

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

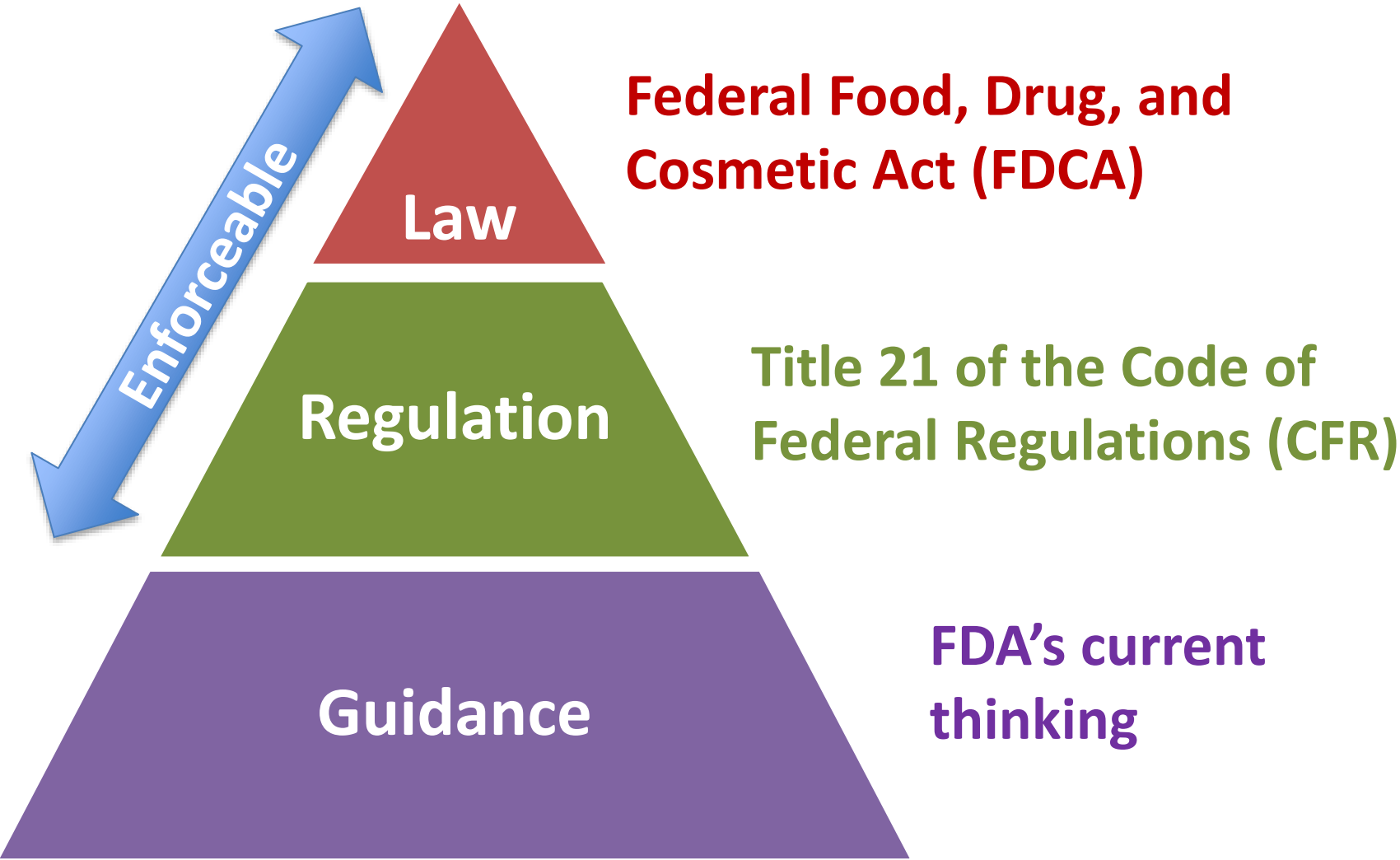
Kelley Simms, PharmD, MS

Commander, US Public Health Service

Consumer Safety Officer

PADE Compliance Team

PADE Legal Framework



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.



✓ Marketed
Or
✓ NOT marketed



Written Procedures Must Address...



Surveillance

- Account for all sources
- Spontaneous
- Solicited
- Internet sources (firm-sponsored)
- Literature

...and more!

Receipt

- ADE info
 - Initial
 - Follow-up
- Receipt from any source

Evaluation

- Seriousness
- Expectedness
- Relatedness
- ADEs from any source
- Follow-up procedures

Reporting

- 15-day Alert Reports
- Non-expedited individual case safety reports (ICSRs)
- Aggregate Reports
- All info must be submitted electronically

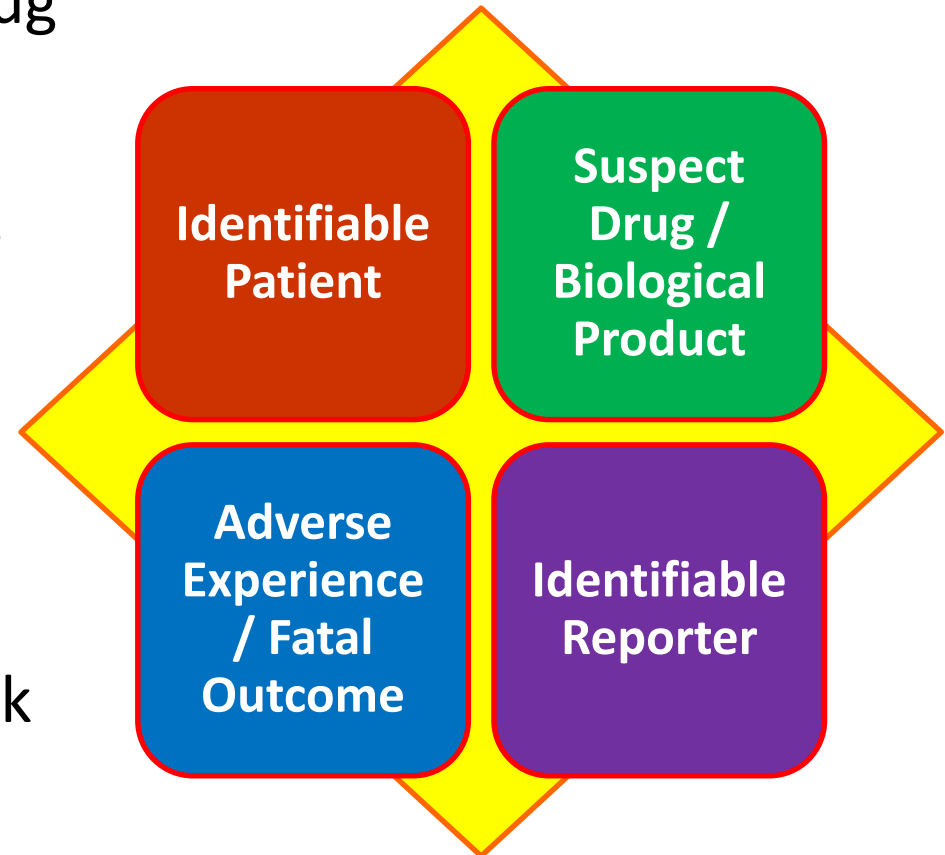
Surveillance

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

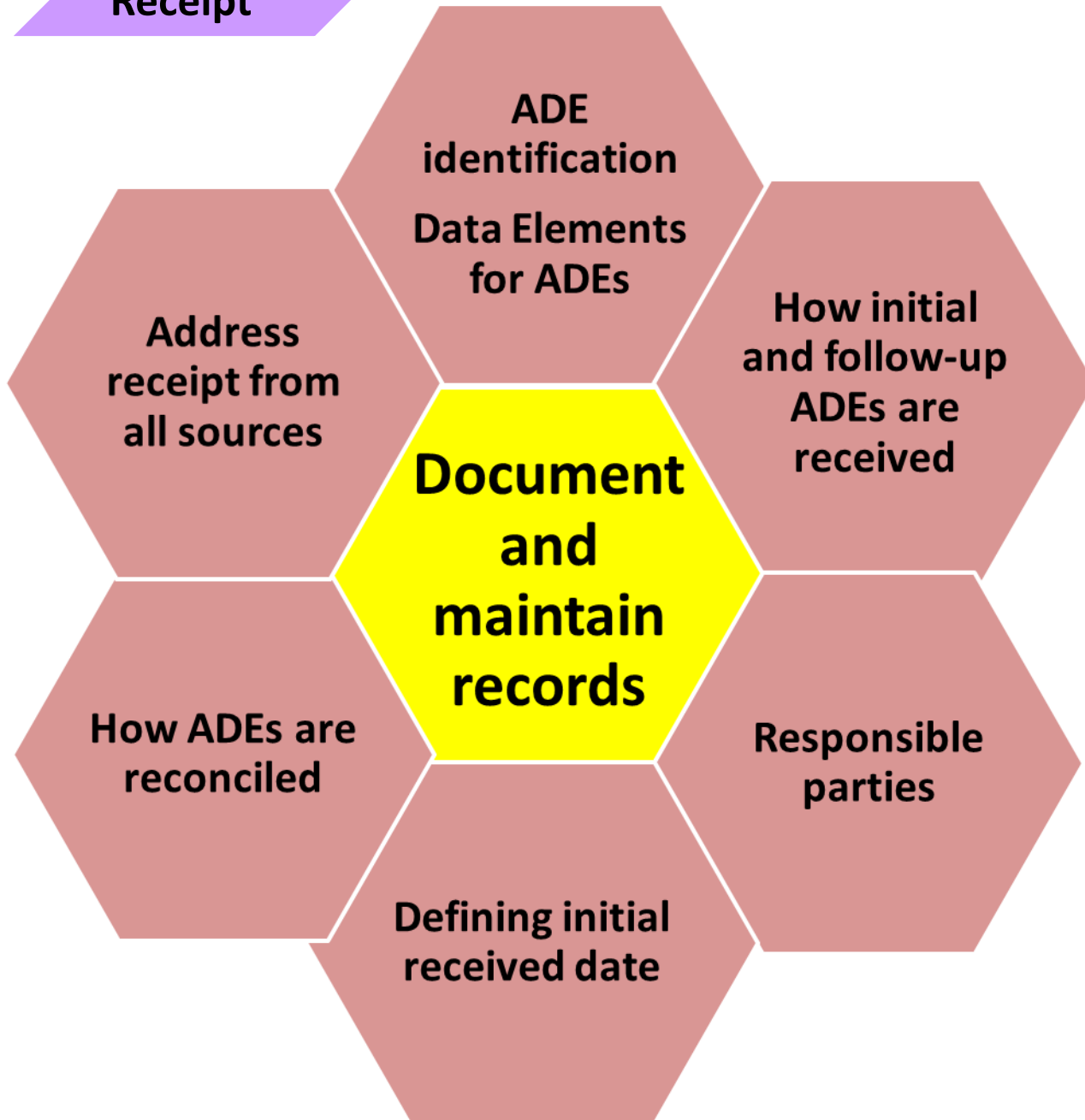
... and many more!

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:
	<ul style="list-style-type: none"> Death Life-threatening Hospitalization Persistent or significant disability Congenital anomaly / birth defect Other serious / important medical event
Expectedness	Unexpected if one of the following:
	<ul style="list-style-type: none"> 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

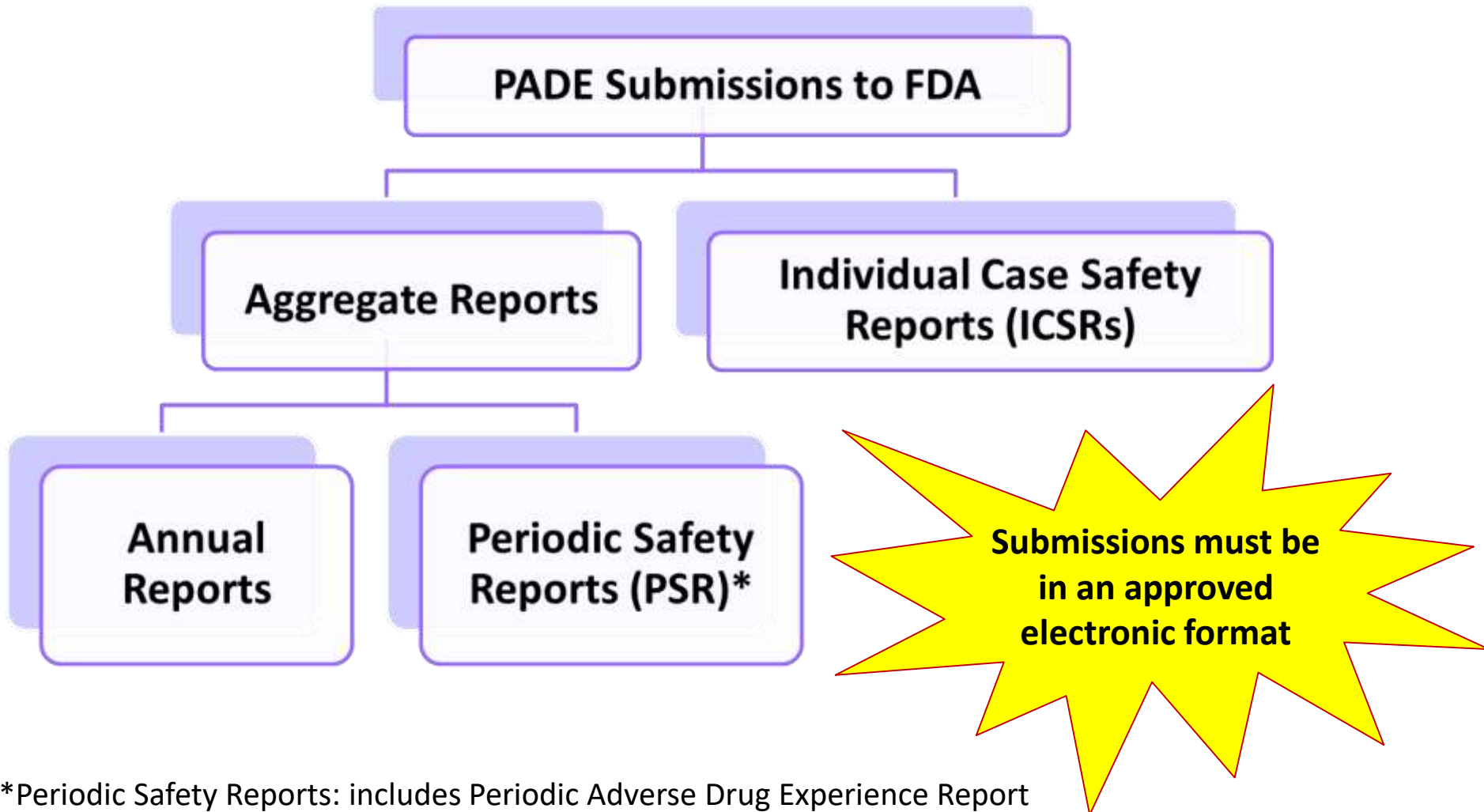
- Promptly review ADE information
- Determine if follow-up is needed, especially if missing data elements
 - Must investigate 15-day Alert Report ADEs
 - Maintain records of follow-up attempts
- Evaluate information for reportability

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 <i>(submit separately from initial ICSR)</i>
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, PBREER 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

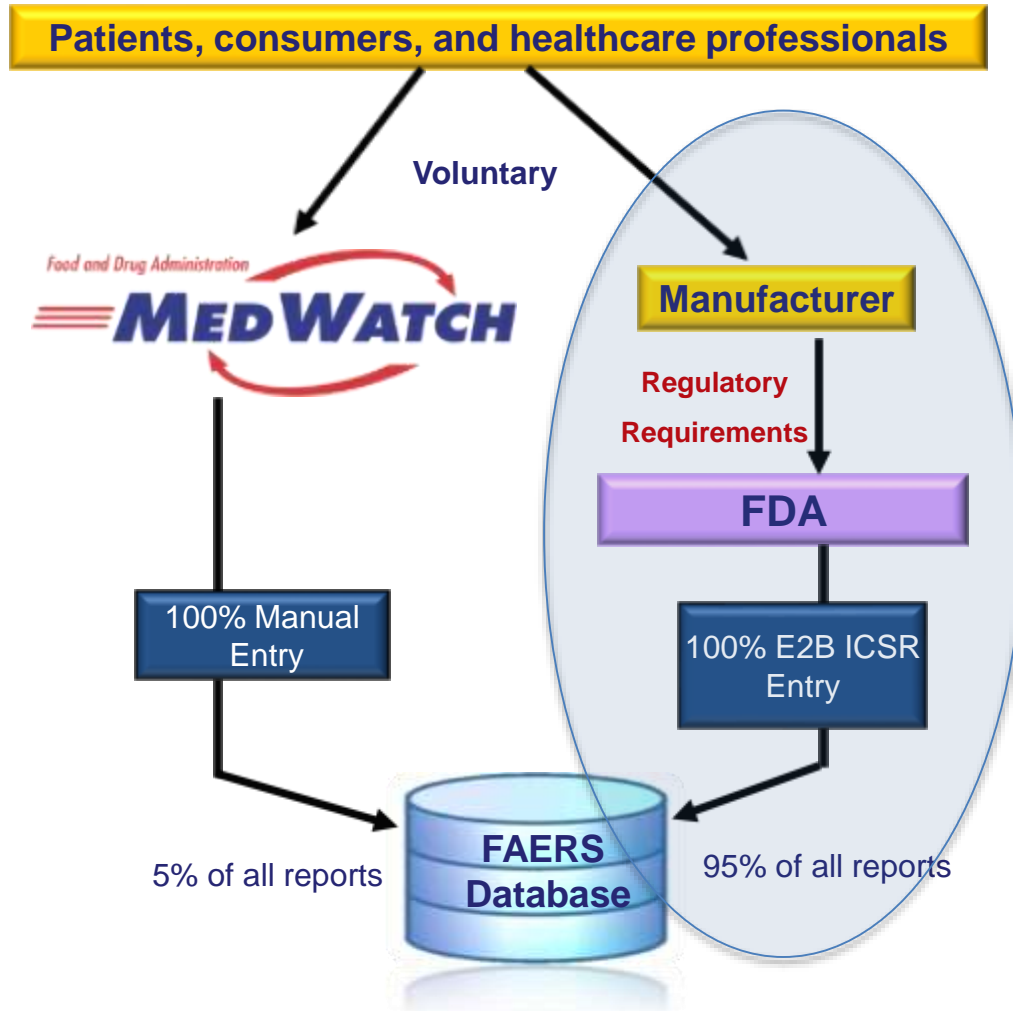
FDA Adverse Event Reporting System (FAERS)

- 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 - **CDER**





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

Document Information

Date Posted:

May 27, 2015

RIN:

0910-AF96

CFR:

21 CFR Parts 310, 314, 329, and 600

Federal Register Number:

2015-12753

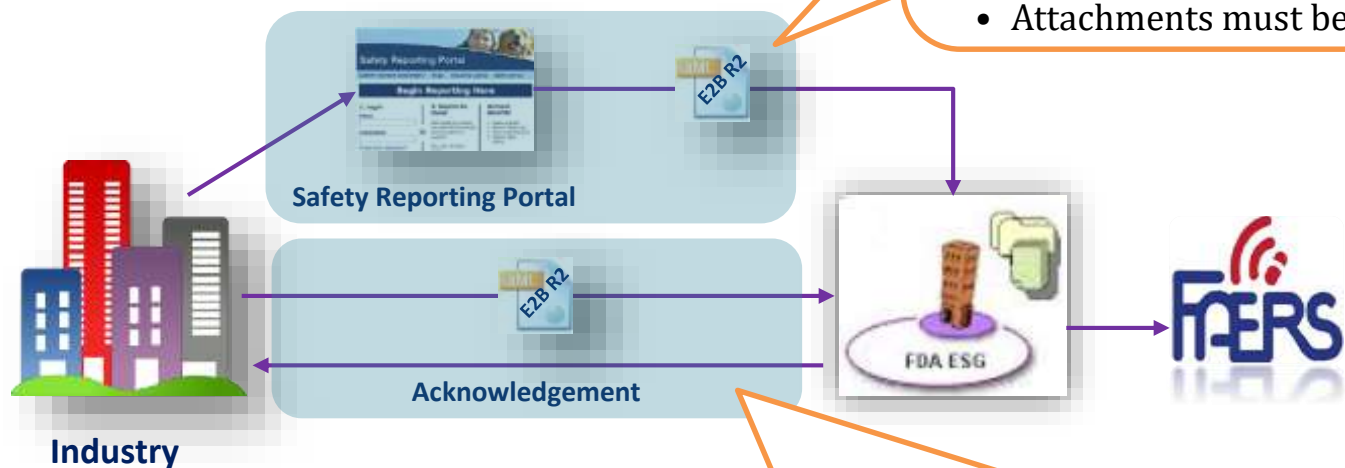
<https://www.regulations.gov/#!/documentDetail;D=FDA-2008-N-0334-0009>

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

ABOUT THE PORTAL SAFETY REPORT DIRECTORY FAQs RELATED LINKS CONTACT US

The Safety Reporting Portal

The Safety Reporting Portal (SRP) streamlines the process of reporting product safety issues to the Food & Drug Administration (FDA) and the National Institutes of Health (NIH).

Whatever your role, (manufacturer, health care professional, researcher, public health official, or concerned citizen), when you submit a safety report through this Portal, you make a vital contribution to the safety of America's food supply, medicines, and other products that touch us all.

1. Login

EMAIL

PASSWORD

[Forgot your password?](#)

Remember me

2. Report As Guest

Not ready to create an account but would like to submit a report?

You can do that here.

Account Benefits

- Save a draft
- Easier follow up
- View submissions
- Faster data entry

Begin Reporting Here

Who Should Submit a Safety Report?

Organizations and people in certain professional roles, such as the following, may be required by law to submit safety reports under some circumstances:

- Food Manufacturers, Processors, Packers, and Holders
- Researchers
- An applicant of an approved drug product or a manufacturer, distributor or packer listed on the label of any drug product
- Drug Manufacturers
- Dietary supplement manufacturers, packers, and distributors

Others, including health care providers, public health officials, and other professionals, as well as consumers and concerned citizens, may voluntarily submit reports if they encounter safety issues with a product and/or unanticipated harmful effects that they believe are related to a product.

[Learn more about mandatory and voluntary reporting.](#)

Reports You Can Submit Through this Portal

FDA safety issues involving:

- Marketed human drug and therapeutic biologics
- Human or animal reportable foods
- Animal drugs
- Animal foods
- Tobacco products
- Dietary supplements

NIH safety issues involving:

- NIH gene-transfer research

For other issues, [find out where to submit your report.](#)

PRIVACY POLICY | FREEDOM OF INFORMATION ACT | ACCESSIBILITY | DISCLAIMER

[Under 18 U.S.C. 1001, anyone who makes a materially false, fictitious, or fraudulent statement to the U.S. Government is subject to criminal penalties.]

Safety Reporting Portal

Welcome Guest HOME FAQs RELATED LINKS CONTACT US FEEDBACK HELP

New Guest Report

You have chosen to use this portal as a Guest reporter.

Reports submitted as a Guest cannot be saved. Therefore, please plan to complete your report in full during this session. If you prefer to save your report and complete it at a later time, please return to the home page and create an account.

* Select the option that best describes what you want to do:

- Start a new report
- Follow-up on a report previously submitted as a guest portal user.
- Follow-up on a report previously submitted as a logged in user.
- None of the above

* Which of the following best describes you?

- Reportable Food Registry Report (mandatory): A food facility or responsible party that manufactures, processes, packs, or holds foods who is submitting a reportable food report.
- Reportable Food Registry Report (voluntary): A federal, state, or local public health official who is submitting a reportable food report involving human and/or animal food.
- Pet Food Report: A veterinarian or veterinary staff member who is submitting a product problem and/or adverse event report involving pet food.
- Pet Food Report: A consumer or concerned citizen who is submitting a product problem and/or adverse event report involving pet food.
- Livestock Food Report: A veterinarian or other professional who is submitting a product problem and/or adverse event report involving livestock food.
- Livestock Food Report: A consumer or concerned citizen who is submitting a product problem and/or adverse event report involving livestock food.
- Animal Drug Report: A marketing authorization holder (manufacturer) for an animal drug who is submitting a report on a product problem and/or an adverse event.
- Tobacco Product Report: A healthcare professional submitting a product problem and/or health-related problem report involving a tobacco product.
- Tobacco Product Report: A consumer or concerned citizen who is submitting a product problem and/or health-related problem report involving a tobacco product.
- Dietary Supplement Report (mandatory): A dietary supplement manufacturer, packer, or distributor who is submitting a mandatory serious adverse event report.
- Dietary Supplement Report (voluntary): A consumer, concerned citizen, or healthcare professional who is submitting a report about an illness, injury, or product problem associated with dietary supplement(s) or a manufacturer, packer, or distributor who is submitting a dietary supplement voluntary serious event and/or product problem report.
- Gene Research Study Report: A clinical trial primary investigator or researcher who needs to report an adverse event involving a gene research study.
- Marketed Human Drug and Therapeutic Biologics Report (mandatory): An applicant, manufacturer, packager, and distributor of human drugs and biological products, other than vaccines who is submitting on a product problem and/or adverse event.
- None of these describe me.

Please contact the FDA.srp@hhs.gov to request access.
Thank you for your interest.

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 (10/10)

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

Form Approved OMB No. 0910-0297, Expires 9/30/2018
See FDA statement on www.fda.gov

Page 1 of 3

FDX Use Only

Note: For date prompts of "dd-mm-yyyy" please use 2-digit day, 3-letter month abbreviation, and 4-digit year; for example, 01-30-2015

A. PATIENT INFORMATION

1. Patient Identifier #

2. Age Year(s) Month(s) Week(s) Day(s)

3. Sex Male Female

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., Defect/ malfunction)

2. Outcome Attributed to Adverse Event (Check all that apply)

Death include date (dd-mm-yyyy)

Life-Threatening Disability or Permanent Damage

Hospitalization - Initial or prolonged Congenital Anomaly/Birth Defects

Other Serious (reporter Medical Events)

Required Intervention to Prevent Permanent Impairment/Damage (Devices)

3. Date of Event (dd-mm-yyyy) 4. Date of this Report (dd-mm-yyyy)

5. Describe Event or Problem

6. Keyword Text/Laboratory Data, including Dates

7. Other Keyword History, including Preexisting Medical Conditions (e.g., allergies, pregnancy, smoking and alcohol use, liver/kidney problems, etc.)

C. SUSPECT PRODUCT(S)

1. Name, Manufacturer/Compounder, Strength

01 - Name and Strength 01 - NDC # or Unique ID

02 - Manufacturer/Compounder 02 - Lot #

03 - Name and Strength 03 - NDC # or Unique ID

04 - Manufacturer/Compounder 04 - Lot #

2. Concurrent Medical Products and Therapy Dates (include treatment of every)

D. SUSPECT MEDICAL DEVICE

1. Brand Name

2. Common Device Name 2b. Procedure

3. Manufacturer Name, City and State

4. Model # 5. Lot # 6. Operator of Device Health Professional Lay User/Patient Other

7. In the Product Compounded? 7. In the Product Over-the-Counter?

01 Yes No 01 Yes No 02 Yes No 02 Yes No

8. Expiration Date (dd-mm-yyyy)

01 02

9. If Incubated, Give Date (dd-mm-yyyy) 10. If Excluded, Give Date (dd-mm-yyyy)

11. Is this a single-use device that was reprocessed and reused on a patient? Yes No

12. If Yes to Item 11, Enter Name and Address of Reprocessor

13. Device available for Evaluation? (Do not send to FDA) Yes No Returned to Manufacturer on: _____

14. Concurrent Medical Products and Therapy Dates (include treatment of every)

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 Self-Report to FDA Yes No UNA

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.

Safety Reporting Portal

HOME | FAQS | RELATED LINKS | CONTACT US | FEEDBACK

My Reports

Draft Reports Click column header to sort the column

Date Saved (EST)	Report ID	Title	Report Type Description
09/13/2013 09:17:09 AM	4430 (S)	SPWR - Medication Stop	SPWR Created by: Ann Goldberg
09/30/2013 07:17:09 AM	5546 (F)	Allergy Product X - Rash adverse event	SPWR/MCN US-ABOPHARMA-1201838 Created by: Joe Smith

Start New Report Edit Delete

Submitted Reports Available for Follow-Up

Submitted as of: _____ ICSR Number (please enter the number only): _____ Search Reset

Submitted Reports. Click column header to sort the column

Date Submitted (EST)	Report ID	ICSR #	Title	Report Type Description
09/13/2013 08:17:09 AM	4431 (S)	120208 (S)	Prescription drug X - adverse event	SPWR - MCN US-ABOPHARMA-1201838 Submitted by: Ann Goldberg
09/13/2013 11:58:22 AM	4432 (S)	1201866 (S)	Allergy Product X - Rash	SPWR - MCN US-ABOPHARMA-1201838 Submitted by: Joe Smith

View View PDF

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 reports 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!](#)

Morning Break

Session 2: REMS Inspections

Risk Evaluation and Mitigation Strategy (REMS) Inspections



Peter Diak, PharmD, MPH

Captain, US Public Health Service
Team Leader, REMS Compliance Team

Haley Seymour, MS

Reviewer, REMS Compliance Team

Objectives

- Provide an overview of the REMS program to help Applicants prepare for BIMO REMS Inspections



- Provide best practices to address inspection findings

Agenda



- Overview of REMS Elements
- Shared System REMS
- The REMS Inspection Process
- Best Practices to Address Inspection Findings
- REMS Specific Issues
- Preparing for REMS Inspections



What is a 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



REMS

- FDAAA, Title IX, Subtitle A, section 901, created new section 505-1 of the Act authorizing FDA to require REMS
- Drug and biologic applicant holders develop REMS programs, FDA reviews and approves them
- REMS programs can be used for a single drug or a class of drugs
- Each REMS has specific safety measures unique to the safety risks associated with a particular drug or class of drugs

REMS Are Enforceable

- REMS must be fully operational before drug introduced into interstate commerce
- Drug may be found to be misbranded (502(y))
- FDA can impose civil monetary penalties for violations of the FD&C Act - 303(f)(4)

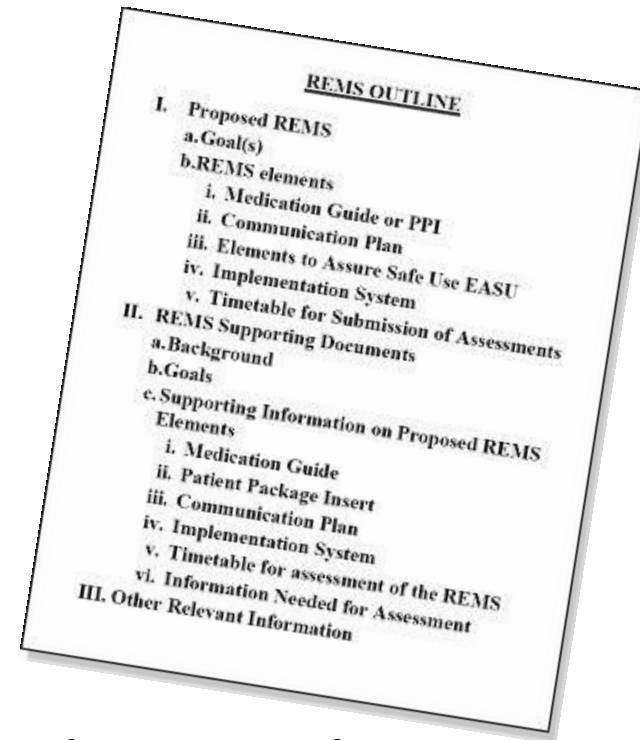


Risks REMS Aim to Mitigate

Example of Risk	Potential REMS action to Mitigate Risk
Serious Infection	Patient education of warning signs of infection prior to prescribing drug
Severe allergic reaction	Healthcare professional must be certified to administer the drug
Liver damage	Monitor liver function while the patient is using the drug
Severe birth defects	Negative pregnancy test prior to dispensing the drug

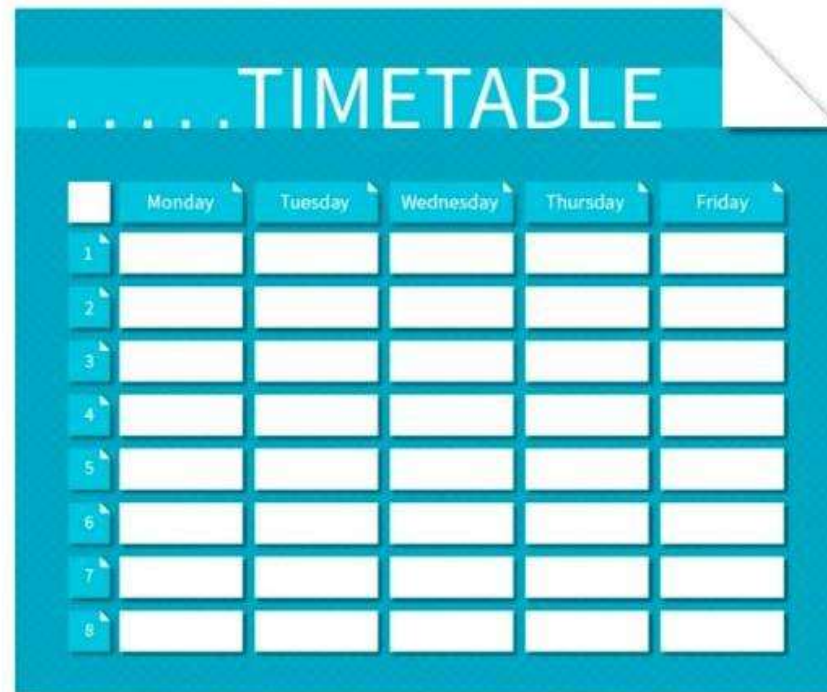
A REMS may include:

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



A REMS must include:

- Timetable for submission of assessments



The image shows a graphic of a calendar titled "TIMETABLE". The calendar has a teal header with the word "TIMETABLE" in white. Below the header is a grid with five columns labeled "Monday", "Tuesday", "Wednesday", "Thursday", and "Friday". The rows are numbered 1 through 8 on the left side. The grid is currently empty, representing a timetable for submission of assessments.

	Monday	Tuesday	Wednesday	Thursday	Friday
1					
2					
3					
4					
5					
6					
7					
8					

Shared System REMS



- Developed for a single drug or biologic product or a class of drug or biologic products
- Includes NDAs and ANDAs
- Single REMS document, REMS materials (except MGs), and supporting documents applicable to all drugs
- Shared database and infrastructure

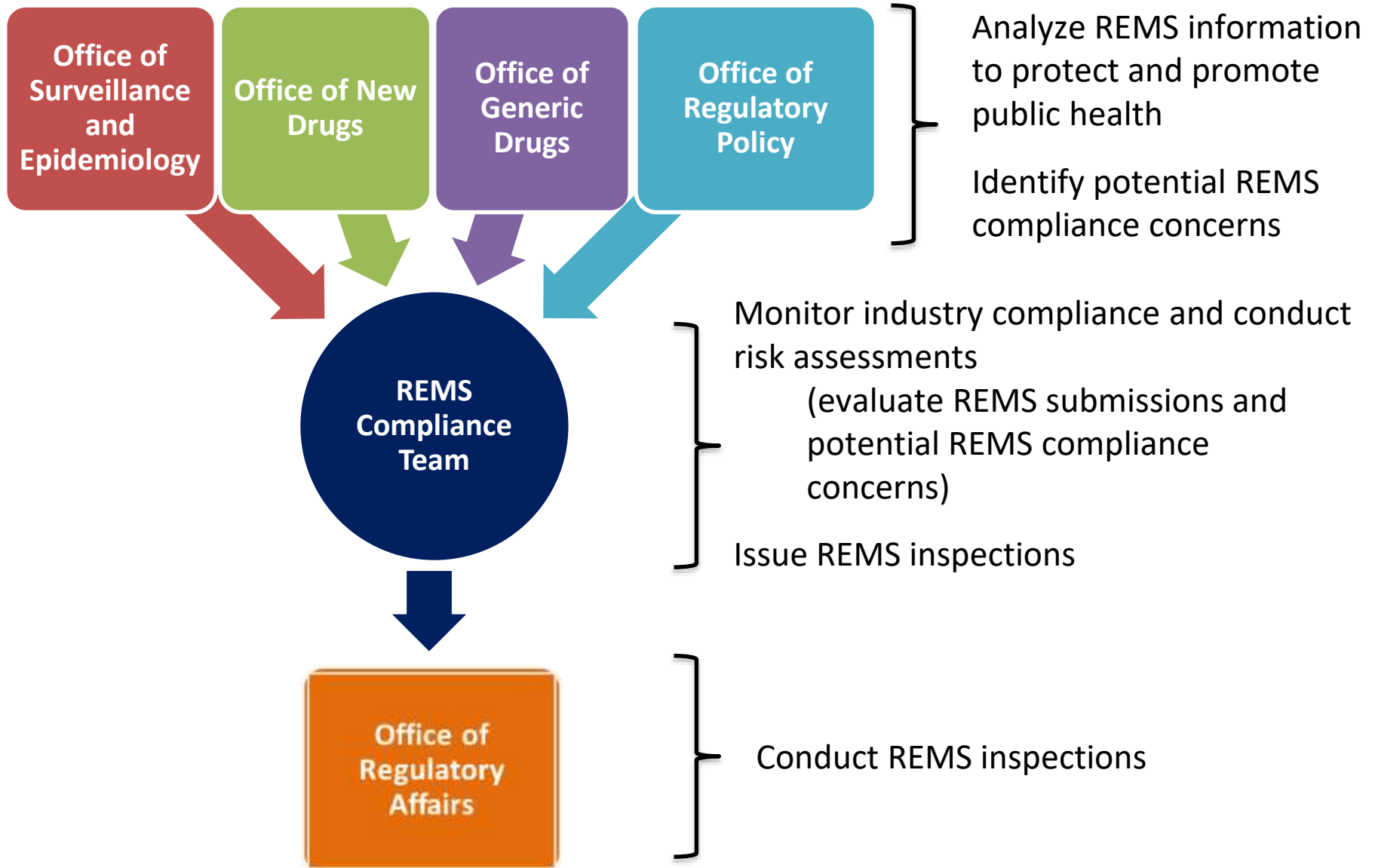


Shared System REMS

Examples of Shared System REMS:

- Isotretinoin – iPLEDGE Program
- Extended-Release and Long-Acting (ER/LA) Opioid Analgesics
- Buprenorphine Transmucosal Products for Opioid Dependence (BTOD)

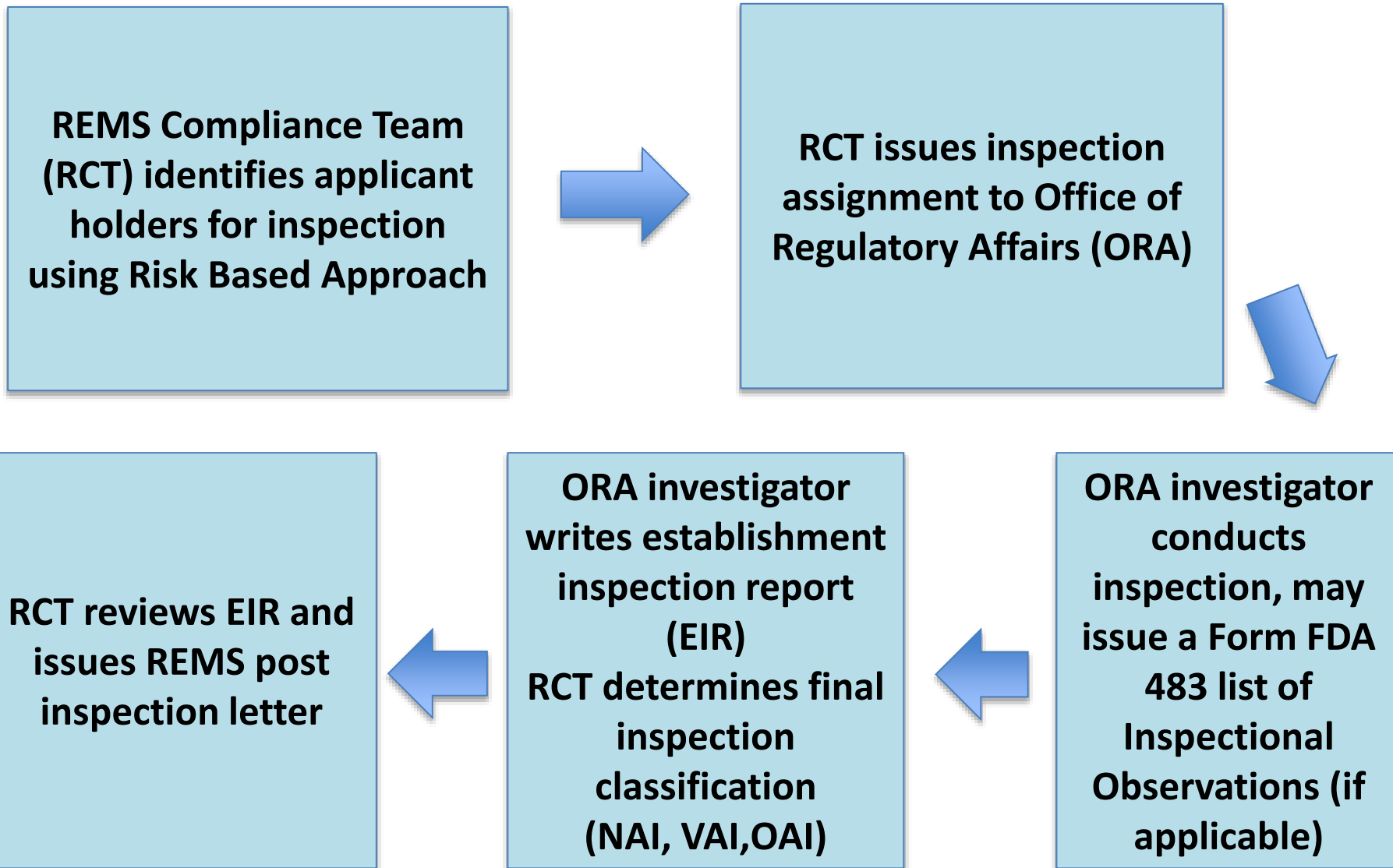
FDA Use of REMS Information



ORA and CDER Work Together



REMS Inspection Process



Purpose of a REMS Inspection

- Verify the REMS is implemented and functioning in accordance to the FDA approved REMS
- Verify information in the REMS assessment report



How do we select REMS to be Inspected?



Site Selection – Risk based approach

- REMS with ETASU never inspected
- REMS with ETASU – issues during previous inspection
- REMS with ETASU – modified since last inspection
- REMS with Communication plans – never inspected (after assessment received if possible)
- REMS – requests from OND/OSE

Possible Inspection Sites

- Sponsor/Applicant
- Call Center
- Vendor/Contract Research Organization



Contractor Inspections

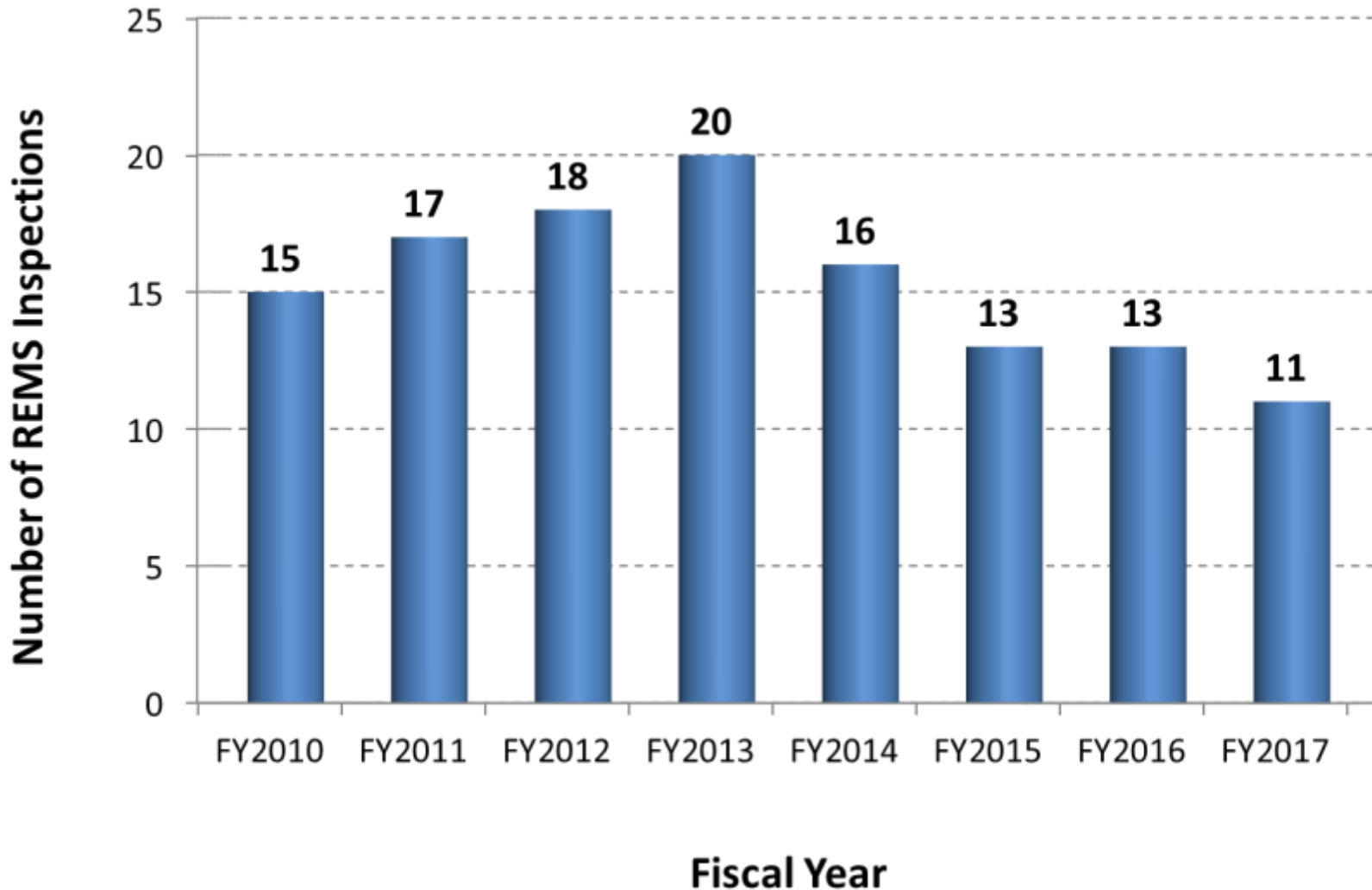
- REMS inspections may be conducted at the Applicant's contractors
- Applicant retains statutory obligation to ensure the REMS functions in accordance to the approved REMS

Contractor Information Collected



- Copy of the contract (financial information may be omitted)
- List of the subcontractors
- Description of the processes or functions performed by the contractor for the REMS program
- Records pertaining to the REMS that are held by the contractor
- REMS training records or standard operating procedures

REMS Inspections Conducted, by Fiscal Year



Inspection Classifications

- **No Action Indicated (NAI)**
 - No objectionable conditions or practices
- **Voluntary Action Indicated (VAI)**
 - Objectionable conditions or practices
 - Not at threshold to take or recommend administrative or regulatory action
- **Official Action Indicated (OAI)**
 - Significant objectionable conditions found
 - Regulatory action recommended

General Information Collected



1. Date the *XYZ* REMS was operational and the date of product launch
2. List of all contractors associated with the *XYZ* REMS to include the point of contact, street address, and phone number of each contractor
3. Contracts with specifications of the contractor's responsibilities
4. Written procedures and training materials
5. Organizational charts



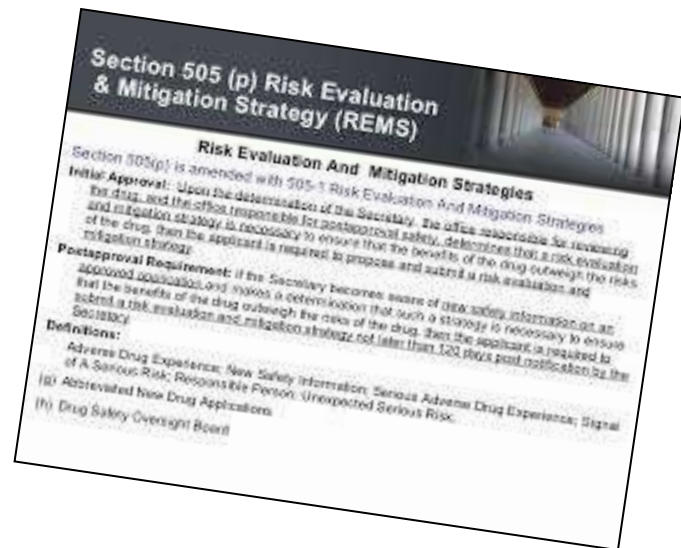


Haley Seymour, MS

Reviewer, REMS Compliance Team

Medication Guides as part of REMS

Medication Guides that are required as part of REMS under Section 505-1 are subject to the assessment and modification provisions of Section 505-1(g) and (h) of the FD&C Act.



Medication Guides

- Required to be dispensed with the drug
- Written in non-technical language
- Standardized format (font size, headers, etc.)
- Provided in ***addition*** to general information sheets (Consumer Medication Information or CMI)



What we look for during an Inspection



1. Is the Medication Guide being distributed to each patient when the drug is dispensed?
2. We collect a copy of the Medication Guide in the version or format (hardcopy) that is provided to each patient



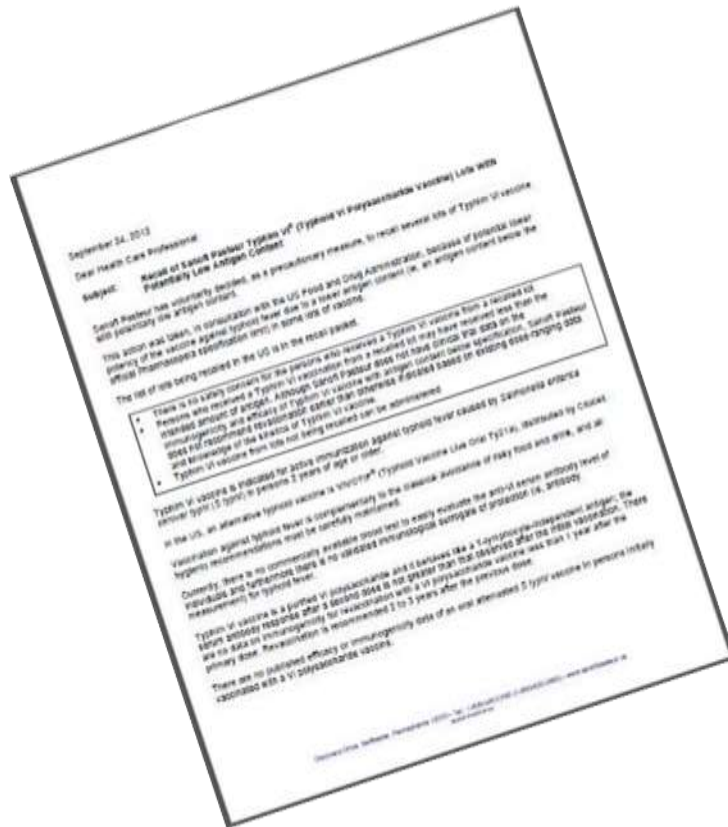
Communication Plan

A Communication Plan is:

- Developed by the applicant holder to support
- implementation of an element of the REMS, and Can inform key audiences (e.g., healthcare providers) about the risk of the drug

Communication Plans can include

Sending letters to Healthcare Providers (e.g., Dear Healthcare Provider letters)



What we look for during an Inspection



1. Were the distribution dates of the Communication Plan in accordance with the dates provided in the REMS document?
2. Were the professional journal communications in the journal as per the dates provided in the REMS document?
3. Is the communication plan available on the REMS website, if applicable?



Possible FDA 483 items for Inspections with a Communication Plan

1. Communication Plan was not distributed to required health care providers, professional societies, etc.
2. Communication Plan was distributed late
3. Not distributing letters to healthcare providers (e.g., Dear Healthcare Provider letters)

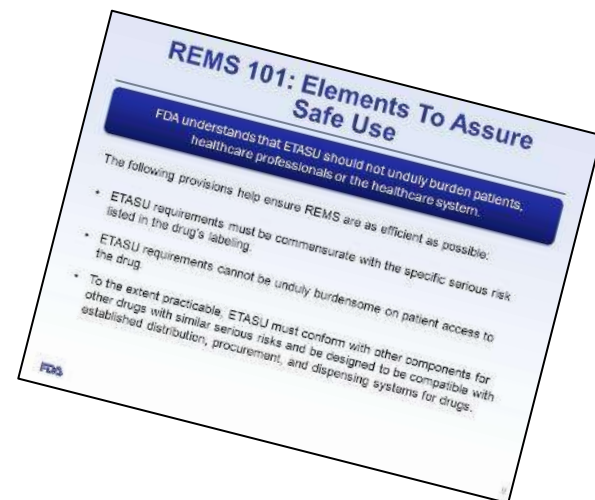


Elements To Assure Safe Use

- Elements to Assure Safe Use (ETASU) may be required to provide safe access for patients to drugs with known serious risks due to inherent toxicity or potential harmfulness
- ETASU is a strategy to mitigate a specific serious risk listed in the labeling of the drug

Elements To Assure Safe Use

- Elements to Assure Safe Use may have 1 or more elements to mitigate the known serious risks associated with the use of the drug.
 - Element A: Healthcare Providers
 - Element B: Pharmacies
 - Element C: Certain Healthcare Settings
 - Element D: Documentation of Safe Use
 - Element E: Monitoring
 - Element F: Registry



Element A



Healthcare providers who prescribe the drug have particular training or experience, or are specially certified. (section 505-1(f)(3)(A))

Examples:

Education program for prescribers

- ER/LA opioid analgesics REMS

Training

- Qsymia REMS

Specially certified

- Caprelsa REMS
- Isotretinoin REMS





Element A: What we look for during an Inspection

- Number of healthcare providers that have received training
- Healthcare provider certification is documented
- Documentation of applicant's activities related to surveillance of the risks addressed by REMS program
- Applicant identifies and addresses non-compliance

Element B

Pharmacies, practitioners, or health care setting that dispense the drug are specially certified. (section 505-1(f)(3)(B))

Examples:

Pharmacy

- Clozapine REMS

Healthcare setting

- Lemtrada REMS



Element B: What we look for during an Inspection



- Documentation of compliance with requirements to become certified – e.g., training, program enrollment, etc.
- Documentation of pharmacy, practitioners or healthcare settings certification process
- Documentation of a validated, secure database of certified pharmacies, practitioners or healthcare settings
- Mechanism that applicant uses to identify and address non-compliant certified pharmacies, practitioners or healthcare settings
- Applicant identifies and addresses non-compliance

Element C

**Drug dispensed to patients only in certain health care setting, such as hospitals
(section 505-1)(f)(3)(C))**

Example:

- Aved REIMS



Element C: What we look for during an Inspection



- Documentation that the drug is shipped only to certified facilities
- Documentation of healthcare setting or wholesalers/distributors enrollment process
- Documentation of the applicant's activities related to compliance with REMS program
- Applicant identifies and addresses non-compliance

Element D

Drug dispensed to patient with evidence or other documentation of safe-use conditions, such as laboratory test results (section 505-1)(f)(3)(D)

Examples:

Patient Enrollment Form

- Tracleer REMS
- Clozapine REMS

Laboratory tests

- Isotretinoin REMS



Element D: What we look for during an Inspection



- Documentation of safe use conditions as described in the approved REMS
- Documentation of REMS Program Call Center activities
- Documentation of maintenance of a validated, secure database
- Applicant identifies and addresses non-compliance

Element E

Each patient using the drug is subject to certain monitoring (section 505-1(f)(3)(E))

Example:

- Clozapine REMS



Element E: What we look for during an Inspection



- Documentation of patient monitoring according to the requirements of the approved REMS
- Documentation of pharmacy, practitioner, patient, or healthcare setting non-compliance
- Applicant identifies and addresses non-compliance

Element F

**Each patient using the drug is enrolled in a registry
(section 505-1(f)(3)(F))**

Example:

Pregnancy registry

- Isotretinoin REMS
- Mycophenolate REMS



Element F: What we look for during an Inspection



- Verify that the registry is in place and all patients are enrolled in a registry
- Documentation of patient registry enrollment non-compliance
- Applicant identifies and addresses non-compliance

Implementation System



To assure safe use, elements B, C and D may include a system through which the applicant is able to take reasonable steps to monitor and evaluate implementation of such elements and work to improve them





Implementation System: What we look for during an Inspection

- Documentation of all processes and procedures to support REMS requirements
- Documentation and maintenance of a validated, secure database of all certified stakeholders in the REMS Program
- Documentation and maintenance of a REMS Program Call Center and a REMS Program website
- Documentation of audits and an ongoing audit plan
- Applicant identifies and addresses non-compliance

Possible Enforcement Action

- Seizure of the drug subject to the REMS
- Injunction
- Civil Monetary Penalties



REMS: Key Points



- The REMS CP is on the FDA's [BIMO Compliance Program Webpage](#)
- REMS can be for a single drug or a class of drugs
- Each REMS is unique (i.e., no two REMS are alike)



Email for REMS Compliance:
CDER-OSI-RMP@fda.hhs.gov

Resources



- **FD&C Act Chapter V: Drugs and Devices**

<http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAAct/FDCAActChapterVDrugsandDevices/default.htm>

- **REMS Guidances**

- **Format and Content of a REMS Document**

<https://www.fda.gov/downloads/Drugs/.../Guidances/UCM184128.pdf>

- **Medication Guides Distribution Requirements and Inclusion in REMS**

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM244570.pdf>

- **REMS@FDA Website**

<http://www.accessdata.fda.gov/scripts/cder/remis/index.cfm>

Resources



- **Risk Evaluation and Mitigation Strategies: Modifications and Revisions – Guidance for Industry (April 2015)**
<http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm441226.pdf>
- **REPORT: Standardizing and Evaluating Risk Evaluation and Mitigation Strategies (REMS) (Sept 2014)**
<http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM415751.pdf>
- **Risk Evaluation and Mitigation Strategies Compliance Program Manual**
<https://www.fda.gov/ICECI/ComplianceManuals/ComplianceProgramManual/ucm255614>



Lunch Break