Postmarketing Drug Safety Compliance: 2019 Inspection Findings

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Center for Drug Evaluation and Research – Small Business and Industry Assistance

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Objectives

1. Identify the role of FDA’s Postmarketing Adverse Drug Experience (PADE) Compliance Program

2. Describe recent PADE inspection findings and trends
Agenda

1. Overview of FDA’s PADE Compliance Program

2. Fiscal Year 2019* Inspection Site Selection

3. Fiscal Year 2019* Inspection Findings and Trends

4. PADE Compliance in a Pandemic Situation

*Fiscal Year 2019 (FY2019): 01-Oct-2018 to 30-Sep-2019
Compliance Mission

Shield patients from poor quality, unsafe, and ineffective drugs through proactive compliance strategies and risk-based enforcement actions

- Ensure CDER-regulated products have reliable evidence of safety and effectiveness, and meet postmarket safety requirements
- Evaluate industry compliance with PADE requirements
- Work to bring inspected entities with significant violations of federal laws and regulations into compliance
Legal Framework

Federal Food, Drug, and Cosmetic Act (FDCA)

Title 21 of the Code of Federal Regulations (CFR)

FDA’s current thinking

Examples of PADE laws and regulations provided at the end of this presentation
PADE Inspection Process

CDER performs risk-based selection of inspection sites

CDER issues inspection to FDA Office of Regulatory Affairs - Bioresearch Monitoring (BIMO) program

BIMO investigator conducts inspection

BIMO investigator provides establishment inspection report (EIR) and initial classification

CDER determines final classification based on EIR, evidence, and firm response

CDER communicates inspection outcome to inspected entity
Inspection Classifications

No Action Indicated (NAI)
Objectionable conditions or practices were not found

Voluntary Action Indicated (VAI)
Objectionable conditions or practices found, but do not rise to the level of regulatory action

Official Action Indicated (OAI)
Regulatory and/or administrative actions recommended, such as: Untitled letter, Warning letter, Regulatory meeting
PADE Compliance Program

Objectives

✓ Assure safe and effective human drugs are available
✓ Verify accuracy, reliability, and timeliness of postmarketing data submitted to FDA
✓ Support FDA reviewers by ensuring that they receive drug safety data required for the continual evaluation of product safety
✓ Monitor industry compliance with PADE reporting requirements
What is an adverse experience?

Any adverse event associated with the use of a drug or biological product in humans, whether or not considered product-related, including:

• Use in professional practice
• Overdose (intentional and accidental)
• Abuse
• Withdrawal
• Failure of expected pharmacological action (lack of effect)
Role of PADE Compliance In Product Lifecycle

Examples of safety data limitations
- Limited / narrow patient population
- Rare adverse events are challenging to identify
- Surrogate endpoints may not predict clinical outcomes
- Short studies (long term effects unknown or not well characterized)

PADE Compliance Program
- Monitor industry compliance with laws and regulations
- Ensure accurate, reliable, timely safety data is submitted to FDA and available to reviewers who evaluate product safety

Postmarketing safety data from real world experience is critical to FDA’s safety surveillance program.
# Who do we inspect for PADE Compliance?

| Application holders | Applicants with approved drugs and therapeutic biologics  
|                       | (prescription and non-prescription)  
|----------------------|----------------------------------|
| Non-Applicants       | Manufacturers, packers, distributors, retailers, and certain others named on product labels  
|                       | (responsibilities vary based on product type)  
| Third parties        | Contractors, vendors, and other third parties  

- New Drug Application (NDA)
- Abbreviated New Drug Application (ANDA)
- Biologics License Application (BLA)
- Approved prescription and non-prescription drugs and therapeutic biologics (NDA, ANDA, BLA)
- Unapproved prescription drugs
- Unapproved non-prescription drugs
- Pharmacovigilance activities conducted on behalf of application holders or non-applicants
Risk-based Site Selection

Firm information
- Corporate changes
- Portfolio (type and number of products)
- Complaints
- Internal FDA information
- Information from other health authorities

Product Portfolio
- New molecular entities
- High-risk
- Patient exposure
- Recalls
- Submissions to FDA
  - Individual Case Safety Reports (ICSRs)
  - Annual reports
  - Periodic reports

Inspection history
- Compliance and inspection history
  - Never inspected for PADE compliance
  - Inspection findings from other program areas
- Firm’s written responses to previous PADE inspections
FY2019 Sites Selected*

* Inspected entities may have more than one risk factor
FY2019 Inspection Classifications*

- NAI
- NAI with discussion items
- VAI (1 observation)
- VAI (2 observations)
- VAI (3+ observations)

* Inspections ending in FY2019
Inspection Observations: FY2017-FY2019*

Late or unreported aggregate safety reports
- FY2019: 22%
- FY2018: 18%
- FY2017: 11%

Late or unreported expedited ICSRs
- FY2019: 19%
- FY2018: 21%
- FY2017: 27%

Inadequate written procedures
- FY2019: 19%
- FY2018: 28%
- FY2017: 30%

Incomplete submissions
- FY2019: 7%
- FY2018: 14%
- FY2017: 6%

Late or unreported non-expedited ICSRs
- FY2019: 7%
- FY2018: 11%
- FY2017: 11%

Records
- FY2019: 8%
- FY2018: 7%
- FY2017: 3%

Other
- FY2019: 6%
- FY2018: 10%
- FY2017: 6%

*Based on inspection end date
PADE Quality Process

Applicants and non-applicants listed on the label are responsible for ensuring compliance with PADE laws and regulations, including activities conducted on their behalf by business partners and third-parties.

**Surveillance**
- Account for all sources, foreign and domestic
- Spontaneous
- Solicited
- Internet sources (firm-sponsored)
- Literature
...and more!

**Receipt**
- Receipt from all sources
  - Initial
  - Follow-up

**Evaluation**
- Evaluate adverse events from all source
  - Seriousness (adverse event outcome)
  - Expectedness (labeling)
  - Causality
  - Follow-up

**Reporting**
- Expedited ICSRs (15-day Alert Reports)
- Non-expedited ICSRs
- Aggregate Safety Reports
- All submissions must be electronic

www.fda.gov
PADE Compliance: Pandemic Situation

FDA Guidance: “Postmarketing Adverse Event Reporting for Medical Products and Dietary Supplements During a Pandemic”

Discusses FDA’s intended approach to enforcement of PADE reporting requirements during a pandemic, considering potential:

• Impacts to the ability to function normally and comply with regulatory requirements

• Reductions in workforce

• Increases in adverse events reported for products used to manage the pandemic

PADE Compliance: Pandemic Situation

**Before**
- Plan and prepare!
- Develop a Continuity of Operations Plan (COOP) for all stages of pandemic

**During**
- FDA expects firms to maintain compliance for products or issues of special concern, as communicated by FDA
- Maintain compliance to the maximum extent possible
- If ability to comply is impacted (e.g. high absenteeism):
  - Implement COOP
  - Document pandemic dates and factors impacting compliance
  - Notify FDA
  - Prioritize report submissions
  - Store certain reports for future submission
  - Maintain records of what was stored and when processes were restored

**After**
- Resume timely reporting of postmarketing safety information
- Prioritize and submit stored reports within 6 months of restoring adverse event reporting process to pre-pandemic state
For More Information...

FDA Website: “Postmarketing Adverse Event Reporting Compliance Program”

Available at:
https://www.fda.gov/drugs/surveillance/postmarketing-adverse-event-reporting-compliance-program

Contact the Pharmacovigilance Compliance Team at
CDER-OSI-ADE@fda.hhs.gov
## PADE Statutory Provisions / Regulations: Prescription Drug Products for Human Use

<table>
<thead>
<tr>
<th>FDCA, Subchapter V, Part A, Section 505 (21 USC §355)</th>
<th>New drugs</th>
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<tbody>
<tr>
<td>21 CFR 310.305</td>
<td>New drugs: Records and reports concerning ADEs on marketed prescription drugs for human use without approved new drug applications</td>
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<tr>
<td>21 CFR 314.80</td>
<td>New drug applications: Postmarketing reporting of ADEs</td>
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<td>21 CFR 314.81(b)(2)</td>
<td>New drug applications: Annual reports</td>
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<td>21 CFR 314.90</td>
<td>New drug applications: Waivers</td>
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<td>21 CFR 314.98</td>
<td>Abbreviated applications: Postmarketing reports</td>
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<td>21 CFR 314.540</td>
<td>Accelerated approval of new drugs for serious or life-threatening illnesses: Postmarketing safety reporting</td>
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<td>21 CFR 314.630</td>
<td>Approval of new drugs when human efficacy studies are not ethical or feasible: Postmarketing safety reporting</td>
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<tr>
<td>21 CFR Part 4, Subpart B</td>
<td>Postmarketing safety reporting for combination products</td>
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## PADE Statutory Provisions / Regulations: Licensed Biological Products for Human Use

<table>
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<tr>
<th>Section</th>
<th>Description</th>
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<tbody>
<tr>
<td>PHS Act, Subchapter II, Part F, Subpart 1 (42 USC §262)</td>
<td>Regulation of biological products</td>
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<td>21 CFR 600.80</td>
<td>Biological products: Postmarketing reporting of adverse experiences</td>
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<tr>
<td>21 CFR 601.28</td>
<td>Biologics licensing: Annual reports of postmarketing pediatric studies</td>
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<tr>
<td>21 CFR 601.44</td>
<td>Accelerated approval of biological products for serious of life-threatening illnesses: Postmarketing safety reporting</td>
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<tr>
<td>21 CFR 601.70</td>
<td>Postmarketing studies: Annual progress reports of postmarketing studies</td>
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<tr>
<td>21 CFR 601.93</td>
<td>Approval of biological products when human efficacy studies are not ethical or feasible: Postmarketing safety reporting</td>
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### PADE Statutory Provisions / Regulations: Unapproved, Non-prescription Products (e.g. OTC monograph)

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<tr>
<td>FDCA, Subchapter VII, Part H, Section 760 (21 USC §379aa )</td>
<td>Serious adverse event reporting for nonprescription drugs</td>
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<tr>
<td>21 CFR 329.100</td>
<td>Postmarketing reporting of ADEs under section 760 of the FDCA</td>
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