DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of Inspector General

Washington, D.C. 20201

NOV 17 2006

TO: Andrew C. von Eschenbach, M.D.
Acting Commissioner of Food and Drugs

FROM: Daniel R. Levinson Daniel R. Levinson
Inspector General

SUBJECT: Review of Corrective Actions Concerning the Human Subject Research Program (A-06-06-00042)

Attached is a copy of our final report on the Food and Drug Administration's (FDA) corrective actions concerning its human subject research program. In a March 21, 2003, letter, the Commissioner of Food and Drugs asked the Office of Inspector General (OIG) to assess the implementation of six corrective actions designed to address problems identified in a clinical study and to prevent future problems in FDA's human subject research program. OIG reviewed and reported on the clinical study in September 2004 (report number A-03-03-00378). This report assesses the implementation of the six corrective actions.

FDA's six centers and two of its offices, which we collectively refer to as centers, must submit their proposed human subject research to FDA's institutional review board (IRB) for approval. Within FDA's Office of the Commissioner, the Office of Science and Health Coordination (Office of Science) carries out administrative activities and maintains a database of human subject research proposals submitted to the IRB.

Our objective was to determine the status, as of October 2005, of the six corrective actions specified in the Commissioner's letter to OIG. The corrective actions direct FDA's centers and the Office of Science to (1) initiate an inventory and audit of clinical studies, (2) examine research monitoring programs and develop quality assurance programs, (3) establish a policy of accountability to the Commissioner, (4) have the Chief Counsel's Office help ensure appropriate "regulatory schemes," (5) provide additional funding for oversight, and (6) initiate a mandatory education and certification program.

The following summarizes the status of the corrective actions:

1. After conducting inventories, the centers submitted to the Office of Science 71 human subject studies that had not been submitted to the IRB for approval or recorded in the IRB database. The Office of Science then added the 71 studies to the database. From March 2003 to October 2005, FDA audited only 3 of the 297 studies listed in the February 11, 2004, database.

2. None of the four centers that we visited had an operational research monitoring program. Three of these centers had started to develop quality assurance programs but had not implemented them. Although the Office of Science had drafted an agencywide quality assurance program, it had not finalized the program.

3. FDA did not have a written policy setting forth the center Directors' accountability to the Commissioner for noncompliance with clinical research requirements. The Directors of three of the four centers we visited said that they were accountable to the Commissioner.

4. The IRB representative from the Office of the Chief Counsel informed us that she helped ensure that clinical research reviewed by the IRB complied with applicable regulations.

5. The FDA Deputy Commissioner for Operations stated that FDA had not provided any additional funds to the Office of Science to strengthen its oversight function and that the Office of Science had not requested additional funds related to this corrective action.

6. In 2002, FDA began requiring its researchers to complete a course on human subject research issues and to pass an examination to receive a certificate of completion. FDA officials reported that they believed that this course met the Commissioner's March 2003 directive.

We recommend that FDA increase its efforts to accomplish the Commissioner's corrective actions.

In its comments on our draft report, FDA agreed with our recommendation. FDA also suggested modifications to our report to ensure that FDA's actions related to the six corrective actions were more accurately stated. After reviewing FDA's comments, we revised the report where appropriate.

Please send us your final management decision, including any action plan, as appropriate, within 60 days. If you have any questions or comments about this report, please do not hesitate to call me, or your staff may contact Joseph J. Green, Assistant Inspector General for Grants and Internal Activities, at (202) 619-1166 or through e-mail at Joe.Green@oig.hhs.gov. Please refer to report number A-06-06-00042 in all correspondence.

Attachment

Department of Health and Human Services

OFFICE OF INSPECTOR GENERAL

REVIEW OF CORRECTIVE ACTIONS CONCERNING THE HUMAN SUBJECT RESEARCH PROGRAM

Daniel R. Levinson
Inspector General

November 2006
A-06-06-00042

Office of Inspector General

http://oig.hhs.gov

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OAS FINDINGS AND OPINIONS

The designation of financial or management practices as questionable or a recommendation for the disallowance of costs incurred or claimed, as well as other conclusions and recommendations in this report, represent the findings and opinions of the HHS/OIG/OAS. Authorized officials of the HHS divisions will make final determination on these matters.

EXECUTIVE SUMMARY

BACKGROUND

Human Subject Research

The Food and Drug Administration (FDA) is responsible for enforcing human subject protection regulations governing clinical investigations of products it regulates under the Federal Food, Drug, and Cosmetic Act. In addition, FDA conducts, funds, and supports human subject research that is governed by the Department of Health and Human Services human subject protection regulations and its own regulations.

FDA's institutional review board (IRB) is generally responsible for protecting the rights and welfare of subjects in research that FDA sponsors, conducts, or funds. FDA's six centers and two of its offices, collectively referred to as centers in this report, must submit their proposed research to the IRB for approval. Within FDA's Office of the Commissioner, the Office of Science and Health Coordination (Office of Science) carries out administrative activities and maintains a database of human subject research proposals submitted to the IRB.

Request for Office of Inspector General Review

In a March 21, 2003, letter, the Commissioner of Food and Drugs asked the Office of Inspector General (OIG) to (1) review certain aspects of a clinical study conducted by an FDA employee and (2) assess FDA's implementation of six corrective actions designed to address problems with the clinical study and to prevent future problems in FDA's human subject research program. We reported on the clinical study on September 20, 2004 (A-03-03-00378). In this report, we assess the implementation of the six corrective actions delineated in the Commissioner's letter: (1) initiate an inventory and audit of clinical studies, (2) examine research monitoring programs and develop quality assurance programs, (3) establish a policy of accountability to the Commissioner, (4) have the Chief Counsel's Office help ensure appropriate "regulatory schemes," (5) provide additional funding for oversight, and (6) initiate a mandatory education and certification program. The centers and the Office of Science are responsible for implementing these corrective actions.

OBJECTIVE

Our objective was to determine the status, as of October 2005, of the six corrective actions specified in the Commissioner's letter to OIG.

SUMMARY OF RESULTS

FDA undertook several efforts to improve its human subject research program, including some that were still underway at the time of this review. The following summarizes the status, as of October 2005, of the corrective actions delineated by the Commissioner:

1. **Inventory and audit.** After conducting inventories, the centers submitted to the Office of Science 71 human subject studies that had not been submitted to the IRB for approval or recorded in the IRB database. The Office of Science then added the 71 studies to the database. From March 2003 to October 2005, FDA audited only 3 of the 297 studies listed in the February 11, 2004, database.

2. **Research monitoring and quality assurance programs.** None of the four centers that we visited had an operational research monitoring program. Three of these centers had started to develop quality assurance programs but had not implemented them. Although the Office of Science had drafted an agencywide quality assurance program, it had not finalized the program.

3. **Accountability to the Commissioner.** FDA did not have a written policy setting forth the center Directors' accountability to the Commissioner for noncompliance with clinical research requirements. The Directors of three of the four centers we visited said that they were accountable to the Commissioner.

4. **Regulatory schemes.** The IRB representative from the Office of the Chief Counsel informed us that she helped ensure that clinical research reviewed by the IRB complied with applicable regulations.

5. **Oversight funding.** The FDA Deputy Commissioner for Operations stated that FDA had not provided any additional funds to the Office of Science to strengthen its oversight function and that the Office of Science had not requested additional funds related to this corrective action.

6. **Education and certification program.** In 2002, FDA began requiring its researchers to complete a course on human subject research issues and to pass an examination to receive a certificate of completion. FDA officials reported that they believed that this course met the Commissioner's March 2003 directive.

RECOMMENDATION

We recommend that FDA increase its efforts to accomplish the Commissioner's corrective actions.

FOOD AND DRUG ADMINISTRATION'S COMMENTS

In its comments on our draft report, FDA agreed with our recommendation. FDA also suggested modifications to our report to ensure that FDA's actions related to the six corrective actions were more accurately stated. After reviewing FDA's comments, we revised the report where appropriate.

FDA's comments are included as the Appendix.

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INTRODUCTION

BACKGROUND

Pursuant to the Federal Food, Drug, and Cosmetic Act, the Food and Drug Administration (FDA) is responsible for enforcing human subject protection regulations governing clinical investigations of products that it regulates under the Act. In addition, FDA conducts, funds, and supports human subject research that is governed by the Department of Health and Human Services human subject protection regulations and its own regulations.

Request for Office of Inspector General Review

In a March 21, 2003, letter, the Commissioner of Food and Drugs asked the Office of Inspector General (OIG) to (1) review certain aspects of a clinical study conducted by an FDA employee and (2) assess FDA's implementation of six corrective actions designed to address problems with the clinical study and to prevent future problems in FDA's human subject research program. We reported on the clinical study on September 20, 2004.[1] We assess the implementation of the six corrective actions in this report.

The Commissioner's letter delineated the following corrective actions: (1) initiate an inventory and audit of clinical studies, (2) examine research monitoring programs and develop quality assurance programs, (3) establish a policy of accountability to the Commissioner, (4) have the Chief Counsel's Office help ensure appropriate "regulatory schemes," (5) provide additional funding for oversight, and (6) initiate a mandatory education and certification program.

Human Subject Research Requirements and Responsibilities

Pursuant to 45 CFR § 46.103(b), an institution (including FDA) must have an institutional review board (IRB) review and approve research involving human subjects. The purpose of the IRB is to ensure that the institution takes appropriate steps to protect the rights and welfare of humans who participate as subjects in research. For research that is subject to Federal regulations, the IRB must approve the research before it begins and provide continued oversight at a level appropriate to the degree of risk to human subjects.

FDA's IRB, the Research Involving Human Subjects Committee, serves as its ethical review committee and is generally responsible for protecting the rights and welfare of subjects in research that FDA sponsors, conducts, or funds. FDA's six centers and two of its offices, collectively referred to as centers in this report, must submit their proposed research to the IRB for approval.[2]

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[1] "Review of Food and Drug Administration's Bone Mass Study" (A-03-03-00378).

[2] The six centers are the Center for Biologics Evaluation and Research (CBER), the Center for Drug Evaluation and Research (CDER), the Center for Devices and Radiological Health (CDRH), the Center for Food Safety and Applied Nutrition (CFSAN), the Center for Veterinary Medicine (CVM), and the National Center for Toxicological Research. The two offices are the Office of the Commissioner and the Office of Regulatory Affairs.

Within FDA's Office of the Commissioner, the Office of Science and Health Coordination (Office of Science) carries out administrative activities related to human subject research, including assisting the IRB and reviewing FDA practices and procedures for protecting human subjects. Along with the centers, the Office of Science is responsible for implementing the six corrective actions delineated by the Commissioner.

Database on Human Subject Research

In 2002, the Office of Science developed a database to track human subject research proposals that the centers submit to the IRB. For each proposal, the database includes an Office of Science-assigned IRB number, the title of the study, the principal investigator's name, the responsible center, the IRB approval date, and continuing review dates. Selected officials of all centers can access the database.

OBJECTIVE, SCOPE, AND METHODOLOGY

Objective

Our objective was to determine the status, as of October 2005, of the six corrective actions specified in the Commissioner's letter to OIG.

Scope

We limited our review of internal controls to those controls relevant to our objective. We did not assess the scientific quality of any FDA research.

We conducted the audit from February 2004 through October 2005 and performed fieldwork at the Office of Science in Rockville, Maryland, and at four centers in the Rockville area. We selected the four centers based primarily on the number of human subject research studies they had submitted to the IRB.

Methodology

To accomplish our objective, we:

- reviewed Federal regulations and Office for Human Research Protections guidance pertaining to human subject protection;[3]

- reviewed "FDA's Internal Standard Operating Procedures for the Research Involving Human Subjects Committee" (IRB procedures), last updated in 2003, to obtain an understanding of FDA procedures and requirements for the conduct of human subject research;

[3]The Office for Human Research Protections, located in the Office of the Secretary of the Department of Health and Human Services, is the regulatory authority that ensures the rights and welfare of human subjects involved in federally funded research.

- held discussions with FDA officials from the Office of Science, Office of the Chief Counsel, and Office of Management;

- obtained a copy of the IRB database, dated February 11, 2004, which listed 297 human subject research studies, and selected 12 studies for review to document FDA's human subject research processes;

- selected four centers to visit—CBER, CDER, CDRH, and CVM—and interviewed the centers' officials;

- discussed with officials of the four centers visited (1) the IRB's requirements for submitting research involving humans, (2) the centers' responsibilities and procedures to meet the IRB's requirements, and (3) the centers' progress toward implementing the Commissioner's corrective actions;

- reviewed documentation from the IRB and the four centers visited to obtain an understanding of FDA's human subject protection program;

- reviewed position descriptions for the Directors of CBER, CDER, CDRH, CFSAN, and CVM and the Senior Associate Commissioner for Regulatory Affairs to determine whether these officials were accountable to the Commissioner; and

- met with FDA officials to discuss our findings and obtain additional information or clarification where needed.

We conducted our review in accordance with generally accepted government auditing standards.

RESULTS OF REVIEW

FDA undertook several efforts to improve its human subject research program, including some that were still underway at the time of this review. The status, as of October 2005, of the six corrective actions delineated by the Commissioner follows.

1. INVENTORY AND AUDIT

Initiate an Inventory and Audit of Clinical Studies

The Commissioner's March 2003 letter stated that FDA would initiate both "an inventory and audit of all clinical studies sponsored by or involving PIs [principal investigators] from any FDA Center to ensure that all are being conducted in accordance with Departmental and FDA regulations and policies."

Inventory Process Completed

In a June 27, 2003, memorandum, the Commissioner directed the centers to survey their respective organizations to determine whether they had accounted for all human subject

research. The Commissioner also instructed the centers to provide any pertinent information resulting from their inventory surveys to the Office of Science to update the IRB database.

During July and August 2003, the centers submitted inventory information to the Office of Science, which used the data to update the IRB database of human subject research.

The centers' inventory process identified 71 human subject studies that Office of Science officials added to the IRB database. According to Office of Science officials, the centers had not submitted these studies to the IRB for approval because they believed that the research was exempt from human subject research regulations. However, in deeming these studies to be exempt, the centers violated the IRB procedures. These procedures authorize only the IRB Chair (or designee) to make exemption determinations. The Office of Science provided us with a copy of the updated database, dated February 11, 2004, listing 297 human subject research studies, including the 71 studies identified during the one-time inventory survey.

According to Office of Science officials, they took several actions to ensure that the centers submit all future human subject studies to the IRB, including:

- updating the 1995 edition of the IRB procedures to better explain the procedures for obtaining IRB approvals and exemptions, including FDA's policy that investigators are not to self-exempt their research;

- creating a Web site on FDA's Intranet to make available to all FDA staff the IRB procedures, IRB forms, all applicable requirements for conducting human research, and training materials;

- developing a new database to track all submissions to the IRB and making the database available to the centers' IRB liaisons and Directors for their oversight purposes;

- ensuring that the centers' IRB liaisons have a direct line to their respective Directors and the responsibility to work with the IRB to help ensure compliance by FDA researchers; and

- orally informing center Directors of the need to maintain documentation of staff training on human subject protection requirements and policies.

Office of Science officials informed us that FDA did not plan to conduct additional inventory surveys to update the database.

Most Clinical Studies Not Audited

From March 2003 to October 2005, FDA audited only 3 of the 297 clinical studies listed in the database. In two of the audits, FDA investigators observed such deficiencies as poor record keeping, missing documentation for subject inclusion/exclusion criteria, no chain of custody for biopsy samples, and a failure to follow IRB requirements. According to FDA

officials, the third audit covered a completed clinical study. Based on the audit, the IRB concluded that the researchers involved had not met IRB and Federal requirements with regard to obtaining approval before conducting the study and obtaining proper consent from the human subjects before using their personal information. Accordingly, the IRB did not allow the investigators to use the data from the study.

2. RESEARCH MONITORING AND QUALITY ASSURANCE PROGRAMS

Examine Research Monitoring Programs and Develop Quality Assurance Programs

In his March 2003 letter, the Commissioner stated that all FDA centers would be required to examine current research monitoring programs and develop specific clinical research quality assurance programs.

Research Monitoring Programs Not Examined and Quality Assurance Programs Not Developed

In his June 27, 2003, memorandum to the centers, the Commissioner specifically asked center officials to evaluate their respective programs for monitoring research studies after IRB approval. He also said that his staff would work with the centers to build on existing programs and define an agency program that establishes standards for all centers.

None of the four centers we visited had an operational monitoring program as of October 2005. Although three centers (CBER, CDER, and CDRH) had started to develop quality assurance programs for human subject research, none of the four centers had implemented a program. In addition, the Office of Science had drafted an agencywide quality assurance program, which, as of October 2005, was awaiting review by the centers and the FDA Deputy Commissioner. Officials at two of the centers we visited (CBER and CDRH) reported that they were awaiting the completion of the agencywide program before finalizing their programs.

3. ACCOUNTABILITY TO THE COMMISSIONER

Establish a Policy of Accountability to the Commissioner

The Commissioner's March 2003 letter stated that FDA would "establish a policy that makes Center Directors directly accountable to the Commissioner for non-compliance with Departmental and FDA policies and regulations regarding clinical research sponsored by their Center or conducted by employees of their Center."

Policy of Accountability Not Established

FDA did not have a written policy setting forth the center Directors' accountability to the Commissioner for noncompliance with clinical research requirements. The Directors of three centers that we visited (CBER, CDRH, and CVM) stated that they were accountable to the Commissioner for research sponsored by their centers or conducted by their employees.

CDER's Director reported that CDER employees must follow its internal operating procedures concerning human subject research. However, these procedures did not state that the Director was accountable to the Commissioner.

In addition, the position descriptions for the Directors of CBER, CDER, and CDRH and the Senior Associate Commissioner for Regulatory Affairs stated that the officials were under the broad administrative direction of the Commissioner. In contrast, the position descriptions for the Directors of CFSAN and CVM did not include any language concerning accountability to the Commissioner.

4. REGULATORY SCHEMES

Have the Chief Counsel's Office Help Ensure Appropriate Regulatory Schemes

In his March 2003 letter, the Commissioner stated that FDA would "instruct the IRB representative from FDA's Office of the Chief Counsel to help assure that clinical research reviewed by the FDA IRB is being conducted under the appropriate regulatory scheme for the product being tested."

Help Provided To Ensure Appropriate Regulatory Schemes

The IRB representative from the Office of the Chief Counsel informed us that she helped ensure that clinical research reviewed by the IRB was conducted under the appropriate regulatory scheme for the product tested. She explained that she received information about proposed clinical research a week or so before each monthly IRB meeting. She then determined whether any FDA regulations applied to the research and, if so, whether the research complied with the regulations.

5. OVERSIGHT FUNDING

Provide Additional Funding for Oversight

In his March 2003 letter, the Commissioner stated that FDA would provide additional funding to the Office of Science to strengthen its oversight of the human subject research program. The funding was to be used to establish a crosscutting program to improve center monitoring and quality assurance programs and to have an independent, outside auditor review these programs and report the findings to the IRB and to the Commissioner.

Additional Funding Not Provided

The FDA Deputy Commissioner for Operations stated that FDA had not provided any additional funds to the Office of Science and that the Office of Science had not requested additional funds related to this corrective action. Also, FDA had not hired an independent, outside auditor.

As an alternative, Office of Science officials explained that the Office of Science had used its existing personnel and a consumer safety official from the Office of Regulatory Affairs to help develop an agencywide quality assurance program. As previously stated, as of October 2005, FDA had not finalized the program.

6. EDUCATION AND CERTIFICATION PROGRAM

Initiate a Mandatory Education and Certification Program

The Commissioner's March 2003 letter stated that FDA would "initiate a mandatory education and certification program for all FDA clinical investigators and key personnel on the scientific, regulatory, and ethical issues regarding clinical research."

Mandatory Course Initiated

In 2002, FDA began requiring its researchers to complete the Office for Human Research Protections "Investigator 101" course. FDA officials reported that they believed that this course met the Commissioner's March 2003 directive.

The course addresses scientific, regulatory, and ethical issues regarding human subject research. FDA requires that researchers pass an examination on the course materials to receive a certificate of completion. In addition, FDA officials told us that they encouraged, but did not require, researchers to participate in continuing education activities, including periodic center refresher courses and courses offered by the Office of Science and the National Institutes of Health.

RECOMMENDATION

We recommend that FDA increase its efforts to accomplish the Commissioner's corrective actions.

FOOD AND DRUG ADMINISTRATION'S COMMENTS AND OFFICE OF INSPECTOR GENERAL'S RESPONSE

In its August 29, 2006, comments on our draft report, FDA agreed with our recommendation. FDA stated that it was committed to ensuring that all clinical studies were of the highest caliber possible and in strict compliance with laws and regulations. FDA also provided technical comments and suggested modifications to our report to ensure that FDA's actions related to the six corrective actions were more accurately stated. After reviewing FDA's comments, we revised the report where appropriate.

FDA's comments are summarized below and included as the Appendix.

Inventory and Audit of Clinical Studies

FDA provided additional information about the 71 studies identified through the inventory process. That information does not affect our conclusion that FDA completed the inventory as directed.

FDA agreed that there could be more audit oversight of clinical studies in the IRB database. However, FDA stated that during our audit period, the budget situation permitted FDA to focus only on high-risk studies. We note that the Commissioner's letter stated that FDA would audit all clinical studies sponsored by or involving principal investigators from any FDA center.

FDA also provided information about the three audits that it had conducted. Based on that information, we revised the report where appropriate.

Accountability to the Commissioner

FDA stated that it had established an effective and interactive policy of accountability to the Commissioner. FDA further stated that the Commissioner's letter did not require a written policy of accountability. While we acknowledge that the Commissioner's letter did not specify that the policy be written, we believe that a written policy would help ensure long-term compliance with clinical research requirements.

Oversight Funding

FDA pointed out that budgetary constraints had prevented additional funding for the Office of Science and provided new information about a personnel assignment referenced in our draft report. We revised our report to reflect the new information. FDA also noted that after our audit period, the Office of Science had received an additional full-time equivalent to work on the agency oversight program.

APPENDIX

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

DATE: AUG 29 2006

TO: Inspector General

FROM: Deputy Commissioner for Operations

SUBJECT: FDA's Comments on OIG Draft Report: "Review of Corrective Actions Concerning the Human Subject Research Program," A-06-06-00042

The Food and Drug Administration (FDA) has completed its review of the OIG draft inspection report entitled OIG Draft Report: "Review of Corrective Actions Concerning the Human Subject Research Program," A-06-06-00042. 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

FDA's Comments on the Office of Inspector General's (OIG) draft report titled "Review of Corrective Actions Concerning the Human Subject Research Program" (A-06-06-00042) dated 7/27/06.

On March 21, 2003, the then Commissioner of Food and Drugs requested that the OIG assess FDA's progress on six corrective actions that FDA stated it would undertake to strengthen oversight of its human subject research program. FDA appreciates the lengthy and thorough efforts that the OIG made to investigate its progress in the strengthening of its human subject research program. We also appreciate the opportunity to comment on the draft report.

General Comments

We agree with the only recommendation made in the draft report (on page 8), that "FDA should increase its efforts to accomplish the Commissioner's corrective actions." Since the date of the OIG evaluation, FDA has continued to make significant progress on its quality assurance program for oversight of its research involving human subjects. We will continue to work on, and increase, our efforts to strengthen the program. We are committed to ensuring that all studies conducted, funded, or supported by FDA are of the highest caliber possible and in strict compliance with applicable laws and regulations.

We do have suggestions, however, for modifications to the draft report, to ensure that FDA's actions related to the six corrective actions are more accurately stated. There are several statements presented in the draft report that contain factual errors or could lead to erroneous conclusions about FDA's oversight of its human subject research program. We also provide some technical comments that clarify certain points.

RESULTS OF REVIEW (page 4)

1. INVENTORY AND AUDIT (page 4)

Initiate an Inventory and Audit of Clinical Studies/Inventory Process Completed

Corrective action #1 stated that the FDA would initiate "an inventory and audit of all clinical studies sponsored by or involving principal investigators from any FDA Center to ensure that all are being conducted in accordance with Departmental and FDA regulations and policies."

The draft report refers to 71 human subject studies that FDA had found in its inventory/audit that had not been submitted to its Institutional Review Board (IRB), the Research Involving Human Subjects Committee (RIHSC), for approval or for recordation in the IRB's internal database that it keeps for tracking and organizational purposes. FDA would like it to be made clear that none of these studies were required under the regulations to have been approved by the IRB prior to initiation. The draft report does

indicate that the centers had believed the research to be exempt, and thus were not submitted. Upon review during the inventory, none of these 71 studies were determined to have needed prior approval by the IRB, although the IRB should have determined the exempt status of the research.

These 71 studies were not recorded in the RIHSC database as revealed by the FDA inventory/audit. The IRB Office subsequently followed up on each of these studies to ascertain its current status. Detailed results of this follow-up were given to the OIG during its review. A summary of the IRB's findings is presented below:

- A large number of the 71 identified studies involved FDA physicians who, as part of their professional development, were working or planning to work as consultants on IRB-approved studies, mainly at the National Institutes of Health (NIH). None of these collaborations involved interaction with study subjects. These collaborations were then either discontinued or a cooperative agreement was developed between the RIHSC and the other IRB as required by 45 CFR 46.114.

- Several of the 71 identified studies were eligible for exemption from IRB review under 45 CFR 46.101(b). Although 45 CFR 46 does not require that those studies falling under the exemptions listed in 45 CFR 46.101 be sent to an IRB for exemption, FDA has an internal policy that researchers should not self-exempt, and the RIHSC database includes information about these exempt studies. Since these studies were identified, FDA has reiterated to its employees, and stated clearly in the RIHSC's Written Procedures, that it is FDA's internal policy that investigators are not to self-exempt.

- The studies determined to be exempt involved either the use of pre-existing, anonymized tissues obtained from either the NIH blood bank or from IRB-approved studies or used anonymized adverse event reports in FDA's public adverse event databases to track surveillance of approved FDA products. All of these studies met the criteria for exemption under the regulations.

- Several of the identified 71 studies were either still in the planning stage or had been planned but never began. A few of the 71 identified studies did not meet the definition of research as outlined in 45 CFR 46.102(d).

We would like to stress that our inventory/audit did not identify any studies that were required to receive IRB approval under the regulations and did not, nor did FDA find any studies that, put any human subjects at any risk.

Most Clinical Studies not Audited (page 5)

We agree that there could be more audit oversight of all of the studies contained in the database. FDA has planned to increase the audits of all of its studies to increase quality assurance. During the time period covered by the draft report, the budget situation only

permitted FDA to focus its attention on, and prioritize its most comprehensive oversight to, high-risk studies. FDA has reviewed the status of the 297 clinical studies listed in the database and does not agree with the draft report's conclusion as expressed in the title of this section. The title implies that FDA provided very little oversight of its ongoing studies. This conclusion is not supported by FDA's review.

The draft report refers to the 297 studies in the IRB database as "clinical studies." In FDA's view, this implies that all are clinical trials that require IRB review. Approximately half of these studies were exempted from IRB review under 45 CFR 46.101(b) and therefore do not receive IRB review or oversight. As such, there would be no reason to audit these particular studies.

Of the remaining studies, almost all of these were studies involving contracts where FDA has funded research in other institutions, mainly in academic settings. For these types of studies, FDA has assigned a project officer to each study. The project officer performs 1-2 site visits per year to check on the progress of the study including determining whether the study is being completed according to the protocol and pertinent regulations. In effect, these site visits substitute for a formal audit as many of the same oversight functions are performed during these visits. Additionally, all of these studies have been reviewed by a second IRB at the institution where the studies are conducted. These IRBs perform additional oversight and quality control.

At the time of the OIG review, we had approximately 64 ongoing studies. FDA would like to stress that its research program encompassing these studies, on the whole, does not include high-risk studies. Our research program is designed to answer regulatory questions about products regulated by FDA in order to better accomplish our missions of protecting the public health. For example, we do not test new drug moieties in humans; instead, the bulk of FDA's human subject studies are to gather information about approved products.

Of the studies ongoing during the period covered by the OIG review, twenty- two involved the use of anonymized tissue samples received by FDA from ongoing IRB-approved studies. These studies were not eligible for exemption under 45 CFR 46.101(b)(4) because the tissue was not pre-existing at the time of approval of the protocol. A number of the ongoing studies used medical information from databases as part of the surveillance of FDA approved products. Six of the ongoing studies were surveys that were not eligible to be exempted under 45 CFR 46.101(b)(2) and most of these involved food issues, such as infant feeding practices or consumer perceptions of labels or food safety issues. Other ongoing studies were in the social science area, i.e. asking subjects to perform a simple operant battery of tests.

Only nineteen of the 64 ongoing studies were ones that either used an approved FDA test article in a research setting or were pharmacokinetic studies of blood levels from subjects prescribed approved FDA drugs as part of their medical care. For example, three of these studies looked at the effect of sunburn on the skin, as part of FDA's regulation of tanning beds and sunscreens. One study looked at the difference in accuracy of approved blood

glucose monitors with either elbow or finger sticks. Three studies looked at differences in drug metabolism with pregnancy. Three of these nineteen studies were audited by FDA during the period covered by the OIG investigation. Two other studies of the nineteen studies were audited by the OIG during this same period.

We believe that it is more appropriate to consider how many of the 19 ongoing studies described in the above paragraph were formally audited by FDA. Within one year, FDA reviewed 15% of its higher-risk studies. Reference to audits of only 3 of 297 clinical trials provides a incomplete picture of FDA's oversight of the studies contained in its database.

The draft report also notes the findings of three audits conducted by FDA in response to specific concerns about the studies. The draft report does not accurately characterize these audits nor the findings and subsequent actions. None of these audits were conducted because of allegations that the health of the human subjects involved was put at risk. The draft report fails to mention that, for the first two audits, although several deficiencies were identified, the auditors concluded that there were no significant violations of the rights or safety of the human subjects. The third audit was conducted on a completed survey of anthrax decontamination workers to evaluate compliance with taking prophylactic antibiotics. The investigators had inadvertently believed that their survey was surveillance, rather than research, and therefore exempt from the regulatory requirements. Thus, there was no ongoing study for the IRB to stop, as the draft report states. The IRB, however, did not allow the investigators to use the resulting data from this study.

3. ACCOUNTABILITY TO THE COMMISSIONER (page 6)

In the Commissioner's March 2003 letter, FDA was directed to "establish a policy to make Center Directors directly accountable to the Commissioner for non-compliance." The draft report concludes that the policy of accountability is not established because of a lack of a written policy to that effect. FDA has established such a policy.

The OIG interviewed four of the six Center Directors in its investigation and it is FDA's understanding that the OIG investigators were emphatically told by all four Center Directors that they felt directly accountable to the Commissioner. The Commissioner, as well as the Associate Commissioner for Science, has communicated this "accountability" directly in conversations with the Center Directors on several occasions. Since these communications, if a problem has occurred with a study, the Center Director is informed by the Commissioner and is intimately involved in all subsequent corrective actions. This procedure has been explained to the OIG on several occasions.

The Commissioner, in his letter to the OIG, did not state that "a written policy" must be produced; rather he was concerned that an effective and interactive policy of accountability be established to strengthen the agency's human subject protection program. This has occurred very effectively within FDA and we have improved the accountability of this program to a remarkable degree.

The draft report notes the position descriptions (PDs) of the Center Directors and the Associate Commissioner for Regulatory Affairs. The draft report acknowledges that the position descriptions for some of the Center Directors are generally worded to state that these officials are under the broad administrative direction of the Commissioner. The PDs for the Directors of CFSAN and CVM are not similarly worded. It is FDA's understanding that the OIG investigators personally interviewed the Director of CVM and was told that he believes he is directly accountable to the Commissioner for not only human subject protection issues (of which there are little to none handled by CVM) but for everything that occurs in the Center. Had the Director of CFSAN been interviewed, he would have reported that he, too, was accountable to the Commissioner. The Directors of the FDA Centers are accountable to the Commissioner for a whole myriad of issues that may not be specifically listed in their PDs.

We believe that FDA has fulfilled corrective action #3 and this section should be changed to reflect that a policy of accountability has been established.

5. OVERSIGHT FUNDING (page 7)

When the Commissioner wrote his March 2003 letter stating that FDA would initiate a mandatory program for all FDA clinical investigators, he had anticipated that additional funds would be available to hire an extra Full Time Employee (FTE) in the Office of Science to develop the quality assurance/quality control (QA/QC) program.

With other competing priorities at FDA, no funds could be made available to the Office of Science to hire any additional FTEs in order to develop the quality assurance program. This information was conveyed to the OIG by the FDA Deputy Commissioner for Operations. The Office of Science had discussions with the Deputy Commissioner on several occasions about this corrective action but understood that with the budget situation, funds could not be given to the Office of Science for this purpose. It was not an issue of whether the Office of Science had requested the additional funds. The draft report does not accurately characterize these discussions.

Funds also were, and are, not available for the purpose of hiring an outside auditor. After assessing the matter, the Office of Science felt confident that its own bioresearch monitoring staff in the Office of Regulatory Affairs could perform this function as they have vast experience in this area and, in fact, often run the training courses for outside auditors.

The Office of Science had limited funds to detail an employee from the Office of Regulatory Affairs for two months to begin the program, but otherwise used its existing personnel. The draft report is incorrect when it states that the Office of Science assigned a clinical science senior advisor from FDA's Office of Good Clinical Practice to work on this program. This correction has been previously conveyed in other written responses to the OIG during the course of the review.

The progress of the development of the QA/QC program in the Office of Science may not have been as rapid as anticipated, because of limited resources, but significant progress has been made and continues to be made. Since the conclusion of the OIG investigation, the Office of Science has now received an additional FTE to work on the agency oversight program and is finalizing the staff manual guide that establishes requirements for implementing a quality systems program to oversee the quality of all FDA-sponsored intra- and extramural research involving human subjects.