National Pharma Audioconference: Lessons of BMS' $515 Million Settlement for Off-label Promotion, Kickbacks and Drug Pricing

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Safety Issues in Off-Label Investigations

- Clinical Trials Issues in Fraud Investigations and Prosecutions
  - Does the clinical data support the off-label use?
    - Research and Development Plans for New (Off-Label) Indications or Populations - company documents can reflect:
      - change in strategy – lack of funding to pursue a new indication or a study in an expanded population;
      - or WORSE – that the indication was studied, but the trial failed to achieve safety/efficacy goals necessary for an approval (and no commensurate change in strategy)

Safety Issues in Off-Label Investigations

- Clinical Trials Issues in Fraud Investigations and Prosecutions
  - Misuse/Misapplication of FDAMA and the Washington Legal Foundation opinion
    - WLF Opinion has limited legal applicability
    - NOT a green light for distribution of any journal article about any use of a product
    - Even within the parameters of WLF – is the information a balanced presentation of what is known about the product?
    - Will an indication for the off-label use or new population be forthcoming based on the data that is being distributed?

Safety Issues in Off-Label Investigations

- Clinical Trials Issues in Fraud Investigations and Prosecutions
  - Critical issue for enforcers – is the off-label use putting patients at unwarranted risk?
  - If drug is not proven to be safe and effective, are patients being deprived of an opportunity for treatment with a proven, FDA-approved product or regimen?
    - Is the off-label "campaign" a disincentive to research?
      - Why conduct studies if the company can still capture significant market share without going to the bother and expense of extensive clinical trials?

Safety Issues in Off-Label Investigations

- Consistent Observations in Off-Label Cases
  - Belief by many inside the Company that the drug was actually safe and effective for the off-label use:
    - Why?
      - Other drugs with similar properties have indications based on good research
      - Preliminary studies were promising
      - But – class effect must be proven like anything else
        - See, e.g., Vioxx

Safety Issues in Off-Label Investigations

- Consistent Observations in Off-Label Cases
  - Why are sales force personnel detailing *e.g.*, pediatricians, when there is no approved indication in this population?
    - Proffered explanations – just sampling, they write anyway, other products in my bag are for the pediatrician – usually fall apart under minimal scrutiny
    - How could this happen – Call Lists traditionally not part of the regulatory/legal review process or auditing activities - Should they be?
    - BMS CIA may reflect current direction of US Attorney's Offices and HHS-OIG on this issue

Safety Issues in Off-Label Investigations

- Consistent Observations in Off-Label Cases
  - Strategic planning documents/financial projections for the brand reflect specific goals for off-label sales as well as tactics for achievement
    - Again, not reviewed as promotional materials, so can escape review by counsel and be very problematic from a defense perspective
    - Lack of awareness of legal/regulatory/compliance implications of internal presentations, e-mails, projections

Safety Issues in Off-Label Investigations

- How is risk minimized and patient safety protected to the greatest extent?
  - Critical examination of *all* data regarding a product as the full clinical picture develops.
  - Ensure that a common understanding of a product's risks, limitations and market potential exists between commercial operations (sales and marketing) and R & D – look at strategic plans and management presentations.
  - Develop review processes that go beyond traditional "compliance" areas such as promotional materials, consultant agreements and content of speaker programs, and also critically assess, e. g.:
    - Development and modification of sales force call lists and Sales Force Incentive Plans
    - Deployment of Consultants – i.e., numbers, activities and fair market value of compensation

Safety Issues in Off-Label Investigations

- **Emerging Issues:**
  - **FDA Amendments Act of 2007 and its New Compliance Obligations**
    - Pediatric Adverse Event Reporting for Newly-Approved Drugs;
    - Clinical Trials Databases and Registry Requirements;
    - Increased Surveillance Requirements for Approved Drugs

Possible Emerging Issues in Enforcement

Clinical Trial Registries

- Previously - Companies under no regulatory or legal requirement to publicly disclose all clinical study results and registry requirements limited
- FDA not required to disclose data in its possession, except in the context of labeling changes, Advisory Committee meetings, etc.
- Registries mainly voluntary in the U.S., with a few exceptions (GSK and Forest settlements with New York Attorney General), NIH database of ongoing studies for serious and life-threatening illnesses

Possible Emerging Issues in Enforcement

- **FDA Amendments Act of 2007**
  - Expansion of Clinical Trials Databases and Registry requirements beyond trials for drugs intended to treat serious and life-threatening conditions.
  - *Required* registration of clinical studies in NIH Clinical Trials Registry
    - "Publicly Available and Searchable Information," about trials must be provided, including status of study; anticipated completion date; description of study; contact information
      - Information must be truthful and not misleading and updated at least annually (unless no changes)

Possible Emerging Issues in Enforcement

- **FDA Amendments Act of 2007**
  - Required submission of study *results* in the "registry and results data bank"
    - "Non-technical" summary of patient demographics and characteristics
    - Primary and secondary outcomes
    - Disclosure of agreements protecting privacy of study subjects
    - Submitted within one year after study is completed (unless certification is made to NIH that there is a pending application with FDA for a new drug or new use)

Emerging Issues in Enforcement

- Clinical Trial Registries – Compliance & Risk Issues
  - What are “full disclosures?”
  - How to characterize the efficacy results
  - How are the safety issues described? Which adverse events are significant enough to be mentioned?
  - Can the data be mischaracterized or otherwise criticized?

Possible Emerging Issues in Enforcement

- **FDA Amendments Act of 2007**
  - Post-approval clinical studies may now be required rather than voluntary
    - FDA must be aware of “new safety information,” i.e., a signal or new and unexpected safety issue, and that post-marketing surveillance is insufficient to clarify the issue.
    - FDA Request and Timetable submitted by Sponsor
    - Penalties now provided for non-compliance
  - Safety Labeling Changes May be Required
    - FDA may require a labeling change if becomes aware of new safety information that it believes should be added to the label
    - Risk Evaluation and Mitigation Strategies (REMS) plan may be required as part of initial approval or subsequently.

Possible Emerging Issues in Enforcement

- **FDA Amendments Act of 2007 – Additional Noteworthy Provisions**
  - Additional User Fees for DTC television ads
  - Pediatric assessments required for *all* applications
  - Expedited reporting of all pediatric adverse events for one year following a pediatric-specific labeling change
  - Changes to pediatric exclusivity provisions