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

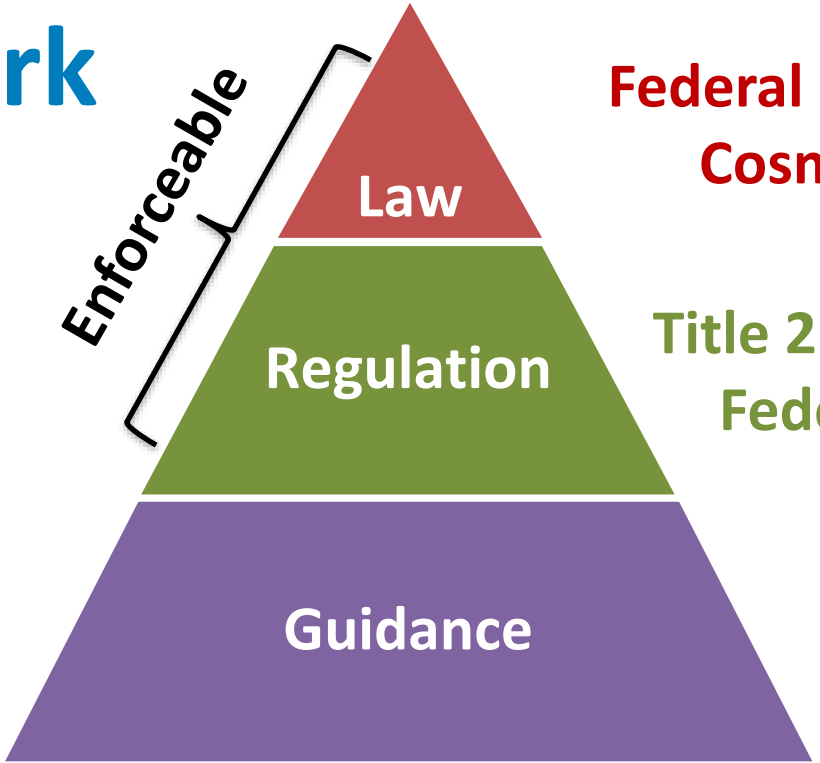
1. Overview of FDA's PADE Compliance Program
2. Fiscal Year 2019* Inspection Site Selection
3. Fiscal Year 2019* Inspection Findings and Trends
4. PADE Compliance in a Pandemic Situation

**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

Legal Framework



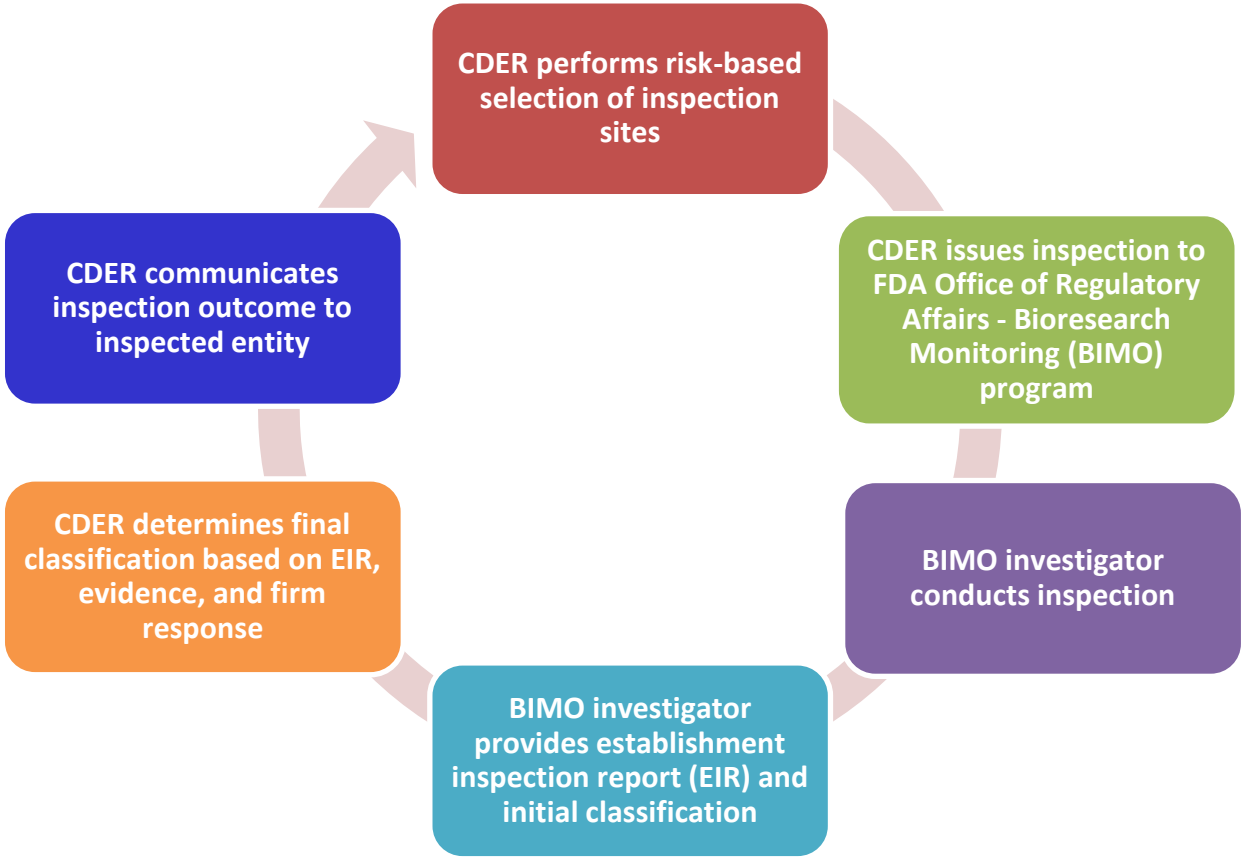
Federal Food, Drug, and Cosmetic Act (FDCA)

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



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

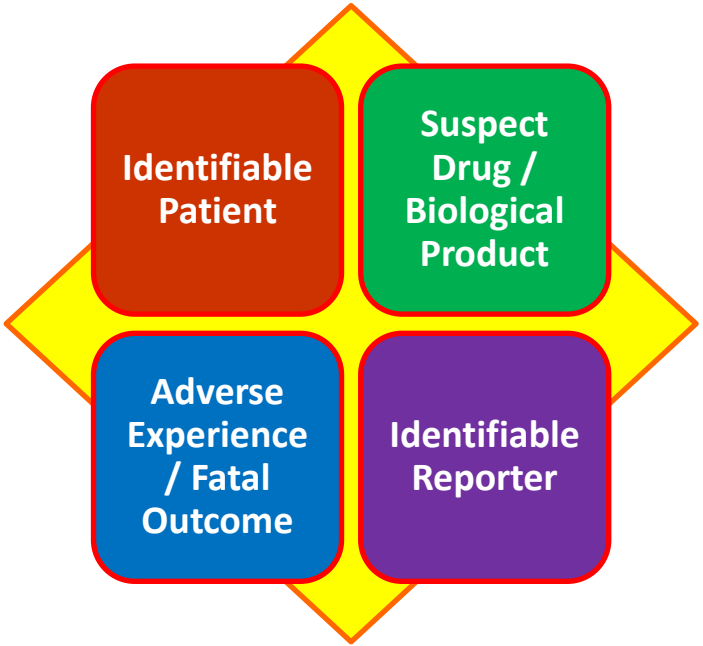
- ✓ Assure safe and effective human drugs are available
- ✓ Verify accuracy, reliability, and timeliness of postmarketing data submitted to FDA
- ✓ Support FDA reviewers by ensuring that they receive drug safety data required for the continual evaluation of product safety
- ✓ Monitor industry compliance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

What is an adverse experience?

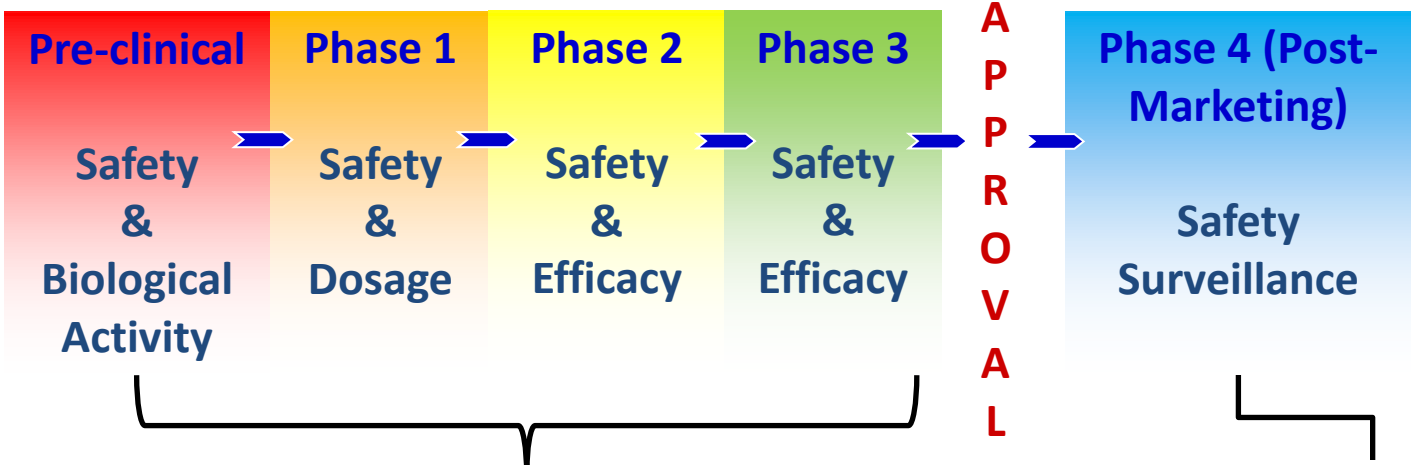
Any adverse event associated with the use of a drug or biological product in humans, whether or not considered product-related, including:

- Use in professional practice
- Overdose (intentional and accidental)
- Abuse
- Withdrawal
- Failure of expected pharmacological action (lack of effect)

Data Elements for Reportable Adverse Experiences



Role of PADE Compliance In Product Lifecycle



Postmarketing safety data from real world experience is critical to FDA's safety surveillance program

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

Who do we inspect for PADE Compliance?

Application holders	Applicants with approved drugs and therapeutic biologics *(prescription and non-prescription)*	• New Drug Application (NDA) • Abbreviated New Drug Application (ANDA) • Biologics License Application (BLA)
Non-Applicants	Manufacturers, packers, distributors, retailers, and certain others named on product labels *(responsibilities vary based on product type)*	• Approved prescription and non-prescription drugs and therapeutic biologics (NDA, ANDA, BLA) • Unapproved prescription drugs • Unapproved non-prescription drugs
Third parties	Contractors, vendors, and other third parties	• 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

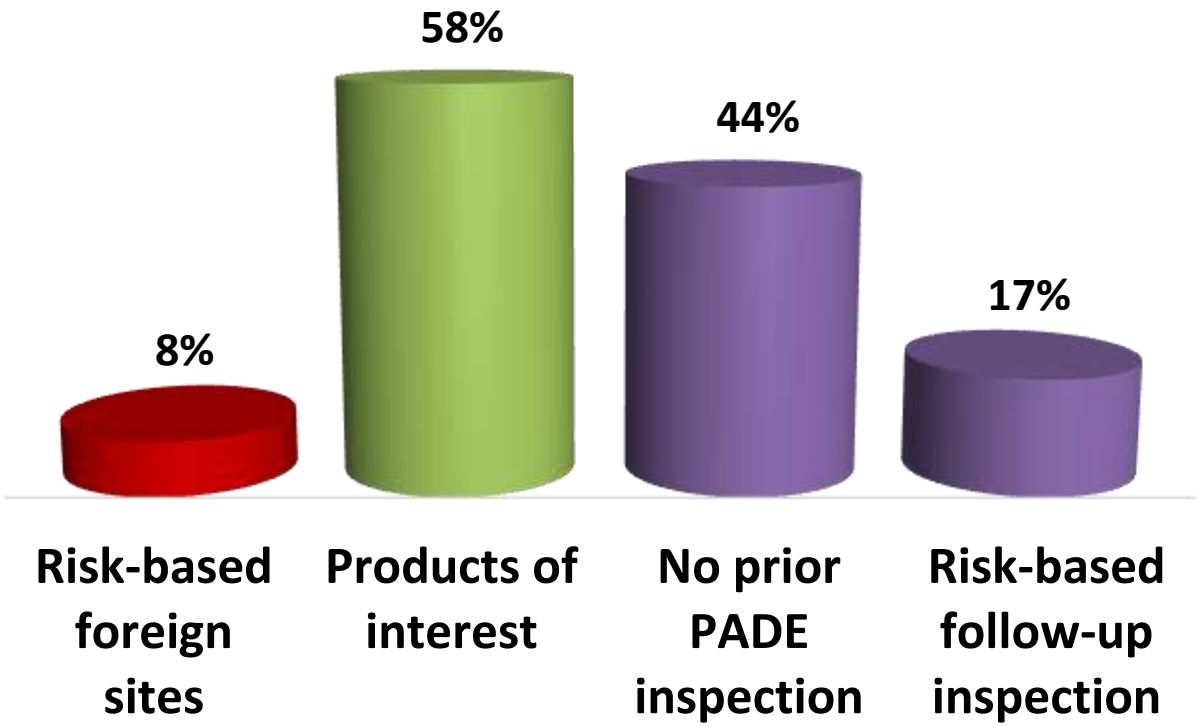
Product Portfolio

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

Inspection history

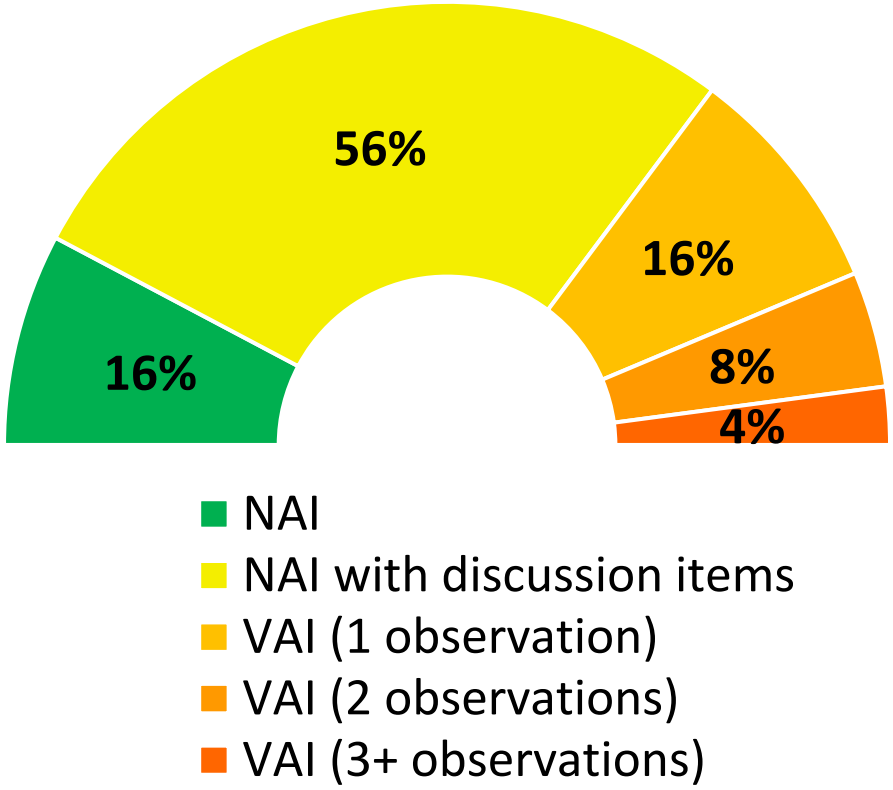
- Compliance and inspection history
  - Never inspected for PADE compliance
  - Inspection findings from other program areas
- Firm's written responses to previous PADE inspections

FY2019 Sites Selected*



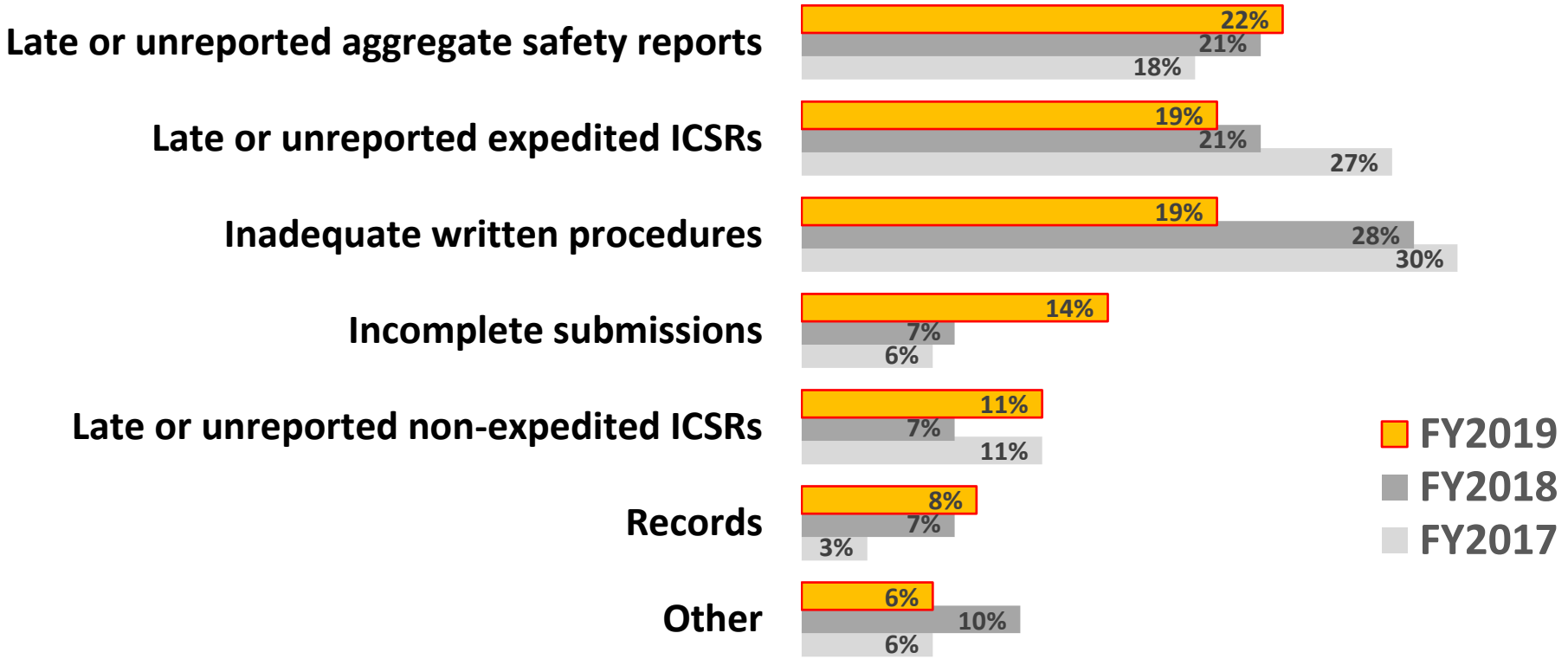
** Inspected entities may have more than one risk factor*

FY2019 Inspection Classifications*



** Inspections ending in FY2019*

Inspection Observations: FY2017-FY2019*



 **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

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

Guidance available at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/postmarketing-adverse-event-reporting-medical-products-and-dietary-supplements-during-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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ADMINISTRATION

PADE Statutory Provisions / Regulations: Prescription Drug Products for Human Use

FDCA, Subchapter V, Part A, Section 505 (21 USC §355)	New drugs
21 CFR 310.305	New drugs: Records and reports concerning ADEs on marketed prescription drugs for human use without approved new drug applications
21 CFR 314.80	New drug applications: Postmarketing reporting of ADEs
21 CFR 314.81(b)(2)	New drug applications: Annual reports
21 CFR 314.90	New drug applications: Waivers
21 CFR 314.98	Abbreviated applications: Postmarketing reports
21 CFR 314.540	Accelerated approval of new drugs for serious of life-threatening illnesses: Postmarketing safety reporting
21 CFR 314.630	Approval of new drugs when human efficacy studies are not ethical or feasible: Postmarketing safety reporting
21 CFR Part 4, Subpart B	Postmarketing safety reporting for combination products

PADE Statutory Provisions / Regulations: Licensed Biological Products for Human Use

PHS Act, Subchapter II, Part F, Subpart 1 (42 USC §262)	Regulation of biological products
21 CFR 600.80	Biological products: Postmarketing reporting of adverse experiences
21 CFR 601.28	Biologics licensing: Annual reports of postmarketing pediatric studies
21 CFR 601.44	Accelerated approval of biological products for serious of life-threatening illnesses: Postmarketing safety reporting
21 CFR 601.70	Postmarketing studies: Annual progress reports of postmarketing studies
21 CFR 601.93	Approval of biological products when human efficacy studies are not ethical or feasible: Postmarketing safety reporting
21 CFR Part 4, Subpart B	Postmarketing safety reporting for combination products

PADE Statutory Provisions / Regulations: Unapproved, Non-prescription Products (e.g. OTC monograph)

FDCA, Subchapter VII, Part H, Section 760 (21 USC §379aa)	Serious adverse event reporting for nonprescription drugs
21 CFR 329.100	Postmarketing reporting of ADEs under section 760 of the FDCA
21 CFR Part 4, Subpart B	Postmarketing safety reporting for combination products