The Regulatory Basis of Post-Marketing Safety

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Outline

- Laws
  - History
  - FDAAA
- Regulations
- Guidances

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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

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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

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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

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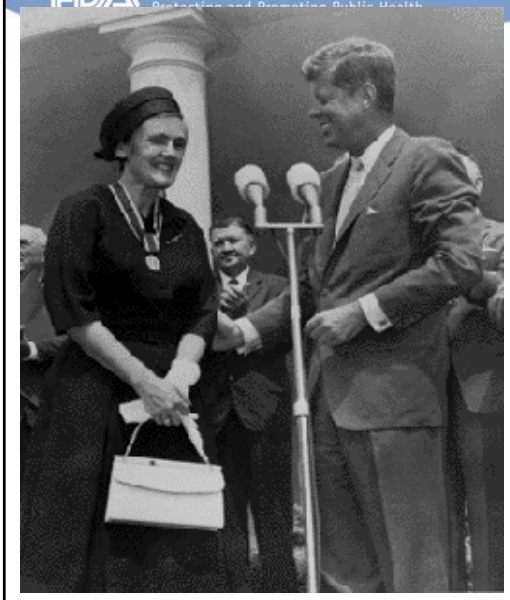

Dr. Frances Kelsey receiving the President's Distinguished Federal Civilian Service Award in 1962, the highest civilian honor available to government employees

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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

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Laws, con't

– 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***

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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...**

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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)

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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

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Regulations

- Also referred to as a “Rule”
- Compiled in the Code of Federal Regulations (CFR)

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Overview of Postmarketing Safety Reporting Requirements

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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

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- **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)

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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

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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

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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

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Periodic Reports (PADER) 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)

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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

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What Do We Require?

- 21 CFR 310.305 – Rx without Approved Application

Must Submit:

– 15-day alert reports and follow-ups

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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

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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

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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

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Guidances
Postmarketing Reporting

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

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Key Guidances (1)

- 1992 Guideline for Postmarketing Reporting of Adverse Drug Experiences
- 1997 Guidance: Postmarketing Adverse Experience Reporting for Human Drug and Licensed Biological Products: Clarification of What to Report
- 2001 Draft Guidance: Postmarketing Safety Reporting for Human Drug and Biological Products Including Vaccines

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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

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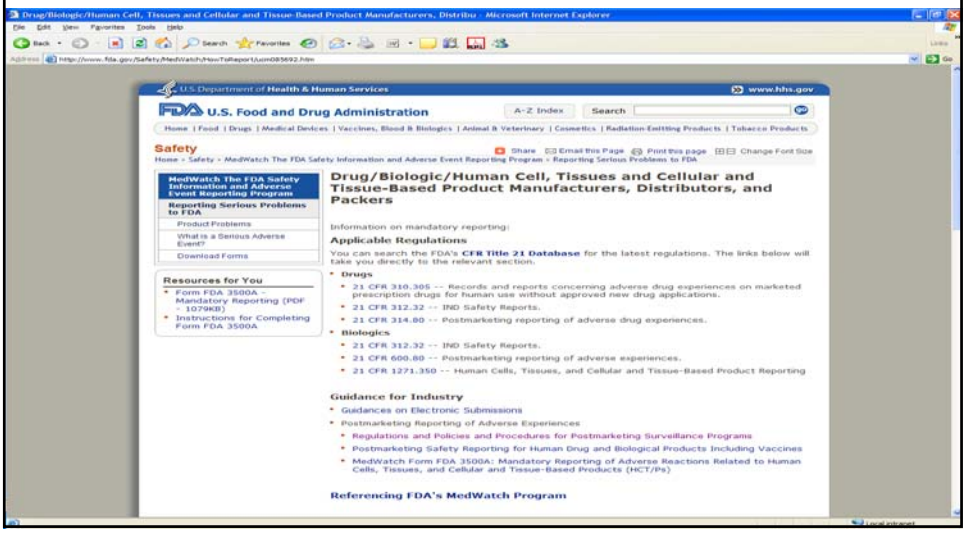
Resources on MedWatch Website

www.fda.gov/Safety/MedWatch/HowToReport/ucm085692.htm



Thank you !!

Questions?