI-05-99-00350	FDA Oversight of Clinical Investigators	June 2000	<a href="http://oig.hhs.gov/oei/reports/oei-05-99-00350.pdf">http://oig.hhs.gov/oei/reports/oei-05-99-00350.pdf</a>
OEI-01-00-00190	The Globalization of Clinical Trials: A Growing Challenge in Protecting Human Subjects	Sept. 2001	<a href="http://oig.hhs.gov/oei/reports/oei-01-00-00190.pdf">http://oig.hhs.gov/oei/reports/oei-01-00-00190.pdf</a>
OEI-01-97-00198	Clinical Trial Web Sites: A Promising Tool to Foster Informed Consent	May 2002	<a href="http://oig.hhs.gov/oei/reports/oei-01-97-00198.pdf">http://oig.hhs.gov/oei/reports/oei-01-97-00198.pdf</a>

**OIG Orange Book FY2001-02**  
**Status of Recommendations (Self-Report from Agency)**

**Public Health Service Agencies**  
*-Biomedical Research-*

**Protect Human Research Subjects by Strengthening Institutional Review Boards**

Report Number:	OEI-01-97-00193	Final Report:	06/1998
	OEI-01-97-00197		04/2000

**Finding**

The effectiveness of institutional review boards (IRBs) is jeopardized by inadequate review time, unavailability of subject matter expertise, inadequate continuing reviews of approved research, conflicts that threaten IRB independence, and inadequate training for investigators and board members.

**Current Law**

In June 2000, the Office for Protection from Research Risks (OPRR) moved from NIH to the Office of the Secretary and is now housed in the Office for Human Research Protections (OHRP). OHRP provides leadership for all 17 Federal agencies that carry out federally funded research under the Common Rule. OHRP works with NIH and FDA in new initiatives for research involving human subjects; FDA retains its enforcement authority to ensure researcher compliance with HHS patient protection and patient consent requirements in FDA-authorized drug and medical device clinical trials.

**Recommendation**

Legislative

Administrative

Material Weakness

We recommended jointly to NIH, OHRP, and FDA that they : (1) recast Federal IRB requirements so that they grant IRBs greater flexibility and hold them more accountable, (2) strengthen continuing protections for human subjects participating in research, (3) enact Federal requirements that help ensure that investigators and IRB members are adequately educated about and sensitized to human-subject protection, (4) help insulate IRBs from conflicts that can compromise their mission in protecting human subjects, (5) recognize the workload pressures that many IRBs face and take actions to moderate them, and (6) reengineer the Federal oversight process.

**Status**

**Management Response**

As part of the Federal-Wide Assurance (FWA) process, OHRP recommends that institutions and their designated IRBs establish educational training and oversight mechanisms to ensure that research investigators, IRB members and staff and other appropriate personnel maintain continuing knowledge of, and comply with, relevant ethical principles; relevant Federal

regulations; written IRB procedures; OHRP guidance, other applicable guidance, State and local laws; and institutional policies for the protection of human subjects. OHRP recommends that IRB members, staff, and research investigators complete relevant educational and institutional training before reviewing or conducting human subject research. In 2003 and 2004, OHRP, FDA, and other Federal agencies sponsored regional training workshops for IRBs, clinical investigators, and clinical staff on good clinical practice and human subject protection issues. FDA and OHRP are working to develop a coordinated process for joint review of protocols under Subpart D regulations of 21 CFR 50.54 and 45 CFR 46.407. FDA published an interim final rule establishing additional safeguards for children in clinical trials involving FDA-regulated products (Federal Register, 66 FR 20598). In addition, FDA has created a new Office of Pediatric Therapeutics, as well as a full Pediatrics Advisory Committee. NIH now requires data and safety monitoring boards (DSMBs) to share summary information with IRBs and has implemented the requirement for monitoring plans for Phase I and Phase II trials, and FDA has issued new draft DSMB guidance. In May 2004, to address conflict of interest concerns, HHS issued a final guidance document, "Financial Relationships and Interests in Research Involving Human Subjects: Guidance for Human Subject Protection," in the Federal Register [69 FR 226393]. In July 2004, OHRP and FDA simultaneously issued proposed rules to require IRBs to register at sites maintained by HHS (69 FR 40556 and 69 FR 40584, respectively). In February 2005, HHS announced new electronic FWA forms required for OHRP approval to simplify the registration process. HHS agencies also worked with the Office for Civil Rights on guidance related to HIPAA privacy issues.

**OIG Orange Book FY2001-02**  
**Status of Recommendations (Self-Report from Agency)**

**Public Health Service Agencies**  
*-Biomedical Research-*

**Improve Recruiting Practices for Human Research Subjects**

Report Number:	OEI-01-97-00195	Final Report:	06/2000
	OEI-01-97-00196		06/2000

**Finding**

Recruitment is a major bottleneck in the flow of drugs developed by industry. Therefore, there is significant pressure for research investigators to recruit subjects quickly. Sponsors and investigators use a variety of recruitment methods (many of which raise concerns) including offering incentives, targeting their own patient bases, seeking additional patient bases, and advertising and promoting their research. Oversight of these recruitment methods is limited.

**Current Law**

In June 2000, the Office for Human Research Protections (OHRP) was established within the Office of the Secretary and took over many of the responsibilities of the former NIH Office for Protection from Research Risks. OHRP is charged with oversight of all research involving human subjects that is conducted or funded by HHS and conducts investigations at research institutions that have signed assurances. Under this new structure, NIH will continue its involvement in the funding and oversight of clinical trials and will coordinate with OHRP in activities related to the protection of human subjects. FDA retains its enforcement authority to ensure researcher compliance with HHS patient protection and patient consent requirements in FDA-authorized drug and medical device clinical trials.

**Recommendation**

**Legislative**       **Administrative**      **Material Weakness**

We recommended jointly to FDA, NIH, and the Assistant Secretary for Health that FDA, NIH, and OHRP clarify institutional review boards' (IRB) authority to review recruiting practices and work with industry, researchers, and ethicists to develop guidelines on appropriate practices. Also, FDA, NIH, and OHRP should require investigator and IRB education and strengthen their oversight.

**Status**

**Management Response**

In 2001, FDA published an interim final rule establishing additional safeguards for children in clinical trials involving FDA-regulated products (Federal Register, 66 FR 20598). NIH also requires data and safety monitoring boards (DSMBs) to share summary information with IRBs and has implemented the requirement for monitoring plans for Phase I and Phase II trials, and

FDA has issued new draft DSMB guidance. FDA is currently updating its human subject protection information sheets to reflect current policies, and as part of this effort, the information sheet guidance on Recruiting Human Subjects will clarify that IRBs should review the recruitment methods and materials proposed by investigators. HHS is considering implementation of new requirements for continuing education in human subject protection for IRB members and staff and institutional officials as part of the Federal-Wide Assurance (FWA) process. OHRP and FDA recently simultaneously issued rules to require IRBs to register at sites maintained by HHS (69 FR 40556 and 69 FR 40584, respectively). In 2003 and 2004, OHRP, partnering with FDA and other Federal agencies, sponsored national and regional training conferences for IRBs, clinical investigators, clinical staff, and institutional officials on good clinical practice and human subject protection issues. To address conflict of interest concerns, HHS issued a final guidance document, "Financial Relationships and Interests in Research Involving Human Subjects: Guidance for Human Subject Protection," in the Federal Register [69 FR 226393] in May 2004. HHS agencies worked with the Office for Civil Rights to develop guidance related to HIPAA privacy issues.

**OIG Orange Book FY2001-02**  
**Status of Recommendations (Self-Report from Agency)**

**Public Health Service Agencies**  
*-Biomedical Research-*

**Strengthen FDA Oversight of Clinical Investigators**

Report Number:            OEI-05-99-00350            Final Report:            06/2000

**Finding**

In general, oversight of clinical investigators by sponsors, institutional review boards (IRB), and FDA is limited and problematic. We found that data integrity concerns, more than human subject protections, drive FDA's oversight of clinical investigators and that the bioresearch monitoring program lacks clear and specific guidelines.

**Current Law**

FDA's bioresearch monitoring program inspects clinical investigators involved in clinical research to ensure the quality and integrity of data submitted to the agency and to protect the rights and welfare of human subjects. In most cases, these inspections occur after clinical work is complete. FDA staff from the Office of Regulatory Affairs conduct on-site inspections as part of the application review process for experimental products for the various centers involved in monitoring the development and testing of new human drugs, biologics, and medical devices.

**Recommendation**

Legislative     **Administrative**    **Material Weakness**

FDA should define cross-center goals for the bioresearch monitoring program and develop criteria to determine whether the program is achieving these goals. In addition, FDA should develop internal guidance on the thresholds that violations must meet to justify disqualifying a clinical investigator from receiving investigational products.

**Status**

**Management Response**

In July 2004, FDA issued a proposed rule to require IRBs to register at sites maintained by HHS (69 FR 40556). HHS simultaneously published a similar IRB registration proposal applicable to research supported or conducted by HHS. In 2003 and 2004, OHRP, partnering with FDA and other Federal agencies and departments, sponsored national and regional training conferences for IRBs, clinical investigators, clinical staff, and institutional officials on good clinical practice and human subject protection issues. FDA also provided faculty for outreach programs and other activities with universities and professional societies, and has created a Web site to provide current information about FDA requirements and guidance for the conduct of clinical studies. FDA and OHRP are also working to develop a coordinated process for joint review of protocols under Subpart D regulations of 21 CFR 50.54 and 45 CFR 46.407. FDA has established a new

unit, the Office for Good Clinical Practice, within the Office of Science Coordination and Communication in the Commissioner's Office to coordinate and direct human subject protection and good clinical practices issues. The Bioresearch Monitoring Program policy and coordination function has been elevated to this Office, and it is responsible for addressing issues identified in the OIG recommendations, specifically defining cross-center goals for the program and developing criteria to determine whether the program is achieving these goals. FDA has also begun implementing an initiative to develop better communication with the European Medicines Agency (EMA) with the goal of improving coordination and communication between FDA and EMA, which would allow information sharing on inspections of clinical study sites.

**OIG Orange Book FY2005**  
**Status of Recommendations (Self-Report from Agency)**

Public Health Service Agencies  
*-Food and Drug Safety-*

**Improve Protection for Research Subjects in Foreign Clinical Trials**

Report Number:            OEI-01-00-00190            Final Report:            09/2001

**Finding**

FDA oversees significantly more foreign research than it did 10 years ago. It cannot assure the same level of human subject protections in foreign trials as in domestic ones. This is especially true in the case of research sites in countries that have limited experience in clinical trials. As a result, key entities overseeing or studying foreign research have raised concerns about some foreign institutional review boards (IRBs).

**Current Law**

In June 2000, the Office for Human Research Protections (OHRP) was established within the Office of the Secretary and took over much of the responsibilities of the former NIH Office for Protection from Research Risks. OHRP is charged with oversight of all research involving human subjects that is conducted or funded by HHS and conducts investigations at research institutions that have signed assurances. Under this new structure, NIH will continue its involvement in the funding and oversight of clinical trials and will coordinate with OHRP in activities related to the protection of human subjects. FDA retains its enforcement authority to ensure researcher compliance with HHS patient protection and patient consent requirements in FDA-authorized drug and medical device clinical trials.

**Recommendation**

Legislative

Administrative

Material Weakness

We directed our recommendations jointly to FDA and OHRP. We recommend that FDA examine ways to obtain more information about the performance of non-US IRBs and help those inexperienced IRBs build their capacities; encourage all non-US investigators participating in research to sign attestations upholding human subject protections; and develop a database to track the growth and location of foreign research. We recommend that OHRP exert leadership in developing strategies to ensure adequate human subject protections for non-US clinical trials funded by the Federal Government and those that contribute data to new drug applications.

**Status**

**Management Response**

OHRP concurred with our recommendations and emphasized that its new International Activities Program will serve as a focal point and coordinating center for HHS's efforts to improve human subject protection. In collaboration with the FDA and the Fogarty International Center, OHRP is

working with a variety of national, regional, and international organizations with a goal of establishing effective education and review processes around the world. In 2004, OHRP sponsored capacity-building workshops for IRB members, gave presentations at international conferences, and began translating key guidance documents into foreign languages. FDA published a proposed rule in 2004, "Human Subject Protection: Foreign Clinical Studies Not Conducted Under an Investigational New Drug Application" (21 CFR 312.120), to promote good clinical practice regardless of the location of the clinical trial. FDA and OHRP have contributed to efforts to strengthen research investigation and harmonize standards through collaboration with the World Health Organization, the Pan American Health Organization, the Council for International Organizations of Medical Sciences, and other organizations. FDA also contributed to the HHS/OHRP/NIH Working Group for Equivalent Protections in developing a HHS report and Federal Register Notice announcing proposed criteria for clinical trials conducted outside of the United States. In addition, FDA has assisted other countries with capacity-building activities for international GCP inspectorates, including Singapore and Australia. An ongoing FDA initiative to develop better communication with the European Medicines Agency will improve coordination between the respective European and FDA programs involving clinical trials. FDA has also provided staff as faculty to professional associations for outreach training programs, as well as creating a GCP Web site for current information about FDA clinical trial requirements.