CLINICAL TRIAL REGISTRIES

Kathleen Meriwether

Assistant United States Attorney
Eastern District of Pennsylvania

UNITED STATES DEPARTMENT OF JUSTICE

Clinical Trial Registries

- REGULATORY BACKGROUND
  - June 2004 – Attorney General of the State of New York, Eliot Spitzer, brings a lawsuit against Glaxo SmithKline
  - Allegations that the Company withheld from the public and prescribers negative clinical trial data about Paxil (paroxetine), the widely used anti-depressant marketed by GSK, particularly negative or inconclusive data from studies conducted in children and adolescents

Clinical Trial Registries

- REGULATORY BACKGROUND
  - June 2004 – Eliot Spitzer sends a Letter of Inquiry to Forest Pharmaceuticals, requesting certain information from Forest relating to off-label uses of Lexapro and Celexa, antidepressants marketed by Forest

Clinical Trial Registries

- REGULATORY BACKGROUND
  - September 2004 – Agreements entered into with GSK and Forest to resolve the complaint and inquiry, respectively
  - Terms of Agreement with each Company required establishment of a Clinical Trial Registry

Clinical Trial Registries

- REGULATORY BACKGROUND
  - GSK Agreement
    - Company agreed post, on-line, results of clinical studies of paroxetine
    - Company will establish an on-line “Clinical Trials Register” that will contain summaries of results from GSK-sponsored clinical studies of *all* of its drugs conducted after December 27, 2000

Clinical Trial Registries

- REGULATORY BACKGROUND
  - Forest Agreement
    - Forest will post on-line the results of clinical studies relating to off-label uses of Lexapro and Celexa in children and adolescents
    - Company agrees to establish an on-line Clinical Trials Registry which will contain summaries of results for all clinical studies conducted after January 1, 2000 and earlier studies that are “relevant” to the use of the drug and care of patients

Clinical Trial Registries

- GSK & Forest Settlements
  - Format of Clinical Trial Data
    - Summaries in format as prescribed in the settlement agreements
    - Summaries have certain limitations – but this is a major advance in the campaign to provide all *useful* information to practitioners to assist independent clinical judgment

Clinical Trial Registries

- What brought about the use of Registries?
  - Publicity about suicide or violent behavior in adolescents taking antidepressants
  - More recently the Vioxx withdrawal raised similar issues – what did the Company know, and when?
  - Companies currently under no regulatory or legal requirement to publicly disclose all clinical study results (in the U.S.)
  - FDA not required to disclose data, except in the context of labeling changes, Advisory Committee meetings, etc.
  - Lack of full disclosure can result in less than optimal decision making

Clinical Trial Registries

- Why is New York State so active?
  - State Attorneys General increasingly using their general powers to protect the public to act in areas traditionally left to the federal government – e.g., drugs, tobacco, securities law, accounting
  - Broad and varied armamentarium possessed by state AGs – Civil Investigative Demands, other pre-complaint discovery – broad powers under state consumer protections
  - Appointment of Jim Sheehan, Associate U.S. Attorney, (E.D. Pa.) to head up the New York State OIG – broad mandate?

Clinical Trial Registries

- Concerns Remain – Company Registries
  - Summaries – how complete are they?
  - Summaries – how balanced are they?
  - Timing of disclosures – significant time lag between the end of a study and the publication of results
  - Who will monitor compliance?
  - Is more information necessarily better?
    - Data inundation – Enron problem?

Clinical Trial Registries

- Concerns Remain
  - Use of Company-sponsored Registries
    - NOT another marketing tool – another avenue for dissemination of off-label information
    - Also, should not be used as a competitive tool – not as a basis for product differentiation, class effect positioning, etc.
    - Links to other sites, solicitation of patients – are these activities proper? Any regulation of the related activities?

Clinical Trial Registries

- WHO – Clinical Trial Search Portal
  - Moving to improve access online to clinical trial data
  - Will not accept submissions from pharmaceutical manufacturers
  - Currently – data from 50,000 trials provided by three registers – Britain, Australia/New Zealand and U.S.
  - Network of registers will be expanded
    - Required to disclose
      - Ownership
      - Governance Structure
      - For-Profit Status

Clinical Trial Registries

- PDUFA 2007 and Post-Marketing Commitments
  - Since 1995 – US FDA has “agreed” with sponsors on Phase IV commitments at an ever-increasing rate
  - However, no increase in regulatory authority or oversight
  - Now – PDUFA 2007 - enhanced enforcement powers:
    - Increased oversight of drug safety post-approval, including:
      - Power to impose labeling changes
      - Improved surveillance of post-marketing adverse events
      - Ability to *require* additional safety studies
    - Establishment of a public database of clinical trials and their results

Clinical Trial Registries

- State Law Requirements:
  - Example - Maine's law requires disclosure of:
    - Summary or purpose of clinical trial;
    - Dates the trial was conducted;
    - "Information concerning the results of the clinical trial, including potential or adverse effects of the drug"
    - Posting of information must be in form and manner acceptable to Maine Department of Health and Human Services.

Clinical Trial Registries

- Challenges for Sponsors:
  - Regulatory – how current are you with your U.S. Phase IV commitments? How to fund, if unbudgeted.
  - Legal – what are the products liability implications of posting data that is inconclusive? Are you exposing yourself to claims? How much information? What data is most important? From whose perspective? Road map for prosecutors/plaintiff's counsel?
    - Timing – how to ensure data posted is the most current and the most rigorous.
    - What happens to the learned intermediary doctrine?
    - Conflicting requirements – FDA, states, WHO, EMEA, etc.
    - Who is managing the overall process?