Statement
Before the Subcommittee on Oversight and Investigations
Committee on Energy and Commerce
United States House of Representatives

The Role of the Food and Drug Administration in Overseeing Subjects Participating in Clinical Trials

Statement of

Joanne R. Less, Ph.D.

Director
Good Clinical Practice Program
Office of the Commissioner
Food and Drug Administration
U.S. Department of Health and Human Services

For Release on Delivery
Expected at 10:00 a.m.
on Thursday, March 26, 2009

INTRODUCTION

Mr. Chairman and Members of the Subcommittee, I am Dr. Joanne Less, Director of the Good Clinical Practice Program in the Office of the Commissioner, Food and Drug Administration (FDA or the Agency), an agency of the Department of Health and Human Services (HHS). I appreciate your invitation to appear here today to discuss FDA's role in overseeing Institutional Review Boards, commonly referred to as "IRBs."

BACKGROUND

For over 40 years, FDA has been committed to protecting the rights, safety, and welfare of subjects who participate in clinical trials of FDA-regulated products. The obligation to protect individuals who volunteer for research, and assume research risks in order to advance public health, therapeutics, and biomedical knowledge, is integral to FDA's mission, and the Agency continually strives to strengthen and promote the human subject protections embodied in our statute and regulations. While measures to protect human subjects are incorporated into all aspects and stages of a clinical investigation, perhaps human subject protection is most clearly embodied in two critical trial activities. The first is the requirement to obtain voluntary, legally effective informed consent from each study subject. The second, which is also the topic of this hearing, is the requirement for independent, ethical review of each clinical trial. Since 1962, with the passage of the Kefauver-Harris Amendments to the Federal Food, Drug, and Cosmetic Act (FD&C Act or the Act), clinical investigators have been required to obtain the informed consent of

subjects who participate in FDA-regulated research. IRB review has been a requirement for studies involving medical devices since 1976 with the enactment of the Medical Device Amendments and, by regulation, for all FDA-regulated research studies since 1981.

However, regulators cannot ensure human subject protection by themselves. The responsibility for human subject protection is one that we share with sponsors, clinical investigators, study monitors, and IRBs. Some studies also include a data monitoring committee, which is an independent group of experts who monitor patient safety and treatment response data. Indeed, every party with a role in the conduct or management of the trial must fulfill those duties and be vigilant in doing so, or subjects could be put at risk.

As I mentioned before, responsibility for protecting the rights, safety, and welfare of human subjects who participate in biomedical research is shared by the sponsor, who is responsible for the overall conduct of the study; the clinical investigator, who conducts the study; the monitor, who verifies information submitted to the sponsor while the study is ongoing; the IRB, which is responsible for ensuring that the research is ethical and that the rights, safety, and welfare of the subjects are protected; and FDA, which has oversight responsibilities for the entire process. As described in more detail below, this network of overlapping responsibilities is key to protecting the rights, safety, and welfare of human subjects who participate in FDA-regulated trials.

OVERSIGHT OF CLINICAL TRIALS

Clinical trials are a means of testing investigational products in human volunteers to see if they should be approved for wider use in the general population. A test article could be a drug, medical device, or biologic, such as a vaccine or a blood product. Test articles are generally studied in laboratory animals or subjected to other types of preclinical testing, such as *in vitro* bench or mechanical testing, before human trials are allowed to proceed. Investigational products having acceptable safety profiles are then moved into clinical trials.

The sponsor of a product to be studied develops an investigational plan, which includes the preclinical supporting data, the scientific justification for the study, a thorough description of the study interventions, plans for monitoring the study, and the informed consent process. The sponsor then selects one or more clinical investigators, appropriately qualified by training and experience, to conduct the trial and evaluate the test article.

In conducting clinical investigations of FDA-regulated products, the investigator is responsible for following the investigational plan and complying with all applicable regulations. Specific responsibilities related to protecting the rights, safety, and welfare of subjects under the investigator's care include, for example, complying with FDA's regulatory requirements for the initial and continuing review and approval of the proposed clinical study, obtaining the voluntary and legally effective informed consent of

each study subject, and promptly reporting any changes in the research activity to the IRB and sponsor prior to implementing them, except where necessary to eliminate apparent immediate hazards to the subjects.

FDA's regulations also require sponsors to monitor their investigations in order to ensure that the study is indeed being conducted according to the investigational plan and study protocol. During the trial, the study monitor may visit the investigational sites or use central monitoring techniques to assess the study's progress. The monitor will review records and case report forms to determine if the investigator is, among other things, accurately reporting adverse events. The monitor will also review the subjects' case histories to verify that the investigator is following the protocol's criteria for including subjects who qualify for the study, and excluding subjects whose medical condition or other factors (e.g., liver or kidney function, concomitant use of other medications) would place them at greater risk of harm if they were allowed to participate in the trial. Instances of noncompliance would be reported to the study sponsor, who must either secure the investigator's compliance or discontinue shipments of the investigational article and terminate the investigator's participation in the study.

I will now describe the responsibilities of the IRB.

WHAT IS AN INSTITUTIONAL REVIEW BOARD?

Under FDA regulations, an Institutional Review Board is a committee that has been formally designated to review, approve, and conduct periodic review of biomedical research involving human subjects. The primary purpose of IRB review is to ensure the protection of the rights and welfare of human subjects participating in the research. To accomplish this purpose, the IRB reviews research protocols, informed consent documents, and other materials (e.g., Investigator's Brochure, recruitment plans, advertising) and decides if the study should proceed.

In accordance with FDA regulations, an IRB has the authority to approve, require modifications in (to secure approval), or disapprove research. But in order to approve a study, the IRB must determine, among other things, that all of the following criteria are met: the risks to subjects are minimized; the risks are reasonable in relation to anticipated benefits; the selection of subjects is equitable; and informed consent is obtained and appropriately documented for each subject. So, for example, the IRB can require modifications to the protocol, informed consent document, or study procedures before it approves the study. And, as I mentioned earlier, under FDA regulations, the IRB also has the authority to disapprove a study. It should be noted that, in addition to protocol deficiencies, a study may be disapproved by an IRB for reasons beyond the protocol itself, such as current workload at the site or limited availability of suitable subjects.

FDA's regulations cover all aspects of an IRB's operations, including membership; procedures for initial, continuing, and expedited review; recordkeeping; and reporting requirements. For example, an IRB must have at least five members of varying backgrounds, including at least one nonscientist, and one nonaffiliated member as well as members who are sufficiently qualified through experience and expertise to review proposed research. An IRB may invite individuals with specialized knowledge to assist in the review of complex issues that require expertise beyond, or in addition to, that available on the IRB. In addition, when ensuring that the IRB is sufficiently qualified to review the research, consideration is also given to race, gender, cultural backgrounds, and sensitivity to the local community attitudes so as to promote respect for the advice and counsel of the IRB in safeguarding the rights and welfare of the subjects. IRB members may not participate in the IRB's review of, nor vote on, any project in which the member has a conflicting interest.

Once a study begins, IRBs have the authority to suspend or terminate approval of research that has been associated with unexpected serious harm to subjects or that is not being conducted in accordance with FDA's regulations or the IRB's requirements. Any suspension or termination of approval must include a statement of the reasons for the IRB`s action and be reported promptly to the investigator, appropriate institutional officials, and FDA. Additionally, the IRB must follow its written procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, and FDA of any unanticipated problems involving risks to human subjects or others; any instance of serious or continuing noncompliance with these regulations or the requirements or

determinations of the IRB; or, as previously mentioned, any suspension or termination of IRB approval. IRBs do not operate in isolation, but rather, they act as part of a larger system intended to collectively ensure the protection of human subjects.

FDA JURISDICTION

FDA has authority over clinical trials involving products regulated by the Agency. This authority includes oversight of studies that are HHS-funded or supported (with joint oversight by FDA and the HHS Office for Human Research Protections (OHRP)), as well as studies that are funded by industry or private parties. FDA's regulations pertaining to IRBs and human subject protection are located at Title 21, *Code of Federal Regulations*, Parts 56 (21 CFR 56; "Institutional Review Boards") and 50; ("Protection of Human Subjects"). These regulations require that each IRB develop written procedures for conducting initial and continuing review of research, determining which studies require more frequent review, ensuring prompt reporting to the IRB of changes in research activity, and ensuring that changes in the research are not initiated without IRB review and approval, except where necessary to eliminate apparent immediate hazards to the human subjects. IRBs must also have, and follow, written procedures for promptly reporting to the IRB, FDA, and institutional officials any unanticipated problems involving risks to human subjects or others, any instance of serious or continuing noncompliance with FDA's regulations or the IRB's requirements, and any suspension or termination of the IRB's approval. These written procedures provide a framework for the

IRB's day-to-day operations and assist FDA's oversight of the IRB by providing a window into how the IRB functions.

There are different types of IRBs. Most IRBs are established and operated by universities, hospitals, and other institutions. While these institutions may receive research awards from the federal government, nonprofit foundations, or other sponsors, these institutionally-based IRBs usually oversee all the clinical research conducted at their institutions, irrespective of the source of the funding for the research. These IRBs are comprised primarily of volunteers (i.e., faculty and staff members of the institution.) A small number of IRBs, often referred to as "independent IRBs," are not affiliated with an institution. Independent IRBs usually provide reviews for industry-sponsored projects conducted outside a university or hospital setting, e.g., in physicians' private offices or clinics. These IRBs also must comply with FDA's IRB regulations at 21 CFR Part 56. In other words, all IRBs that review FDA-regulated research, whether institutionally-based or independent, are subject to the same regulatory requirements.

INSPECTIONS AND ENFORCEMENT

Each year, FDA's field staff conduct on-site inspections of Bioresearch Monitoring (BIMO) facilities, including sponsors, monitors, clinical investigators, IRBs, and laboratories that conduct nonclinical safety studies (including animal toxicity studies) to support FDA-regulated research. The Agency performs these inspections to evaluate the

inspected party's practices and procedures and to determine compliance with applicable regulations.

FDA applies the same oversight, scrutiny, and inspectional practices to independent IRBs as it does to IRBs that are linked to an academic or other institution. FDA conducts both surveillance and directed inspections of IRBs, and the Agency uses risk-based criteria to select these entities for surveillance inspections. For example, FDA places a higher priority on inspecting IRBs that are new or have not been previously inspected, IRBs that had previously been found to be out of compliance, and IRBs that are reviewing research involving high-risk products or vulnerable populations, such as pediatric subjects. During these inspections, FDA's inspectors will select one or more FDA-regulated studies in the IRB's inventory. The inspector will review the IRB's procedures and records, such as meeting minutes, membership rosters, progress reports, and correspondence with the clinical investigator. The inspector will follow the selected studies through the IRB's entire process, and interview key IRB staff. FDA's goal is to reconstruct the IRB's activities and ensure that the IRB's focus is on human subject protection, and that any controverted issues are resolved to the IRB's satisfaction. FDA also conducts directed (or "for-cause") inspections of IRBs for which complaints have been received. During a directed inspection, FDA focuses on the issues or study identified in the complaint and determines if there is evidence to substantiate the complaint.

If the FDA inspector uncovers a regulatory violation, the Agency may take further action. For minor deviations, FDA generally issues a letter describing the deficiency and provides reference to relevant regulations or guidance. For more serious violations, such as failure to ensure informed consent or failure to conduct continuing review of studies, FDA may issue a Warning Letter requesting that the IRB submit a corrective action plan within 15 days that describes how the IRB will correct the violations. FDA generally conducts follow-up inspections to ensure that the violations were corrected.

FDA may also impose administrative sanctions on an IRB found to be out of compliance with FDA's regulations. For example, FDA may withhold approval of studies that are reviewed by the IRBs, direct that no new subjects be enrolled in ongoing studies, or terminate ongoing studies, provided that doing so would not endanger study subjects. FDA may also impose specific restrictions, such as prohibiting the IRB from approving studies using expedited review procedures. FDA may also initiate disqualification proceedings against an IRB or its parent institution if the IRB has refused or repeatedly failed to comply with FDA's regulations and the noncompliance adversely affects the rights, safety, or welfare of the study subjects.

FDA EFFORTS TO IMPROVE OVERSIGHT OF CLINICAL TRIALS - HUMAN SUBJECT PROTECTION/BIORESEARCH MONITORING (HSP/BIMO) INITIATIVE

HSP/BIMO Initiative

In 2006, FDA launched the HSP/BIMO Initiative under the auspices of the Agency's Critical Path Initiative. The HSP/BIMO Initiative is aimed at modernizing and strengthening the Agency's oversight and protection of subjects in clinical trials and the integrity of resulting data.

For the past two years, the Agency has been working diligently to develop and issue new regulations and guidance to improve the conduct of clinical trials and enhance human subject protection. For example, FDA has long been aware that multiple individual adverse event (AE) reports were routinely submitted to IRBs, without any accompanying analysis or context as to their relevance to subject safety. As a consequence, IRBs have been struggling to manage the overwhelming volume of reports. To reduce this burden on IRBs and help provide for a more focused review, FDA issued guidance to assist sponsors and investigators in differentiating between AEs that are unanticipated problems that must be reported to an IRB and those that are not. In a similar vein, FDA has issued guidance on use of a centralized review process, data retention when a subject withdraws from a study, IRB review of Humanitarian Use Devices, and other topics, with the expectation that such guidance will reduce burdens, improve IRBs' efficiency, and allow IRBs to give more attention to critical human subject protection activities.

Earlier this year, FDA issued regulations that require all IRBs to register through an electronic system maintained by OHRP. Besides contact information for the IRB, the registration system includes the number of protocols involving FDA-regulated products reviewed during the preceding 12 months and a description of the types of FDA-regulated products involved in the protocols reviewed. These registration requirements will enable the Agency to more precisely identify IRBs that review FDA-regulated research, assist FDA in providing educational information to IRBs, and help us to identify IRBs for inspection.

Clinical Trial Transformation Initiative [1]

Another effort to improve the quality of clinical trials and strengthen human subject protection is embodied in the Clinical Trial Transformation Initiative (CTTI). The result of a public-private partnership between FDA and Duke University, CTTI includes representatives from government, industry, patient advocacy groups, professional societies, and academia. CTTI's overarching goal is to identify practices which, if broadly adopted, are likely to increase the quality and efficiency of clinical trials. One of CTTI's first initiatives is a project to assess various clinical trial monitoring methods and thereby assist sponsors in selecting the most appropriate techniques for a specific trial. Other areas that CTTI may consider include exploring alternative models for IRBs in order to reduce

[1] www.trialstransformation.org

duplication of effort in multisite clinical trials and identifying strategies to enhance the informed consent process.

FDA Internal Task Force

FDA has also established a task force to ensure that all pending and future recommendations related to the Agency's oversight of clinical trials raised by Congress, the HHS Office of the Inspector General (OIG), and the General Accounting Office (GAO) are fully addressed. For example, the OIG recommended that FDA establish procedures to enhance communication between its field and headquarters staff, develop criteria for initiating certain regulatory actions, and provide additional training to its staff in a number of areas. To address these recommendations, FDA recently added a section to the Compliance Program Guidance Manual (CPGM) chapter on Clinical Investigator Inspections that defines threshold criteria for issuing Warning Letters or notices initiating disqualification proceedings to clinical investigators, and includes instructions for determining if clinical investigators provided required financial disclosure information to trial sponsors.

In addition, FDA has developed and implemented internal procedures and guidance documents to provide direction to inspectional staff and to ensure consistency, transparency, and timeliness in FDA's process for disqualifying clinical investigators who repeatedly or deliberately fail to comply with regulations for human subject protection and the conduct of clinical investigations. Under Section 306 of the FD&C

Act, FDA has the authority to, among other actions, debar certain persons from the drug industry, such as companies and individuals convicted of crimes related to the drug approval process. FDA has finalized a guidance that consolidates the authority to initiate and pursue debarment actions within one Agency office. The new document also establishes specific procedures and timeframes for initiating, pursuing, and finalizing debarment actions.

Targeted Inspection Strategy

Finally, although FDA has traditionally conducted the majority of its BIMO inspections in association with the submission of a marketing application or as a part of its investigation of a complaint, the Agency has been focusing more on inspections of ongoing studies. This will allow the Agency to identify potential problems while a study is still active, enabling the implementation of corrective actions to minimize risks to human subjects and to preserve the integrity of the clinical trial. FDA has also been improving its follow-up of violative inspections and working to identify alternative methods to select IRBs for inspection. From information gleaned during clinical investigator and sponsor inspections, FDA works to identify potential problems with IRB operations and communications that might signal the need for an IRB inspection. This oversight includes investigations and enforcement if noncompliance with regulations in the operation of an IRB is apparent.

EDUCATIONAL ACTIVITIES

It is FDA's strong belief that educating IRB members, chairs, and administrators fosters understanding of the human subject protection regulations and enhances their ability to assure that the rights and welfare of human subjects participating in research are protected. To that end, in partnership with OHRP and other organizations, FDA participates in numerous national and regional educational conferences and workshops on human subject protection, research ethics, and good clinical practice. FDA continues to issue guidance on these issues, and responds to over 1,500 questions each year received from sponsors, investigators, and IRBs in an e-mail account dedicated to this purpose.

CONCLUSION

In conclusion, FDA remains committed to strengthening human subject protection and improving its oversight of IRBs and other parties who conduct, oversee, or manage clinical trials. FDA has taken steps to ensure that recommendations regarding the Agency's oversight of clinical trials, including IRBs, are fully addressed. While FDA has already implemented a number of changes to its clinical trial oversight activities, the Agency continues to look for and welcome input about new approaches and opportunities to fulfill these responsibilities. This concludes my statement and I would be happy to address any questions.

Please visit the Agency's Web site at *www.fda.gov/placeholder* to view FDA's HSP/BIMO Initiative Accomplishments Update