Risk Management Strategy for the Pharma and Biotech Product Lifecycle:
New Regulatory and Legal Focus and Approach

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Stephen Paul Mahinka
Morgan Lewis, Washington, D.C.
smahinka@morganlewis.com

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Increasing Focus on Risk Management – Litigation Challenges

- Product liability litigation
  - Vioxx litigation
  - Hormone replacement therapy (HRT) litigation
  - Baycol litigation
- New litigation focus on marketing/promotion and on data from ongoing clinical studies

Increasing Focus on Risk Management – Regulatory Activities

- Enhanced reviews of NDAs for safety data by FDA
- Enhanced focus by FDA on safety labeling and updates of labeling
- Effect of new clinical trials registries (e.g., clinicaltrials.gov)
- New FDA Guidance documents on risk management programs
- Enhanced FDA focus on Phase IV post-marketing clinical studies
- Potential CMS comparative studies of clinical effectiveness and "coverage with evidence development" policy

Increasing Focus on Risk Management – Regulatory Activities

Labeling issues:

- Need to fully incorporate risks and warnings
- New FDA regulation (Jan. 2006) – drug labeling approval preempts state law
  - Will increase consultation with and need for written responses from FDA on risk labeling inclusion and exclusion
  - Mechanisms to add warnings to labeling (prior approval supplement; changes-being-effected supplement)

Increasing Focus on Risk Management – Regulatory Activities

FDA risk management programs:

- New FDA Guidance documents (March 2005):
  - Premarketing Risk Assessment
  - Development and Use of Risk Minimization Action Plans (RiskMAP)
  - Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment
- Focus is to identify and characterize the nature, frequency, and severity of product risks
- RiskMAPs intended to minimize product risks and provide specific objectives to ensure effectiveness of the plan

Increasing Focus on Risk Management – Regulatory Activities

Recent RiskMAPs

- Roche/Accutane® (acne): physician training; letter of understanding; negative pregnancy tests; patient contraception; tracking system
- GSK/Lotronex® (IBS): physician education; prescribing program compliance; patient-physician agreement; patient education
- Biogen Idec & Elan/Tysabri (MS): mandatory registry; patient information; preliminary MRI required; available only through authorized doctors or centers

Increasing Focus on Risk Management – Regulatory Activities

FDA – Phase IV studies

- Increasing FDA use of Phase IV studies as a condition of NDA approval
- GAO Report, "Improvement Needed in FDA's Post-market and Oversight Process" (March 2006)
  - Calls for improved tracking of post-market studies
  - Calls for expansion of FDA's statutory authority to impose post-marketing studies
- OIG Report, "FDA's Monitoring of Postmarket Study Commitments" (June 2006) – critical of FDA's current oversight of Phase IV
- Proposed legislation

Increasing Focus on Risk Management – Regulatory Activities

FDA and CMS focus on promotional activities

- Effect of reporting of clinical trials to public databases
- Dissemination of off-label use information and off-label studies

Potential CMS development of drug use data

- Potential effect on risk management of CMS' coverage with evidence development (CED) policy (July 2006), conditioning Medicare reimbursement on collection of data, including off-label use.
- Potential effect on risk management of comparative effectiveness studies/trials

Increasing Focus on Risk Management – Regulatory Activities

Potential CMS development of drug data (cont'd)

- Potential use of CMS Medicare prescription drug claims data as a source of drug safety and outcomes information
- Potential access to private claims databases (e.g., Blue Cross Blue Shield Ass'n testing of "Blue Heath Intelligence" database and possible partnering with CMS)

Increasing Focus on Risk Management – Regulatory Activities

Need for a proactive risk management strategy

- Integrating science issues/regulatory aspects/litigation planning
- Operative throughout the product lifecycle
  - Product development/pre-market approval/post-market promotion and distribution/and post-market trials/evidence

Proactive Risk Management Strategy for the Pharma/Biotech Product Lifecycle

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Emerging Risk Management Strategy Issues

Need to address emerging risk management strategy issues:

- Effect of more widespread use of risk management action plans by FDA
  - Effects of narrow or restricted distribution of products (12-18 months) on development of safety profile data
  - Market and economic effects of consequent reduction of the period of unrestricted sales during the patent life of the product
    - Potential need for corresponding patent term extension

Emerging Risk Management Strategy Issues

- Potential impact of increased use of surrogate markers in clinical trials for approvals
  - Reduced scope and size of clinical trials and of risk predictive capability
- Potential impact of increase in use of staged launches of products to restricted patient populations
  - effect on scope of product experience data
  - effect on scope of warnings/labeling

Emerging Risk Management Strategy Issues

- Effect of increased use of pharmacogenomics
  - Potential development of differing safety profiles for both broader and narrower groups
- Effect of changes in promotional focus
  - Potential reduction of DTC advertising (e.g., PhRMA guidelines) on initial launch
  - Potential increase in physician training and product use education at launch

Emerging Risk Management Strategy Issues

- Effect of increasing interaction between FDA and CMS/OIG activities
  - Effect of CMS activities regarding comparative effectiveness and coverage based on evidence, including off-label use
  - Effect of OIG fraud and abuse investigations covering off-label use and marketing on reporting of risks and safety labeling
- Effect of increasing use of outsourcing of clinical trials on coordination of evidence generated by co-development partners; CROs undertaking clinical trials; third-party manufacturers, co-marketing and co-promotion partners

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