RESEARCH SUMMIT AUDIO CONFERENCE JANUARY 30, 2003
IRB COMPLIANCE PROGRAM
10 minutes

(a) Compliance Oversight Mechanisms of IRBs, and
(b) Recent citations of non-compliance following IRB inspections

Before discussing FDA's oversight mechanisms, I want to give you some background information of FDA's compliance program. FDA's bioresearch monitoring program was established in 1977. FDA has a strong history protecting human research subjects based on regulations at Title 21 Code of Federal Regulations Part 50 and 56. It was Congress that mandated that FDA develop and implement an agency-wide compliance program.

The objective of FDA's Compliance Program with respect to IRBs is to achieve IRB compliance with the regulations. The Compliance Program attempts to improve IRB performance by providing information and guidance to IRBs and by applying administrative actions for IRBs seriously out of compliance with regulations.

FDA has three Centers that issue IRB inspections (Center for Drug Evaluation and Research, The Center for Biologics Evaluation and Research, and the Center for Devices and Radiological Health). (Also, the Center for Food Safety and Applied Nutrition can request an IRB inspection, although it rarely does.) The Centers use the same basic criteria when choosing which IRB to inspect. They choose IRBs that

- Have reviewed and approved research-projects of FDA-regulated products
- Require re-inspections after having received a Warning Letter in the recent past,
- have not been inspected in the past 5 or more years or
- that have never been inspected,
- that are part of a complaint; and
- a Center can have a special project or program, for example the Center for Devices has a special program to inspect IRBs to examine how IRBs protect vulnerable populations.

There are two groups of people who are responsible for the inspection of IRB facilities.

The first group of people who are responsible are the Center's personnel. Each Center has a Division that is responsible for issuing requests for IRB inspections. These Centers are located in the Washington DC area. The Centers initiates an IRB inspection by sending a memo to the FDA District Office in which the IRB is located.
The second group of people who are responsible are the Field Investigator who actually conduct the IRB inspection. Field Investigators are located in the 22 FDA District Offices situated throughout the United States.

FDA has 22 District Offices not 50. So you readily see that each state does not have its own FDA District Office. One District Office may provide coverage for three states while another District Office may provide coverage for only one state.

After the FDA District receives the Center's memo requesting an IRB inspection, the District Office sends an FDA Field Investigator to the IRB to conduct the inspection of the IRB's facilities. One or more Field Investigators may go on an IRB inspection. In addition, a representative from the Center that issued the inspection may participate in the inspection. The FDA Field Investigator uses the Compliance Program Manual instructions and any special instructions from the Center when performing the inspection. An IRB inspection usually lasts from 2 to 5 days or more if needed

The first part of my presentation is the Compliance Oversight Mechanisms of IRBs.
The Techniques used by the Field Investigators during the inspections are found in the FDA's Compliance Program Manual for the inspections of IRB facilities. This 18 page manual describes the requirements and techniques of the inspection. The manual is on the Internet at http://www.fda.gov/ora/cpgm/default.htm. I strongly suggest that you download this manual. It may prove to be an interesting resource for your IRB.

The mechanisms of an IRB inspection include four components. After I list them for you, I'll briefly discuss each one.

1) Interviews

2) review of the IRB's **written procedures** and comparison with requirements 21 CRF 56
3) review of **IRB records** and comparison with requirements at 21 CFR Parts 50 and 56.
4) the **EXIT** meeting with management (Form FDA 483, discussions between FDA and management).

***1) The first component of the IRB inspection is the Interview:**
INTERVIEWs are conducted with the Chair, members of the Board, IRB administrators and staff, institutional officials, and sometimes clinical investigators. The interview includes questions about IRB membership, functions and operations, and records. Field Investigators will continue the interviews until the FDA investigator has an understanding of how the IRB operates.

***2) The second component of an FDA inspection of an IRB facility is the review of the IRB's written Procedures.**
The Field Investigator will want to spend some time reviewing the IRB's standard operating procedures. The Field Investigator will note whether the written procedures are in sufficient detail to describe how the IRB will meet the requirements at 21 CFR 56.108 (IRB Functions and Operations), and whether the written procedures compare favorably with the information gathered during the interviews.

***3) The third component of the IRB inspection is a review of the IRB records and reports**
The Field Investigator will select research studies to review. Some of these studies may be listed in the assignment from the FDA Center. However, Field Investigators may select protocols of their own choosing.
FDA field investigator will ensure the IRB has maintained the following records and reports required by 21 CFR 56.115:

- the protocol, consent forms, continuing review reports, adverse event reports, and statements of new findings that were given to subjects;
- IRB minutes

Other records that Field Investigators will review are:

- Correspondence between the IRB and the clinical investigator
- The IRB membership roster, and
- Other records that the Board may have for example, protocol or investigator suspensions or terminations.

The 4th component of the FDA's inspection of IRB facilities is the Exit meeting with IRB management.

At the conclusion of the inspection the FDA Field Investigator meets with the IRB chairperson and anyone whom the chairperson wants present. During this meeting, the Field Investigator may give a Form FDA 483 to the most responsible person at the meeting. The Form FDA 483 is titled "inspectional observations." It notifies the IRB's management in writing of significant objectionable conditions that were observed during the inspection (for example non-compliance with Code of Federal Regulations). The issuance of this written communication is mandated by law and FDA policy. Only significant observations are included on the Form FDA 483. Other observations are "discussed" with the IRB's management at the exit meeting.

After the Field Investigator completes the IRB inspection the Field Investigator writes a report and sends it to the Center that requested the inspection. The Center personnel analyzes the inspectional report and writes a letter to the IRB. The letter describes the Center's assessment of the IRB's performance. More often, the letter that is sent to the IRB describes two, three or more areas in which problems have been found.

If the Center personnel analyzes the inspectional report and finds numerous objectionable conditions or practices and finds there was evidence of failure to adequately protect human research subjects a **Warning Letter** is sent to the IRB. This letter describes the noncompliance and requests that the IRB respond within 15 working days with **corrective actions** that the IRB plans to take to achieve compliance.

The SECOND Part of my presentation is to describe
COMMON IRB DEFICIENCIES found during FDA inspections

- The IRB's **written procedures are incomplete** or it lacks sufficient detail.

- IRB written procedures are not being followed.
- Another common finding is that the **expedited review process** does not comply with regulations. For example, FDA has seen IRBs conduct all

continuing reviews using the expedited review process. Some IRBs use the expedited review and approval for emergency use.

- **Emergency use** is used many more times than once. Emergency use is sometimes confused with "compassionate or single use."

- **Failure to perform adequate continuing review**. For example, not all members received the continuing review materials. *Continuing review is done by a subcommittee that submits a report with their recommendation for approval and the Board votes on the Subcommittee's report. *The voting process for continuing research is made by block voting, whereby the chair announces that the protocols for continuing review are open for discussion and questions. If no discussion or questions, or after discussion and questions only one vote takes place. *Continuing review is not conducted at least annually. *

- The **minutes** of the IRB meeting fail to show sufficient detail of IRB actions or provide the basis for requiring changes in or disapproving research or the informed consent; or fail to document the comings and goings of the IRB members to ensure that a majority of the members are present to review and vote on the research.

- **The Vote** is not recorded properly, for example **the number of members** that vote For, the **number of members** that vote Against, and **the number that abstained** is not given. We sometimes see the terms "vote for approval was unanimous" or "the IRB voted to approve"

- **Adverse events** not being adequately reviewed – for example, small bowl obstruction in a peritoneal chemo therapy subject. When reported at the IRB meeting, the IRB minutes recorded "no comment." (this is also an issue with respect to IRBs cutting and pasting the same remark for each adverse event.)

- Another deficiency that is often noted is that the **majority of members are not present during the vote** and yet the vote was taken anyway.

- Often the **nonscientific** member is **not present**.

- Some IRBs **fail to notify FDA when a study is suspended or terminated**.