The Regulatory Basis of Post-Marketing Safety

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Outline

• Laws
  – History
  – FDAAA
• Regulations
• Guidances
Laws – The Beginning*

1906: Federal Food & Drugs Act
   – The Jungle
      • Prohibited the sale of adulterated or misbranded drugs
      • Did not require that drugs be approved by FDA
      • Truthful labeling, definition of a drug, claims allowed unless provable as untrue, ingredients not required

*FDA History Page: [http://www.fda.gov/AboutFDA/WhatWeDo/History/default.htm](http://www.fda.gov/AboutFDA/WhatWeDo/History/default.htm)

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Food Drug and Cosmetic Act & Selected Amendments

– 1938: Food, Drug and Cosmetic Act
   – Elixir of Sulfanilamide
      • New drugs must be shown safe before marketing
         – Results submitted to FDA in a New Drug Application
      • Must have adequate labeling for use
Food Drug and Cosmetic Act & Selected Amendments

– 1962: Kefauver-Harris Drug Amendments
  – Thalidomide
    • Safe AND effective
    • Require mfrs to report adverse events
    • Advertisements must disclose risks as well as benefits

Dr. Frances Kelsey receiving the President's Distinguished Federal Civilian Service Award in 1962, the highest civilian honor available to government employees
Laws, con’t

– 2006: Dietary Supplement and Nonprescription Drug Consumer Protection Act (Public Law 109-462)
  • Requires reporting of serious adverse events for dietary supplements and non-approved nonprescription drugs
    – Such as OTC monograph products

– 2007: Food and Drug Administration Amendments Act (FDAAA)
  • Signed September 27, 2007
  • Huge – size and impact
  • Reauthorized
    – PDUFA – funding for postmarketing drug safety activities
    – Medical Device User Fee & Modernization Act (MDUFMA)
    – Best Pharmaceuticals for Children Act (BPCA)
    – Pediatric Research Equity Act (PREA)
  • New authorities for drug safety
FDAAA Considerations Postapproval

• When new safety information about a serious risk or effectiveness of an approved REMS becomes available after approval that:
  – needs to be in the label
  – might warrant a Risk Evaluation and Mitigation Strategy
  – might warrant a Medication Guide
  – might best be addressed through a postmarketing study or clinical trial...

Food and Drug Administration Amendments Act of 2007 - Title IX

• ...FDA can apply 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)
New Safety Information

• Must have new safety information in order to apply these FDAAA-related new authorities postmarketing
• New safety information is a serious risk that we have become aware of since the drug was approved
• Source can be clinical trial, adverse event report, postapproval study, literature (or other scientific data FDA deems appropriate)
• Can be based on a reanalysis of existing data

Regulations

• Also referred to as a “Rule”
• Compiled in the Code of Federal Regulations (CFR)
Overview of Postmarketing Safety Reporting Requirements

Post-Marketing Reporting of Adverse Experiences
21 Code of Federal Regulations (CFR)

- 310.305 – Rx without Approved Application
- 314.80 - Postmarketing drugs - NDAs
- 314.98- Generic drugs - ANDAs
- 600.80- Biologics – BLAs

Public Law 109-462
- Dietary Supplement and Nonprescription Drug Consumer Protection Act
**Regulatory Definition of Serious**
- Death
- Life-threatening
- Inpatient Hospitalization (initial or prolonged)
- Disability/Incapacity
- Congenital anomaly/Birth Defect
- Important medical events – medical judgment – jeopardize patient/subject and require medical/surgical intervention to prevent serious outcomes

**Expected** - included in current labeling

**Unexpected** – not included in current labeling

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**15-day Alert Report**

**NDAs, BLAs, ANDAs, and Marketed Unapproved Rx Drugs**

- Serious AND Unexpected Adverse Experience
- Foreign or Domestic
- Includes scientific literature of case reports or result of a formal clinical trial
- From postmarketing study ONLY if applicant concludes there is a reasonable possibility the drug caused the adverse experience
- Report as soon as possible
- In no case later than 15 calendar days of initial receipt of information by the applicant (or receipt of follow-up info)
15-day Alert Report
OTC (without application)

- All Serious Adverse Experiences
- Must include a copy of the label with the report
- Domestic only
- Report as soon as possible
- In no case later than 15 business days of initial receipt of information by the responsible person
- Follow-up Information – within 15 business days
  - Only required for info received within 1 year of initial report

When is there enough to report an adverse experience to FDA?

- Minimum four elements:
  - Identifiable patient
  - Identifiable reporter
  - Suspect drug or biological product
  - Adverse event or fatal outcome
Periodic Safety Reports

- Periodic Adverse Drug Experience Reports (PADER) - NDAs and ANDAs: 21 CFR 314.80
- Periodic Adverse Experience Reports - BLAs: 21 CFR 600.80
- Both submitted quarterly for the first three years after approval and annually thereafter
- ICH-E2C Format: Periodic Safety Update Reports (PSURs) – companies need an approved waiver to submit this format for the Periodic

What’s In Them?

- Individual Reports
  - Domestic spontaneous reports
    - no foreign, literature, or postmarketing studies
    - Other than serious and unexpected
- Summary Portion
  - Narrative summary & analysis of 15-day alert reports
  - Line listing of 3500As included
  - History of actions taken since last report because of adverse experiences - labeling changes or studies initiated
- Individual Reports can be submitted on 3500A form (and attached to paper Periodic) or as ICH E2B ICSRs (submitted via FDA electronic gateway)
What Do We Require?

• 21 CFR 314.80 - Drugs – NDAs
  21 CFR 314.98 - Generic drugs - ANDAs
  21 CFR 600.80 - Biologics - BLAs

Must Submit:

– 15-day alert reports and followups

– Periodic Adverse [Drug] Experience Reports

What Do We Require?

• 21 CFR 310.305 – Rx without Approved Application

Must Submit:

– 15-day alert reports and follow-ups
What Do We Require?

- Public Law 109-462 - OTC without an Approved Application

Must Submit:

- 15-day reports and follow-ups for ALL SERIOUS EVENTS – labeled & unlabeled

Proposed Rules
Safety Reporting Requirements for Human Drug and Biological Products
Proposed Rule

Content:
- Harmonize U.S. requirements with ICH-developed guidelines
  - Requires PSUR submission
- Medication error reports
- Much more

• Status: Published in Draft March 14, 2003
  - Comment review and final rule development in progress

Postmarketing Safety Reports for Human Drug and Biological Products: Electronic Submission Requirements

• Content:
  - Requires all mandatory postmarketing safety reports to be submitted electronically in a format the agency can process, review and archive

• Status:
  - Published on August 21, 2009
  - Comments closed November 19, 2009
Guidances
Postmarketing Reporting

www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

Key Guidances (1)

• 1992 Guideline for Postmarketing Reporting of Adverse Drug Experiences
• 2001 Draft Guidance: Postmarketing Safety Reporting for Human Drug and Biological Products Including Vaccines
Key Guidances (2)

- 2009 Guidance: Postmarketing Adverse Event Reporting for Nonprescription Human Drug Products Marketed without an Approved Application
- 2008 Draft Guidance: Postmarketing Adverse Event Reporting for Medical Products and Dietary Supplements During Pandemic Influenza
- 2008 Draft Guidance: Providing Regulatory Submissions in Electronic Format--Postmarketing Individual Case Safety Reports

Resources on MedWatch Website
www.fda.gov/Safety/MedWatch/HowToReport/ucm085692.htm
Thank you!!

Questions?