Introduction to FDA’s Clinical Research Review Process

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What This Talk Will Cover

- Basics of FDA application review
- FDA’s regulatory expectations for acceptance of non-U.S. clinical studies
- Some problems encountered by FDA reviewers
- The interface between regulatory review and clinical trial inspection
FDA Oversight of Clinical Research Occurs at Two Levels

- Review Process

- On-Site Inspections
  - Manufacturing (GMPs)
  - Bioresearch Monitoring (GLPs, GCPs)

In the United States, FDA Review is Required:

- To Obtain a Research Permit for human study
  - Investigational New Drug Application (IND)
  - Investigational Device Exemption (IDE)
- During research under that permit
  (IND: Phases 1, 2 and 3; IDE: pilot and pivotal studies)
- To Obtain a Marketing Permit
  - New Drug Application (NDA)
  - Premarket Approval (PMA) or Premarket Notification [510(k)] for devices
- During (or post-) marketing under that Marketing Permit
Where are Drug Applications Reviewed?

- Within CDER (Center for Drug Evaluation and Research), there is an Office of New Drugs
  - 17 Review Divisions (grouped in 6 Offices of Drug Evaluation)
  - Approximately 60 staff per Review Division
  - Organized by Therapeutic Area

and an Office of Generic Drugs

Where are Device Applications Reviewed?

- Within the Center for Devices and Radiological Health (CDRH) - 2 Offices
  - Office of Device Evaluation (ODE)
  - Office of In Vitro Diagnostic Evaluation and Safety (OIVD)
- ODE = 5 Divisions, approximately 350 reviewers
- OIVD = 3 Divisions, approximately 60 reviewers
- Branches organized by therapeutic/diagnostic area
Reviews are Conducted by Teams of Specialists

For CDER:
- Medical Officer
- Consumer Safety Officer/Project Manager
- Statistician
- Chemist
- Pharmacologist(s)
- Human Biopharmaceutics specialist
- Bioresearch Monitoring (BIMO) reviewer
- A single review team will generally follow a drug from its IND application through the NDA “approval” decision and into post-marketing

Reviews are Conducted by Teams of Specialists

For CDRH:
- Lead reviewer
- Medical/clinical reviewer
- Engineer (Material, Mechanical, Electrical)
- Statistician
- Patient labeling reviewer
- Manufacturing reviewer
- Bioresearch Monitoring (BIMO) reviewer
- Others as appropriate (e.g., toxicology, microbiology, biocompatibility, software, human factors, optics)
**Bioresearch Monitoring (BIMO) Reviewer**

- Part of the review team in CDER/CBER/CDRH
  - Represents Center’s “Office of Compliance”
  - Advises the review team on
    - Oversight of the study (e.g., monitoring plans)
    - Subject protection/GCP-related issues
    - When/what to inspect
  - Translates any identified “GCP concerns” into the inspection assignment
  - Reports back to the review team during/after the inspection

**IND and IDE Review**

- The focus of the IND and IDE reviews is on safety and on ensuring that the study will provide useful information once completed
  - Review teams can recommend:
    - Stopping a study (“clinical hold” for drugs; refusal or withdrawal of an IDE for devices)
    - Changes to the study protocol or Investigator's Brochure
    - Additional examinations or laboratory tests
    - Limits to the number of subjects or number of sites (or increases in the number of subjects)
Review of IND and IDE Applications

- Review team has 30 days to review the initial IND/IDE application
- No News = Good News

Product Development Under an IND or IDE

- Review Team Monitors
  - New Protocols (IND amendments; IDE supplements and 5-day reports)
  - Safety reports
  - Annual reports
  - Additional chemistry/bench, animal toxicology, microbiology data, device biocompatibility data
- Review team is available to consult/meet with sponsors: advise on protocol design, advise on drug/device development plan
Under the IND: If Problems...

- “Clinical Hold”
  - Legal order to delay or stop the study in the U.S.
  - May be imposed at any time/phase of study if:
    - Subjects would be exposed to unreasonable risk (includes manufacturing problems)
    - Investigator’s Brochure is misleading, erroneous, or materially incomplete
    - Investigator is not qualified
    - The study is not designed to achieve its stated objectives
  - An inspection may be assigned

Marketing Applications: Science from Source Data

- The focus of FDA NDA and PMA review is on the data itself and on data analyses, NOT on expert reports or summary statements
  - Ability to independently review and analyze primary data
  - Primacy of data quality and integrity
  - Perspective that can reveal the failings of summary reports and even peer-reviewed publications
Marketing Application Review

- Standard for Approval:
  - Drugs = Substantial evidence of safety and effectiveness from adequate and well-controlled investigations
  - Devices = Valid scientific evidence of safety and effectiveness
- Output: Application decision and product label

Non-U.S. Studies

- FDA has no absolute requirement that there be a U.S. study(-ies) to support a U.S. drug marketing application (NDA) or device marketing application (PMA) or submission [510(k)] in the U.S.
- Applications/submissions can and have been entirely supported by non-U.S. studies
- Non-U.S. studies must meet criteria for acceptance by FDA
Non-U.S. Studies   -2-

- The application must be signed by an attorney, agent, or other authorized official who resides or maintains a place of business within the U.S.

Non-U.S. Studies   -3-

- FDA can accept non-U.S. data for purposes of FDA review in two ways:
  - For drugs, if the non-U.S. studies/sites voluntarily operate under a U.S. research permit (IND) as designated by the sponsor
  - Under FDA regulations for accepting non-U.S. data in support of NDAs and PMAs
Non-U.S. Studies -4-

- FDA regulations for accepting “Foreign Studies Not Conducted Under an IND” have been in place since 1975
- Finalization of an update has just occurred (Apr ‘08)
  - FDA’s regulatory expectation for non-U.S. studies submitted in support of an NDA is now linked to compliance with internationally recognized GCP
- FDA will require not just certification but also certain documentation supporting GCP compliance
- FDA is planning to revise the PMA regulation to mirror the proposed change to the IND regulation

Required Documentation Reflects FDA’s Risk-Based Approach

- Investigator’s qualifications
- Description of the research facility(-ies)
- Information about the IEC(s)
- A summary of the IEC’s decision
- A description of how informed consent was obtained
- A description of what incentives, if any, were provided to subjects to participate
Required Documentation Reflects FDA’s Risk-Based Approach

- A description of how the sponsor monitored the study
- A description of how investigators were trained to comply with GCP
- Protocol, product and study summary information
- Provision (and authority) for FDA to validate the data through an on-site inspection

Non-U.S. Studies - 5 -

- If/once non-U.S. studies/data are accepted for FDA review, they are reviewed to the same standards as studies/data from the U.S.
**Review Teams are Guided by “Good Review Practices”**

- SOPs and standard review formats are available for FDA reviewers to assist in conducting their application reviews.
- FDA has also developed diagrams of how CDER review teams do their work and meet timeframes.
Some Problems Reviewers Encounter -1-

- Failure of studies to meet statutory requirements for establishing safety/efficacy
  - Unsuccessful drug/device
  - Poor study design
  - Bias in the design or execution of the study
- Failure to follow GCP
  - Compromise to data integrity and/or human subject protection

Some Problems Reviewers Encounter -2-

- Failure of the sponsor to follow the protocol and/or its predetermined plan for data analysis
- Underreporting of adverse events
- Selective reporting of studies, study data and/or study analyses
Interactive Exercise

The Interface Between Review and Inspection

Review Team
Bioresearch Monitoring Reviewer
Inspection Team

- The Bioresearch Monitoring Reviewer is part of both the Review Team and the Inspection Team
On-Site Inspections Complement In-House Review

- Through the Bioresearch Monitoring Reviewer, GCP Inspections are closely coordinated with FDA’s in-house review.
- Both processes (review and inspection) seek to ensure protection of research subjects and the quality of studies and data.

Reviews Must be Completed On Schedule

- Schedules are addressed in U.S. law for both drug/biologics reviews and for medical device reviews.
  - This includes time to assign and complete pre-approval GCP inspections.
Review Teams make use of Advisory Committees

- Each review division has an associated advisory committee available to consult on New Drug Applications and Premarket Approvals
  - Members are appointed for specified terms
  - Non-FDA employees
  - Scientific experts; community representative
- Committees are purely advisory; FDA review team makes the decisions

Review Decision

- For NDA or PMA, action may be:
  - Approval
  - Approvable
  - Not Approvable
- For 510(k),
  - Substantially Equivalent (SE)
  - Not Substantially Equivalent (NSE)
Review continues after a product is approved...

- Phase 4 (Post-approval) commitments
- Advertising and promotional material
- Field alert reports (drug quality or labeling problems)
- Annual reports
- Spontaneous adverse event reporting
Disclaimer:

The information within this presentation is based on the presenter's expertise and experience, and represents the views of the presenter for the purposes of a training workshop.

What This Lecture will Address/Review

- Key Activities in a Clinical Trial
  - The Process Approach
- Brief History of GCP (U.S. and international)
- Goals and Principles of GCP
- Roles and Responsibilities Under GCP
  - Investigators
  - Sponsors/Contract Research Organizations
  - Ethics Committees