Good Clinical Practice Compliance

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ROPES & GRAY

Agenda?

- GCP compliance “rules”
  - What is the law?
  - What other (non-binding) standards apply?
  - What are the unwritten expectations?
- Factors are affecting the current environment
- Enforcement changes
- What’s next?

What is the law?

- FFDCA § 505(i)
  - Authorizes FDA to promulgate regulations for exempting investigational new drugs from NDA approval requirement
- FDA Regulations
  - 21 C.F.R. Part 312, Subpart D (Duties of Sponsors, Investigators)
  - 21 C.F.R. Part 50 (Informed Consent)
  - 21 C.F.R. Part 56 (Institutional Review Boards)
  - 21 C.F.R. Part 54 (Investigator Financial Disclosure)

What is the law?

- 21 C.F.R. § 312.50 (General Duties of Sponsors)
  - Selecting qualified investigators
  - Providing investigators with the information needed to conduct the investigation properly
  - Ensuring proper monitoring of the investigation
  - Ensuring that the investigation is conducted in accordance with the protocol contained in the IND
  - Maintaining an effective IND with respect to all investigations
  - Ensuring that FDA and all participating investigators are promptly informed of significant new adverse effects or risks

What is the law?

- Specific Sponsor Obligations
  - Drug accountability and disposition
  - Obtaining information from the investigator (Form 1572)
  - Clinical protocol
  - Financial disclosure information (Part 54)
  - Selecting monitors
  - Investigator Brochure
  - Secure compliance from or terminate noncompliant investigators
  - Halting study in case of unreasonable risk to subjects
  - Recordkeeping and record retention
  - FDA inspection access
- IND safety reports (21 C.F.R. § 312.32)

What is the law?

- Non-IND studies: conditions of FDA acceptance to support an IND or marketing application
  - Well-designed and well-conducted
  - Conducted in accordance with good clinical practice (GCP)
  - FDA able to validate the data through an onsite inspection if necessary
  - Record retention

What other standards apply?

- FDA Non-Binding Guidance
  - Safety Reporting Requirements for INDs and BA/BE Studies (Draft)(2010)
  - IRB Continuing Review After Clinical Investigation Approval (Draft)(2010)
  - Adverse Event Reporting to IRBs – Improving Human Subject Protection (2009)
  - CGMP for Phase 1 Investigational Drugs (2008)
  - Establishment and Operation of Clinical Trial Data Monitoring Committees (2006)
  - Using a Centralized IRB Review Process in Multicenter Clinical Trials (2006)
  - Use of Clinical Holds Following Clinical Investigator Misconduct (2004)
  - INDs for Phase 2 and Phase 3 Studies: Chemistry, Manufacturing, and Controls Data (2003)
  - Financial Disclosure by Clinical Investigators (2001)
  - Computerized Systems Used in Clinical Trials (1999)
  - ICH E6 Good Clinical Practice: Consolidated Guidance (1996)
  - Guideline for the Monitoring of Clinical Investigators (1988)

What other standards apply?

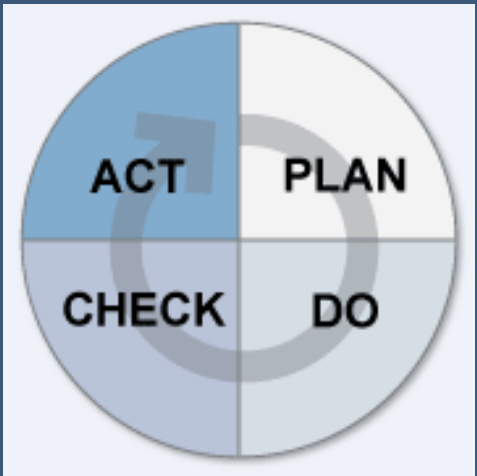
- FDA Non-Binding Guidance: Topical Information Sheets
  - Frequently Asked Questions – Statement of Investigator (Form FDA 1572)(2010)
  - Data Retention When Study Subjects Withdraw from FDA-Regulated Clinical Trials (2008)
  - Waiver of IRB Requirements for Drug and Biological Product Studies (2006)
  - Acceptance of Foreign Clinical Studies (2001)
  - Charging for investigational products (1998)
  - Recruiting study subjects (1998)
  - Non-local IRB review (1998)
  - Payment to research subjects (1998)
  - Sponsor-Investigator-IRB relationship (1998)
  - Guide to Informed Consent (1998)
  - Treatment Use of Investigational Drugs (1998)
  - Drug Study Designs (1998)
  - Evaluation of Gender Differences (1998)

What other standards apply?

- International Guidance
  - ICH E6 Good Clinical Practice: Consolidated Guidance (1996)
  - Declaration of Helsinki
  - Council for International Organizations of Medical Sciences (CIOMS) International Ethics Guidelines for Biomedical Research Involving Human Subjects

What does FDA expect?

- FDA public statements on “Quality Risk Management” in clinical trials
- Can’t “inspect in” quality
- ISO quality management system involving a closed feedback loop



(http://www.iso.org/iso/iso_catalogue/management_standards/understand_the_basics.htm)

What does FDA expect?

- What should be covered in clinical trials QRM system?
  - Protocol design
  - Monitoring of protocol adherence
  - Data collection
  - Data analysis
- Implementation of QRM system
  - Implement an integrated system addressing key risks to data quality/integrity and subject protections
  - Use I.T. to detect irregularities (e.g., late data, data alterations)
  - Address human factors like staff qualifications, financial conflicts, manual data handling, and accountability

What does FDA expect?

- FDA now conducting inspections of sponsor's clinical trial "quality systems"
  - Select products in early, mid, and late development phases
  - Link with clinical investigator (site) inspections
  - "Require" submission of sponsor's "quality risk management system," including monitoring plan

What factors are affecting the current environment?

- OIG, “The FDA’s Oversight of Clinical Trials” (2007)
- Congressional investigation of Ketek clinical trials (2008)
- OIG, “The FDA’s Oversight of Clinical Investigators’ Financial Information” (2009)
- GAO, “Oversight of Clinical Investigators: Action Needed to Improve Timeliness and Enhance Scope of FDA’s Debarment and Disqualification Processes for Medical Product Investigators” (2009)
- GAO, “Human Subjects Research: Undercover Tests Show the IRB System is Vulnerable to Unethical Manipulation” (2009)
- OIG, “Challenges to FDA’s Ability to Monitor and Inspect Foreign Clinical Trials” (2010)

FDA Enforcement

- Options to address regulatory violations (CPGM 7348.810)
  - Warning and Untitled Letters
  - Re-inspection
  - Termination of an exemption (IND, IDE, INAD)
  - Refusal to approve or license
  - Withdrawal of approval (PMA, NDA, NADA)
  - Implementation of the Application Integrity Policy
  - Initiation of stock recovery
  - Seizure of test articles
  - Injunction
  - Criminal prosecution
  - Referral to other Federal, state, and local agencies

FDA Enforcement

- Traditional approach
  - Site selection based on highest enrollment or other qualitative risk perception
  - Several sites per application
  - If significant violations identified at some sites, FDA performed sensitivity analysis excluding those sites
  - Data at other sites assumed to be reliable
  - If data held up under sensitivity analysis, application could be approved

FDA Enforcement

- New approach
  - Risk-based site selection using multifactor algorithm
  - If first round of inspections shows significant violations, conduct second round
  - Systems-based inspection of sponsor or CRO
  - Request 3rd party audit of representative sites
  - Compare 3rd party audit with sponsor monitoring reports and FDA inspections
  - Assess whether violations were limited to FDA-inspected sites
  - Hold sponsor and CRO accountable for inadequate monitoring and failure of quality systems by rejecting data, issuing Warning Letter, or conducting follow up inspections

What's next?

- Proposed Rule, "Reporting Information Regarding Falsification of Data" (Feb. 2010)
- Revised Compliance Policy Guide
- Guidance for Contract Research Organizations

Questions?

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