

Regulatory Education
for Industry (REdI)
Fall 2015

**FDA SMALL
BUSINESS** AND
INDUSTRY ASSISTANCE
REdI Conference

Chrissy J. Cochran, PhD

Director (acting)
Division of Enforcement and Postmarketing Safety
Office of Compliance
Office of Scientific Investigations/CDER





Topics

- Investigational New Drug (IND) safety reporting requirements (pre-market)
- Postmarket Adverse Drug Experience reporting requirements (PADE, postmarket)
- Electronic Safety Reporting Rule (eSRR)



ADVERSE EVENT OVERVIEW



What is an adverse event?

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

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



... and many more!



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

MEDWATCH
FORM FDA 3500A (2/13)

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

Form Approved OMB No. 0910-0281, Expires: 03/31/2015
See OMB website for details

Page 1 of 3

A. PATIENT INFORMATION

1. Patient Name: [Red circle around this field]

2. Age at Time of Event: [Red circle around this field]

3. Sex: [Red circle around this field]

4. Weight: [Red circle around this field]

B. ADVERSE EVENT OR ADVERSE PROBLEM

1. Adverse Event and/or Product Problem (e.g., defect/malfunction)

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

3. Date of Event (mm/dd/yyyy)

4. Date of This Report (mm/dd/yyyy)

5. Describe Event or Problem

C. SUSPECT PRODUCT (p)

1. Name (Give Abbrev Strength & Indication)

2. Date, Frequency & Route Used

3. Therapy Dates (If patients, give dates; Event(s) (if not applicable)

4. Containers for Use (Indicate)

5. Event Abated After Use Stopped or Dose Reduced?

6. Lot #

7. Event Reappeared After Rechallenge/Use?

8. NDC or Unique ID

9. Concurrent Medical Products and Therapy Dates (Include treatment of event)

D. SUSPECT MEDICAL DEVICE

1. Brand Name

2. Common Device Name

3. Manufacturer Name, City and State

4. Model #

5. Operator of Device

6. If Implanted, Give Date (mm/dd/yyyy)

7. To this a Single-use Device that was Reprocessed and Reused on a Patient?

8. If Yes to Item No. 7, Enter Name and Address of Reprocessor

9. Device Available for Inspection? (Do not send to FDA)

10. Concurrent Medical Products and Therapy Dates (Include treatment of event)

INITIAL REPORTER

1. Name and Address

2. Health Professional?

3. Occupation

4. Initial Reporter Also Sent Report to FDA?

MedWatch Form FDA 3500A

1. Suspect drug product
 - Order not specified in regulations
2. Identifiable patient
 - Each Form FDA 3500A should refer to only 1 patient
 - Privacy-> report should not include patient names and addresses
3. Adverse event
4. Identifiable reporter



AE Term: Expectedness

- Based on current labeling (Investigator Brochure, Prescribing Information, Drug Facts, etc.)
 - Expected – described in labeling
 - Unexpected – not described in labeling
 - Includes events with greater severity or specificity than described in the label

-----ADVERSE REACTIONS-----

Most common adverse reactions (incidence >3% and greater than with placebo):
Nasopharyngitis, upper respiratory tract infection, headache, and fatigue (6.1)

An AE report of migraines with vision loss may be considered unexpected

An AE report of fatigue would be considered expected



AE Term: Seriousness

- AE with one or more of the following outcomes
 - Death
 - Life-threatening (in that specific case, not theoretical)
 - Inpatient hospitalization or prolongation of existing hospitalization
 - Persistent or significant disability/incapacity
 - Congenital anomaly/birth defect
 - Other serious / important medical events

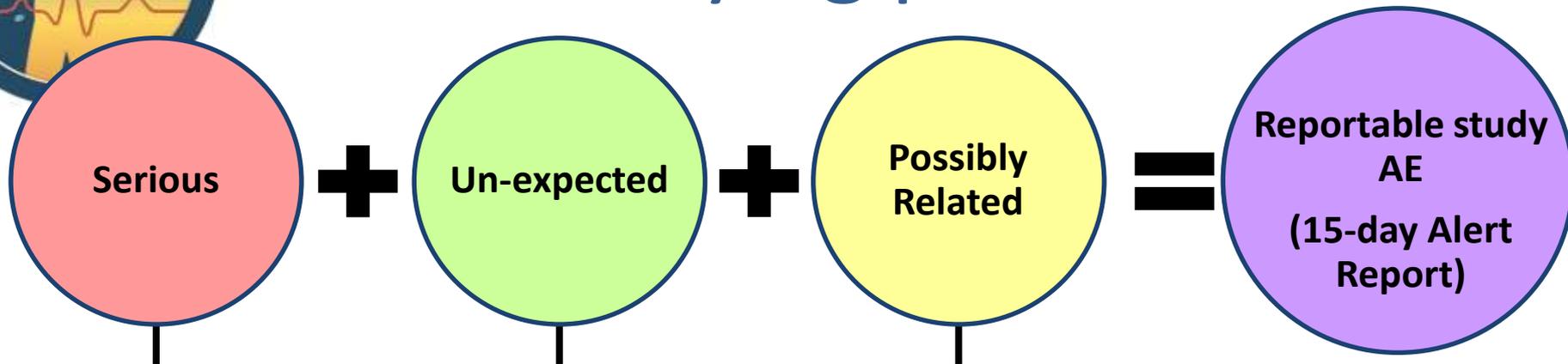
Serious (regulatory outcome) is different than severe (clinical judgment)



IND SAFETY REPORTING



Classifying premarket AEs



Results in ≥ 1 of the following outcomes:

- Death
- Life-threatening
- Inpatient/prolonged hospitalization,
- Persistent or significant disability
- Congenital anomaly / birth defect
- Other serious / important medical event

Not listed in current investigator brochure

or

Greater severity or specificity than AE listed in brochure

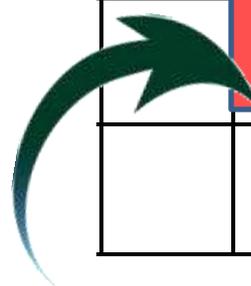
Reasonable possibility that the drug caused AE



What to report

Calendar for the month of _____

Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
0						
	15					



Initial receipt of AE information

- ▶ Serious, unexpected, possibly related study AEs from any source
- ▶ Foreign or domestic
- ▶ Initial and follow-up

Submit within 15 calendar days via:

- eCTD to the IND application
- Phone, fax, email if application not in eCTD

© Freestyle.com



How does FDA receive AEs?

Subject -> Clinical Investigator

Other studies, animal testing, inc. rate of AE

Per protocol

Sponsor receives AE

AE submitted to all IND investigators

15 calendar days

Electronic Reporting to FDA via eCTD, or phone, fax, email

AE submitted to the IND application

Domestic: Form FDA 3500A

Foreign: Form FDA 3500A or CIOMS I



IND Safety Reporting

- Expedited IND safety reporting
 - Uninformative reporting
 - Underlying disease
 - Common occurrence in population
 - Study endpoints
- Time commitment
 - Sites
 - Sponsor
 - IRB
 - FDA
- Final Rule, Guidance
- Inspections



POSTMARKET ADVERSE DRUG EVENT SAFETY REPORTING



Written Procedures

Surveillance

Receipt

Evaluation

Submission

- Spontaneous sources
- Solicited information

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

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

- ICSRs
 - 15-day Alert Reports
 - Periodic Reports
- Aggregate Reports
 - Annual
 - Periodic



Sources of ADE Reports

- Literature
 - Includes published material and unpublished manuscripts
 - Only need to report **serious unexpected** ADEs that are case reports or from a formal clinical trial
 - Must include full text of the article in English with the ADE

- Study (solicited)
 - ADE from organized data collection
 - Examples: postmarketing studies, registries, patient support programs, etc.
 - Only need to report serious unexpected ADEs as 15-day reports if there is a **reasonable possibility that the drug caused** the ADE



Individual Reports: 15-day & Periodic

Expedited (15-day)

- Serious and unexpected ADEs
- Foreign and domestic
- Submit within 15 calendar days of receipt of information

Periodic

- Serious expected ADEs
- All non-serious ADEs
- Submitted with quarterly or annual periodic report

		Based on product label	
		Expected	Unexpected
Based on outcomes	Serious	Serious / Expected	Serious / Unexpected
	Non-serious	Non-serious / Expected	Non-serious / Unexpected

Potential 15-day Report



Individual Reports: Initial & Follow-up

- Initial
 - Considered reportable when 4 minimum elements are known (Day 0)
 - Promptly investigate ADEs, especially if missing any of the minimum elements
- Follow-up
 - Maintain records of follow-up attempts
 - Required for 15-day Alert Reports
- Submit initial and follow-up 15-day ADEs separately

**Electronic submissions
required as of June 10,
2015**

*****ICSRs CANNOT BE
SUBMITTED IN PDF*****



How does FDA receive PADEs?

Consumers, patients, healthcare professionals, etc.

Voluntary



Voluntary



Literature, studies, registries, sales force, etc.



Firm receives AE

Mandatory



MedWatch Online Voluntary Reporting Form (3500)



The FDA Safety Information and Adverse Event Reporting Program

BEGIN

Form FDA 3500B or submit online



Electronic Reporting to FDA via XML, or Safety Reporting Portal

Domestic: Form FDA 3500A

Foreign: Form FDA 3500A or CIOMS I



AE entered into the FAERS database



Aggregate Reports: Periodic

- Timing (based on FDA approval date)
 - Quarterly for 3 years (submit within 30 days of close of the quarter)
 - Annually thereafter (submit within 60 days of approval date)
- Contents
 - Narrative summary and analysis
 - 15-day ADEs: analysis
 - Periodic ADEs: line-listing and Form FDA 3500A for each ADE
 - Actions taken due to ADEs
- Formats: PADER, PSUR, PBRER
 - Electronic
 - Submit Periodic Report as PDF
 - Submit ICSRs as XML file via Electronic Submission Gateway



Expedited Safety Reporting

Pre - 21 CFR 312.32(c)(1)	Post - 21 CFR 314.80(c)(1)
Serious and unexpected suspected	Serious and unexpected
Clinical trials or any other source	Any source
15 calendar days	15 calendar days
Causal relationship	No causality assessment



ELECTRONIC SAFETY REPORTING RULE



Electronic Safety Reporting

- Food and Drug Administration Safety and Innovation Act - 2012
- Section 1136 - Requires the submission of reports to applications to be in an electronic format





eSRR Timeline

- Final Rule published in Federal Register –June 10, 2014
- The rule went into effect June 10, 2015
- CDER delayed enforcement of eSRR to September 8, 2015





eSRR requirements

- Requires electronic format for reporting Individual Case Safety Reports (ICSRs; MedWatch; Form FDA 3500A)
- Provides that periodic ICSRs may be submitted individually or in batch prior to PADER due date
- Provides for which fields should be completed on an ICSR



Approved Electronic Formats

1. E2B submissions over the Electronic Submission Gateway (ESG) – in place since March 2005

No PDF files!



2. ***New Method***

Safety Reporting Portal (SRP)





E2B Submissions



- Database to database
- Must be submitted in XML-syntax (file type)
- Delivery confirmation
 - Message Delivery Notice from ESG
 - FAERS acknowledgement





SRP - <https://www.safetyreporting.hhs.gov>

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.

Begin Reporting Here

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

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.](#)

Firms with an account login to access the SRP





Email Confirmation

Subject: Safety Report ID FPSR7374 Submission Confirmation

Your initial Marketed Human Drug and Therapeutic Biologics Report, Submitted by: UserFirstname UserLastname, MCN: MCN0000, ID FPSR7374, was successfully submitted on 8/25/2015 2:42:08 PM EST to the FDA, and it was issued an Individual Case Safety Report Number (ICSR) of 1103423.

Thank you for using the Safety Reporting Portal.

Please do not reply to this message. Replies to this message are routed to an unmonitored mailbox. If you have questions please refer to the Portal's Contact Us page for further instructions.



My Report History in SRP

Safety Reporting Portal

HOME FAQs RELATED LINKS CONTACT US FEEDBACK HELP LOGOUT

My Report History

My Account

My Group

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 (I)	Small Pharma Health Report	SPHR Created by: Ann Goldberg
09/30/2013 07:17:09 AM	5546 (F)	Small Pharma Health Report	SPHR-MCN: US-ABCPHARMA-1201806 SPHR Created by: Joe Smith

Click on the Add button to add an item

Start New Report Edit Delete << Page 1 of 1 >>



My Report History in SRP

(1) 09/13/2013 09:17:09 AM 4430
 Small Pharma Health Report
 SPHR Created by: Ann Goldberg

Submitted Reports Available for Follow-Up

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

Submitted Reports. Click column header to sort the column

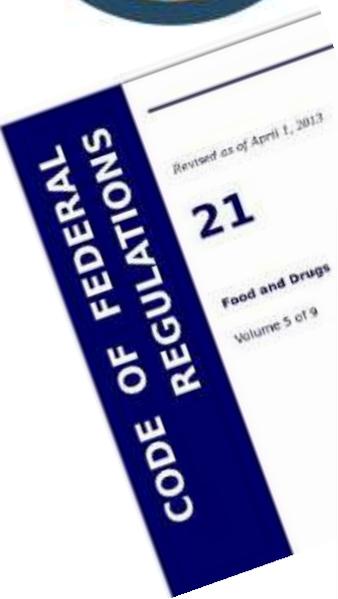
Date Submitted (EST)	Report ID	ICSR#	Title	Report Type Description
09/15/2013 10:36:22 AM	4431 (1)	1202006 (1)	test_SPHR_091513	SPHR - MCN: US-ABCPHARMA-1202006 Submitted by: Ann Goldberg
09/17/2013 11:36:22 AM	4432 (1)	1201806 (1)	test_SPHR_091713	SPHR - MCN: US-ABCPHARMA-1201806 Submitted by: Ann Goldberg

Click on the Add button to add an item

|<<Page 1 of 1 >>|



Statutory Provisions & Regulations



21 CFR 312.32	IND: investigational new drugs
21 CFR 314.80	NDA (Rx and OTC): postmarketing reporting
21 CFR 314.81(b)(2)	NDA, ANDA (Rx and OTC): annual reports
21 CFR 314.90	Waivers
21 CFR 314.98	ANDA
21 CFR 310.305	Rx without approved applications (e.g., DESI drugs)
21 CFR 314.540	Subpart H (accelerated for serious or life-threatening illnesses)
21 CFR 314.630	Subpart I (human studies not ethical or feasible)



References

- Safety Reporting Requirements for INDs and BA/BE Studies guidance
 - <http://www.fda.gov/downloads/Drugs/.../Guidances/UCM227351.pdf>
- IND Safety Reporting Requirements final rule
 - <http://www.gpo.gov/fdsys/pkg/FR-2010-09-29/pdf/2010-24296.pdf>
- Federal register eSRR posting June 10, 2014
 - <http://www.regulations.gov/#!documentDetail;D=FDA-2008-N-0334-0009>
- Draft Guidance: Providing Submissions in Electronic Format — Postmarketing Safety Reports
 - <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm072369.pdf>
- FAERS Electronic Safety Reporting website ★
 - <http://www.fda.gov/drugs/guidancecomplianceregulatoryinformation/surveillance/adversedrugeffects/ucm115894.htm>



Chrissy J. Cochran, PhD

Chrissy.Cochran@fda.hhs.gov



Please complete the session survey:

[surveymonkey.com/r/DRG-D1S3](https://www.surveymonkey.com/r/DRG-D1S3)