

## DRUG SAFETY INITIATIVES AT THE FOOD AND DRUG ADMINISTRATION

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## Topics

- Safety First initiative
- Early communications on drug safety
- Implementation of the Food and Drug Administration Amendments Act of 2007 (FDAAA), Public Law 110-85, 121 Stat. 823.

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## Safety First Initiative

- Better FDA management of drug safety issues
- Better management of internal discussions on drug safety issues
- Better communication about drug safety issues

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## Resources for Postmarket Drug Safety

- The Prescription Drug User Fee Act of 1992 gave FDA resources to better manage pre-market reviews of drugs
- Although the ability to identify drug risks before approval is limited by available data, until 2003, PDUFA did not authorize FDA to use fees for postmarketing drug safety activities
- Now, under PDUFA IV, Congress has provided substantial user fee funding for postmarket drug safety

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## Resources Will Be Used To Better Manage Drug Safety Activities

- New Deputy Division Directors in each review division will be responsible for managing postmarket drug safety issues
- This will better focus responsibility and accountability
- Issues will be tracked and managed using workplans with milestones and goal dates
- Multidisciplinary teams will address each issue
- Conflicts between team members will be better managed and handled at the appropriate level

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## Drug Safety Communications

- March, 2007, FDA issued Guidance on Communicating Drug Safety Information to the Public. The Guidance can be found at <http://www.fda.gov/cder/guidance/index.htm>
- Guidance reflected FDA's commitment to communicate important information about drug safety in a timely manner, in some cases while it was still being evaluated.

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## Drug Safety Communications

- 2007
  - 4 Early Communications (began in August)
  - 10 Public Health Advisories
  - 21 Healthcare Professional Sheets
- 2008 First Quarter
  - 6 Early Communications
  - 5 Public Health Advisories
  - 3 Healthcare Professional Sheets

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## We Recognize the Need For Many Communication Vehicles

- Drug Safety Newsletter, published quarterly
- Drug Safety Podcasts  
<http://www.fda.gov/cder/drug/podcast/podcast.htm>
- Consultations with the Drug Safety Oversight Board and the Risk Communication Advisory Committee to obtain advice on communications

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## FDAAA Overview

- 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

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## 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)

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## New Requirements Are Enforceable

- May not introduce drug into interstate commerce if in violation of provisions
- Drug may be found to be misbranded
- FDA can impose civil penalties for violations of the Act.

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## Section 505(o)(3) - Postmarket Studies and Surveillance

- FDA may require studies at the time of approval, or after approval based on new safety information
- Requirement must be based on scientific data and is limited to certain specific purposes:
  - To assess a known serious risk related to the use of the drug involved
  - To assess signals of serious risk related to the use of the drug
  - To identify an unexpected serious risk when available data indicates the potential for a serious risk

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## Postmarket Studies and Surveillance

- Before requiring a study, FDA must find that adverse event reporting and the active postmarket risk identification and analysis system (to be established under the Act) will not be sufficient to meet the purposes described previously
- Before requiring a clinical trial, FDA must determine that a post approval study or studies (e.g., epidemiology) will not be sufficient

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## Postmarketing Studies - Implementation

- Since FDAAA took effect, when we have identified the need for additional clinical or observational studies that are necessary to address one of the purposes in section 505(o), we have made it a post-marketing requirement.
- We have issued some approval letters since FDAAA took effect that contain such requirements. Examples include Cimzia, and Treximet. These approval letters can be found at [drugs@fda.gov](mailto:drugs@fda.gov).

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## Study/Trial Requirements

- When we impose a post-marketing study or trial requirement, in accordance with FDAAA, we require the sponsor to submit:
  - A timetable for completion of the study or trial
  - Periodic reports on the status of the study, including difficulties encountered, and for each *required* trial or *trial otherwise undertaken by the sponsor*. Status reports must state:
    - Whether enrollment has begun
    - Number of participants enrolled
    - Expected completion date
    - Difficulties completing
    - Registration information regarding [clinicaltrials.gov](http://clinicaltrials.gov).

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## Sec. 505(o)(4) - Safety Related Labeling Changes

- New authority to require labeling changes based on new safety information
- New safety information as defined in the statute is information tied to a serious risk associated with the drug of which FDA has become aware since the drug was approved
- Strict timelines for negotiating changes
- Applies to Rx drugs only (not OTC's under an NDA); applies to generic drugs if no innovator marketing

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## Safety Labeling Changes

- FDA must promptly notify sponsor if becomes aware of new safety information that should be included in the labeling of the drug
- After notification, sponsor must *within 30 days*:
  - Submit a supplement proposing changes, or
  - Notify FDA that they do not believe a labeling change is warranted, and state why not

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## Safety Labeling Changes

- FDA must promptly review supplement or statement, and if disagrees, must initiate discussions
- Discussions may not extend for more than 30 days after the response to the notification that safety labeling changes are needed, unless FDA decides extension warranted
- Within 15 days of conclusion of discussion, FDA may issue an Order directing sponsor to make whatever labeling change FDA deems appropriate to address new safety information
- Within 15 days from receipt of Order, sponsor must submit supplement containing the labeling change, or
- Within 5 days, sponsor may appeal using regular dispute resolution procedures
- FDA may accelerate timelines if concludes labeling change necessary to protect public health

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## Safety Labeling Changes - Enforcement

- If person has not submitted a supplement within 15 days of the order, or within 15 days of conclusion of any dispute resolution procedures, person is in violation, and same enforcement mechanisms as for studies apply

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## Sec. 505-1 - Risk Evaluation and Mitigation Strategies (REMS)

- Pre-approval: FDA may determine REMS is needed to ensure that the benefits of the drug outweigh the risks of the drug, inform the sponsor, and require sponsor to submit a REMS
- Post-approval: 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

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## REMS - Elements

- Only required element is a timetable for submission of assessments of the REMS
- Required timetable:
  - Assess 18 months, 3 years, and 7 years after REMS approved
  - FDA may specify other shorter or longer frequencies,
  - FDA can eliminate assessments after 3 years if determines serious risks of the drug have been adequately identified and assessed and are being adequately managed

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## REMS Elements - 505-1(e)

- MedGuides (if meets regs) and PPI (if insert may help mitigate serious risk of the drug)
- Communication plan if FDA determines plan may support implementation of an element of the REMS
- Plan may include: letters to healthcare providers, disseminating info about the REMS to encourage implementation; disseminating information through professional societies about any serious risks of the drug and any protocol to assure safe use

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## Elements to Assure Safe Use – 505-1(f)(3)

- 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

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## Elements to Assure Safe Use

- Must be commensurate with the specific serious risk listed in the labeling
- Can't be unduly burdensome on patient access to the drug, considering patients with serious or life-threatening diseases, patients who have difficulty accessing healthcare, and
- To the extent practicable, to minimize the burden on the healthcare delivery system, must conform with other elements for other drugs with similar serious risks and be designed to be compatible with established distribution, procurement, and dispensing systems for drugs.

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### Drugs Approved Before FDAAA

- On March 27, 2008, FDA issued a Federal Register Notice identifying drugs approved before FDAAA passed that are deemed to have REMS because they had in effect on date of enactment elements to assure safe use
- By September 21, 2008, holder of an application for which REMS deemed in effect must submit a proposed REMS

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### Definition of New Safety Information (505-1(b))

*“Information derived from a clinical trial, an adverse event report, a postapproval study, or peer-reviewed biomedical literature; data derived from the postmarket risk identification and analysis system...or other scientific data deemed appropriate by the Secretary about --*

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### Definition of New Safety Information (cont'd)

- “(A) a serious risk or an unexpected serious risk associated with use of the drug that the Secretary has become aware of (that may be based on a new analysis of existing information) since the drug was approved, since the REMS was required, or since the last assessment of the approved REMS; or*
- (B) the effectiveness of the approved REMS obtained since the last assessment of the strategy.*

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