Overview of Postmarketing Safety Reporting and Pharmacovigilance in CDER

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“The opinions expressed are those of the author and not necessarily those of the FDA.”
Safety in the Lifecycle of FDA-regulated Products

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Components of Postmarket Drug Safety System

- Spontaneous Reports
- Medication Error Reports
- Active Surveillance
- Observational Studies
- Drug Utilization Studies
- Clinical Trials

Existing Knowledge
Scope of Regulations

- Approved Rx’s under NDAs, ANDAs, BLAs (21 CFR 314.80, 314.98, 600.80)
  - *Drugs, therapeutic biologics, Generics, Rx’s switched to OTC status*
- Unapproved or non-approved NDA or non-NDA Rx’s or pre-1938 “grandfathered” drugs (21 CFR 310.305)
- OTC (monograph’d non-NDA non-Rx) drugs (Section 760 of FDC Act)
Safety Reporting for Combination Products

• Includes drug/device, biologic/device, drug/biologic, or drug/device/biologic combos, examples:
  – Drug-eluting stent
  – Insulin-containing prefilled pen device
  – “Kit” containing biologic vial plus separate syringe for drug combination in same package
  – “Cross labeled” products- different/separate products but labeling states using one with the other product
Who gets these combination product reports?

• Lead center that has the approved application
• Lead Center will have the review responsibility
• Centers will communicate and share reports/discuss cross-center issues as needed
Report Sources

• Spontaneous or voluntary from the public-
  Direct reports
• Mandatory from the sponsors or
  manufacturers of the approved FDA
  regulated products
  – Spontaneous
  – Studies, domestic or foreign
  – Scientific literature publications
  – Foreign, including foreign regulatory authorities
Reporting of Serious Adverse Events and Medication Errors

Reporting Directly to FDA

- **Online**
  - www.fda.gov/medwatch

- **Download the form**
  - Mail
  - Fax 1–800–332–0178

- **Telephone**
  - 1-800-FDA-1088
How Postmarketing Reports Get to FDA

Patients, consumer, and healthcare professionals

Voluntary → FDA MedWatch

5% of all reports

Voluntary → Manufacturer

95% of all reports

FDA MedWatch

Manufacturer

Regulatory Requirements

FDA

FAERS Database
Reporting In To MedWatch

1. Patient Identifier
2. Product
3. Event or Problem
4. Reporter
Manufacturer’s Reports

• Based on outcomes and expectness
• 15-day ( Expedited) Alert reports
  • Serious and unexpected events
• Periodic reports- quarterly for 3 years after approval and annually thereafter, include-
  • Individual serious labeled and all non-serious event reports
  • Descriptive or narrative summary and analysis (in PADER, PSUR or PBRR format) of reports in period
FDA Adverse Event Reporting System (FAERS)

- AE report data from 1969
- >7 million records
- Database re-engineered in 1997 to accommodate electronic submission standards (E2B and M2)
- Data available on the web
  - Potential Signals of Serious Risks/New Safety Information Identified from the FDA Adverse Event Reporting System (FAERS)
  - Quarterly data files of raw data extract
FAERS Entered Case Counts
1996 – 2012*

*Search: 09/2013
What Do We Do With the Reports?

• Evaluate cases from all data sources
• Identify safety signals
• Assess signals further beyond case review
• Recommend regulatory actions
• Communicate safety information
Data Sources

- FAERS
- Scientific literature
- Drug Quality Reporting System (DQRS)
- World Health Organization (WHO)
- Drug use data
- Epidemiological research contract databases
- Foreign regulatory authorities
International Sources

• Through FDA’s Office of International Policy
• Participates ICH or CIOMS Expert Working Groups related to safety
• Provides FAERS reports quarterly to WHO and has access to WHO’s foreign data
• Holds videoconferences with
  – EMA/monthly
  – Australia, Canada and New Zealand/bi-monthly
  – Exchange/share PV findings for globally marketed products
Use of Data Mining/Empirica Tool

• Systematically analyzing FAERS by using statistical methodology for disproportionality or “higher-than-expected” product event combinations

• Case report evaluation and other safety information should accompany data mining result analysis
Case Evaluation

- Use sound clinical knowledge to search the databases for relevant cases to develop a case series
- Follow-up with reporter when needed for clinical details and documentation of diagnosis
- Establish temporal relationship between product and AE, e.g., dechallenge/rechallenge
- Identify comorbidities, underlying diseases, risk factors, role of concomitant meds
Case Evaluation (cont’d)

• Biological plausibility
• Consistent with known pharmacological effects
• Support from pre-clinical studies or clinical trials findings
Beyond Case Review

- Case reports – putting into perspective by epidemiologic assessment
- Calculation of reporting rate in the exposed population with available usage data when appropriate.
- Comparison of reporting rates
  - against estimates of background occurrence rate in the general population.
  - to similar products within a class or products across product class
- Proposal of additional studies
Safety Signals

• New unlabeled adverse events
• An observed increase in severity or specificity in a labeled event
• New drug-drug interactions
• Newly identified at-risk population subgroup
• Product quality problems
• Confusion with product design- dosing, delivery system, product names, labeling, or packaging
Other Safety Related Activities

• Product quality, Drug Counterfeiting
• Emergency product-related outbreaks/adverse event clusters
• Safety of medical counter measures/Counter-terrorism products
• Collaboration with CFSAN, CDRH, CDC, etc.
• Liaison with patient and health professional organizations
Regulatory Actions on Safety Issues

- Labeling changes- ADRs, Precautions and Warnings; Boxed Warnings
- Risk Evaluation and Mitigation Strategy (REMS): medication guides, communication plans, elements to assure safe use (ETASUS)
- Issue requiring postmarketing studies (observational claims, registry studies etc)
- Communication to the public- Drug Safety Communications, "Dear Healthcare Provider" letters, FDA Talk Papers, Press Releases, Public Health Advisories/Alerts, MedWatch website postings
- Market withdrawal
Active Surveillance

• FDA’s Sentinel Initiative
  www.fda.gov/safety/FDAsSentinelInitiative/ucm2007250.htm
  – Use large databases from multiple sources
  – Cover a large number of lives
    • 25 million in 2010
    • 100 million in 2012
  – Two components:
    • Mini Sentinel and Federal Partners Collaboration
• **Stay Informed**

• Subscribe to MedWatch
  – E-list
  – Text alerts
  – Twitter
  – RSS feeds
Drug Safety and Availability

Information for consumers and health professionals on new drug warnings and other safety information, drug label changes, and shortages of medically necessary drug products.

Drug Safety Communications

- FDA Drug Safety Podcast RSS Feed
- FDA Drug Safety Communication: New risk factor for Progressive Multifocal Leukoencephalopathy (PML) associated with Tysabri (natalizumab)
- FDA Drug Safety Communication: New risk factor for Progressive Multifocal Leukoencephalopathy (PML) associated with Tysabri (natalizumab)
- More Drug Safety Communications

Drug Shortages

- Current Drug Shortages
- Resolved Drug Shortages
- Drugs to be Discontinued

Drug Recalls

- Novartis Consumer Health Inc. Issues Voluntary Nationwide Recall Of Certain Over-The-Counter Products Due To Potential Presence Of Foreign Tablets Or Chipped Or Broken Tablets Or Gelcaps
Questions?