CDER SBIA Webinar Series

U.S. FOOD & DRUG ADMINISTRATION

Postmarketing Drug Safety and Inspection Readiness

June 19, 2018
Center for Drug Evaluation and Research (CDER)
Small Business and Industry Assistance (SBIA) Webinar

United States Food and Drug Administration (FDA)
CDER / Office of Compliance
Office of Scientific Investigations (OSI)
Division of Enforcement and Postmarketing Safety (DEPS)
Postmarket Safety Branch (PSB)

This one file contains all the slides used in the MORNING sessions for the webinar.

Agenda

Session 1:

Postmarketing Adverse Drug Experience (PADE) Inspections

Session 2:

Risk Evaluation and Mitigation Strategies (REMS) Inspections

Session 3:

Inspection Readiness

Session 1:
PADE Inspections

Outline

- Objectives
- PADE Laws and Regulations
- Written Procedures
- Business Relationships and Agreements
- Electronic Reporting

Objectives

1. Gain an understanding of PADE laws and regulations for products regulated by CDER
   - New Drug Applications (NDA) products
   - Abbreviated New Drug Applications (ANDA) products
   - Biologic License Applications (BLA) products
   - Unapproved, prescription products
   - Unapproved, non-prescription products (e.g. over-the-counter (OTC) monograph products)
2. Recognize best practices for a PADE program

PADE Inspections: Overview of Laws and Regulations

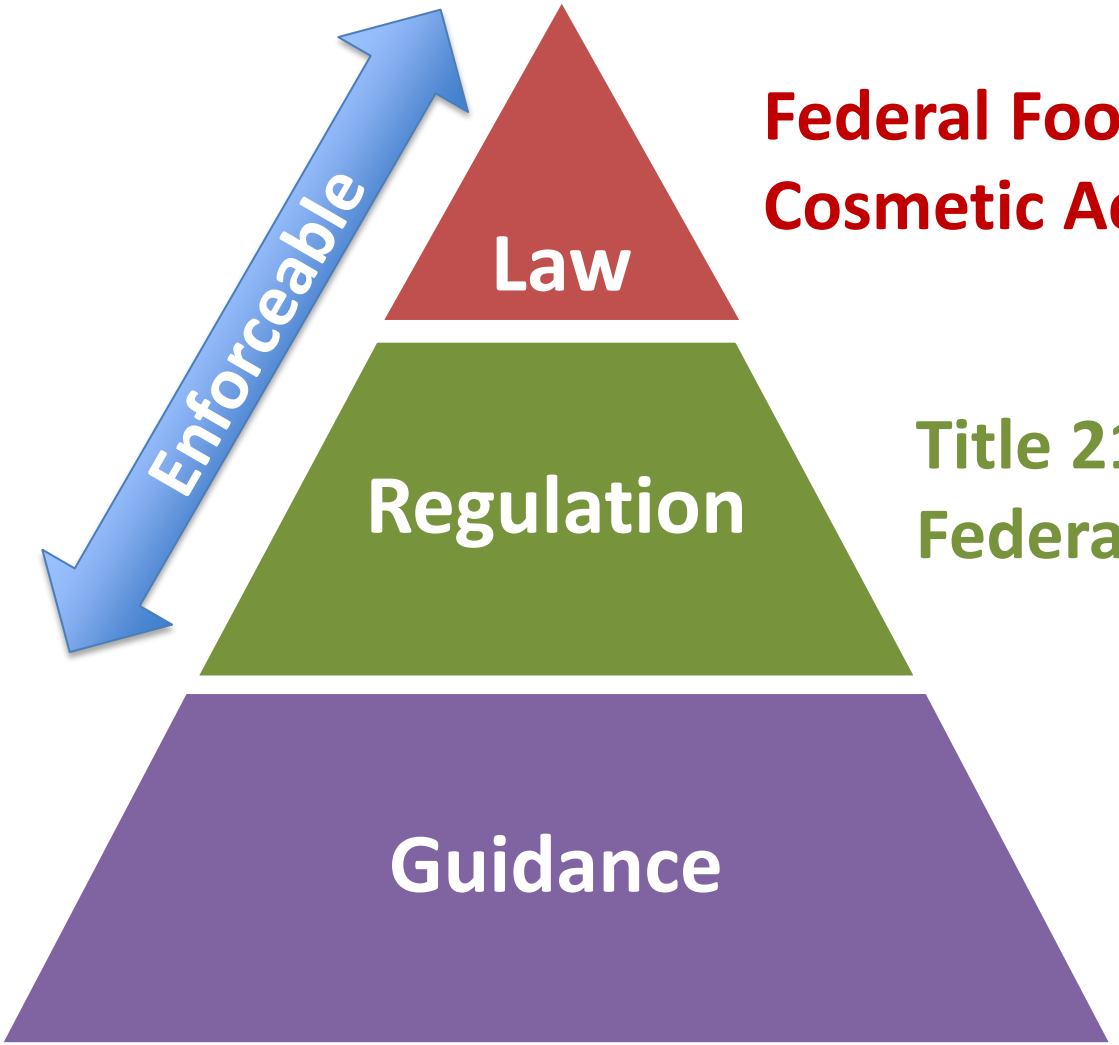
Kelley Simms, PharmD, MS

Commander, US Public Health Service

Consumer Safety Officer

PADE Compliance Team

PADE Legal Framework



Federal Food, Drug, and Cosmetic Act (FDCA)

Title 21 of the Code of Federal Regulations (CFR)

FDA's current thinking

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 (21 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

PADE Inspections: Written Procedures

Diane Bruce, PharmD

Namita Kothary, PharmD, RAC (US)

Consumer Safety Officers

PADE Compliance Team

Written Procedures

- Required in PADE Regulations
  - 21 CFR 310.305: Unapproved prescription products
  - 21 CFR 314.80: Approved application drug products
  - 21 CFR 600.80: Approved application or licensed biologic products

- Not required for unapproved, non-prescription (OTC monograph) products covered under FD&C Act (Section 760)

Approval vs. Marketing

Once a drug is approved, applicant holders MUST receive, evaluate, and report all adverse drug experiences (ADEs) to FDA, even if the drug is not marketed.

Written Procedures Must Address…

Surveillance	Receipt	Evaluation	Reporting

• Account for all sources
• Spontaneous
• Solicited
• Internet sources (firm-sponsored)
• Literature
 	
…and more!
	• ADE info
	  • Initial
	  • Follow-up
	
	• Receipt from ***any*** source
		• Seriousness
		• Expectedness
		• Relatedness
		
		• ADEs from ***any*** source
		
		• Follow-up procedures
			• 15-day Alert Reports
			• Non-expedited individual case safety reports (ICSRs)
			• Aggregate Reports
			• All info must be submitted electronically

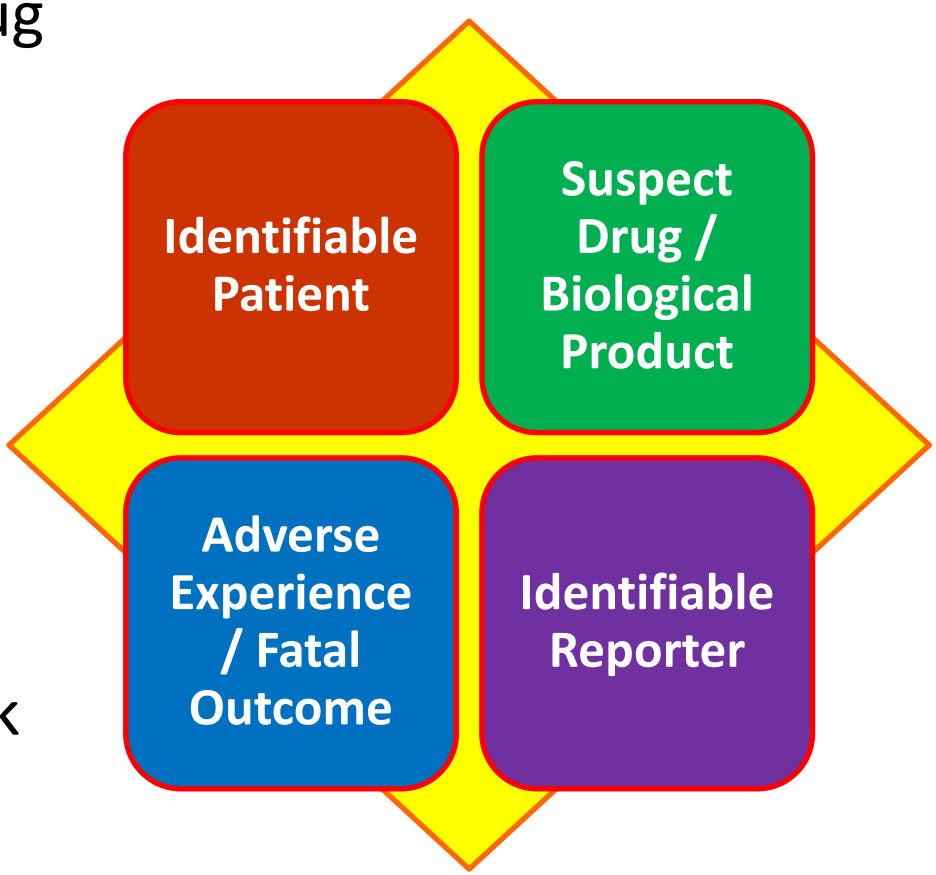
Surveillance

What is an ADE?

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

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

Data Elements for Reportable ADEs



Spontaneous ADEs: Examples of Sources

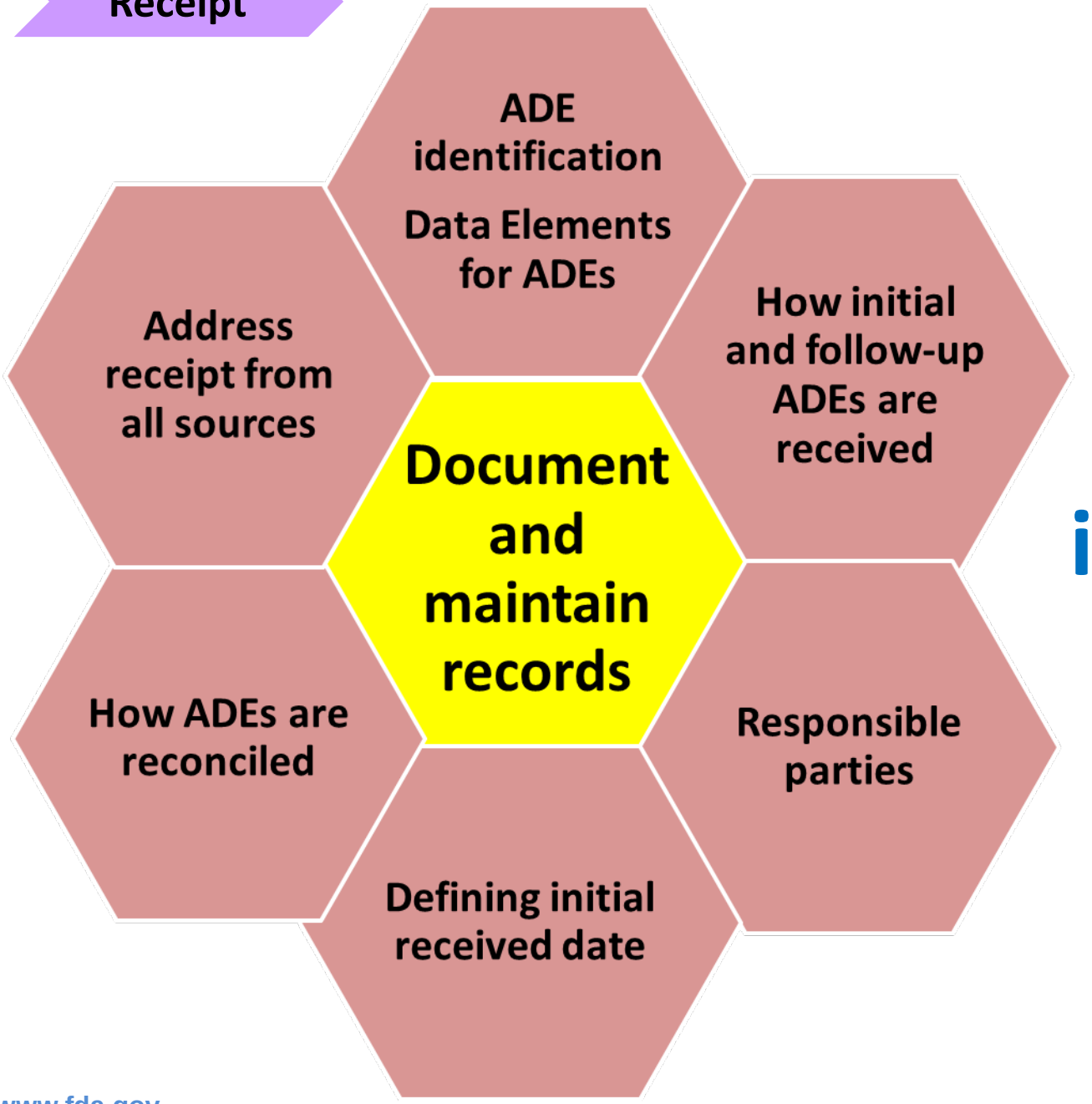
… and many more!

Solicited ADE: Examples of Sources

Systematic collection of data involving solicitation of ADE information

Receipt

Receipt of ADE information



Evaluation

Evaluating ADEs

Seriousness	**Serious if ≥1 of the following outcomes:**
	Death Life-threatening Hospitalization Persistent or significant disability Congenital anomaly / birth defect Other serious / important medical event
Expectedness	**Unexpected if one of the following:**
	Not listed in current labeling Greater severity or specificity than ADE listed in label
Relatedness	**Impacts reporting of solicited ADEs**
	Related if there is a reasonable possibility that the drug caused ADE

Determine Reportability

Expedited (15-day Alert Reports)

NDA, ANDA, BLA, and unapproved prescription drugs: Submit within 15 calendar days of information receipt

- Spontaneous: serious, unexpected ADEs
- Solicited: serious, unexpected, possibly related ADEs

OTC Monograph products: Submit serious, domestic ADEs within 15 business days of information receipt

Non-expedited (Periodic ICSRs)

NDA, ANDA, BLA: Submit with periodic safety report

- Spontaneous: serious, expected ADEs
- Spontaneous: non-serious ADEs
- Not applicable for literature, study, or foreign ADEs

Not applicable for unapproved prescription and OTC monograph products

Review and Investigate ADEs

- Promptly review ADE information
- Determine if follow-up is needed, especially if missing data elements
  - Must investigate 15-day Alert Report ADEs
  - Maintain records of follow-up attempts
- Evaluate information for reportability

Reporting

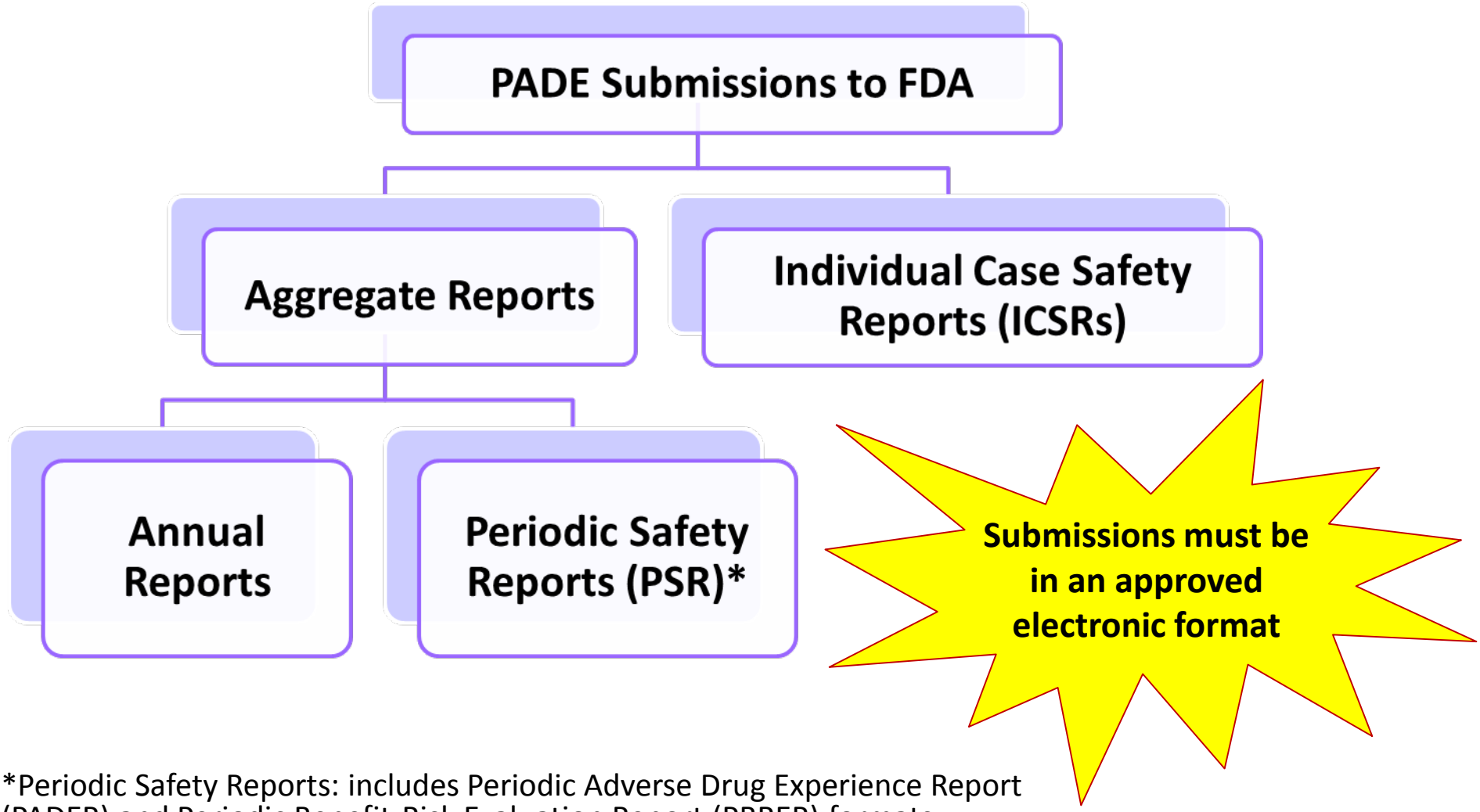
Who is responsible for PADE reporting?

- 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

Reporting to FDA



*Periodic Safety Reports: includes Periodic Adverse Drug Experience Report (PADER) and Periodic Benefit-Risk Evaluation Report (PBRER) formats

Submitting ICSRs

- Must submit electronically via Electronic Submission Gateway (ESG) or Safety Reporting Portal (SRP)
- Reportable when 4 basic data elements are known

	Expedited ICSRs	Periodic ICSRs	Follow-up ICSRs *(submit separately from initial ICSR)*
NDA, ANDA, BLA	Submit within 15 calendar days	Submit with PSR	Expedited ICSRs: Submit within 15 calendar days Non-expedited: Submit with next PSR
Unapproved prescription products	Submit within 15 calendar days	Not-applicable	Expedited ICSRs: Submit within 15 calendar days
OTC monograph products	Submit within 15 business days	Not-applicable	Submit information received within one year of the initial report within 15 business days

Aggregate Safety Reports

- Applies to approved NDAs, ANDAs, and BLAs
- Must submit electronically to eCTD
  - ICSRs must be submitted via ESG or SRP

	Post approval	Time period	Submission due
Annual Report	All years	Annually	within 60 days of US approval date
PADER*	First 3 years	Quarterly	within 30 days of close of quarter
	>3 years	Annually	within 60 days of US approval date

**Firm may apply for waivers for PADER requirements (e.g., use of International Birth Date, PBRER format)*

Waivers

- Firms may request waivers for certain PADE requirements
- Waivers stay with the application, even if the application transfers firms
- Examples of PADE waivers
  - Submit PBRER instead of PADER
  - To not submit non-serious, expected ADEs
  - High volume of ADEs associated with legal cases
  - Submit periodic reports on a date other than the US approval date (e.g. international birth date)
  - Paper submissions

PADE Inspections: Business Relationships and Agreements

Richard Abate, RPh, MS

Team Lead

PADE Compliance Team

Using Contractors for Pharmacovigilance Activities

Oversight of PV contractors

- Any PADE activities can be outsourced to a third party (e.g. vendor, contractor, consultant, or other pharmacovigilance provider)

- However, the applicant or non-applicant named on the label remains responsible for compliance

Business Partners – A Source of Safety Data

Business Partners

- Joint development & marketing of drugs
- Contract manufacturers
- Drug safety data generated needs to be collected and exchanged between partnering firms (any source of ADEs)
- Laws and regulations govern the exchange, review, & reporting of safety data
  - 21 CFR 314.80(c)(1)(iii)
  - 21 CFR 310.305(c)(3)
  - 21 CFR 600.80(c)(1)(iii)
  - FDCA, Subchapter VII, Sec 760

Business Partners as a Source of ADE Data

- Business partners are potential “sources” of ADE data
  - Firms must establish written procedures (agreements) regarding any business partner that might get safety data

- Written agreements with business partners
  - Safety Data Exchange Agreements or SDEAs
  - Pharmacovigilance (PV) Agreements
  - Contracts / Work orders

Written Agreements with Business Partners

There is no "one size fits all"

Written Agreements with Business Partners should explain:

1. **What data get exchanged?**

   - ✓ *Serious ADEs or all ADEs [21 CFR 314.80(c)(1)(iii)]*
   - ✓ *Ensures ADEs sent to a business partner are actually received (and vice versa)*

There is no "one size fits all"

2. **When does the exchange take place?**

   - ✓ *Timelines for non-applicants sending serious ADEs to applicants is no more than 5 calendar* days [21 CFR 314.80 (c)(1)(iii)]

   - ✓ *Do exchange timelines facilitate compliance with reporting requirements*

3. **What provisions ensure that terms of the agreement are met?**

   - ✓ *Reconciliation of data, meetings, or audits of business partners*

There is no "one size fits all"

4. **Who prepares aggregate reports (PADERs/PBRERs) for FDA?**

   - ✓ *When activity for safety reports is contracted to affiliates, the applicant holder remains responsible for compliance*

5. **How are ICSRs and aggregate reports submitted to FDA?**

   - ✓ *Who is responsible*
   - ✓ *Timelines, method and format for submission, submission confirmations*

Electronic Reporting of Individual Case Safety Reports

Suranjan De, Deputy Director
Regulatory Science Staff
Office of Surveillance and Epidemiology, CDER

Objective

- Understand electronic reporting of Individual Case Safety Report (ICSR)

Outline

- Introduction to FAERS
- Why an electronic ICSR submission requirement
- Submission Methods
- Submission of Periodic Safety Reports
- Future state of electronic submission
- References

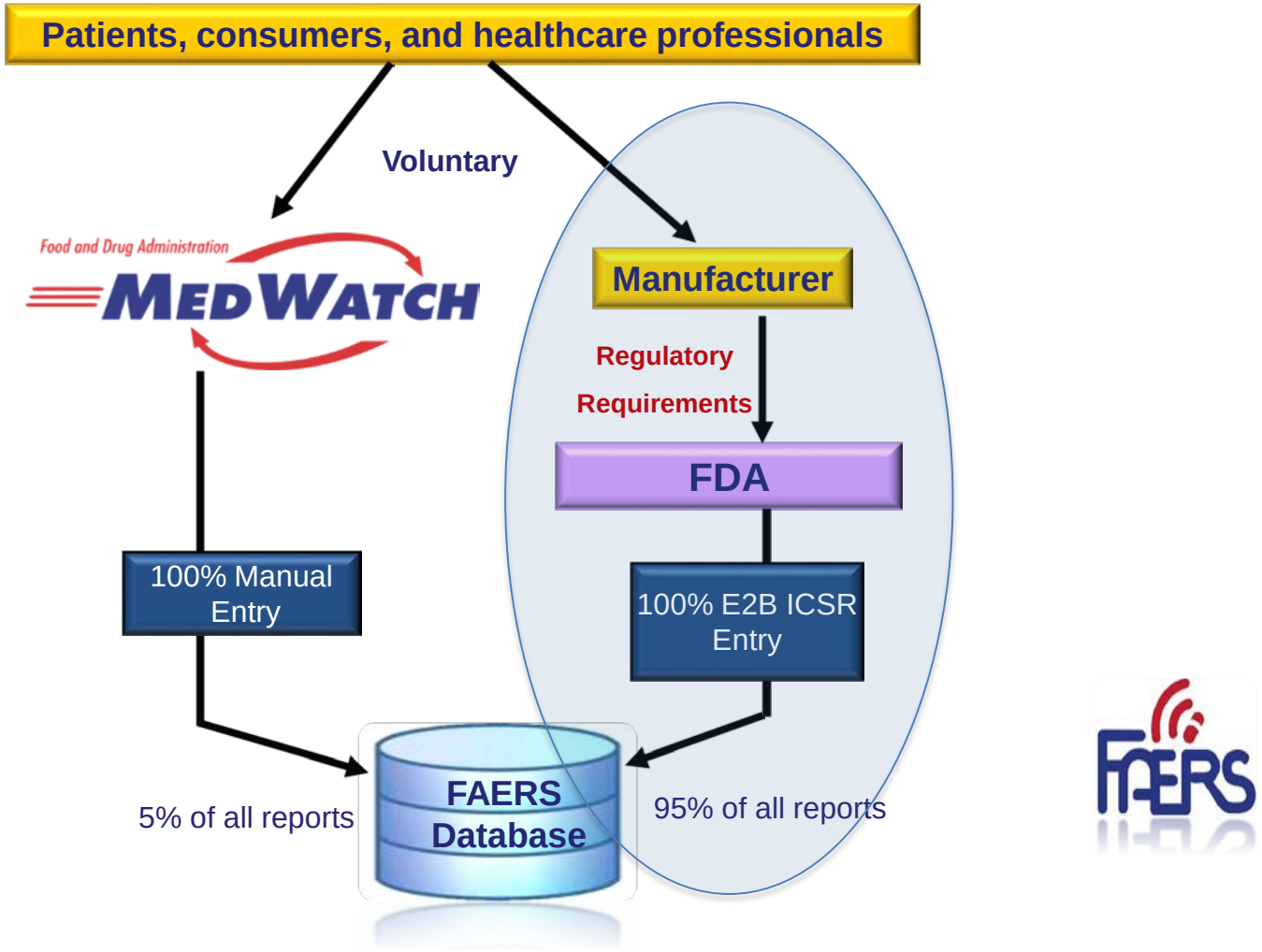
Electronic Reporting of ICSRs

FDA Adverse Event Reporting System (FAERS)

- FDA's postmarketing safety surveillance database for drugs and therapeutic biologics
- FDA uses FAERS data to monitor, identify and analyze adverse event and medication errors
- FDA staff in CDER and CBER regularly examine the FAERS database as part of routine safety monitoring
- When a safety signal is identified from FAERS data, it is further evaluated

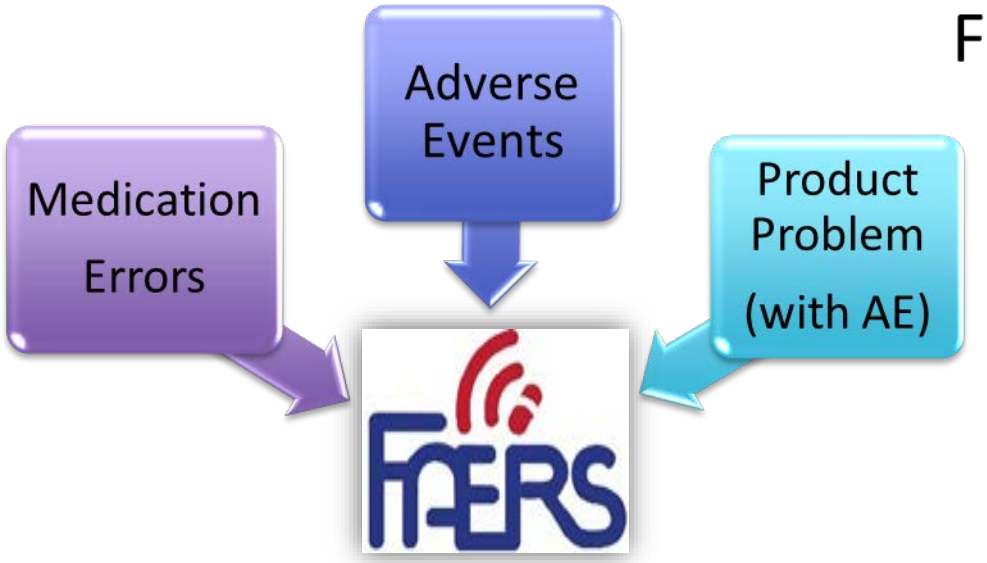
Electronic Reporting of ICSR

How post-marketing adverse event reports get to FDA



Electronic Reporting of ICSR

What Reports are in the FAERS Database?



For

Drugs and therapeutic biologics (Rx + OTC) - **CDER**

Tissue products, therapeutic blood products - **CBER**

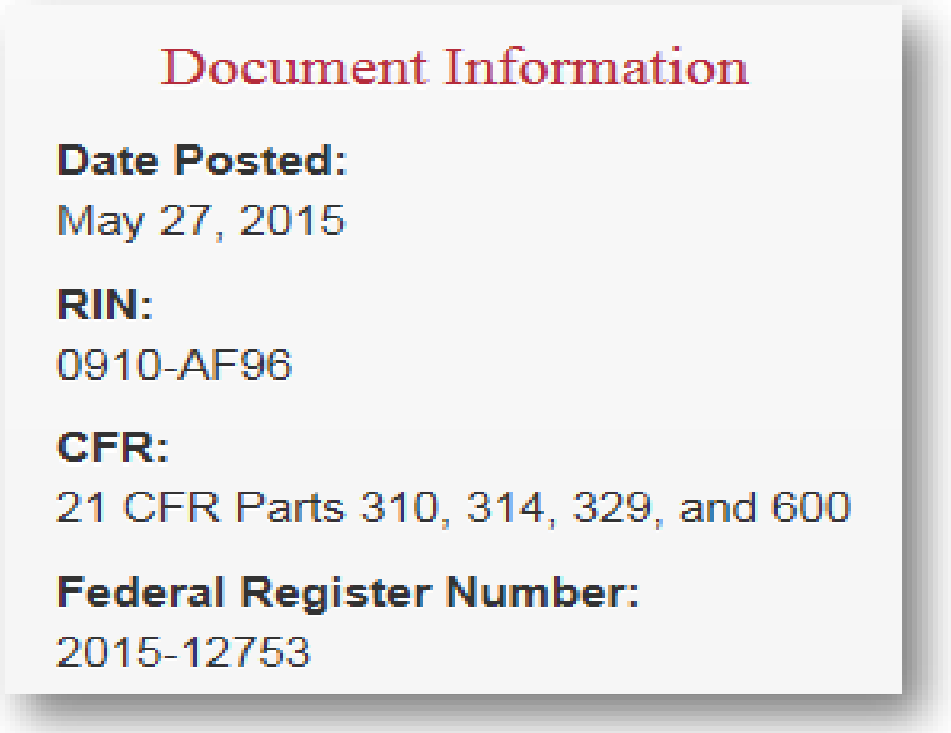
Electronic Reporting of ICSRs

Postmarketing Safety Reports for Human Drug and Biological Products; Electronic Submission Requirements

- **Submit safety reports in an electronic format** that FDA can process, review, and archive
- **Improve** the Agency's systems for **collecting and analyzing** postmarketing safety reports
- **Enable** Agency to **more rapidly review** postmarketing safety reports, **identify and evaluate** emerging safety problems, and **disseminate** safety information in support of FDA's public health mission
- Electronic submission of ICSRs **enhances** global pharmacovigilance by **facilitating electronic transmission and exchange of appropriate information** from ICSRs among regulatory bodies and regulated entities through use of **common data elements and transmission standards**

Electronic Reporting of ICSRs

Postmarketing Safety Reports for Human Drug and Biological Products; Electronic Submission Requirements



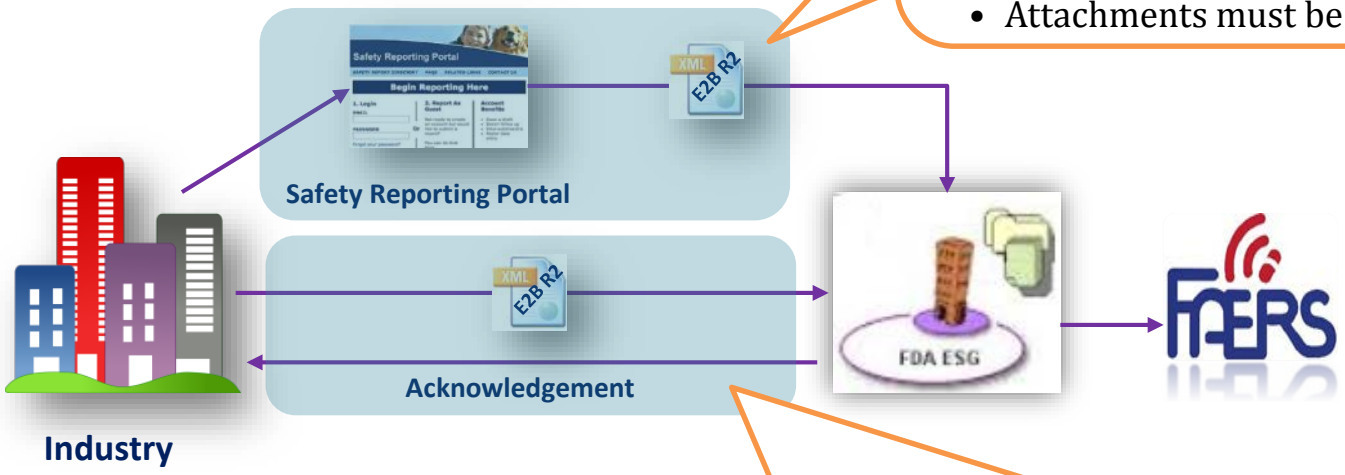
https://www.regulations.gov/#!documentDetail;D=FDA-2008-N-0334-0009

Electronic Reporting of ICSRs

Submission Methods

- There are two options for submitting ICSRs electronically

- **The Safety Reporting Portal (SRP) by manually entering data via web form**
  - Do not have database-to-database capability
  - Must have an account to access the portal site
  - Gateway partners cannot use the SRP
  - Attachments must be in the PDF format

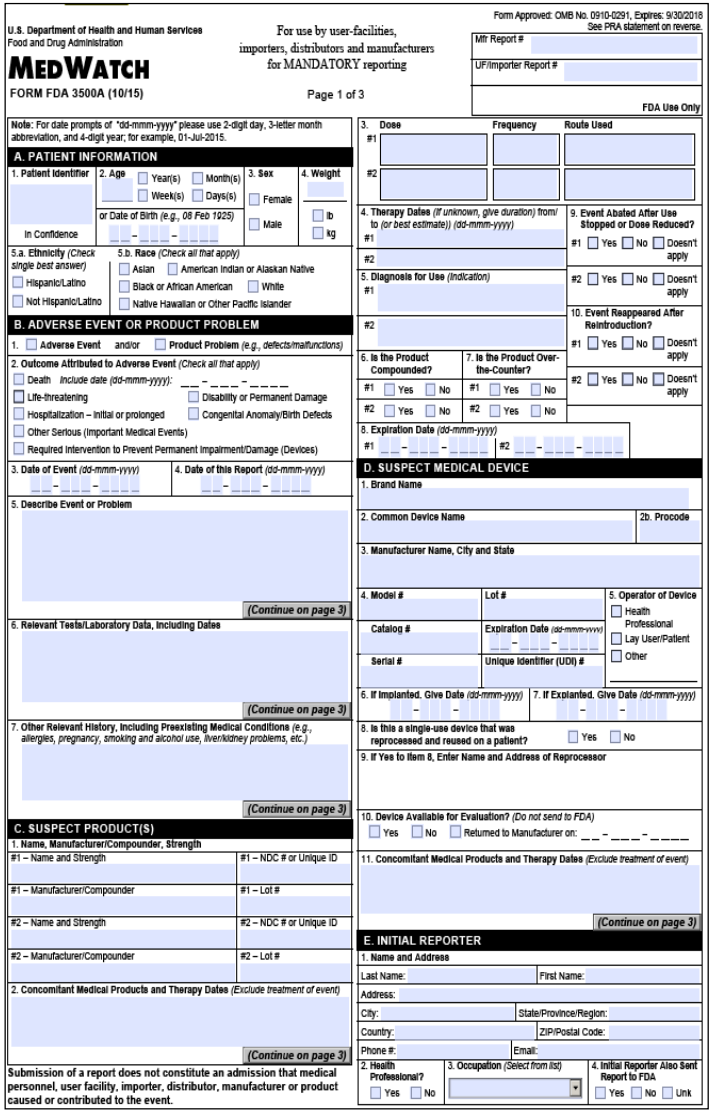


- **Database-to-database transmission ("E2B")**
  - Use standardized ICH E2B(M) data elements
  - ICSRs must be submitted in the XML format
  - Attachments must be in the PDF format

Safety Reporting Portal (SRP)

Safety Reporting Portal (SRP)

SRP is based on the data elements from the MedWatch 3500A



U.S. Department of Health and Human Services
Food and Drug Administration

MEDWATCH

FORM FDA 3500A (10/15)

For use by user-facilities, importers, distributors and manufacturers for MANDATORY reporting

Page 1 of 3

Form Approved: OMB No. 0910-0291, Expires: 9/30/2018
See PRA statement on reverse.

Mfr Report #
UF/Importer Report #
FDA Use Only

Note: For date prompts of "dd-mmm-yyyy" please use 2-digit day, 3-letter month abbreviation, and 4-digit year; for example, 01-Jul-2015.

A. PATIENT INFORMATION

1. Patient Identifier
In Confidence
2. Age — Year(s) Month(s) Week(s) Days(s)
or Date of Birth (e.g., 08 Feb 1925)
3. Sex — Female Male
4. Weight — lb kg
5.a. Ethnicity (Check single best answer) — Hispanic/Latino; Not Hispanic/Latino
5.b. Race (Check all that apply) — Asian; American Indian or Alaskan Native; Black or African American; White; Native Hawaiian or Other Pacific Islander

B. ADVERSE EVENT OR PRODUCT PROBLEM

1. Adverse Event and/or Product Problem (e.g., defects/malfunctions)
2. Outcome Attributed to Adverse Event (Check all that apply)
Death Include date (dd-mmm-yyyy): ___ - ___ - ____
Life-threatening; Disability or Permanent Damage; Hospitalization – initial or prolonged; Congenital Anomaly/Birth Defects; Other Serious (Important Medical Events); Required Intervention to Prevent Permanent Impairment/Damage (Devices)
3. Date of Event (dd-mmm-yyyy)
4. Date of this Report (dd-mmm-yyyy)
5. Describe Event or Problem
(Continue on page 3)
6. Relevant Tests/Laboratory Data, Including Dates
(Continue on page 3)
7. Other Relevant History, Including Preexisting Medical Conditions (e.g., allergies, pregnancy, smoking and alcohol use, liver/kidney problems, etc.)
(Continue on page 3)

C. SUSPECT PRODUCT(S)

1. Name, Manufacturer/Compounder, Strength
#1 – Name and Strength; #1 – NDC # or Unique ID
#1 – Manufacturer/Compounder; #1 – Lot #
#2 – Name and Strength; #2 – NDC # or Unique ID
#2 – Manufacturer/Compounder; #2 – Lot #
2. Concomitant Medical Products and Therapy Dates (Exclude treatment of event)
(Continue on page 3)

Submission of a report does not constitute an admission that medical personnel, user facility, importer, distributor, manufacturer or product caused or contributed to the event.

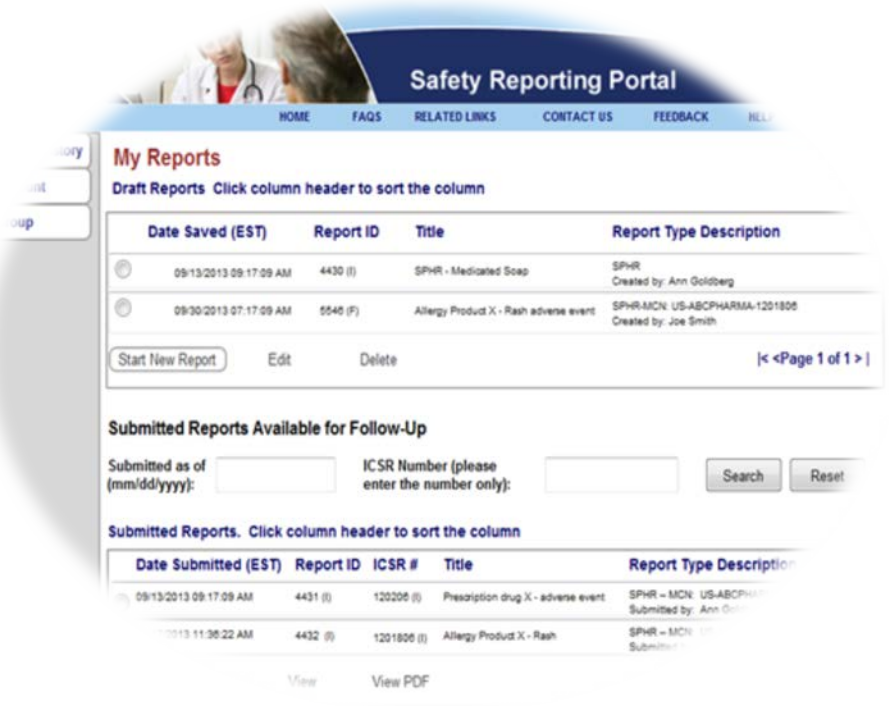
3. Dose — Frequency — Route Used
#1
#2
4. Therapy Dates (If unknown, give duration) from/to (or best estimate)) (dd-mmm-yyyy)
#1
#2
5. Diagnosis for Use (Indication)
#1
#2
6. Is the Product Compounded? Yes No
7. Is the Product Over-the-Counter? Yes No
8. Expiration Date (dd-mmm-yyyy)
#1 ___ - ___ - _____ #2 ___ - ___ - _____
9. Event Abated After Use Stopped or Dose Reduced? #1 Yes No Doesn't apply; #2 Yes No Doesn't apply
10. Event Reappeared After Reintroduction? #1 Yes No Doesn't apply; #2 Yes No Doesn't apply

D. SUSPECT MEDICAL DEVICE

1. Brand Name
2. Common Device Name; 2b. Procode
3. Manufacturer Name, City and State
4. Model # ; Lot #
Catalog # ; Expiration Date (dd-mmm-yyyy)
Serial # ; Unique Identifier (UDI) #
5. Operator of Device: Health Professional; Lay User/Patient; Other
6. If Implanted, Give Date (dd-mmm-yyyy)
7. If Explanted, Give Date (dd-mmm-yyyy)
8. Is this a single-use device that was reprocessed and reused on a patient? Yes No
9. If Yes to Item 8, Enter Name and Address of Reprocessor
10. Device Available for Evaluation? (Do not send to FDA) Yes No Returned to Manufacturer on: ___ - ___ - _____
11. Concomitant Medical Products and Therapy Dates (Exclude treatment of event)
(Continue on page 3)

E. INITIAL REPORTER

1. Name and Address
Last Name: First Name:
Address:
City: State/Province/Region:
Country: ZIP/Postal Code:
Phone #: Email:
2. Health Professional? Yes No
3. Occupation (Select from list)
4. Initial Reporter Also Sent Report to FDA? Yes No Unk



Electronic Reporting of ICSRs

Submitting Periodic Safety Reports (PSR)

Periodic safety reports are comprised of a **descriptive portion** and **non-expedited ICSRs** (21 CFR 314.80 and 600.80), regardless of the format.

- **Descriptive Portion:**
  - Use **Electronic Common Technical Document (eCTD)** specifications to submit the descriptive portion electronically.
  - **Indicate** in the descriptive portion that the **ICSRs have been submitted electronically** as XML files to the FDA Electronic Submissions Gateway (ESG) or via the Safety Reporting Portal (SRP).
- **Non-expedited ICSRs:** must be submitted as described in the options **on or before** the periodic safety report due date. Do NOT submit expedited ICSRs previously submitted.

Electronic Reporting of ICSRs

Future state of electronic submission

- "FDA Regional Implementation Specifications for ICH E2B(R3) Implementation: Postmarket Submission of Individual Case Safety Reports (ICSRs) for Drugs and Biologics, Excluding Vaccines" posted on June 23, 2016
- Follow core ICH E2B R3 with a few regional requirements
- Regional Elements
  - Ethnicity
  - Race
  - Drug descriptor
    - Combination
    - Compounding

Challenge Question #1

1. Methods to submit ICSR.

a. Database-to-database
b. Safety Reporting Portal
c. Paper MedWatch
d. a and b

Answer: D

Challenge Question #2

True or False?

Periodic report are comprised of two parts: the Descriptive portion and the Non-expedited ICSRS

Answer: True

Electronic Reporting of ICSRs

References

- FDA Adverse Event Reporting System (FAERS) - Electronic Submission
  http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm115894.htm

- FDA issues final rule on postmarketing safety report in electronic format
  http://www.regulations.gov/#!documentDetail;D=FDA-2008-N-0334-0009

- Specifications for Preparing and Submitting Electronic ICSRs and ICSR Attachments
  https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/UCM601820.pdf
- Steps to Submitting E2B(R2) ICSRs Electronically in the XML Format
  http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm115914.htm

- Electronic Common technical Document (eCTD)
  http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm

Questions for the Panel

Click for resources:

- Guidance for Industry: Compliance Policy for Combination Product Postmarketing Safety Reporting
- Guidance for Industry: Providing Regulatory Submissions In Electronic Format - Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications
- Guidance for Industry: Postmarketing Adverse Event Reporting for Nonprescription Human Drug Products Marketed Without An Approved Application

Open Q&A begins shortly – type in your questions now.

Please send any questions we do not have time for to:
CDERSBIA@fda.hhs.gov

Learn about other resources from CDER Small Business & Industry Assistance:
Visit Our Website!