FOOD AND DRUG ADMINISTRATION AMENDMENTS ACT OF 2007 (FDAAA) and Risk Evaluation and Mitigation Strategies (REMS)

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FDAAA

- Title I – PDUFA
- Title II – MDUFMA
- Title III – Peds Devices
- Title IV – PREA
- Title V – BPCA
- Title VI – Reagan/Udall
- Title VII - COI
- Title VIII – Clinical Trials Database
- Title IX – Postmarket Drug Safety
- Title X – Food Safety
- Title XI – Misc. Provisions

Title IX – Drug Safety

- New authorities to:
  - Require postmarketing studies and clinical trials
  - Require sponsors to make safety related labeling changes
  - Require sponsors to develop and comply with risk evaluation and mitigation strategies (REMS)
- Subtitle A took effect March 25, 2008, 180 days after enactment
- Subtitle B took effect Sept. 27, 2007

Risk Evaluation and Mitigation Strategies (REMS) (505-1)

REMS apply to:

- Approved prescription drugs and biologics
- Generic drug with special limitations and adaptations
  - 505-1(i)

Pre-approval REMS

- FDA may determine REMS is needed *to ensure that the benefits of the drug outweigh the risks of the drug*
- Certain factors must be considered:
  - Size of population likely to use drug
  - Seriousness of disease
  - Expected benefit of drug
  - Expected duration of treatment
  - Seriousness of known or potential adverse events
  - Whether the drug is an NME

Post-approval REMS

- If no REMS in effect, FDA may determine REMS is needed and require sponsor to submit *if the Secretary becomes aware of new safety information* and determines that *such a strategy is necessary to ensure that the benefits of the drug outweigh the risks of the drug*
- If FDA requires REMS, sponsor must submit within 120 days, or within such other reasonable time as FDA requires to protect the public health

REMS Elements

- Only required element is a timetable for submission of assessments of the REMS (505-1(d))
- Optional Elements:
  - MedGuides (if meets regs) and PPI (if insert may help mitigate serious risk of the drug) (505-1(e))
  - Communication plan if FDA determines plan may support implementation of an element of the REMS (505-1(e))
  - Elements to assure safe use (505-1(f)(3))
  - Implementation system (505-1(f)(4))

Timetable for assessment

Required timetable:

- Assess by 18 months, by 3 years, and in the 7th year after REMS approval
- FDA may specify other shorter frequencies
- FDA can eliminate assessments after 3 years if we determine *serious risks of the drug have been adequately identified and assessed and are being adequately managed*

Elements to Assure Safe Use

- Healthcare providers who prescribe the drug have particular training or experience or special certifications
- Pharmacies, practitioners, or healthcare settings that dispense the drug are specially certified
- The drug may be dispensed only in certain healthcare settings
- The drug may be dispensed to patients with evidence of safe-use conditions
- Each patient must be subject to monitoring
- Patients must be enrolled in a registry

Findings for ETASU

- The drug can be approved only if such elements are required as part of a REMS to mitigate a specific serious risk listed in the labeling, or would be withdrawn if elements are not part of REMS
- For a drug initially approved without elements to assure safe use, other elements (e.g., a MedGuide, communication plan) are not sufficient to mitigate a serious risk.

Implementation of REMS

- Take reasonable steps to monitor, evaluate, and work to improve implementation by healthcare providers and other participants
- Only applies to certain ETASU

REMS and Generic Drugs

- Generic drugs are only subject to MedGuides or PPIs, and elements to assure safe use
- If there was a communication plan for the innovator, FDA must carry out the plan when a generic is approved
- Generics must use a single shared system or obtain a waiver

Enforcement of New Title IX Authorities

- Person may not introduce drug into interstate commerce if in violation of post-marketing requirements, safety label change order, or REMS requirements (505(o) and (p))
- Also in violation if fails to conduct a postmarket study under section 506, Part 314, subpart H, or Part 601, subpart E
- Misbranding charges - 502(y) and 502(z)
- Civil penalties – 303(f)(4)

Responsible person (505(o)(2)(A))

- Person who submitted a covered application that is pending; or
- holder of approved application

Misbranding

- 502(y)
  - For drugs subject to a REMS if the responsible person fails to comply with sections 505-1(d) (minimal REMS elements), 505-1(e) (additional potential REMS elements), or 505-1(f) (safe access to drugs with known serious risks)
- 502(z)
  - Drugs for which the responsible person violates section 505(o)(3) (post-market studies and clinical trials) or 505(o)(4) (drug safety labeling changes)

Civil Penalties

- Civil Penalties – Any responsible person who violates sections 505(o) (post-market studies, clinical trials, labeling), 505(p) (REMS), or 505-1 (REMS) shall be subject to a civil money penalty of:
  - $250,000/violation – **but** not to exceed $1 million for all violations adjudicated in a single proceeding; or
  - For a continuing violation after notice by the Secretary, $250,000/first 30 days, then doubled for every 30-day period thereafter – **but** not to exceed $1 million/30-day period or $10 million for all violations adjudicated in a single proceeding.
  - The Secretary shall consider efforts to correct violations in assessing civil penalties.

Drugs Deemed to have REMS

- Sec 909 states that drugs approved before FDAAA with elements to assure safe use were deemed to have REMS
- On March 27, 2008, we issued FR notice (73 FR 16313) identifying 16 drugs/biologics deemed to have REMS
  - Proposed REMS submitted by September 21, 2008

FDAAA Update
March 25 – September 9, 2008

- Of 102 CDER and CBER approvals of applications and efficacy supplements
  - 13 included approved REMS
    - 11 actions were Medication Guide only REMS
    - 2 REMS had Elements to Assure Safe Use
    - 3 REMS had Communication Plans
  - 18 approval letters required postmarketing studies or clinical trials
- Post-approval actions:
  - FDA exercised authority to require postmarketing studies or clinical trials based on new safety data 3 times
  - FDA exercised authority to require safety labeling changes 4 times, all involving multiple applications

Questions?