Collaborating with FDA- Get Involved with the FDA MedWatch Adverse Event Reporting Program

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Learning Objectives

• Introduce the FDA Office of Health and Constituent Affairs (OHCA)
• Share examples of ways to advance FDA messages and be involved in FDA processes
• Describe the FDA MedWatch Program
• Identify the types of adverse events and product problems that should be reported to FDA
• Explain how to submit a report to the FDA MedWatch Program
• Summarize how to obtain safety information from FDA MedWatch
FDA Regulates $1 Trillion Worth of Products a Year

Every morning when you wake up and

brush your teeth
put in your contact lenses
microwave your breakfast
take your medicine
feed your pet
select a lipstick
go grocery shopping
get a flu shot or a mammogram….

You have been touched by the U. S. Food and Drug Administration.
Assessment question-
Which is **Not** Regulated by the FDA

A) Aspirin
B) Anti-lice shampoo
C) Insect repellent
D) Lipstick
Assessment question-
Which is *Not* Regulated by the FDA

a. Spam
b. Puppy food
c. Chocolate covered cherries
d. Frozen spinach
e. Imported caviar
Assessment question-
Which is *Not* Regulated by the FDA

a. Illegal heroin use
b. Veterinary tetracycline
c. Barbiturates
d. Medical oxygen
e. Methadone
Assessment question-
Which is *Not* Regulated by the FDA

a. Kidney dialysis machine
b. Tongue depressor
c. Toothpaste
d. Fluoridated toothpaste
e. Hair dryer
Assessment question -
Which is **Not** Regulated by the FDA

a. Tamper-resistant packaging for over-the-counter (OTC) drugs
b. Child-proof packaging for OTC drugs
c. Plastic containers for soft drinks
d. Valentine heart box containing chocolates
e. Tube containing medical ointment
FDA In Your Neighborhood
FDA's Office of Health and Constituent Affairs (OHCA) serves as the liaison between FDA and stakeholder organizations to educate constituents on FDA related issues and activities.
Collaboration and Engagement Examples

• Webinars
• Publishing
• Memorandum of Understanding
• MedWatch
Advance our Reach through Webinars
Advance our Reach through Publishing

High doses of loperamide can cause serious cardiac events

FREDERICK A. MAHLER

FDA is warning that taking higher-than-recommended doses of the over-the-counter (OTC) and prescription antidiarrheal medicine loperamide, including through abuse or misuse of the product, can cause serious cardiac events, including torsades de pointes, cardiac arrest, ventricular tachycardia, syncope, and death. The risk of these serious cardiac events may also be increased when high doses of loperamide are taken with other drugs that can interact with loperamide.

The majority of reported serious heart problems occurred in individuals who were intentionally misusing and abusing high doses of loperamide to achieve a feeling of euphoria.

Background
Loperamide is approved to help control symptoms of diarrhea, but it is sold under the OTC brand name Imodium A-D at store shelves, and as generics. It is important not to exceed the total daily dose that is recommended on the drug label. Loperamide is approved for use in single doses of 4 mg for the first dose, followed by 2 mg after each loose stool for adults. The maximum approved total daily dose is 8 mg per day for OTC use and 16 mg per day for prescription use. Dosing for children depends on the age of the child and is not recommended for use in children younger than 2 years.

Loperamide can interact with other drugs that are cytochrome (CYP) 3A4 inhibitors (e.g., simvastatin, alendronate, erlotinib, cyclosporine, and clarithromycin), and other drugs that are cytochrome (CYP) 3A4 inhibitors (e.g., gefitinib, and pimozide) and cytochrome 2C19 inhibitors.

Safety data
In the 20 years between when loperamide was first approved in 1998 and 2015, FDA received reports of 46 cases of serious heart problems associated with use of loperamide. Thirty-eight of these cases resulted in hospitalizations, and 10 patients died.

In the majority of severe cases, individuals intentionally abused loperamide. Some patients also misused loperamide by taking higher-than-recommended doses to treat their diarrhea. In the most severe cases, individuals self-treated with doses ranging from 70 mg to 1400 mg per day, which is 4 to 330 times the recommended dose. In several cases, individuals continued taking loperamide despite the risk of serious adverse cardiac events.

In the majority of severe cases, individuals intentionally abused loperamide.

Summary of safety labeling changes
As part of FDA's MedWatch program, changes to the boxed warnings in the labeling of drugs and biologics that are approved are compiled quarterly. These and other labeling changes are searchable in the Drug Safety Labeling Changes (DLC) database, where data is available to the public in downloadable and searchable formats. Boxed warnings are routinely used to highlight (1) an adverse reaction so serious in proportion to the potential benefit from the drug that it is essential that the reaction be considered in assessing the risks and benefits of using the drug, and (2) serious adverse reactions that can be prevented or reduced in frequency or severity by appropriate use of the drug, and (3) situations in which FDA approved a drug with limitations in case use so that FDA concluded that the drug can be safely used only if distribution or use is restricted. The following changes to boxed warnings were identified in the October 10 search of the Drug Safety Labeling Changes (DLC) database over the time range July 1, 2016, through September 30, 2016.

Class of Systemic Fluoroquinolone Antibacterial Drugs, including Avolin (ciprofloxacin hydrochloride), Cipro (ciprofloxacin hydrochloride), Cipro IV (ciprofloxacin hydrochloride injection), Cipro XR (ciprofloxacin hydrochloride extended-release tablets), Levaquin (levofloxacin extended-release tablets), Noroxin (norfloxacin hydrochloride) and Noroxin (norfloxacin hydrochloride, extended-release tablets), refer to www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm and the report of labeling changes for specific new drug application.

Updated Quinolone Boxed Warning

WARNING: SERIOUS ADVERSE REACTIONS INCLUDING TENDONITIS, TENDON RUPTURE, PERIPHERAL NEUROMYOPATHY, CENTRAL NERVOUS SYSTEM EFFECTS AND EXACERBATION OF MYASTHENIA GRAVIS

• Fluoroquinolones, including Product, have been associated with disabling and permanently irreversible serious adverse reactions that have occurred together including:
  - Tendinitis or tendinopathy
  - Peripheral neuropathy
  - Central nervous system effects

• Discontinue (Product) immediately and avoid the use of fluoroquinolones, including (Product), in patients who experience any of these serious adverse reactions. Fluoroquinolones, including (Product), may exacerbate muscle weakness in patients with myasthenia gravis. Avoid (Product) in patients with known history of myasthenia gravis.

• Because fluoroquinolones, including (Product), have been associated with serious adverse reactions, reserve (Product) for use in patients who have no alternative treatment options for the following indications:
  - Acute bacterial sinusitis
  - Acute bacterial exacerbation of chronic bronchitis
  - Acute exacerbation of chronic bronchitis (for Cipro XR and Noroxin)
  - Uncomplicated urinary tract infections
  - Acute bacterial sinusitis for infections
  - Acute exacerbation of chronic bronchitis (for Cipro XR and Noroxin)
  - Uncomplicated urinary tract infections
  - Acute exacerbation of chronic bronchitis
  - Acute bacterial sinusitis

Updated Krystexxa (kedrinasali) Boxed Warning

WARNING: ARACHNIDIASIS AND INFUSION REACTIONS; GDP DEFICIENCY ASSOCIATED MEMOLYSIS AND METHEMOGLOBINEMIA (Title Updated)

Addition of

- Serum patients at risk for GDP deficiency prior to starting Krystexxa. Hemolytic and methemoglobinemia have been reported with Krystexxa in patients with GDP deficiency. Treat asymptomatic Krystexxa in patients with GDP deficiency.
Advance our Reach through MOUs

MedWatch: a Vehicle to Engage with FDA

1. A way to send information *IN* to FDA
2. A way to get safety information *OUT* from FDA

www.fda.gov/medwatch
What is a drug as defined by the FDA?
A drug is any product that is intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease and that is intended to affect the structure or any function of the body.

Drug Approval Process

1. **Drug Developed**
   - Drug sponsor develops a new drug compound and seeks to have it approved by FDA for sale in the United States.

2. **IND Application**
   - The sponsor submits an Investigational New Drug (IND) application to FDA based on the results from initial testing that include:
     - The drug's composition and manufacturing
     - A plan for testing the drug on humans
   - **IND REVIEW**
     - FDA reviews the IND to assure that the proposed studies, generally referred to as clinical trials, do not present a significant risk to human subjects or an unreasonable risk of harm.
     - FDA also verifies that there are adequate informed consent and human subject protection.

3. **20-80**
   - The typical number of healthy volunteers used in Phase 1; this phase emphasizes safety. The goal here in this phase is to determine what the drug's most frequent side effects are and, often, how the drug is metabolized and excreted.

4. **100's**
   - The typical number of patients used in Phase 2; this phase emphasizes effectiveness. This goal is to obtain preliminary data on whether the drug works in people who have a certain disease or condition. For controlled trials, patients receiving the drug are compared with similar patients receiving a different treatment—usually a placebo or a different drug. Safety continues to be evaluated, and short-term side effects are studied.

5. **1000's**
   - The typical number of patients used in Phase 3. These studies gather more information about safety and effectiveness, study different populations and different dosages, and uses the drug in combination with other drugs.

At the end of Phase 2, FDA and sponsors discuss how large-scale studies in Phase 3 will be done.

Note: FDA's Center for Drug Evaluation and Research (CDER) evaluates new drugs before they can be sold.

The center's evaluation not only prevents quackery, but also provides doctors and patients the information they need to use medicines wisely. CDER ensures that drugs, both human and veterinary, are effective and their health benefits outweigh their known risks.
“Every product that FDA approves carries some risk...Sometimes there are risks that only come to light after a medical product gets on the market and is used in a larger number of patients, for a longer period of time, and in patients whose health characteristics are different from those of the patients studied before approval."

- Norman Marks, M.D., retired MedWatch Medical Officer
MedWatch - Reporting IN

Anyone can report a problem
MedWatch Reporting IN

• One person can make a difference.
Assessment question

True or False. You must be a healthcare professional in order to submit a report to MedWatch.

False
MedWatch - What to Report

• Serious events
• Medication errors
• Product quality problems
• Potential for error
• Non-serious events
Reporting IN – Serious events

• Any event that:
  – Is fatal
  – Is life-threatening
  – Is permanently disabling
  – Requires/ prolongs hospitalization
  – Causes a birth defect
  – Requires intervention to prevent permanent impairment or damage
  – Potential for harm/close calls (drugs or devices)
FDA is also interested in cases where the potential for harm exists.

Such reports help FDA identify and better understand the risks associated with medical products.
Potential Errors

• Prescribing
  – handwriting, abbreviations

• Miscommunication of Orders/Nomenclature
  – sound alike, look alike
Potential Errors

• Label/Packaging
  – placement of information
  – expression of strength/dose
  – readability of label
  – inappropriate labeling during repackaging
MedWatch Reporting-
VOLUNTARY

Clinician Form 3500  Consumer/Patient Form 3500B
MedWatch Reporting - MANDATORY

MANDATORY Form 3500A

- User Facilities (medical devices)
- Manufacturers
  - Drugs
  - Biologics
  - Human Cell and Tissue Products
  - OTC Products
  - Medical Devices
Responsive Design

- First for FDA website
- Screen will adjust to device used to access web page: i.e. tablets, smartphone
How do I report?

Report A Problem

www.fda.gov/medwatch
MedWatch Online Voluntary Reporting Form

Welcome

Begin report as a:

Health Professional
(FDA Form 1500)

Consumer/Patient
(FDA Form 2500)

What to Report to FDA MedWatch:

Use the MedWatch form to report adverse events that you observe or suspect for human medical products, including serious drug side effects, product use errors, product quality problems, and therapeutic failures for:

- Prescription or over-the-counter medicines, as well as medicines administered to hospital patients or at outpatient infusion centers
- Biologics (including blood components, blood and plasma derivatives, allergenic, human cells, tissues, and cellular and tissue-based products (HCT/Ps))
- Medical devices (including in vitro diagnostic products)
- Combination products
- Special nutritional products (infant formulas, and medical foods)
- Cosmetics
- Foods/beverages (including reports of serious allergic reactions)

What Not to Report to FDA MedWatch:

- Tobacco: Tobacco product problems should be reported to the Safety Reporting Portal.
- Vaccines: Report vaccine events to the Vaccine Adverse Event Reporting System (VAERS) online at https://vaers.hhs.gov/vaersb/index
- Investigational (study) drugs: Report investigational (study) drug adverse events as required in the study protocol and send to the address and contact person listed in the study protocol.
- Mandatory recording by regulated industry:
  - Drugs and Biologics
    - Applicable Regulations
    - Devices
- Reporting on Dietary Supplements
- Reporting on Veterinary Medicine Products
- Reports FDA Does Not Handle (e.g., CPSC, FTC, State Health Departments) and Others to Send Them

Note: If you need help accessing information in different file formats, see Instructions for Downloading Viewers and Players.

MedWatch Home | Safety Info | How to Report | Download Forms | Join Email
How do I report?

- Online
- Mail/Fax
- By Phone
  1-800-332-1088

www.fda.gov/medwatch
The FDA will accept your adverse event report by which of the following methods?

A) Mail
B) Online submission
C) Fax
D) All of the Above
Four Minimum Elements

- Patient Identifier
- Event or Problem
- Reporter
- Product
Assessment Question

Case #1

Health care worker ST reported male patient ABC123 started Drug X at 5 mg daily for type 2 diabetes on February 11, 2015. The patient developed liver failure.

Question: Does Case #1 contain the four elements needed to file this report into the MedWatch database?

A  Yes
B  No
What makes a good report a Great report?
• 59-year-old male ABC123 with type 2 diabetes, hyperlipidemia, and hypertension. No history of liver disease.
• Started Drug X on February 11, 2015.
• Other medications: Drug Y and Drug Z.
• Labs drawn on Feb 11 revealed Liver enzymes, INR, creatinine, and bilirubin all within normal limits.
• No alcohol use.

• 8 weeks after starting Drug X patient presented to ER with 5 day history of jaundice, dark urine, and nausea/vomiting.
• He was admitted to ICU and subsequently diagnosed with acute liver failure.
• Drug X stopped upon admission.
• Viral hepatitis was ruled out.
• 7 days after stopping the medication, all lab values returned to normal.
• Reported by ST
What Happens to Your MedWatch Report?

- Report is captured in a database
- FDA safety evaluator use a variety of methods to screen database
How can MedWatch Reports Result in Product Changes?

- Update the product label
- Request a change in the product’s design, process, packaging, or distribution
- Request a product recall
MedWatch-Safety OUT

• Subscribe to MedWatch
  – E-list
  – Twitter
  – RSS feeds
Vancomycin Hydrochloride for Injection, USP by Hospira: Recall - Particulate Matter in Vial

[Posted 01/25/2017]

AUDIENCE: Pharmacy

ISSUE: Hospira, Inc. is voluntarily recalling one lot of Vancomycin Hydrochloride for Injection, USP (NDC: 0409-6510-01, Lot 591035A, Expiry Date 1NOV2017), to the hospital/retail level due to a confirmed customer report for the presence of particulate matter within a single vial. The product is packaged in a vial containing 1x100 mL vial. The lot was distributed from August 2016 through September 2016 in the United States.

If particulate is administered to a patient, it may result in local swelling, irritation of blood vessels or tissue, blockage of blood vessels and/or low-level allergic response to the particulate. The risk is reduced by the possibility of detection, as the label contains a clear statement directing the physician to visually inspect the product for particulate matter and discoloration prior to administration.

BACKGROUND: Vancomycin Hydrochloride is indicated for the treatment of serious or severe infections caused by susceptible strains of methicillin-resistant staphylococci.

RECOMMENDATION: Anyone with an existing inventory of the recalled lot should stop use and distribution and quarantine the product immediately. Inform health care professionals in your organization of this recall. If you have further distributed the recalled product, please notify any accounts or additional locations which may have received the recalled product from you. Further, please instruct entities that may have received the recalled product from you that if they redistributed the product, they should notify their accounts, locations or facilities of the recall to the hospital/retail level. Hospira will be notifying its direct customers via a recall letter and is arranging for impacted product to be returned to Stericycle in the United States.

Healthcare professionals and patients are encouraged to report adverse events or side effects related to the use of these products to the FDA's MedWatch Safety Information and Adverse Event Reporting Program:

• Complete and submit the report Online: www.fda.gov/medwatch/report
• Download form or call 1-800-332-1088 to request a reporting form, then complete and return to the address on the pre-addressed form, or submit by fax to 1-800-FDA-0178

[01/24/2017 - Press Release - FDA]
**FDA Case Studies**

**FDA MedWatch Adverse Event Reporting Curriculum Case Study**

**DRUGS, DEVICES, & BIOLOGICS: Health professionals encounter adverse events with medicinal products and learn about reporting to FDA MedWatch**

"I'm not sure," Chris replied. He took a few moments to think. "I find my skin was getting lighter, but I didn't think anything of it since I used to use that patch in the same place and that area isn't exposed much to light." "Well, discrimination like this is sometimes a sign of melasma, or loss of color pigment in the skin." [Image 12x35 to 709x455]

**FDA MedWatch Adverse Event Reporting Curriculum Case Study: Instructor’s Guide**

**LEARNING OBJECTIVES**
- Identify how to receive safety information from the FDA.
- Identify how to submit a quality medical product complaint report to FDA.
- Explain how reports are used by FDA to investigate and attribute events, and to take action to ensure safety.
- Review the definitions of drug, device, and biologic.

**TOPICS**
- Adverse event reporting: Maximum, forms: 2050, 2050A, 2050B, 2050C, Drugs, Devices, Biologics.

**ASSUMPTIONS**
This case study is based on the assumption that the student has a background in pharmacology who took a course on adverse drug reactions.

**SUGGESTED APPROACH**
1. Improving Students: Students are expected to read the case study prior to the training session.
2. Engaging Students: The training session should consist of a discussion of the case study and completion of a Reflection Form.
3. Intervening Students: The training session should address group discussion of the case study. In-class discussion is possible.

**STUDENT ACTIVITIES Before Case**
- Review the following materials before class:
  - MedWatch Newsletter: http://www.fda.gov/ForHealthProfessionals/LearningActivities/default.htm

**STUDENT ACTIVITIES During Case**
- Review the following materials before class:
  - MedWatch Newsletter: http://www.fda.gov/ForHealthProfessionals/LearningActivities/default.htm

**FDA Drug Information Curriculum Case Study: Instructor’s Guide**

**FDA Useful Drug Information for Clinicians: Practicing clinicians seek available information on a new drug before making a treatment decision**

If they listened closely, the patients in the cardiology wing of San Valley hospital could hear them. Several pairs of rubber-soled shoes dragged the ground to quick paces as they tried to keep up with the flurry of Dr. Michael Carpenter, attending physician and director of the cardiology department. In his wake, the small talking doctors and chief resident, Dr. Amanda Baird, made a sound as they followed with each word and gesture. As the nurses, residents, and interns began their daily rounds, Carpenter asked: "How is the heart of that patient doing today?"

"I'm not sure," Dr. Baird replied. "I heard from her nurse that she has been having some chest pain and I just thought I should let you know before we head to the clinic today." Carpenter continued, "Take her back to San Valley at the age of 48 after she experienced severe chest pain and fell unconscious at her son's graduation party. Then blue, she stopped breathing, and the emergency team rushed her to the hospital quickly, but there was no palpable pulse."

**LEARNING OBJECTIVES**
- Identify an online resource for FDA’s drug review materials based: www.fda.gov/Drugs/ReviewApplications.
- Determine if a drug or biological marketed in the U.S. has been discussed at an FDA advisory committee meeting.
- Gain an understanding of the FDA advisory committee's role in promoting a product's benefits and risks.
- Explain the characteristics of a new molecular entity (NME).
- Gain an understanding of risk evaluation and mitigation strategies (REMS) and their role.

**TOPICS**
- FDA Drug Information Resources: Drugs@FDA, Risk Evaluation and Mitigation Strategies, U.S. Food and Drug Administration (FDA) Cardiome, LTD, FDA Drug Shortages Program

**ASSUMPTIONS**
This case study is based on the assumption that the target audience is undergraduate students in health disciplines who are unfamiliar with FDA drug information resources.

**SUGGESTED APPROACH**
1. Preparing Students: Students are expected to read the case study prior to the training session.
2. Engaging Students: The training session should consist of a discussion of the case study.
3. Immersing Students: The training session should emphasize group discussion of the case study. Students should be encouraged to review the materials before the training session.

**STUDENT ACTIVITIES**
- Review the following materials before class:
  - What is Drugs@FDA?
  - Drugs@FDA is a searchable database of drug product labels and approval-related documents, including reviews, approval letters, and current and archived labeling.
- True or False: Advisory Committee members are FDA employees.

**Answer**
- True or False: Advisory Committee members are FDA employees.

**Answer**
- Answer: Drugs@FDA is a searchable database of drug product labels and approval-related documents, including reviews, approval letters, and current and archived labeling. The marketing applications they review include data about the safety and effectiveness of human drugs. The committees receive summary information about the drug applications and copies of FDA’s review of the application documents, based on this information, advisory board members vote on whether to recommend approval of the drug or not. The final decision is made by the FDA Commissioner and depends on the recommendation of the advisory committee.
Reporting Tutorial – MedWatchLearn

• Online practice portal
  – Students/Health Professionals
  – Consumers Section
  – Learn how to fill out a MedWatch Report

www.fda.gov/medwatchlearn
Reporting Tutorial - MedWatch Learn

MEDWATCH LEARN

FDA MedWatch Learn teaches students, health professionals, and consumers how to complete the forms necessary to report a serious side effect or problem with a medical product or device. You have the opportunity to practice filling out FDA Form 3500 (for health professionals) or FDA Form 3500B (for consumers).

Learn more about MedWatch medical product safety or submit an actual report.

To start, select either “Students and Health Professionals” or “Consumers.”

This site performs best with Internet Explorer 9 or higher, or recent versions of Firefox, Safari, and Chrome web browsers. If you are having trouble viewing or printing pages, try updating your browser to the latest available version.

Page Last Updated: 05/29/2013
Note: If you need help accessing information in different file formats, see Instructions for Downloading Viewers and Players.
MedWatch Learn v1.0
Assessment Question

What is MedWatch?

A. A way to send information to FDA on problems with medical products
B. A way to receive safety information from FDA
C. Both A and B
Thank You!
Questions?

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