ARNOLD & PORTER LLP

The U.S. Approach to Risk Management

Daniel Kracov

Track II: Pharmacovigilance and Drug Safety
Risk Management: - EU and US Developments
International Pharma Congress

May 28, 2008

FDA Amendments Act of 2007 (FDAAA) and Drug Safety

- The most significant amendments to the Federal Food, Drug, and Cosmetic Act (FFDCA) in years…but FDAAA is generally considered inadequate by key Democrats, so more legislation to come.

- The law broadens user fee-funded postmarket safety-related activities -- no time limitation and can be used for:
  - Reviewing safety information on approved drugs, including adverse event reports;
  - Developing and using improved data collection systems; and
  - Developing and using improved analytical tools to assess potential safety problems (including accessing external databases).

- Establishes new statutory "Risk Evaluation and Mitigation Strategy" framework

- New authority to require studies, trials and labeling changes

- New enforcement tools

Risk Evaluation and Mitigation Strategies (REMS)

- The legislation provides a new statutory framework for integrating risk evaluation and mitigation into drug reviews and post-market pharmacovigilance.
  - An evolution from prior law, which provided funding for development of FDA risk management guidance and review of voluntary risk minimization plans.
  - Many of the risk minimization tools in the legislation are already in use in certain existing drug approvals (under Subpart H / Risk Minimization Action Plans (RiskMAPs)).

REMS Standards

- A REMS proposal may be required for New Drug Applications (NDAs), Biologic License Applications (BLAs), Abbreviated New Drug Applications (ANDAs), and major supplements if FDA "determines that a risk evaluation and mitigation strategy is necessary to ensure that the benefits of the drug involved outweigh the risks of the drug."
- FDA will consider:
  - The patient population, seriousness of the disease, expected benefit, duration of treatment, and seriousness of known or potential adverse events.
  - The background incidence in the population likely to use the drug and whether the drug is a new molecular entity.
- REMS may be required post-approval if based on new safety information.
  - Submission within 120 days after notification

REMS Requirements

- The REMS for a drug or biologic must include a timetable for submission of assessments.

- The Secretary may require one or more of the following elements:
  - a Medication Guide or patient package insert;
  - a risk communication plan; and
  - use and distribution restrictions.

REMS Distribution and Use Restrictions

- Under REMS Framework
  - Providing patients with safe access to drugs with known serious risks that would otherwise be unavailable
  - Secretary may include such elements "as are necessary to assure safe use of the drug, because of its inherent toxicity or potential harmfulness."
  - Secretary must determine –
    - The drug, which has been shown to be effective, but is associated with a serious adverse drug experience, can be approved only if, or would be withdrawn unless, such elements are required as part of the REMS
    - Other REMS elements are insufficient to mitigate such serious risk

REMS Distribution and Use Restrictions (cont.)

- "Elements to ensure safe use" may require that –
  - Health care providers who prescribe the drug have particular training or experience or are specially certified (must be available at reasonable cost to providers from a "frontier area" in a widely available method (on-line or mail) as approved by the Secretary)
  - Pharmacies, practitioners, or health care settings that dispense the drug are specially certified (must be available to providers in "frontier areas")
  - The drug be dispensed to patients only in certain health care settings, such as hospitals
  - The drug be dispensed to patients with evidence or other documentation of safe use conditions, such as lab results
  - Each patient using the drug be subject to certain monitoring
  - Each patient using the drug be enrolled in a registry

REMS Distribution and Use Restrictions (cont.)

- Conditions on "elements to ensure safe use" –
  - Must be commensurate with the specific serious risk listed in the labeling of the drug
  - Must -- considering the risk -- not be unduly burdensome on patient access to the drug, considering in particular –
    - Patients with serious or life-threatening disease or conditions,
    - Patients who have difficulty accessing health care (such as patients in rural or medically underserved areas).
  - To the extent practicable, so as to minimize the burden on the health care delivery system, such elements should –
    - Conform with elements to assure safe us for other drugs with similar, serious risks, and
    - Be designed to be compatible with established distribution, procurement, and dispensing systems for drugs

Distribution and Use Restrictions (cont.)

- Applicant may be required to monitor, evaluate, and work to improve implementation
- Within 30 days of the date on which one or more of these restrictions is imposed, the restrictions must be posted publicly by the Secretary with an explanation of how such elements will mitigate the observed safety risk
- REMS restrictions may be used to permit expanded access for patients with off-label, serious or life-threatening diseases or conditions
- Waivers permitted in certain public health emergencies (countermeasures)
- Secretary should seek evaluation of such elements by the FDA Drug Safety and Risk Management Advisory Committee
  - At least annually, for one or more drugs

REMS Submissions

- Processes for moving existing drugs with distribution or use restrictions into REMS framework
- On March 27, 2008, FDA issued a notice identifying the drugs and biologics deemed to have REMS
  - The manufacturers must submit a proposed REMS by September 21, 2008
  - FDA developing guidance on the preferred content and format of a proposed REMS
  - Brand names of products deemed to have a REMS in effect:
    - Plenaxis, Lotronex, Letairis, Tracleer, Clozaril, Fazaclo ODT, Tikosyn, Soliris, Ionsys, Actiq, Accutane, Amnesteem, Claravis, Sotret, Revlimid, Mifeprex, Tysabri, ACAM2000, Xyrem and Thalomid

REMS Timetables and Dispute Resolution

- The law requires submission of REMS assessments at 18 months, three years, and seven years.
  - The Secretary may eliminate assessments after the three-year period if the serious risks of the drug are being adequately managed.

- The law includes a process/timeline for the resolution of REMS-related disputes, including a review conducted by the Drug Safety Oversight Board (DSOB)

Recent Example: Entereg® (alvimopan)

- Indicated for restoration of bowel function after bowel resection surgery
- Approved May 20 with a REMS
  - Inpatient use, not to exceed 15 doses
  - No pediatric use
  - Hospital certification
  - Educational materials to health care professionals
  - Regular assessments

Evaluation of REMS Elements

- The law requires the Secretary, through the Drug Safety and Risk Management Advisory Committee, to evaluate whether various REMS elements:
  - assure safe use of a drug;
  - limit patient access; or
  - place an undue burden on the healthcare system.
- With input from patients and health care providers, the Drug Safety and Risk Management Advisory Committee will issue or modify guidance about how to implement REMS.

Postmarket Studies and Clinical Trials

- New FFDCA Section 505(o)
  - FDA authority to require postapproval studies and clinical trials from "responsible person" for a pending or approved "covered application" (NDA (Rx) or BLA).
  - Can be required "…on the basis of scientific data deemed appropriate by [FDA], including information regarding chemically-related or pharmacologically-related drugs"
  - Permitted purposes:
    - to assess a known serious risk,
    - to assess signals of a serious risk related to the use of the drug, or
    - to "identify an unexpected serious risk when available data indicates the potential for a serious risk."

Postmarket Studies and Clinical Trials

- For pending applications, FDA must notify the responsible person of the need for a postapproval study or clinical trial by deadlines established in user fee performance goals, and the sponsor must submit a timetable for its completion and periodic status reports.
  - Decision can be appealed by following FDA dispute resolution procedures

Postmarket Studies and Clinical Trials

- Limitations:
  - In order to require a postapproval study, FDA must first determine that currently required postmarket reports will be insufficient to assess or identify the risk.
  - Can be applied to a previously approved application if such determination is based on *new safety information*
  - A clinical *trial* may not be required unless FDA determines that a postapproval *study or studies* will not be sufficient to meet the statutory purposes

Enforcement: REMS and Study Requirements

- Failure to comply with the following requirements would render a drug misbranded.
  - FDC Act § 505(o) – Post-approval studies/trials
    - FDC Act, Sec. 502(z) (21 U.S.C. 352(z))
  - FDC Act § 505(p) – Maintain compliance with REMS
    - FDC Act, Sec. 502(y) (21 U.S.C. 352(y))
  - FDC Act § 505-1 – REMS Submission
    - FDC Act, Sec. 502(y) (21 U.S.C. 352(y))

Civil Penalties: REMS and Study Requirements

- FDAAA includes civil penalties for manufacturer violations of REMS and study requirements:
  - Penalties of $250,000 per violation (up to $1 million) in a single proceeding. FDC Act, Sec. 303(f)(4)(A)(i) (21 U.S.C. 333(f)(4)(A)(i))
  - For continued violations after the Secretary has provided notice, $250,000 for the first 30-day period, doubling for each subsequent 30-day period, not to exceed $1 million in a 30-day period and $10 million for all violations adjudicated in a single proceeding. FDC Act, Sec. 303(f)(4)(A)(ii) (21 U.S.C. 333(f)(4)(A)(ii))
- In determining the amount of the civil penalty for continued violations, the Secretary will take into account whether the responsible person is making efforts toward correcting the violation. FDC Act, Sec. 303(f)(4)(B) (21 U.S.C. 333(f)(4)(B))

Sentinel Initiative Announced May 22, 2008

- Long-term effort to create a national electronic system for monitoring medical product safety
- Sentinel System
  - Targeted queries of patient registry data, insurance claims data, and other large health care (private and governmental) information databases
  - Plan to link data from Medicare Part D (outpatient drug benefit) to hospital and physician data (Medicare Parts A and B)
  - Privacy protections

Dan Kracov
Arnold & Porter LLP
daniel.kracov@aporter.com
(202) 942-5120