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Amarex Clinical Research
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FDA Meetings
Global Regulatory Submissions
Global Clinical Trials
Statistics & Data management
Strategy Implementation
Pre-Clinical Assays

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RAPS Annual Conference, Philadelphia, Sep 13-16, 2009

India Essentials, Sep 14, 2009 – 1:30-3:00 PM

Amarex’s
India Business Workshop
Germantown (Washington DC area)
Sep 11, 2009

• Various kinds of grants available
• Eligibility requirements
• Application Process
• Time-lines and milestones
• Application review process
• Terms of the grants
• Logistics of US-India Development projects
• And much more..

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Preparing for an FDA Audit for GCP Compliance

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Why Does FDA Audit Sites?

- To use the money paid for NDA review
- They like giving us a hard time
- To show that they can
- They like to travel at tax-payers’ expense
- We have done something seriously wrong
- Process Validation

It’s the Law: FDA is responsible for assuring that the products it approves are safe for people: developed, manufactured, reported and distributed appropriately
Who Gets Audited?
- Everyone
- Randomly
- Selected Few: high priority targets
- When there is an accident

Who Gets Audited by FDA?
- File for an approval application NDA/PMA
- High Risk Product
  - Used in vulnerable population
  - Used in large populations
  - New technology, unknown mechanism, etc.
- High Risk Process
  - Safety concerns at clinical sites
  - Inadequate process controls (SOPs, Monitoring, etc)

An FDA Audit: Are you next?
The FDA may conduct announced or unannounced inspections of clinical investigator sites for various reasons such as:
- Routinely to verify data that has been submitted to the Agency
- As a result of a complaint to the Agency about the conduct of the study at the site [i.e., "for cause"]
- In response to sponsor concerns or termination of the clinical site
- At the request of an FDA review division
- And related to certain classes of investigational products that the FDA has identified as products of special interest in its current work plan (i.e. targeted inspections based on current public health issues).

What is Subject to FDA Audit?
- Everything
  - Laboratory processes (GLP)
  - Clinical process (GCP)
  - Sites, investigators, etc
  - Manufacturing processes (GMP)
  - Safety Reporting processes (GRP)

Sponsor Audits (QA) Vs FDA Audit
- Sponsor Audits:
  - "Silent Topic" at FDA: No explicit regulatory requirement for auditing by sponsor.
  - Routine sponsor audit reports would not be requested by FDA.
  - Not *required* but *essential*. Without audit there is no way to know if the system is working.
- FDA Audits
  - are becoming more frequent.
  - ICH GCP guideline E6-5.19 and 6.11.

How Frequent are FDA Audits?
- It’s a daunting task
  - More studies; more sites; greater volume at each site
  - About 50,000 clinical studies under IND
  - Expansion and fluidity of clinical investigator pool
  - "New" players in new roles (CRO’s, SMO’s)
  - More participation by "vulnerable" subjects
  - Global process
  - GLP, GCP, GMP, distribution, safety reporting issues
  - Lack of surprise inspections
  - New technologies
  - Electronic record-keeping
  - Higher communication
  - Information age
  - Higher level of awareness
  - Accidents are amplified

Not frequent enough
Who are the FDA auditors?

- Enforcement arm of the FDA:
  - Office of Compliance, Division of Scientific Investigations
  - The Bioresearch Monitoring (BIMO) program
  - Since 1976, about 600 auditors
  - Either work for FDA headquarters (Washington DC area) or regional offices
- Trained in FDA auditing manual
- Experienced in fraud detection

Audit

- Audit = Process validation: Process to establish documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its pre-determined specifications and quality characteristics.

Processes must exhibit
Well-Organized, Well-Documented
Common Sense

FDA Audit

Objective: To detect Misconduct

Key Regulations

- Good Laboratory Practices: 21 CFR 58
- Good Clinical Practices: 21 CFR 312 and ICH E6
- Good Manufacturing Practices: 21 CFR 211, 21 CFR 820
- Compliance Program Guidance Manual

FDA Enforcement Policy

- Compliance with regulations is expected
- Industry is constantly monitored and given opportunity to correct/prevent violations
- Enforcement response metered to the severity of violation
- No tolerance for fraud, intentional violation or gross negligence
- Enforcement based on science, logic
- Works with local, state, federal and international health officials
- Maximize enforcement resources

Prohibited Acts

- Adulteration or misbranding of products
  - All unapproved products
- Shipping or receiving above products
- Facilitating creation of above products
- Refusal to allow FDA inspection

Note: FDA oversight is over products it approves, process oversight is indirect. Processes leading to no viable application for approval might never get audited, e.g., R&D is not directly audited, only when used to support an application.
What constitutes Misconduct?

- Recognizing Research Misconduct
  - Research misconduct means *Falsification of data* in proposing, designing, performing, recording, supervising or reviewing research, or in reporting research results.
  - Falsification of data includes creating, altering, recording, or omitting data in such a way that the data do not represent what actually occurred.
  - Safety risk, reliability of data

  **If it is not written it wasn’t done, if it’s written and not done it is fraud**

- Misconduct in Clinical Research
  - The Misconduct Scale
    - Innocent Ignorance
    - Lack of knowledge of regulations
    - Incomplete or incorrect CRF
    - Non-preserving source documents
    - Surprising Sloppiness
    - In-attention to detail
    - Lack of supervision
    - Protocol “shortcuts”
    - Malicious Malfeasance
    - Deliberate falsification of data (Fraud)
  - Sponsor’s obligation: Detecting, Correcting and Preventing Misconduct
  - FDA Sanctions for Misconduct

GCP: Good Clinical Practices

- Apply to all human studies to support an application for research (IND, IDE) or marketing approval (NDA/PMA)
  - Direct or contracted studies
  - iRB approval also required
- FDA *does not* provide a GCP certification
  - Lots of guidance (http://www.fda.gov/oc/gcp/regulations.html)
  - Private vendors do GCP training and validation
  - All studies need to be GCP compliant, without exception

GCP Basics

- Site Organization and Personnel
  - Qualified physicians and safety personnel
  - Training, safety, management
  - Quality Assurance
  - Distribution of responsibilities
- Facilities
  - Visiting area, consenting area
  - Pharmacy procedures
  - Study procedures (SOPs, manuals, etc)
- Protocol management
  - Sample handling
  - Record keeping and documentation

So, FDA contacted you…

- Most FDA audits are scheduled about 1-2 weeks in advance
  - Surprise audits do occur
  - 1-2 weeks notice could be a surprise for you if you are not prepared
- Almost all audits are study/application specific
- Almost all audits are safety related
- Being selected for audit by FDA does not necessarily imply fault on your part
- Be courteous and professional
- FDA auditor is a person doing his/her job

Before FDA visits

- Contact the sponsor
  - Inform of the dates, ask advise
  - Sponsor might be able to provide a consultant
- Make a Plan
- Do a thorough check of documentation
  - Organize and clean-up
  - Study document and process review
  - All internal audit findings (QC and QA issues)
Before FDA visits

- Prepare staff
  - Mock interviews
    - Two questions and a request:
      - What do you do?
      - How do you do the work?
      - Show me
    - Assign responsibilities for interacting
  - Trouble-shoot
    - Identified issues and their potential resolution

The FDA Investigator is here!

- Access should to controlled
  1. Inspector announces himself/herself
  2. Wait in reception area
  3. QA/Regulatory personnel escort to designated area
  4. Check credentials, never try to copy (it's illegal)
  5. FDA 482 presented, documents requested
  6. Introductions and orientation, hospitality
  7. Always escort to all the areas of the company that he/she wants to visit/examine
  8. Personnel access to be controlled and recorded

FDA Inspection: Dos and Don’ts

- Make readily accessible: Source documents
  - SOPs, manuals
  - Study documentation
  - Raw data access (Labs)
  - Training files
- Make readily accessible: Facilities
  - Labs
  - Clinics
  - Patient areas
- Be available, make senior management aware of progress

FDA Inspection: Final Minutes

- Exit interview
  - Summarize findings
  - Clear any misimpressions
  - Document discussions
- FDA Inspector has two options
  - No findings (you are very good!!)
  - Findings (FDA 483)
    - Nobody’s perfect, don’t get shocked
    - Don’t argue or get defensive
    - Respond in writing at a later date
    - FDA 483 and your response becomes public information

FDA Inspection: Dos and Don’ts

- Make good notes, everything is being recorded
- Keep everyone calm
  - People get nervous and defensive
  - Train people to only say what they know not what they believe
  - Never make unsubstantiated comments
  - If you don’t know, say so, don’t make up!
- Good hospitality and personable people make the process flow (Plenty of chocolate helps)
Common Audit Findings (from 483s)

- GCP:
  - Documentation issues
  - Safety Reporting violations
  - Inadequate training records
  - Informed consent improper
  - Protocol violations, e.g., Inclusion/exclusion criteria violations
  - Procedural violations
    - Study processes inadequately followed
    - Source document and CRF mismatch

FDA Sanctions

- Individuals, Companies and Institutions involved in FDA regulated research
  - Clinical Investigators
  - Sponsors, CROs, Monitors
  - Laboratories
  - Institutional Review Boards (IRBs)
- Applications and data submitted to FDA

When the FDA means business!

- FDA 483

International Sites

- Reasons for audit of non-US sites
  - Insufficient domestic data
  - Large percent domestic data
  - Conflicting results from US and non-US sites
  - Suspension of fraud, full financial disclosure or human subject protection violation
- Frequency of non-US site audits
  - Increasing due to trends in more non-US data
  - Increasing number of non-US audits
- Most investigator training required
  - Little or no experience
  - FDA’s international offices make surprise audits a reality

"Diligence is the mother of good luck."
Benjamin Franklin

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