Session 3
FDA Audits and Findings

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Objective

The purpose of this session will be focus on the role and findings of FDA audits, the reasons for FDA audit procedures and the result of recent FDA inspections

1. Background / Reasons for Inspections US FDA
2. BioResearch Monitoring Program
3. FDA Inspection Process
4. Other Actions / Sanctions
5. Inspectional Findings
The Food, Drug and Cosmetic Act of 1938:

- Drugs had to be **safe** before it could be marketed.
- Authorized factory inspections.
- Required submission of marketing application, but if US FDA did not act on it, it was automatically approved.
1962 – Kefauver-Harris Drug Amendment

- required firms to prove drug was not only safety, but also provide substantial evidence of effectiveness for the product’s intended use.

- required US FDA to specifically approve marketing application before the drug could be marketed.
Reasons for Inspections

Primary reason for inspection: verification of data in support of a marketing application, **NOT** to evaluate the scientific validity.

➢ Thalidomide manufactured by German firm Chemie Grunenthal
Types of Inspections

1. Surveillance / Routine / Workplan
2. Compliance
3. For cause (complaints, fraud, criminal activity)
US FDA BioResearch Monitoring Program

**Purpose:** To conduct on-site inspections of both clinical and non-clinical studies performed to support research and marketing applications / submissions to the agency

- This is not limited to drug or device or foods or biologics or veterinary drugs only
- This is not limited studied performed only in the USA.
- Does include the review of the marketing application
Good Clinical Practice Regulations

- 21 CFR 50 – Protection of Human Subjects
- 21 CFR 54 – Financial Disclosure by Clinical Investigators
- 21 CFR 56 – Institutional Review Board
- 21 CFR 312 – Investigational New Drug Application
- 21 CFR 320 – Bioavailability & Bioequivalence Req.
- 21 CFR 812 – Investigational Device Exemptions
US FDA Policies for Inspections

- CPMG 7348.001 – In Vivo Bioequivalence
- CPGM 7348.808 – Good Laboratory Practice
- CPMG 7348.809 – Institutional Review Board
- CPMG 7348.810 – Sponsor, CRO & Monitors
- CPMG 7348.811 – Clinical Investigator and Sponsor Investigator
Each Center has a department responsible for pre-clinical and clinical trial activities as they affect their product type (food, drug, device, biologics, veterinary)

DFI coordinates between these Centers to inspectional to coordinate inspectional activities
"Player" in US FDA & their Roles

- US FDA Headquarters
  - Reviewers
  - Office of Compliance
  - Office of Enforcement
  - Office of Regulatory Affairs
- Field Staff
Major Players / Review Flowchart

Sponsor

Submit marketing application

Application approval / rejection

US FDA

Review / Evaluate of application by Center

Site Inspection by Field
FDA INSPECTION PROCESS
INSPCTION

- Inspections of CI, S/M, CROs are usually application driven
- IRB inspections are usually conducted on workplan basis
- Audits of these organizations are conducted in accordance to their respective compliance programs
Inspection of S/M-CROs-IRB

Inspection usually covers:

- Relevant SOPs
- Training
- Monitoring reports
- Organization structure
- Staff qualifications
- Meeting minutes

- Systems
  - Computer,
  - (S)AE review
  - Audit
  - Monitoring
  - Reporting
  - Site Selection

- Etc
Inspection of Clinical Investigator

- Coverage is usually study specific.
- Inspection is conducted
  - in accordance to CPGM7348.811
  - to ensure adherence to 21 CFR 50, 54, 56, and 312 (for drugs)
  - to ensure adherence to study protocol
  - to ensure patient protection
REGULATORY PROCESS
Regulatory Process (after inspection)

1. Establishment Inspection Report written

2. Levels of review of the EIR
   a. Supervisor (Classification Recommendation)
   b. Center / Reviewer / Assigning Center (Final Classification)
   c. General Counsel

3. Classification
   a. NAI – No Action Indicated
   b. VAI – Voluntary Action Indicated
   c. OAI – Official Action Indicated
Regulatory Action / Sanctions
Regulatory Action / Sanctions

1. Administrative Action
2. Civil / Criminal Action
Regulatory Action / Sanctions

- Administrative Action / Sanction
  - Untitled Letter
  - Warning Letter
  - Study Disqualification
  - Clinical Study Hold
  - Clinical Investigator Disqualification
  - Application Integrity Policy
Regulatory Action / Sanctions

- Administrative Action
  - Increase intensity of inspection
  - Inspection of other related parties
  - Notification of other regulatory agencies
    - Medicare / Medicaid
    - Medical / Pharmacy / Nursing Boards
  - Notification of other clinical trial sites
  - Notification of Sponsor
  - Notification of Institutional Review Board
Regulatory Action / Sanctions

- Legal Sanction
  - Seizures of test article
  - Injunction
  - Civil Money Penalties
  - Criminal Prosecution
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Site Inspection by Field
Inspectional Findings
Inspectional Findings

The Investigation was not conducted in accordance with the investigational plan.

Specifically, there is no documentation that the blind was maintained as there is no documentation that the examiner and the investigator providing the treatments were not the same person.

21CFR810.100 and ICH 4.5.1
Inspectional Findings

The investigation was not conducted in accordance with the investigational plan.

Specifically, the investigator failed to sign and date on all the forms where data was collected and failed to edit errors as specified by protocol section 16.1.

21 CFR 812.110(b) and ICH 1.27, 4.5
The investigation was not conducted in accordance with the investigational plan. For example:

The study was not conducted as a blinded study as:

1. There is no documentation who conducted the post treatment evaluations for at least one of the two post treatment evaluations for 20 of the 20 subjects’ records reviewed.

2. “YW” who provided the treatments was present for at least one post treatment for two of the 20 subjects’ records reviewed.

21 CFR 812.110(b) and ICH 1.27, 4.5
Inspectional Findings

The investigation was not conducted in accordance with the investigational plan. For example:

A final report to the reviewing ethics committee was not submitted within three months after completion of the study.

There is no documentation final report has been submitted to the ethics committee since the study completion, October 2006. This was also required by protocol section 17.6.

21 CFR 812.150(a)(6) and ICH 4.10
Inspectional Findings

Data reported on the case report form, which are derived from source documents, were not consistent with the source documents nor were the discrepancies explained as required by protocol section 19.

Specifically, there were at least nine data points in the source document which was not consistent with the case report form. In addition, for Subject #38, the source document for Week 6 examination results were transcribed onto the case report form for weeks 6 and 12 examination results.

21 CFR 812.140 and ICH 4.9.2
Inspectional Findings

Informed consent was not obtained from the study subjects prior to study enrollment for two of the 45 subjects.

21 CFR 812.100(d) and ICH 2.9
Initials / Acronyms
Initials / Abbreviations

- **BIMO** = Bioresearch Monitoring Program
- **CDER** = Center for Drug Evaluation and Research
- **CFR** = Code of Federal Regulations
- **CPMG** = Compliance Program Guidance Manual
- **CRO** = Contract Research Organization
Initals / Abbreviations  

- **DFI** = Division of Field Investigation
- **DFFI** = Division of Foreign Field Investigation
- **FD&C Act** = The Food, Drug and Cosmetic Act
- **GCP** = Good Clinical Practice
- **ICECI** = Inspections, Compliance, Enforcement, and Criminal Investigation
- **PI** = CI = Principal Investigator = Investigator
谢谢
Thank You