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U.S. DRUG SAFETY : Compliance Basics

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AGENDA

- Basic Safety Reporting
- FDAAA Changes
- OTC Drugs and Dietary Supplements

Global Compliance Concerns

- Non-aligned pharmacovigilance practices among divisions, geographic entities or product groups
- REMS complications
- Clinical trial.com summaries
- Mismatched day zero terms
- Recalcitrant third parties
- Social networking sites
- Inspectors making new law
- Dawn raids
- Government “transparency” publicity
- Criminal investigations and fraud and abuse implications

Start with the United States

BASICS FOR AUDITS AND CONTRACTS

Statute: FFDCA SECTION 505(k)(1)

- Establish and maintain records, and make reports of data relating to clinical experience and other data or information, received or otherwise obtained by the applicant with respect to the drug
- Must permit FDA to have access to these records

IND REQUIREMENTS

21 C.F.R. § 312

- "Ensuring that FDA and all participating investigators are promptly informed of significant new adverse effects or risks" 21 C.F.R. § 312.50
- Selecting qualified investigators
- Sponsor Shall Promptly Review All Relevant Safety Information, Domestic and Foreign
- Sponsor Must Submit to FDA and All Participating Investigators
  - Written safety report of any serious and unexpected adverse experience associated with use of a drug
  - Written safety report of any laboratory finding in animals that suggests significant risk for human subjects
  - 15 DAYS

IND: Critical Reports

- Sponsor must report unexpected fatal or life-threatening ADEs associated with the use of a drug by phone or fax
- No later than **7 calendar days** after sponsor's initial receipt of information
- For safety reports, must investigate and report any relevant follow-up information as soon as it is available

NDA: REPORTING REQUIREMENTS

21 C.F.R. § 314

- Postmarketing Reporting of Adverse Drug Experiences
  - 15-day reports
  - Follow-up reports
  - Periodic reports
- Field Alert Reports
- Annual Reports
- papers

ADE INFORMATION

- Promptly Review All ADE Information, Including:
  - commercial marketing
  - postmarketing clinical investigations
  - postmarketing epidemiological studies
  - reports in scientific literature
  - unpublished scientific information
  - Social networking

15-DAY ALERT REPORTS

- Must Submit Report for Each ADE That is *Serious and Unexpected*, Whether Foreign or Domestic
- Not Later Than **15 Calendar Days** After Initial Receipt of Information by the Applicant
  1. Must Promptly Investigate All 15-Day Alert Report ADEs
  2. Must Submit Follow-Up Reports Within 15 Calendar Days of Receipt of New Information

PV AGREEMENTS

- Information Obtained Pursuant to Agreements With Co-Development, Co-Promotion, or Co-Marketing Partners Can Trigger FDA Reporting Requirements
- 15-Day Alert Requirements: Clock Can Start When Partner or Affiliate Obtains Information

PERIODIC REPORTS

- Must Report Each ADE Not Reported in 15-day Reports in Quarterly Intervals for 3 Years From Date of Approval, Then Annually
  - Narrative summary and analysis
  - Case report forms
  - History of actions since last report because of ADEs
- Does Not Apply to ADE Information From Postmarketing Studies, Scientific Literature, and Foreign Marketing Experience

PART 11

- Electronic Records and Signatures
- Compliance is a Slippery Slope – Impossible to do it Only Part of the Way
- Currently Precatory
- Attention to Interface Issues, Security, and Data Integrity

FOOD AND DRUG ADMINISTRATION AMENDMENTS ACT OF 2007

- "Responsible Parties" Have Duty to Report to clinicaltrial.gov
  - Must Designate Manufacturer or Sponsors Of Trial as RP
- Definitions For Clinical Trial Posting:
  - "Serious Adverse Events"
    - Anticipated And Unanticipated
    - Drugs, Biologics And Devices
  - "Frequent Adverse Event"
    - Exceed Frequency Of 5% With Any Arm Of Clinical Trial
  - FDA To Issue Regulations By 2010

FDAAA

FDAAA Definitions For Post-Market Studies and Surveillance:

- FDA May Require Clinical Trials Or Studies To
  - Assess “Signals” Of Serious Risk
  - Identify “Unexpected Serious Risk”
    - Not in Labeling
  - May Have To Monitor Health Care Providers, Pharmacists To Ensure Safe Use (FDCA § 505-1(f)(3)-(5))

FDAAA

- Risk Evaluation and Mitigation Strategy (REMS) Requirement May Be Imposed Based Upon "New Safety Information"
  - "New Safety Information" May Be Derived From:
    - Clinical Trials
    - Adverse Event Reports
    - Post-approval Studies
    - Peer-reviewed Biomedical Literature
    - Data Derived From The Post-market Risk Identification And Analysis System, Or
    - "Other Scientific Data Deemed Appropriate" By FDA
    - A "New Analysis Of Existing Information"

OTC DRUGS AND DIETARY SUPPLEMENTS

The Dietary Supplement and Nonprescription Drug Consumer Protection Act ("AER Act")

- "Applies to "Responsible Persons
  - Manufacturer
  - Packer
  - Distributor

    whose name(s) appears on the label of an OTC or dietary supplement product.
- Submit SAERs to FDA within fifteen (15) days
- For One Year After Submitting SAER, Must Update SAER's With Any "New Medical Information" Within Fifteen (15) Days Of Receipt
- Label to include domestic address or telephone number to which AERs/SAERs can be reported