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)

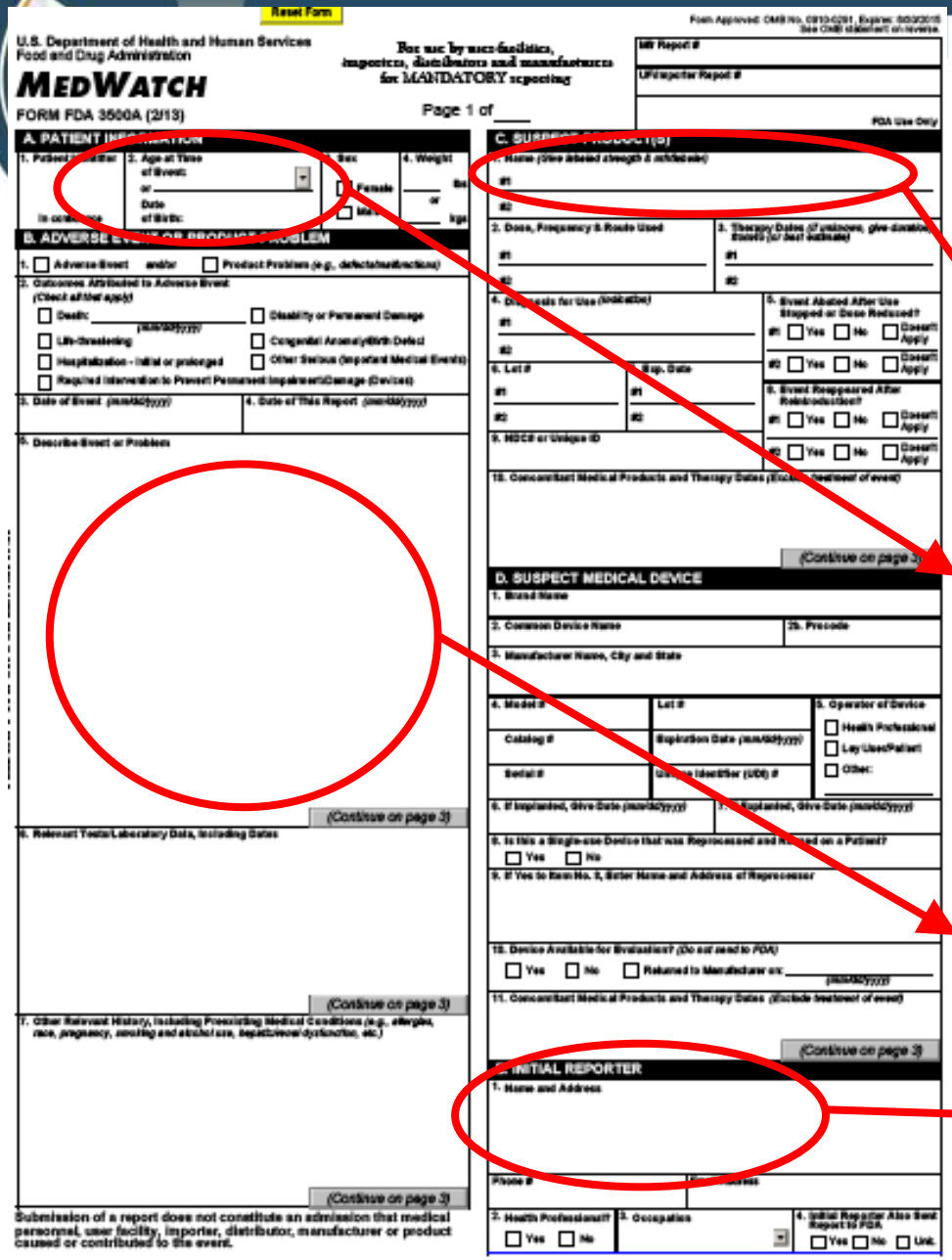
ADVERSE EVENT OVERVIEW

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 user facilities, importers, distributors and manufacturers for MANDATORY reporting

Page 1 of ___

A. PATIENT INFORMATION

B. ADVERSE EVENT OR PRODUCT PROBLEM

C. SUSPECT PRODUCT(S)

D. SUSPECT MEDICAL DEVICE

E. INITIAL REPORTER

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.

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

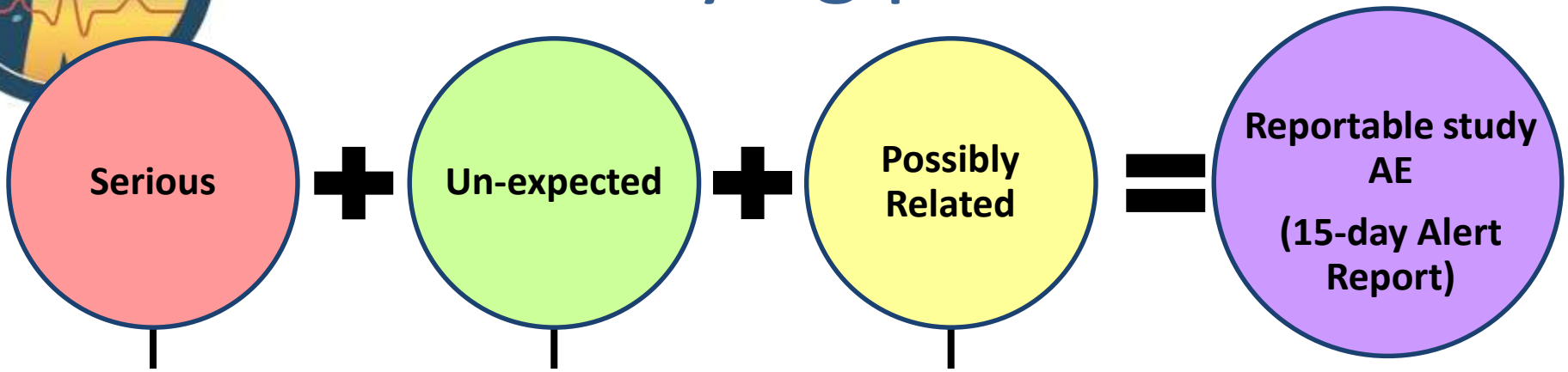
AE Term: Seriousness

- 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

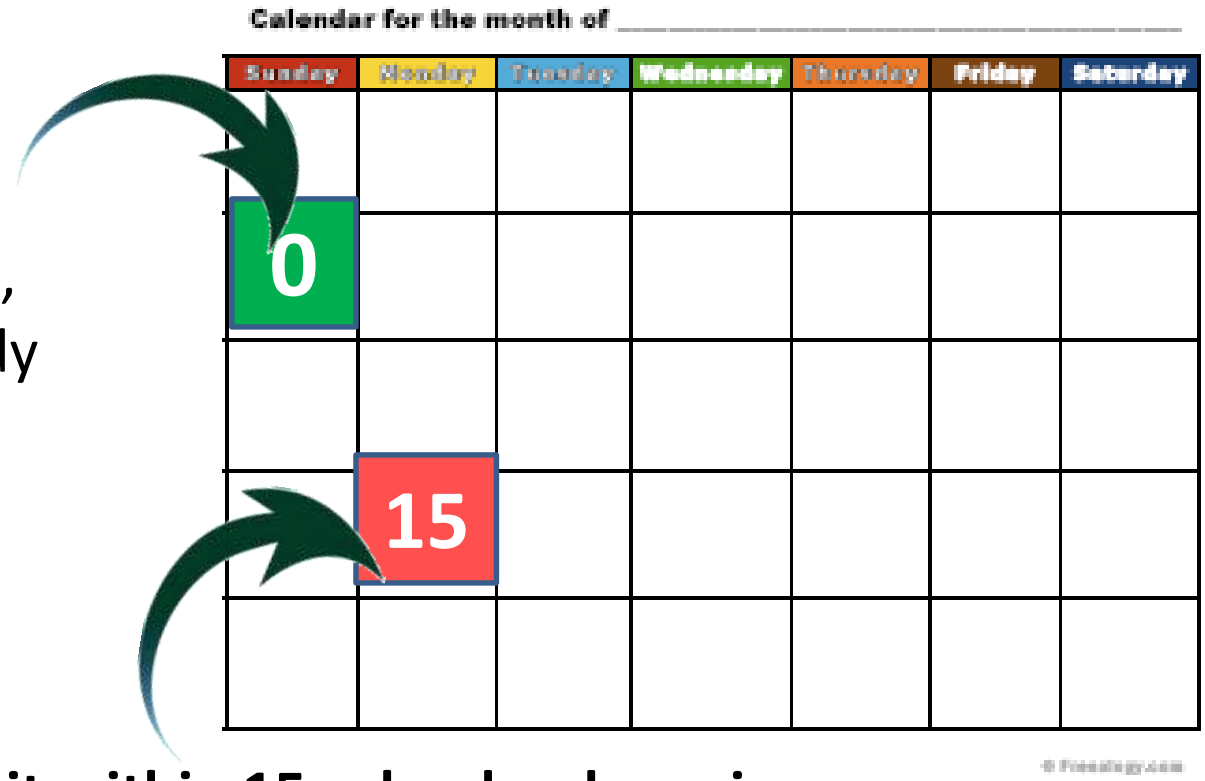
Greater severity or specificity than AE listed in brochure

Reasonable possibility that the drug caused AE

What to report

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

How does FDA receive AEs?

Subject -> Clinical Investigator

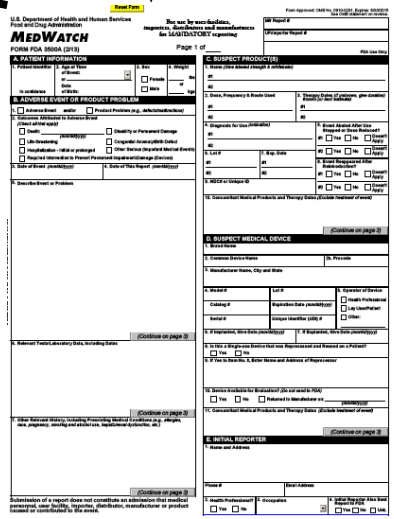
Other studies, animal testing, inc. rate of AE

Per protocol

Sponsor receives AE

AE submitted to all IND investigators

15 calendar days


MEDWATCH
FORM FDA 3500A (2/13)

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

Literature, studies, registries, sales force, etc.

Voluntary

Firm receives AE

Mandatory

MedWatch Online Voluntary Reporting Form (3500)

MEDWATCH 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

Firms with an account login to access the SRP

Email Confirmation

Subject: Safety Report ID FPSR7374 Submission Confirmation

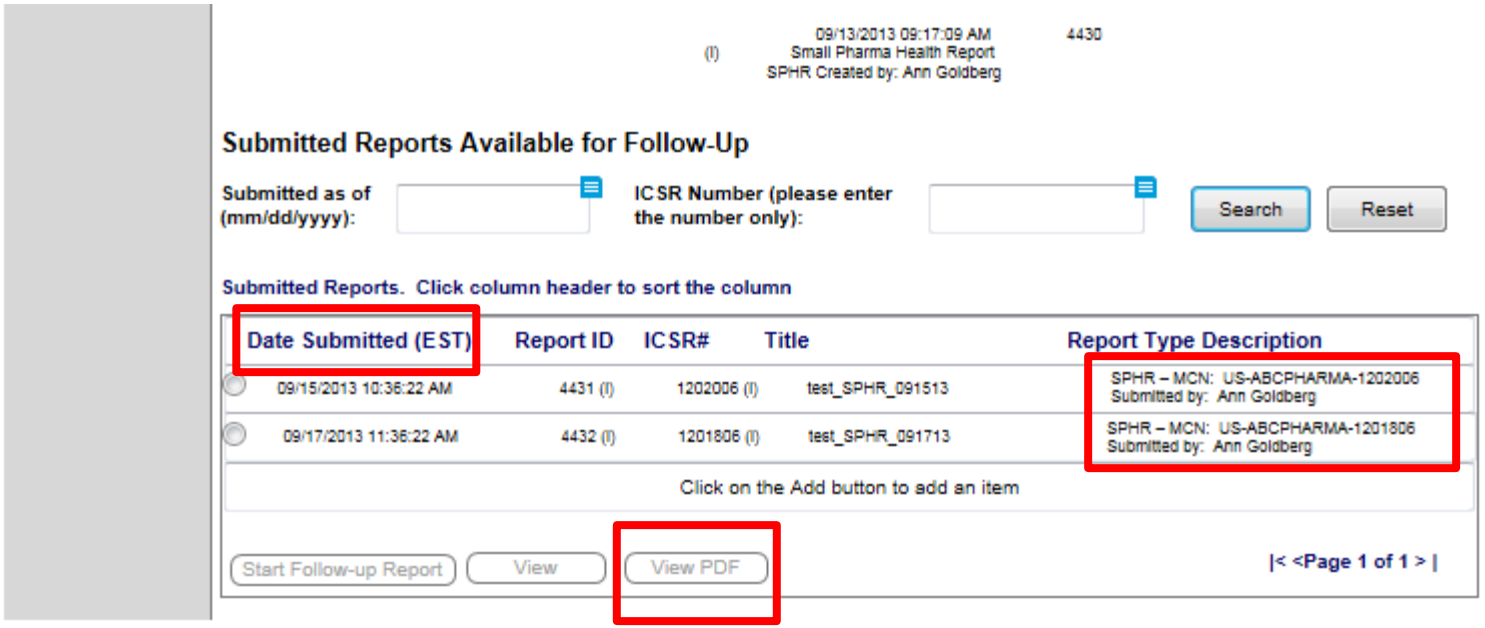
Your initial Marketed Human Drug and Therapeutic Biologics Report, Submitted by: UserFirstname UserLastname, MCN: MCN0000, ID FPSR7374, was successfully submitted on 8/25/2015 2:42:08 PM EST to the FDA, and it was issued an Individual Case Safety Report Number (ICSR) of 1103423.

Thank you for using the Safety Reporting Portal.

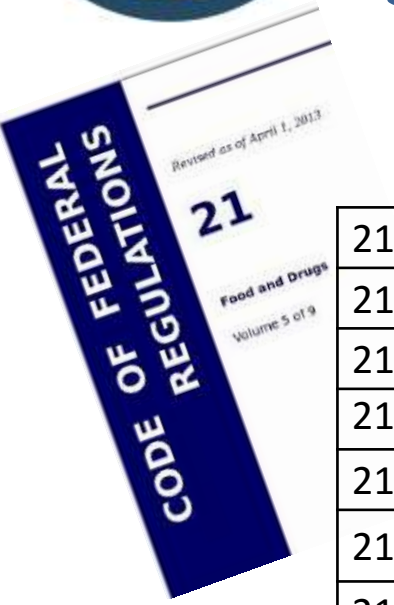
Please do not reply to this message. Replies to this message are routed to an unmonitored mailbox. If you have questions please refer to the Portal's Contact Us page for further instructions.

My Report History in SRP

My Report History in SRP



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

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