Drug Pharmacovigilance Under CDER

Moderator: Paula Katz, Special Counsel, Covington & Burling

Panelist: Cynthia Schnedar, Executive Vice President, Regulatory Compliance, Greenleaf Health

Panelist: Brian Malkin, Of Counsel, Arent Fox
Drug Pharmacovigilance Under CDER

FDANews Conference: Post-market Surveillance
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Session I
Speakers: Cynthia Schnedar, Greenleaf Health
Brian Malkin, Arent Fox
Moderated by Paula Katz, Covington & Burling LLP
Topics We Will Cover

- Structure and function of post-market offices within CDER
- Use of registries and Phase IV Data
- Post-market field alerts, adverse drug reports, and Medwatch benefits and best practices of post-market monitoring
- Submission of post-marketing reports and process analysis
- FDA’s Adverse Event Reporting System (FAERS)
- Safety signal detection
- Use of data mining
- Regulatory actions: warnings, precautions and adverse reactions
- Sentinel System
- FDA’s new efforts to address drug shortages
- Increasing role of social media in post-market surveillance
- Communicating safety issues that are effective and compliant
- Product liability litigation and how to avoid it
What is Pharmacovigilance?

- The science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other drug-related problems.
  - WHO definition
Structure and function of post-market offices within CDER: Office of Surveillance & Epidemiology

- **Office of Surveillance & Epidemiology**
  - Monitors and evaluates the safety profiles of drugs throughout life cycle
  - Maintains a system of post-marketing surveillance and risk assessment programs to identify adverse events that did not appear during the drug development process
  - Evaluates more than 1.5 million adverse event reports submitted every year to FDA’s MedWatch program.
  - 2 offices (PV & Epi, and Med Error/Risk Prevention)

- **Office of Pharmacovigilance and Epidemiology (OPE)**
  - Division of Pharmacovigilance (DPV I & DPV II)
    - Safety Evaluators and Medical Officers detect safety signals and assess safety-related issues for all marketed drug and therapeutic biologic products.
    - Evaluate AE report data, literature, and preclinical, clinical, and pharmacologic information to provide scientific and clinical evaluation to inform regulatory actions and communications for safe use of the marketed products
Structure and function of post-market offices within CDER: Office of Surveillance & Epidemiology (cont’d)

- Division of Epidemiology (DEPI I & DEPI II)
  - Epidemiologists conduct active drug safety surveillance using Sentinel System, conduct epidemiologic studies using observational data resources, and review drug safety-related epidemiologic study protocols and study reports that are required of manufacturers as post marketing requirements (PMRs) and commitments (PMCs).
  - **Agency lead** in ensuring that the observational post marketing studies conducted by sponsors meet the best practices in epidemiology and can provide robust and actionable evidence to inform regulatory decision making following initial approval.
  - Evaluate safety signals by putting them into context of drug use (calculating reporting rates, existing body of evidence, FDA-sponsored epidemiologic studies)
  - Quantify and characterize drug safety risks detected through spontaneous reports or through systematic review of literature.
  - SMEs for the observational data aspects of use of real world evidence. They also provide data that aid in increasing the FDA’s ability to request regulatory impact studies such as those authorized under Best Pharmaceuticals for Children Act (BPCA).
Structure and function of post-market offices within CDER: Office of Surveillance & Epidemiology (cont’d)

- **Drug Utilization Analysis Staff**
  - Sales & other health care data to determine utilization levels and treatment patterns in the US to support regulatory decision-making in FDA/CDER
  - Maintains an expertise in pharmacy practice, health care delivery, and pharmacoepidemiology principles to evaluate and interpret these data.

**Office of Medication Error Prevention and Risk Management (OMEPRM)**

- **Division of Medication Error Prevention and Analysis (DMEPA)**
  - Monitoring and preventing medication errors related to drug names, labeling, packaging, and design

- **Division of Risk Management**
  - Provides risk management expertise on development and implementation of programs and initiatives to support the Center’s policies related to REMS
Field Alert Reports

- NDA or ANDA “applicant” must submit a field alert report (FAR) to FDA with information concerning:
  - Any incident that causes drug or labeling to be mistaken for another article
  - Any bacterial contamination
  - Change or deterioration in the drug product
  - Failure of distributed batches to meet specifications

- Submission required within three business days of applicant receipt of information
FARs Draft Guidance

- Posted in Federal Register July 19, 2018
- Comments to docket due September 17, 2018
- FARs as “part of an early warning system to protect public health.”

Recommendations:
- who should file (A/NDA applicant)
- what triggers FAR submission
- when to file
- what to include
- how to follow up
- logistics (Form 3331 & 3331a)

Compliance and enforcement outcomes
Biological Product Deviation Reports (BPDRs)

- BLA holder must report on any event associated with manufacturing or testing of BLA product that represents:
  - A deviation from CGMP, applicable regs/standards, or applicable standards that may affect safety, purity, or potency of product; or
  - An unexpected or unforeseeable event that may affect safety, purity, or potency

AND

- Occurs in BLA-holder’s facility or a contracted facility
- Due asap but no more than 45 calendar days
FDA Inspections and Enforcement

- FDA routinely inspects application holders for PV compliance
- 483s and Warning Letters
  - Failure to develop (or follow) adequate written PV procedures
    - Particular issue with contract partners
  - Late or missing reports
  - Improper adjudication of events
    - E.g., 15-day alert report versus PADER
  - Failure to maintain proper records
  - Failure to submit or timely submit FARs
- Failure to follow PV requirements is grounds for withdrawal
Drug Pharmacovigilance

Under

CDER

Brian J. Malkin
Counsel
Arent Fox LLP
Overview

- Use of Registries & Phase IV Data
- Submission of Post-Marketing Reports & Process Analysis
- Safety Signal Detection
- Use of Data Mining
- Regulatory Actions: Warnings, Precautions, & Adverse Reactions
- Increasing Role of Social Media in Post-Market Surveillance
- Communicating Safety Issues that are Effective and Compliant
- Product Liability Litigation & How to Avoid It
Use of Registries and Phase IV Data

Registries

- Real-world databases used to track how patients respond to particular drugs
- May be required for accelerated/fast track products to gather post-approval data and make up for more limited IND data
- Data can develop Phase IV commitments

Phase IV Commitments

- Required often as a condition of approval for post-approval research
- Required sponsor annual reports within 60 days of original approval on progress under section 130 of the Food and Drug Administration Modernization Act of 1997 including certain public reports – FDA’s public database updated 4x/year
- Also required to report on status of safety studies required by FDA for both known safety risks and studies to ascertain potential risks based on safety signals observed post approval
- Other special study commitments include pediatric studies and post approval of certain fast-track products, e.g., animal efficacy rule
Under 21 CFR 314.80, post-marketing safety reports must be submitted to FDA for the following:

- 15-day Expedited Alert reports: serious and unexpected adverse experience from all sources (domestic and foreign)

Periodic Adverse Events Reports

- Domestic spontaneous adverse events that are:
  - Quarterly for the first 3 years, then annually
Submission of Post-Marketing Reports & Process Analysis (cont’d)

FDA Defines Serious Outcomes as:

- Death
- Life-threatening adverse experience
- Inpatient hospitalization – new or prolonged
- Persistent/significant disability or incapacity
- Congenital birth defect
- Other serious: based upon appropriate medical judgment, these AEs may jeopardize the patient & require intervention to prevent a serious outcome

21 CFR 314.80 (a) 29
Developing a Case Series

Identify a well-documented case in FAERS, published literature, data mining, or other sources to identify a safety signal.

Using knowledge of the disease’s clinical course, formulate a case definition, which may include both clinical features and laboratory findings, sometimes even demographic information, if the safety signal is for a specific population.

Complete thorough database search for more cases.
Principles of Case Evaluation

- Temporal relationship
- Causality assessment – World Health Organization, the Uppsala Monitoring Centre (WHO-UMC):
  - Certain
  - Probable/Likely
  - Possible
  - Unlikely
  - Conditional/Unclassified

- Key factors in causality assessment including, but not limited to
  - Dechallenge/rechallenge
  - Comorbidities
  - Concomitant medications
  - Consistent with pharmacological effects (biologic plausibility)
Submission of Post-Marketing Reports & Process Analysis (cont’d)

Good Post-Marketing Event Reports Include:

- Description of adverse event
- Suspected and concomitant product therapy details (e.g., dose, dates of therapy)
- Patient characteristics (e.g., age, sex, baseline medical condition)
- Co-morbid conditions, family history, other risk factors
- Documentation of the diagnosis
- Clinical course and outcomes
- Relevant therapeutic measures and laboratory information
- Any other relevant information
- Dechallenge and rechallenge information
- Reporter contact information
Signal Strengthening through Collaboration

- Collaboration within Division of Pharmacovigilance: Office of Surveillance and Epidemiology
- Epidemiology, including Drug Use
- Evaluate observational studies
- Quantify a drug-event association
- Calculate reporting rates
- Risk Management
- Develop Risk Evaluation and Mitigation Strategy (REMS)
- Collaboration with other FDA offices and regulatory agencies
Safety Signal Detection

What is a Safety Signal?

- Information that arises from one or multiple sources (including observations and experiments), which suggests a new potentially causal association, or a new aspect of a known association, between an intervention and an event or set of related events, either adverse or beneficial.

Select Sources of Possible Safety Signals

- Routine pharmacovigilance
  - FAERS
  - Data mining
  - Periodic Safety Update Reports from drug manufacturers

- Study results
- Medical literature
- Media
- New Drug Application (NDA) safety database
- Outside inquiry
- Foreign Regulatory Agencies
- Others
Monitoring FAERS for Safety Signals

- Safety Evaluators are assigned a drug portfolio
- Weekly FAERS “inbox” for newly received reports
- Risk-based principles utilized for report screening

### FAERS Cases By Product Name, Case Type, Outcome

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<th>Product Name</th>
<th>Total Cases</th>
<th>Expedited (15-Day)</th>
<th>Direct</th>
<th>Periodic</th>
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<td>0</td>
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### FAERS Cases by MedDRA Preferred Terms (PT)

<table>
<thead>
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<th>MedDRA PTs</th>
<th>Total Cases</th>
<th>Percent of Total</th>
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<tr>
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</tr>
<tr>
<td>Distinct Total Cases</td>
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Use of Data Mining

- Mathematical tool identifies higher-than-expected frequency of product-event combinations
- Tool for hypothesis generation; does not prove causation
- Supplements FAERS data review
- Does not replace expert clinical case review
Regulatory Actions: Warnings, Precautions, Adverse Reactions

- Product information changes
- Pharmacovigilance activities – enhanced surveillance (e.g., expedited reporting), registry, epidemiology studies
- Risk Evaluation and Mitigation Strategy (REMS) – Communication plan, restricted use
- Drug Safety Communication (DSC)
- Market withdrawal
Increasing Role of Social Media in Post-Market Surveillance

- FDA first asked for input on how social media can be used in post-market surveillance in 2014
  - Found that patients are more likely to post drug-related adverse events on Twitter than report them to the FDA
  - 4,401 reports resembling adverse events, among a sample of 61,402 posts collected from 6.9 million tweets sent between Nov. 2012 and May 2013 versus 1,400 AEs reported to FAERS during a similar timeframe

- “Internet/Social Media Platforms with Character Space Limitations—Presenting Risk and Benefit Information for Prescription Drugs and Medical Devices” (2014)
  - Includes recommendations for providing Internet/social media space-limited benefit/risk information (e.g., Twitter) and paid-search-results links (e.g., Google and Yahoo)
Up-to-date and clarifies how to correct misinformation created or disseminated by independent third parties on the Internet/social media platforms

Information must respond to misinformation and must:

- Be relevant and focused to misinformation
- Be accurate and include data if needed
- Be labeling-consistent and non-promotional
- Post in the same media or reference it
- Disclose manufacturer is providing this information, including a copy or link to labeling
Increasing Role of Social Media in Post-Market Surveillance (cont’d)

- Social media can augment current surveillance systems (MedWatch type reporting <10% adverse drug reactions (ADRs)) but is it reliable?

- Consumers do not use terms in medical lexicons
  - More creative phrases, descriptive symptom explanations, and idiomatic expressions
    - Example: “messed up my sleeping patterns” to report a “sleep disturbance”
  - ADR v. indications with informal style, deviating from grammar and misspellings, making word searches difficult
    - Example: Works to calm mania or depression but zonks me and scares me about diabetes issues
      - Indication – mania; ADR – drowsiness; risk – diabetes

- Capturing ADRs in social media still in infancy – what is its role?
Communicating Safety Issues that are Effective & Compliant

- Consider audience
- Be complete and clear about purpose
- Simple, clear message – not overly wordy, understandable
- Provide with empathy
- Report with benefits/risks – natural element of all drugs
- Report uncertainty
- Choose appropriate method
- Seek feedback – check that message is understood and adjust
- Involve patients/focus groups
- Consider potential issues of polypharmacy
- Consider labeling/handling & storage issues, potential for dispensing errors
Many jurisdictions impose post-sale duty to warn especially for drugs

Legal standard: seller knows potential for harm & patients would otherwise be unaware of the harm; warning can be effectively communicated and expected to act on information; risk of harm justifies warning

Courts impose duty of care to continue to monitor and test for post-approval risks

Continuous duty to update risks – not just benefits

ADRs and signals need to be monitored and reported to authorities and considered along with concomitant drug use and its impact

Plaintiff’s attorneys latch onto failure to warn or inadequate warnings, including post-approval information, if not updated in product labeling

- Continue to monitor and update safety information (generally OK to do without preapproval) as well as benefits (generally requires product approval before adding/modifying)
Other Compliance Prevention Tactics

- Maintain culture of regulatory compliance
- Do not shield or insulate executives
- Develop and maintain effective training for compliance
- Develop quality metrics and follow them throughout organization
- Run audits before/between inspections and take corrective action
- Fix FDA/state authority observations/483 violations and evaluate full quality system for developing better cGMP compliance
- Re-run audits after inspections and take corrective action
Questions?

Brian J. Malkin
brian.malkin@arentfox.com
202-857-6240
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Cynthia Schnedar
Executive Vice President, Regulatory Compliance
Greenleaf Health, Inc.
WHO  Definition of Pharmacovigilance

The science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other drug-related problems.

See: https://www.who.int/medicines/areas/quality_safety/safety_efficacy/pharmvigi/en/
Sentinel

FDA’s medical product active safety surveillance system

• To assess the use, safety, and effectiveness of regulated medical products
• To develop data, informatics, and methodologic capabilities to support these activities

Key Components:

• Distributed data network of 18 Data Partners
• Electronic healthcare data
• Common data model
• Sophisticated quality assurance process

Created in response to a U.S. Congressional mandate

See: https://www.fda.gov/safety/fdas-sentinel-initiative
FAERS - FDA Adverse Event Reporting System

Computerized database of spontaneous reports
- Voluntary communication from an individual (e.g., healthcare professional, consumer)
- Mandatory reporting requirements for manufacturers

Contains human drug and therapeutic biologic reports
How Postmarketing Reports Get to FDA

Source: FDA Drug Topics: An Overview of Pharmacovigilance in the Center for Drug Evaluation and Research (CDER). March 26, 2019
Postmarketing Adverse Drug Experience - PADE

PADE Regulations Require Written Procedures to address:

• Surveillance
• Receipt
• Evaluation
• Reporting
Who is responsible for PADE reporting?

**Application holders for approved products**
- NDA
- ANDA ("generics")
- BLA (including biosimilars)

**Non-application holders (manufacturers, packers, and distributors) named on the label of:**
- Approved products
- Unapproved products (prescription and OTC monographs)

**Non-applicants must report serious ADEs to applicant within 5 days or submit 15-day alerts directly to FDA**
Responsibility for Contractors and Business Partners

• Sponsor can outsource any PADE activities, but applicant remains responsible for compliance

• Business partners are potential “sources” of ADE data so applicant must establish written procedures regarding safety data
Site Selection for PADE Inspection – Risk based approach

- Date of Last PADE Inspection
- Past Compliance History
- Identified Deficiencies
- Acquisition of NDA or ANDAs
- Product Safety Concerns

FDA Compliance Program, Chapter 53 - 7353.001, Postmarketing Surveillance and Epidemiology: Human Drug and Therapeutic Biological Products: https://www.fda.gov/media/84969/download
PADE Inspection Coverage

- Written procedures
- Organization, roles, and responsibilities
- Safety Contracts/Agreements
- Business partners
- Training documents
- Confirmations for electronic submissions
PADE Inspection Coverage

• Waivers

• Root cause analyses and corrective actions for deviations

• Product list (approval date, status, etc.)

• Late or missing periodic reports

• Late or missing annual reports

• Late, missing, incomplete, or inaccurate 15-day reports

• ADEs from all sources

FDA Compliance Program, Chapter 53 - 7353.001, Postmarketing Surveillance and Epidemiology: Human Drug and Therapeutic Biological Products: https://www.fda.gov/media/84969/download
PADE Inspection Trends: PADE Citations of Form FDA 483 (FY2015-FY2017)

Source: Postmarketing Drug Safety and Inspection Readiness, June 19, 2018
Center for Drug Evaluation and Research (CDER) Small Business and Industry Assistance (SBIA) Webinar

Fault to develop adequate written procedures, 27%
Late, unreported, or incomplete Aggregate Report, 26%
Late or unreported 15-day Alert Reports, 28%
Other, 19%

Incorrect submission, 1%

Late or unreported non-expedited ICSRs, 8%
Failure to review, 3%
Follow-up, 3%
Incomplete ICSR, 2%
Recordkeeping, 2%
REMS
Risk Evaluation and Mitigation Strategy

• A required risk management plan that uses risk minimization strategies beyond professional labeling to ensure that the benefits of the drug outweigh the risks

• Each REMS has specific safety measures unique to the safety risks associated with a particular drug or class of drugs

• Applicants develop REMS programs; FDA reviews and approves them
FDA Use of REMS Information

Source: Postmarketing Drug Safety and Inspection Readiness, June 19, 2018
Center for Drug Evaluation and Research (CDER) Small Business and Industry Assistance (SBIA) Webinar
Site Selection for REMS Inspection – Risk based approach

- REMS with ETASU
- REMS with issues identified during previous inspection
- REMS modified since last inspection
- REMS identified with issues by Office of New Drugs or Office of Surveillance and Epidemiology
- REMS with issues identified during review of REMS assessment report
- REMS that have never been inspected
- REMS not inspected in the last 2-3 years
Possible Inspection Sites

- Sponsor/Applicant
- Call Center
- Vendor/Contract Research Organization
Focus of Inspection Will Depend on Type of REMS

- Medication Guide (MG)
- Communication Plan (CP)
- Elements to Assure Safe Use (ETASU)
- Implementation System

Source: FDA Compliance Program, Chapter 53 - 7353.001c, Risk Evaluation and Mitigation Strategies
REMS are Enforceable

- REMS must be fully operational before drug introduced into interstate commerce

- Drug may be found to be misbranded (502(y))

- Possible Enforcement Actions Include:
  - Seizure of the drug subject to the REMS
  - Injunction
  - Civil Monetary Penalties
Drug Shortages

The CDER Drug Shortage Staff (DSS) defines a drug shortage:

• A shortage exists when the “total supply of all versions of the approved product available at the user level will not meet the current demand. A registered alternative manufacturer will not meet the current and/or projected demands for the potentially medically necessary use(s) at the user level”

What Causes Shortages?

• FDA estimates that 65% of all drug shortages are caused by manufacturing and quality issues.

Sources:
Michael Kopcha, Director, Office of Pharmaceutical Quality (February 2016) FDA Voice blog,
Capt Val Jensen Associate Director of the Drug Shortage Staff, CDER and Cynthia Schnedar, Director, Office of Compliance, CDER (April 2015) FDA Voice blog
Major Reasons for Drug Shortages

• A major reason for these shortages has been quality/manufacturing issues.
• Other reasons include:
  o Production delays at the manufacturer
  o Delays companies have experienced receiving raw materials and components from suppliers.
  o Discontinuations. Older drugs are sometimes discontinued by companies in favor of newer, more profitable drugs.
  o Limited capacity for raw material suppliers
  o Difficulty in scaling up production in a short period of time
  o Natural disasters (Hurricane Maria and the IV shortage)
  o Increased patient need (Ex: in a particularly bad flu season)

• With fewer firms making older sterile injectable drugs, there are a limited number of production lines that can make these drugs. The drugs are low profit, providing little incentive for new competition. Thus, this small number of manufacturers and limited production capacity for older sterile injectables, combined with the long lead times and complexity of the manufacturing process for injectable drugs, results in these drugs being vulnerable to shortage.
Drug Shortages

How does CDER DSS Identify shortages?

- DSS utilizes information from manufacturers, distributors, and market share data to determine if a shortage exists.
- DSS also considers newly approved products on the market and the capacity of the manufacturer of the newly approved product as well as information conveyed to patients and providers.

When FDA identifies a shortage they have protocols in place to minimize their impact including:

- Expediting the review of new applications for generic drugs when potential shortage issues arise with approved drugs.
- Invested in emerging technologies that could modernize drug manufacturing to prevent quality issues and product failures that cause shortages.

Source: Current and Resolved Drug Shortage list.