Medication Errors: A CDER Perspective

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Team Leader
Division of Medication Error Prevention and Analysis
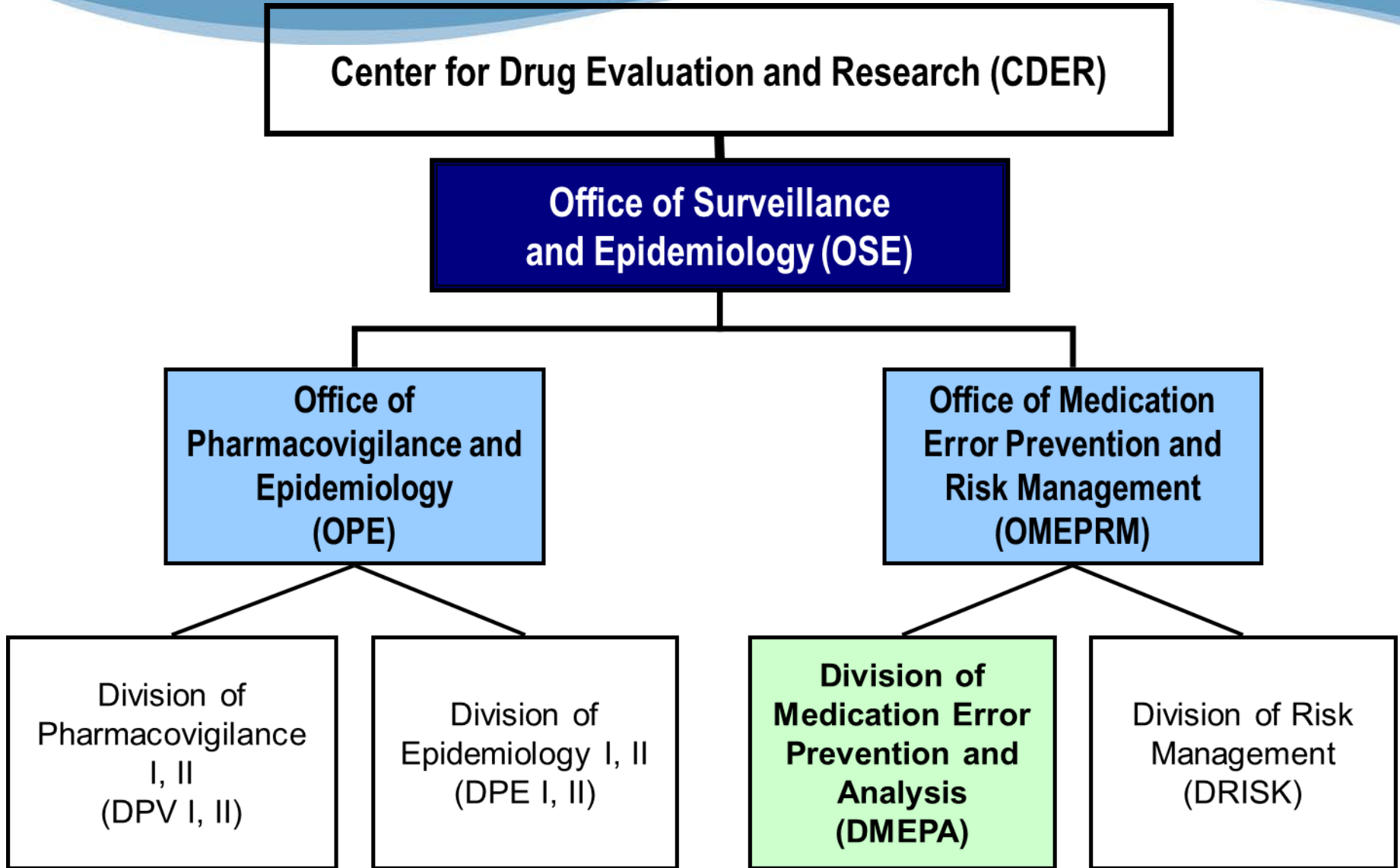**Office of Medication Error Prevention and Risk Management**
Office of Surveillance and Epidemiology
June 25, 2015

U.S. Food and Drug Administration
Protecting and Promoting Public Health

Objectives of the Presentation

- Describe Division of Medication Error Prevention and Analysis' role and responsibilities and its mission.

- Describe sources and types of Medication Errors.

- Describe how you can help identify, prevent, and mitigate medication errors.

Center for Drug Evaluation and Research (CDER)

Office of Surveillance and Epidemiology (OSE)

Office of Pharmacovigilance and Epidemiology (OPE)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Division of Pharmacovigilance I, II (DPV I, II)

Division of Epidemiology I, II (DPE I, II)

Division of Medication Error Prevention and Analysis (DMEPA)
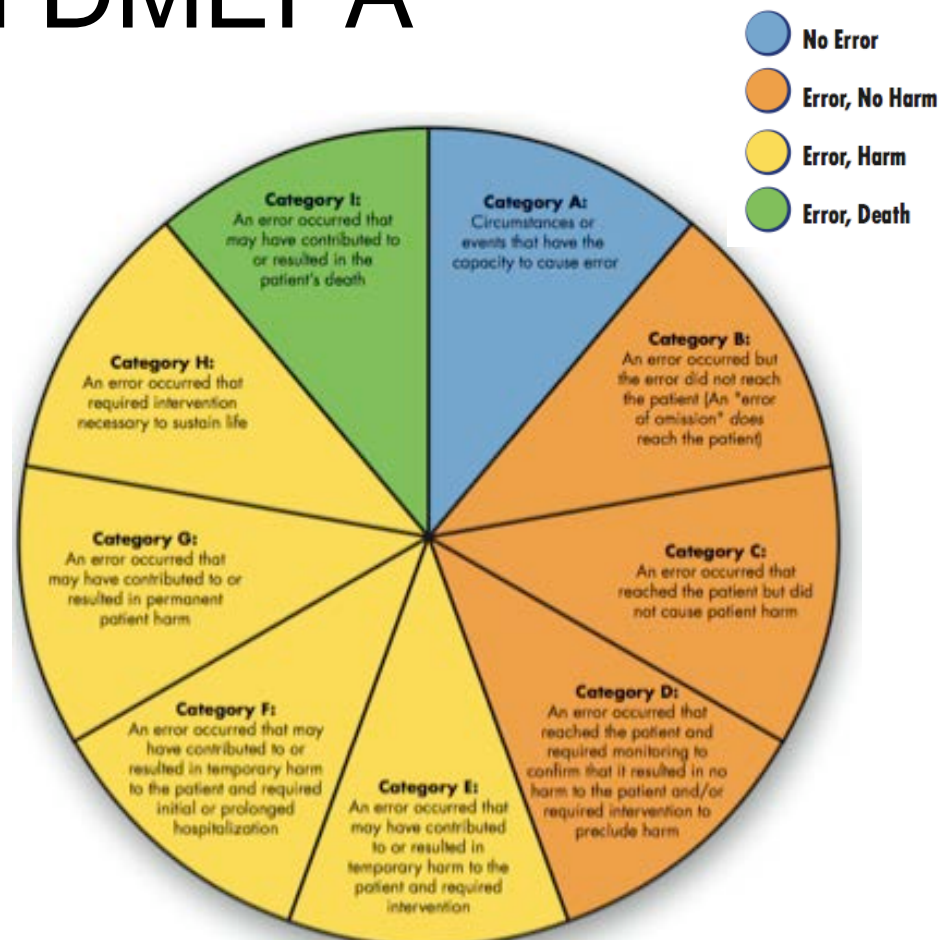
Division of Risk Management (DRISK)

DMEPA

- Division of Medication Error Prevention and Analysis
  - Healthcare professionals with varied backgrounds (i.e., pharmacists, nurses, physicians)
  - 43 FTE's
  - Aligned by therapeutic areas
- DMEPA created ~1999

Definition of "Medication Error" for FDA and DMEPA

We define medication error in accordance with NCCMERP, which states …it is any <u>preventable</u> event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer

Legend:
- No Error
- Error, No Harm
- Error, Harm
- Error, Death

Category I: An error occurred that may have contributed to or resulted in the patient's death

Category A: Circumstances or events that have the capacity to cause error

Category B: An error occurred but the error did not reach the patient (An "error of omission" does reach the patient)

Category H: An error occurred that required intervention necessary to sustain life

Category G: An error occurred that may have contributed to or resulted in permanent patient harm

Category C: An error occurred that reached the patient but did not cause patient harm

Category F: An error occurred that may have contributed to or resulted in temporary harm to the patient and required initial or prolonged hospitalization

Category E: An error occurred that may have contributed to or resulted in temporary harm to the patient and required intervention

Category D: An error occurred that reached the patient and required monitoring to confirm that it resulted in no harm to the patient and/or required intervention to preclude harm

National Coordinating Council for Medication Error Reporting and Prevention.
Available at: www.nccmerp.org. Accessed 10/30/13.

5

DMEPA's Mission and Regulatory Authority

- To increase the safe use of drug products by minimizing use error that is related to the naming, labeling, and/or packaging of drug products.

- Our regulations and guidelines are intended for industry and not healthcare providers.

Responsibilities

- Pre-marketing Risk Assessment Reviews:
  – Proprietary Name
  – Labeling and Packaging
  – Human Factors

- Post-marketing Activities
  – Medication error signal surveillance and analysis
  – Medication error cases evaluation and reviews
  – Collaboration with ISMP for medication error surveillance, analysis, and prevention
  – Drug Safety Communications and Consumer Updates
  – Research

Responsibilities, Cont.

- Additional Activities:
  - Guidelines, MAPP, Regulation Development, and PDUFA negotiations
  - Input on Risk Evaluation and Mitigation Strategies (REMS), when related to mitigating the risk of medication errors
  - Committee Involvement (NCC MERP, USP's Safe Medication Use and Nomenclature Standards, and CDER LNC)

Draft Guidances

- Safety Considerations for Product Design to Minimize Medication Errors (Draft, 2012)
- Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (Draft, 2013)
- Best Practices in Developing Proprietary Names for Drugs (Draft, 2014)

Draft Guidance for Industry: **Safety Considerations for Product Design to Minimize Medication Errors**

- Provides sponsors with a set of principles for developing Rx and OTC drug products using a systems approach to minimize medication errors relating to product design
- Describes methods for proactive risk assessments of proposed product design and the container closure
- Draft issued December 13, 2012
- Comment period closed February 2013 (comments under review and consideration)
- http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM331810.pdf

10

Examples of Known Problems Due to Product Design

- Solid Oral Dosage Forms
  - Inadequate differentiation of strengths
  - Imprint codes as a critical identifier

Examples of Known Problems Due to Product Design

- Solid Oral Dosage Forms
  - Product resembles candy
  - Choking hazard
    - Sticky coating
    - Large size
    - Larger cross sectional area
    - Propensity for swelling
  - Too hard/Too friable
- Product Line Extensions
  - Creating extended-release product strength(s) that overlap in strength(s) with immediate release products

12

Examples of Known Problems Due to Product Design

- Dosing Devices not appropriate for dosages to be measured
- Difficult to see dose markings on dosing device
- Intravenous Products
  - 2 step dilution for a product already in solution
    - Overdoses due to failure to dilute product
    - Improper doses due to incorrect dilution
- Co-packaging of special diluent
  - Diluent separated from dry powder
  - Confusing diluent as drug

13

Examples of Known Problems Due to Product Design

- Topical products packaged in container/ closures that look similar to eye, ear, nasal, or oral products

14

Examples of Known Problems Due to Product Design

- Capsules for inhalation swallowed whole

15

Draft Guidance for Industry: **Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors**

- Provides sponsors with a set of principles and recommendations for ensuring that critical elements of product labels and labeling are designed to promote safe use
- Focuses on safety aspects of Rx container label and carton labeling design
- Draft issued April 24, 2013
- Comment period closed June 24, 2013 (comments under review and consideration)
- http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm349009.pdf

Principal Display Panel (PDP)

Proprietary Name

Established Name or Proper Name

Product Strength

Warning/ Cautionary Statements

Route of Administration

NDC 50242-070-01

Gazyva™
(obinutuzumab)
Injection

1000 mg/40 mL
(25 mg/mL)

For Intravenous Infusion After Dilution.
Single-Use Vial. Discard Unused Portion.
No preservative.

Rx only

Genentech

1 vial
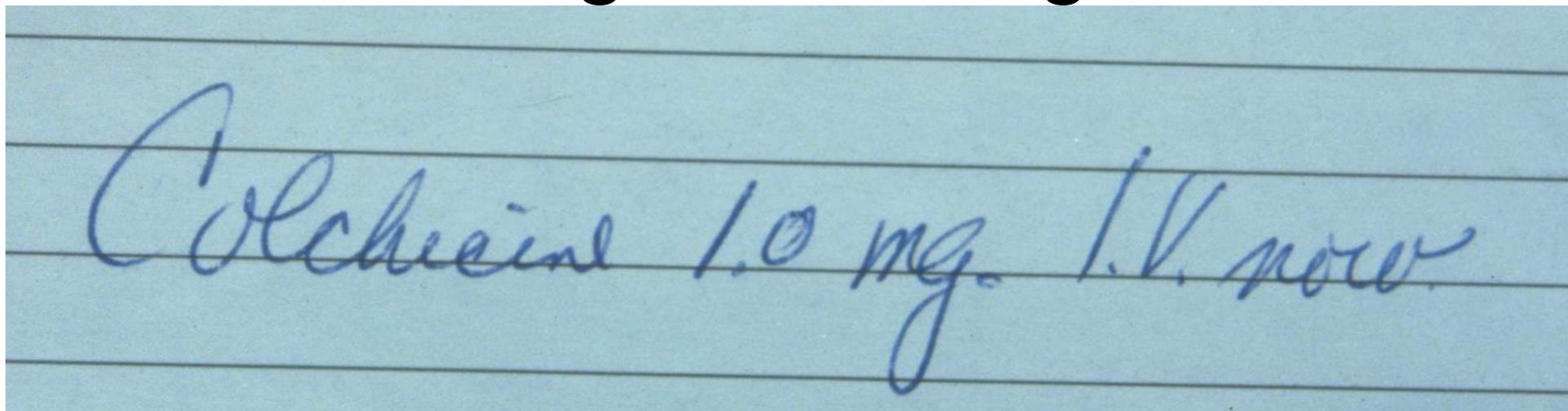
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Dangerous Abbreviations, Acronyms, and Symbols: General Considerations

- Certain abbreviations, acronyms, and symbols are dangerous and should not be used
  - Misinterpretations can lead to mistakes
- Non-standardized abbreviations, symbols, and dose designations can also lead to mistakes
- Refer to The Joint Commission's "Do Not Use" list (http://www.jointcommission.org/assets/1/18/do_not_use_list.pdf)
- Refer to the Institute for Safe Medication Practices (ISMP) "List of Error Prone Abbreviations, Symbols, and Dose Designations" (http://www.ismp.org/tools/errorproneabbreviations.pdf) 18

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Use of Abbreviations & Trailing/Preceding Zeros

Look-alike Container Labels and Carton Labeling: General Considerations

- Encourage Sponsors to create labels and labeling sufficiently distinct from that of their other products

- Consider when products are customarily stored side-by-side or near one another

Look-alike Container Labels and Carton Labeling: General Considerations

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Example, Before and After

Draft Guidance for Industry: **Best Practices in Developing Proprietary Names for Drugs**

- Proprietary name is a critical element in use of drug products

- Intent is to help sponsors develop proprietary names that do not cause or contribute to medication errors or otherwise contribute to the misbranding of the drug

- Proprietary names that are similar phonetically or in their spelling or orthographic appearance, or are otherwise confusing or misleading, may lead to errors

- Applies to Rx and OTC products

- http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm398997.pdf

23

Aspects of Proposed Proprietary Name Assessment

- Misbranding Review
- Safety Review
  - Pre-screening
  - Misleading or error-prone assessment
  - Look-alike and/or sound/alike assessment

Misbranding

- Suggestion that a drug is safer or more effective than has been demonstrated by appropriate scientific evidence
- A fanciful proprietary name may misbrand a product by suggesting that it has some unique effectiveness or composition when it does not

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Safety Assessment-Prescreening

- Things to avoid
  - Obvious similarity to other names
  - Inclusion of medical/coined abbreviations
  - Inclusion or reference to inert or inactive ingredients
  - For combination drug products: avoid suggesting the name of one or more, but not all active ingredients
  - Inclusion of USAN stem
  - Using the same root name for a product that does not share at least one common active ingredient
  - Reusing a proprietary name of a different discontinued drug product

Safety Assessment-Misleading or Error-Prone Attributes

- Evaluated on case-by-case basis whether appropriate or misleading or error-prone
  - Inclusion of product-specific attributes
  - Use of modifiers
  - Brand name extensions
  - Dual proprietary name
  - Drug names used outside the US
  - Rx to OTC switch
  - Use of sponsor name in the proprietary name

27

Safety Assessment Look-alike/Sound-alike to Other Names

- Several Components Are Assessed:
  - Similarity in printing, writing, speech
  - Name Simulation Studies
  - Similarity of names by using FDA's Phonetic and Orthographic Computer Analysis (POCA) program and assessment of POCA scores. (http://www.fda.gov/Drugs/ResourcesForYou/Industry/ucm400127.htm)

Post-Marketing Activities - Medication Error Surveillance

- Sources (also see links at the end of the presentation):
  - Reporting by pharmaceutical companies
  - MedWatch (Voluntary Reporting from HCP and patients) (http://www.fda.gov/Safety/MedWatch/)
  - ISMP Communications [http://www.ismp.org/Newsletters/default.asp]
  - Division of Drug Information (DDI) Inquiries
  - Literature
  - Etc.

Outcomes of Post-Marketing Case Evaluation

- Changes to labels and labeling
- Changes to product design
- Changes to proprietary name of the product
- Drug Safety Communications and Consumer Updates
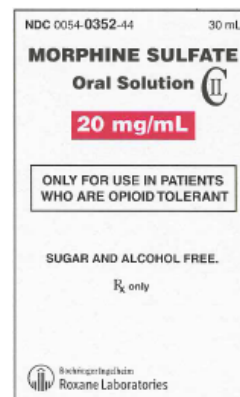- Literature

Example of Changes to the Labels and Labeling

- Morphine Case Study:
  - Oral solution strength confusion
    - 20 mg/5 mL bulk bottles (100 mL & 500 mL)
    - 100 mg/5 mL 120 mL bottle

Figure 1. Unapproved Morphine Sulfate Oral Solution 20 mg/mL previously marketed by Roxane.

Figure 2. Morphine Sulfate Oral Solution 20 mg/5 mL by Roxane.

31

Example of Changes to the Labels and Labeling-Morphine

- Recommendations
  - Oral Solution
    - Differentiate strengths by using contrasting colors, boxing, or some other means
    - Express strength of concentrated solution as 100 mg/5 mL
    - Increase prominence of product strength

- Before

- After

32

Morphine Sulfate Labeling Changes

33

Example of Change in Container Closure System Design

- Benadryl Gel Case Study

  – Reported cases of administration of Benadryl Topical Gel via oral route instead of topical due to design of the container closure system

Example of Change in Container Closure System Design
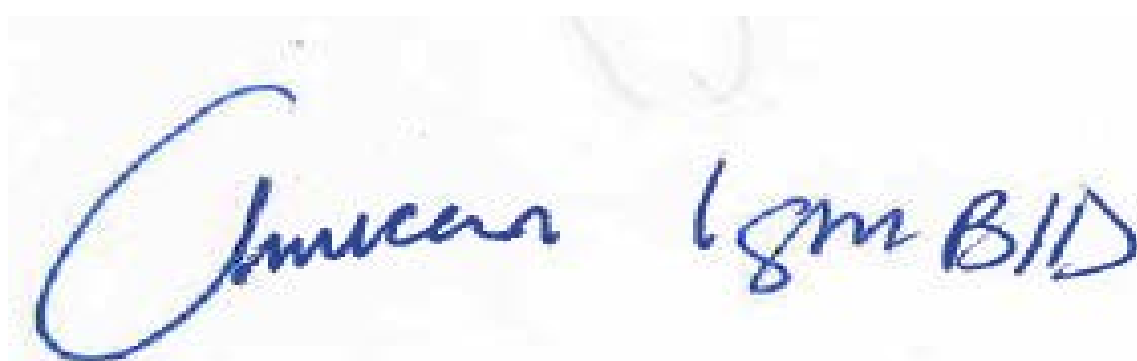
- Before

- After

35

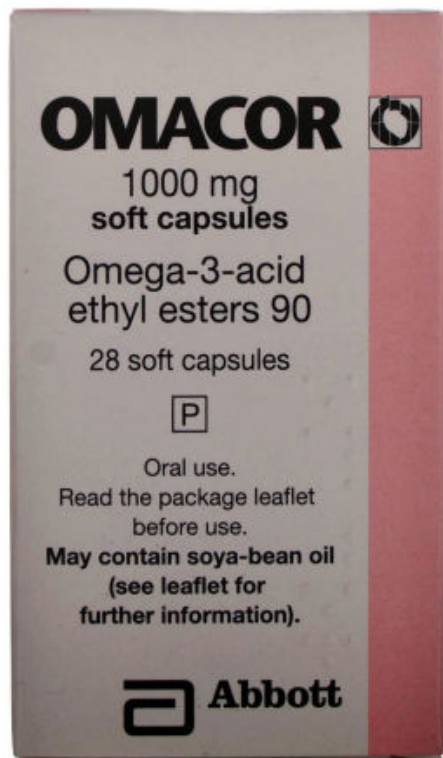# Example of Proprietary Name Change

- Case Study: Amicar or Omacor
    - FDA received reports of name confusion between Omacor and Amicar despite differences in product's strength or dosage form. One case resulted in hospitalization due to shortness of breath, dizziness, and headache.

Example of Proprietary Name Change

- Before

- After

Example of Proprietary Name Change

- Case Study: Kapidex vs. Casodex
  - FDA received reports of name confusion between Kapidex and Casodex despite differences in the products' strengths.
  - Kapidex was re-named to Dexilant to help

Photo courtesy of Takeda Pharmaceuticals

38

Examples of Drug Safety Communications

- FDA Drug Safety Communication: Serious medication errors from intravenous administration of nimodipine oral capsules
  - Multiple reports of intravenous administration of nimodipine oral capsules resulting in patients' death and serious adverse events
  - http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm220386.htm

Examples of Drug Safety Communications

- FDA Drug Safety Communication: Medication errors resulting from confusion between risperidone (Risperdal) and ropinirole (Requip)
  - Large number of reports in which patients were given Risperdal instead of Requip, and vice versa. Several cases resulted in patients hospitalization due to adverse events such as confusion, lethargy, altered mental status, ataxia, hallucinations, tiredness, tingling, etc.

- http://www.fda.gov/Drugs/DrugSafety/ucm25880 5.htm

40

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Example of Consumer Update

- Fentanyl Patch Can Be Deadly to Children

Young children have died or become seriously ill from accidental exposure to a skin patch containing fentanyl, a powerful pain reliever. As a result of this, the Food and Drug Administration (FDA) is issuing a Drug Safety Communication to warn patients, caregivers and health care professionals about the dangers of accidental exposure to and improper storage and disposal of the fentanyl patch.

- Consumer update is based on multiple post-marketing cases of accidental exposure in children that led to death and hospitalization.

41

Example of Journal Articles

- Accidental Pediatric Exposure to Imidazoline Derivatives (journal of Emergency Nursing, Volume 39, Issue 1, Pages 59–60, January 201)
    - Describes accidental pediatric administration of Visine and other ophthalmic and nasal imidazoline derivatives due to several factors including non-child resistant container closure. Majority of cases resulted in hospitalization due to adverse events such as nausea, vomiting, dizziness, somnolence, hypotension, bradycardia, seizures, and central nervous system depression.

    - The article informed how to identify imidazoline derivative poisoning if children present with above symptoms.

How to Help Identify, Prevent, and Mitigate Medication Errors

- Understand FDA's role and responsibilities related to medication errors.

- Be able to find information regarding medication errors and their prevention at your institution from multiple resources.

- Report Medication Errors to FDA through MedWatch so we can evaluate them.

- Disseminate information related to medication error prevention appropriately to your staff.

Finding Information-Resources

- Regulations 21 CFR 200s, 300s and 600s
    - http://www.ecfr.gov/cgi-bin/textidx?tpl=/ecfrbrowse/Title21/21tab_02.tpl
- DMEPA's Issued Draft Guidances
    - http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM331810.pdf

    - http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm349009.pdf

    - http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm398997.pdf

Finding Information-Resources

- POCA
  - http://www.fda.gov/Drugs/ResourcesForYou/Industry/ucm400127.htm

- MedWatch
  - http://www.fda.gov/Safety/MedWatch/

- FDA Medication Error Website
  - http://www.fda.gov/drugs/drugsafety/medicationerrors/

- ISMP Website and their Letters
  - http://www.ismp.org/

  - http://www.ismp.org/Newsletters/default.asp

Finding Information-Resources

- ISMP's "List of Error Prone Abbreviations, Symbols, and Dose Designations"
    - http://www.ismp.org/tools/errorproneabbreviations.pdf
- Joint Commission
    - http://www.jointcommission.org
- Pharmacist's Letter
    - http://pharmacistsletter.therapeuticresearch.com/home.aspx?cs=CEPDA&s=PL&AspxAutoDetectCookieSupport=1
- NCCMERP
    - www.nccmerp.org

Reporting Information-Links and Contacts

- Division of Drug Information (DDI)
    - http://www.fda.gov/AboutFDA/CentersOffices/Officeof MedicalProductsandTobacco/CDER/ucm082585
    - druginfo@fda.hhs.gov
    - Phone (855) 543-3784 or (301) 796-3400
    - Fax (301) 431-6353
    - Address:
    10001 New Hampshire Ave, Silver Spring, MD 20993

Question

Which one of the following statements is FALSE?

A. DMEPA does pre-marketing assessment of the proposed proprietary names

B. DMEPA visits hospital pharmacies to inspect medications in stock and provide advice regarding placement of products

C. DMEPA issued a Draft Guidance regarding Safety Considerations for Product Design to Minimize Medication Errors (Draft, 2012)

Question

All of the following are examples of actions FDA may take in response to post-marketing medication errors, EXCEPT:

A. Revisions to a carton of the product

B. Revisions to the prescribing information labeling

C. Publishing a drug safety communication (DSC)

D. Requesting a change in the ownership of the product's application

Questions