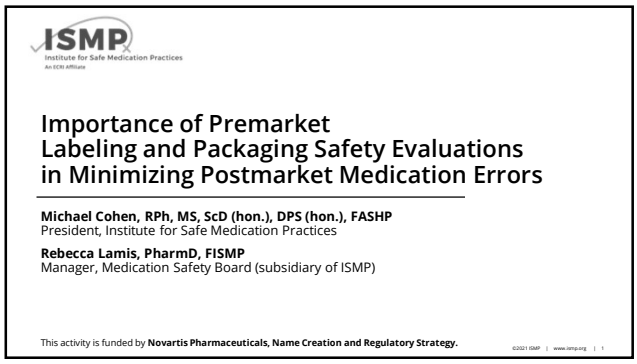
Importance of Premarket Labeling and Packaging Safety Evaluations in Minimizing Postmarket Medication Errors



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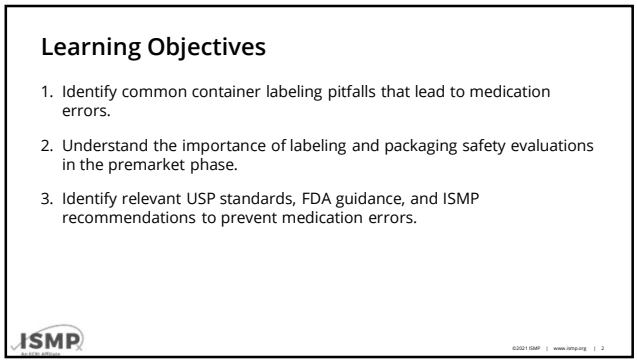

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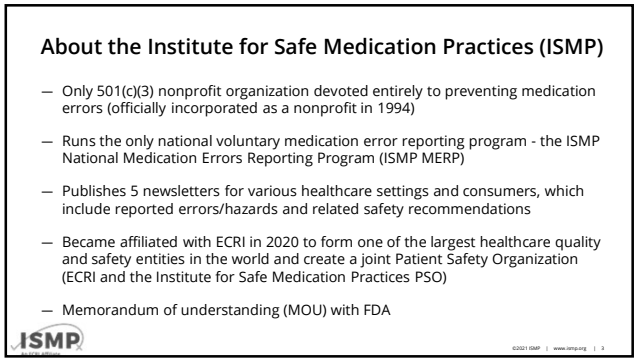

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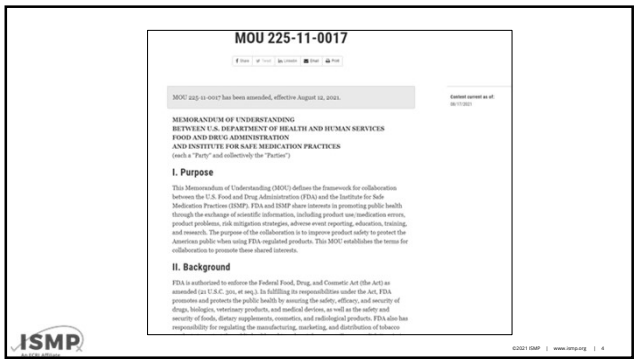
Importance of Premarket Labeling and Packaging Safety Evaluations in Minimizing Postmarket Medication Errors



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6

Importance of Premarket Labeling and Packaging Safety Evaluations in Minimizing Postmarket Medication Errors

About Medication Safety Board (MSB)

- Subsidiary of ISMP
- Dedicated to assisting the pharmaceutical and other healthcare industries with improving the safe use of their medication-related products
- Editorial wall between MSB and the editors of ISMP's acute care newsletter
- Offers various safety consulting services to prevent or reduce the risk of medication errors related to packaging and labeling or the use of medication-related devices/technology, including:
  - **Package and label review or design**
  - **Focus/provider advisory groups**
  - **Risk assessments**
  - **Remediation of product-related medication errors**

7

Premarket Safety Evaluations of Labeling/Packaging

- Background:
  - **Less progress has been made to ensure labeling/packaging safety evaluations are conducted compared to premarket safety testing of medication brand names**
  - **ISMP continues to receive error reports related to look-alike products and misleading container labeling, including repeat issues (more than 25% of reports)**
- Goal:
  - **Proactively identify and prevent (or minimize) the risk of medication errors related to product labeling/packaging premarket, before they can reach patients and potentially result in harm**
  - **Pharmaceutical companies should conduct labeling/packaging safety evaluations on a premarket basis**

8

Label Attributes

- Drug Name (Brand/Generic)
- Concentration/Strength
- Route of Administration
- Warnings
- Container Size (Volume/Tablet Number)
- Additional Information/Statements
- Barcode
- Expiration Date and Lot Number
- Manufacturer Information
- Container Brand Name
- Graduated Markings (bags, syringes)
- Overall Layout/Format
- Use of Color
- Product Differentiation

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Product Name and Concentration/Strength

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Error-Prone Label Conditions

- Product name
  - Brand and/or generic names not the most prominent information
  - Brand and/or generic names overshadowed by graphic design, corporate dress/logo
  - No distinction among IV bags with different base solutions
  - Product name more prominent than "Diluent" on diluent container
- Concentration/Strength
  - Concentration/strength not prominently displayed
  - Injectable product strength only expressed as a per mL concentration rather than the total amount per container volume
  - Different concentrations/strengths or volume sizes of same medication not well-differentiated
  - Use of error-prone abbreviations or dose/strength/quantity expressions

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Product Name Overshadowed By Company Logo

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Lack of Distinction Among Different Base Solutions

ISMP Medication Safety Alert! 2021;26(3):1-4.

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"Diluent" Not Prominent Compared to Product Name

Original Labels

Revised Labels

ISMP Medication Safety Alert! 2021;26(7):2.
ISMP Medication Safety Alert! 2019;24(5):2-3.
ISMP Medication Safety Alert! 2015;20(21):1-2.

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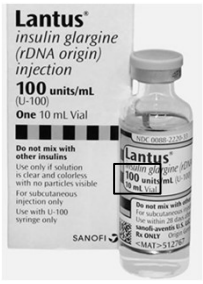
Total Amount Per Container Listed in Confusing Manner

- Lantus 100 units/mL vial was turned slightly
- Nurse saw "100 units" with "10" directly under it
- Nurse assumed concentration was 100 units/10 mL and administered 9 mL (900 units) instead of 90 units
- Patient given dextrose infusion immediately after nurse realized mistake



ISMP Medication Safety Alert! 2016;21(23):1-2.

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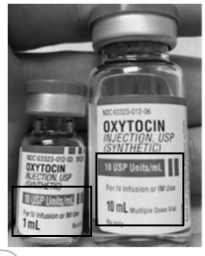
Importance of Premarket Labeling and Packaging Safety Evaluations in Minimizing Postmarket Medication Errors

Total Amount Per Container Not Listed



- Technician intended to compound oxytocin 30 units in 500 mL of normal saline, using three 1 mL vials
- Instead, three 10 mL vials were used, resulting in a concentration of 300 units per 500 mL
- Incorrect infusions were administered to several patients; no harm reported

ISMP Medication Safety Alert! 2020;25(22):1-3.

16

Total Amount Per Container Not Listed; Use of Error-Prone Abbreviation

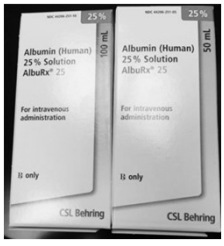
Original Labels

Revised Labels

ISMP Medication Safety Alert! 2020;25(9):4.
ISMP Medication Safety Alert! 2018;23(17):1-2.

17

Same Package Size, but Different Volume



ISMP Medication Safety Alert! 2021;26(7):1.
ISMP Medication Safety Alert! 2017;22(17):3.

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Route/Warning Statements and Preparation Instructions

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Error-Prone Label Conditions

- Route of Administration and Warning Statements
  - **Route and/or warnings not prominently displayed**
  - **Use of negative (vs. affirmative) warnings**
  - **Absent warning/cautionary statements**
- Preparation Instructions
  - **Unclear admixture and/or product preparation instructions**
  - **Expiration date and storage instructions after reconstitution are absent**

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Warning Not Prominent

- Gebauer's Ethyl Chloride spray applied as a numbing agent to patient's toe prior to procedure
- Electrocautery was used during the procedure, causing ignition of the ethyl chloride
- Patient received first-degree burns on toe, requiring wound care

ISMP Medication Safety Alert! 2018;23(5):1-4.

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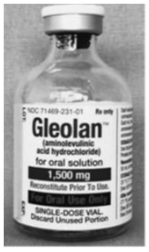
Importance of Premarket Labeling and Packaging Safety Evaluations in Minimizing Postmarket Medication Errors

Route/Warning Difficult to Read/Not Prominent



- Gleolan (aminolevulinic acid) is an optical imaging agents intended for oral use
- "For Oral Use Only" warning is hard to read due to the poor color contrast ratio and is not very prominent

*Also concerning is that it is packaged in what appears to be a parenteral vial; could potentially be administered accidentally as an IV injection

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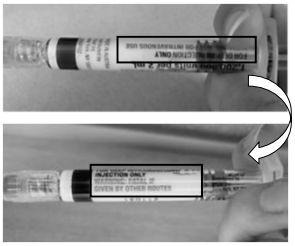
ISMP Medication Safety Alert! 2018;23(25):2-3.

22

Route/Warning Listed as A Negative Statement

- Prefilled syringe label of penicillin G benzathine was upside down for right-handed practitioners
- "NOT" in the route warning statement ("NOT FOR INTRAVENOUS USE") was blocked by the plunger
- Label was revised to address these issues



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ISMP Medication Safety Alert! 2019;24(10):3-4.
ISMP Medication Safety Alert! 2017;22(20):1-2.

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Barcode, Lot Number, and Expiration Date

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Error-Prone Label Conditions

- Barcodes
  - **Placed on the curvature of the container**
  - **Lack of a barcode on the overwrap or not scannable through the overwrap**
  - **Lack of or unreadable barcode on the immediate container or on each individual unit dose package**
  - **Presence of multiple barcodes**
- Expiration Dates and Lot Numbers
  - **Confusing expiration dates that do not follow the standard format (USP General Chapter <7>):**
    - YYYY-MM-DD or YYYY-MM (or MMM if displaying the month in letters)
  - **Expiration date and lot number mistaken for each other**
  - **Embossed, difficult to read or find expiration dates and lot numbers**

25

Barcode Placed on Curvature of Container

ISMP Medication Safety Alert! 2021;26(5):1.
ISMP Medication Safety Alert! 2020;25(1):1.
ISMP Medication Safety Alert! 2017;22(21):1-3.

26

Inability to Scan Barcode

- Lack of barcode on the overwrap of an IV bag (in addition to the immediate container)
- Inability to scan barcode on IV bag when in overwrap due to placement of the overwrap seam

ISMP Medication Safety Alert! 2017;22(2):1.

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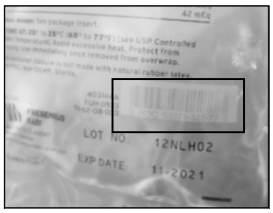
Importance of Premarket Labeling and Packaging Safety Evaluations in Minimizing Postmarket Medication Errors

Multiple Barcodes and Difficult to Read Barcodes

- Multiple barcodes

- White barcodes on clear bags



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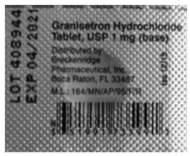
ISMP Medication Safety Alert! 2020;25(3):1-2.
ISMP Medication Safety Alert! 2021;26(3):1-4.

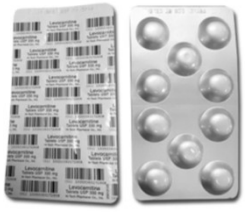
28

Barcode Issues with Unit Dose Packaging

- Inability to scan barcode



- Barcodes do not line up with individual tablets



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ISMP Medication Safety Alert! 2019;24(24):3-4.
ISMP Medication Safety Alert! 2019;24(24):3-4.

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Lack of Barcode on Immediate Container

- Hospital purchased over-the-counter (OTC) oxymetazoline hydrochloride decongestant spray, 0.05%
- The bottle though lacked a barcode and could not be scanned at the bedside
- Instead, nurses had to scan the barcode on the product's carton, which is usually discarded after opening

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ISMP Medication Safety Alert! 2019;24(21):3-4.

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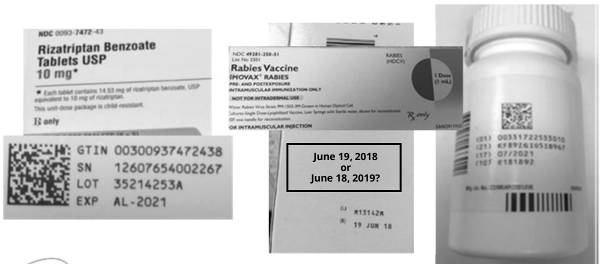
Confusing Expiration Date and/or Lot Number



ISMP Medication Safety Alert! 2019;24(24):4-5.
ISMP Medication Safety Alert! 2019;24(19):1-2.

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General Chapter <7> *Labeling*
CHANGE TO EXPIRATION DATE FORMAT

July 31, 2020

Patient Safety Challenges[1]

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Overall Layout/Format
Use of Color

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Importance of Premarket Labeling and Packaging Safety Evaluations in Minimizing Postmarket Medication Errors

Error-Prone Label Conditions

- Overall layout/format
  - **Crowded; lack of white space**
  - **Content not grouped by topic**
  - **Use of all capital letters vs. mixed case letters**
  - **Small font size (unreadable)**
  - **Placement on actual container not considered (e.g., how the label will appear when holding a syringe or when on a bottle that is hung upside down)**
- Use of color
  - **Poor color contrast ratio**
  - **Use of embossed labels**
  - **Lack of color used to differentiate similar products**
  - **Color used to "color code" products**

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Crowded Content; Use of All Capital Letters

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ISMP Medication Safety Alert! 2021;26(3):1-4.

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Use of Color

- Labels should employ judicious use of color to maximize legibility of the text and readability of the information presented
- Color Coding
  - **Systematic, standard application of color**
  - **Aid in classification and identification**
  - **Example: black cap on vial of potassium chloride concentrate injection**
- Color Differentiation
  - **Makes certain features stand out**
  - **Distinguish one item from another**
- Color Matching
  - **Example: when a medical device attaches a yellow plug to a yellow receptacle (color has no meaning other than it matches two items)**

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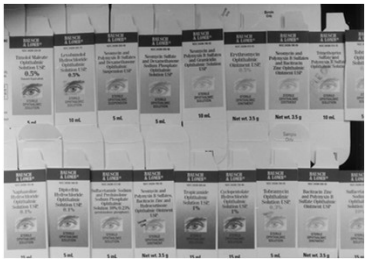
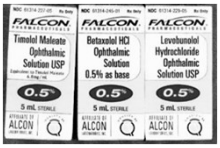
Importance of Premarket Labeling and Packaging Safety Evaluations in Minimizing Postmarket Medication Errors

Color Coding Ophthalmic Products





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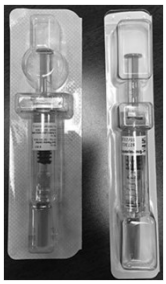
Use of Color on Syringe Plungers

Enoxaparin and methylnaltrexone (Relistor)



Enoxaparin and fondaparinux

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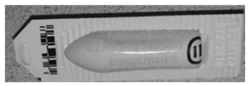
ISMP Medication Safety Alert! 2015;20(16):2-3.

38

Poor Color Contrast Ratio and Embossed Labels



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ISMP Medication Safety Alert! 2018;23(4):1-5.

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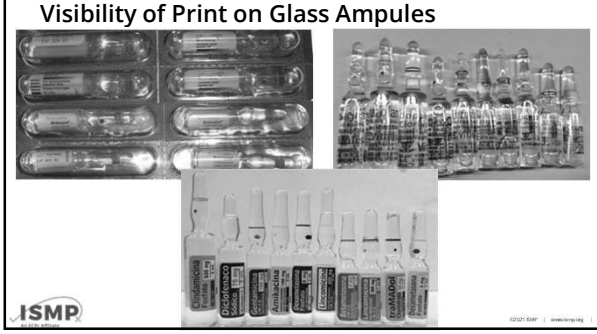
Visibility of Print on Glass Ampules



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Look-alike Labels

Rebecca Lamis, PharmD, FISMP
Manager, Medication Safety Board (subsidiary of ISMP)
rlamis@ismp.org

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Contributing Factors

- Same or similar container size
- Overlapping design elements and color schemes (particularly with products from the same company)
- Same or similar cap color (vials)
- Stored in proximity to one another
  - **Alphabetically due to name**
  - **Same storage requirements (e.g., in the refrigerator)**
  - **Overlapping clinical use**
- Other similarities
  - **Amber vials**
  - **Overwrap**
  - **Same carton size**

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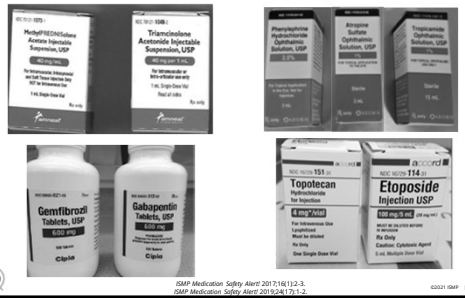
Importance of Premarket Labeling and Packaging Safety Evaluations in Minimizing Postmarket Medication Errors

Look-Alike Products: Same Manufacturer



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ISMP Medication Safety Alert! 2017;16(1):2-3.
ISMP Medication Safety Alert! 2019;24(17):1-2.

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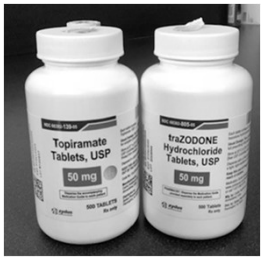
Look-Alike Products: Same Manufacturer



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ISMP Medication Safety Alert! 2021;26(16):1-3.

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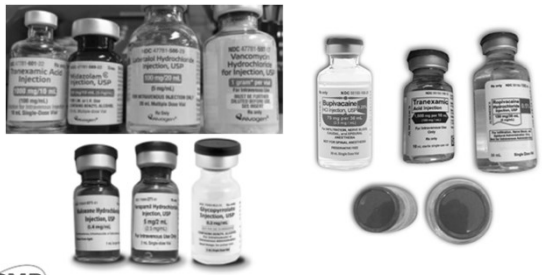
Look-Alike Products: Same Manufacturer



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ISMP Medication Safety Alert! 2020;25(18):1-2. *ISMP Medication Safety Alert!* 2020;25(25):5.
ISMP Medication Safety Alert! 2019;24(10):1-2. *ISMP Medication Safety Alert!* 2019;24(8):2.

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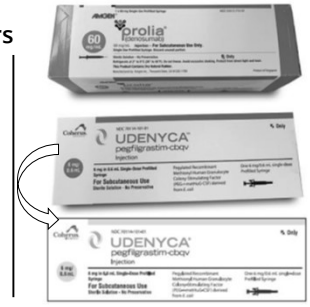
Look-Alike Products: Different Manufacturers

- Multiple mix-ups reported between Prolia and Udenyca prefilled syringes.
- Each packaged in similar green and white cartons, with the concentration listed in a green circle in the same location.
- Both products stocked in oncology and infusion centers, are refrigerated, and may be stored near each other.



ISMP Medication Safety Alert! 2019;24(17):1-2.
ISMP Medication Safety Alert! 2020;25(2):4.

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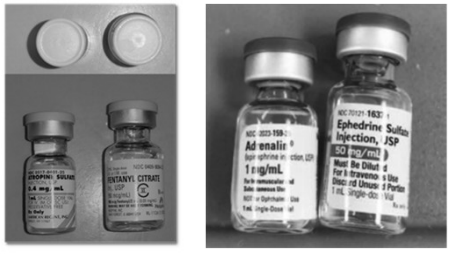
Look-Alike Products: Different Manufacturers



ISMP Medication Safety Alert! 2020;25(21):3-4.

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Look-Alike Products: Cap Color

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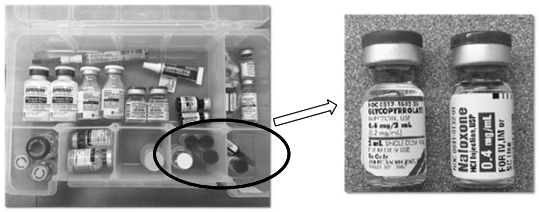
Look-Alike Products: Cap Color



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Look-Alike Products: Cap Color

- Vials of metoprolol were stocked in the wrong bin with rocuronium
- Anesthesiologist administered metoprolol instead of rocuronium, causing an unexpected drop in the patient's blood pressure

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Packaging Issues

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Two Tablets/Capsules Contained in Package

- Venclexta 20 mg ordered; pharmacy dispensed 40 mg (two 20 mg unit dose packages)

- Granisetron 1 mg prescribed; pharmacy dispensed 2 mg (one blister pack)

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ISMP Medication Safety Alert! 2020;25(10):1-2.
ISMP Medication Safety Alert! 2019;24(22):1-2.

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Two Tablets/Capsules Contained in Package

- Aprepitant 80 mg capsules are available in a two-dose blister
- Aprepitant dose is 125 mg on day 1, and 80 mg on days 2 and 3 (80 mg each day)
- A nurse initially thought that both 80 mg capsules were to be administered on day 2, which would have resulted in an overdose

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ISMP Medication Safety Alert! 2021;26(11):3.

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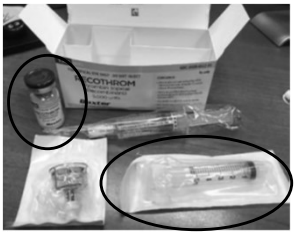
Packaging Doesn't Match Route/Intended Use

- Topical thrombin is intended for application to the surface of bleeding tissues as an aid to hemostasis
- Accidental systemic use can lead to extensive intravascular clotting and death
- Supplied in vials; some products available as a kit that includes a Luer syringe, which can lead to accidental intravenous (IV) administration



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ISMP Medication Safety Alert! 2020;25(22):3-5.

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Importance of Premarket Labeling and Packaging Safety Evaluations in Minimizing Postmarket Medication Errors

Topical Thrombin: Case Report

A patient was receiving both IV coagulation factor for hemophilia and topical recombinant thrombin (Recothrom) to treat surgical wound oozing. The nurse took both syringes containing the IV coagulation factor and the Recothrom into the patient's room. After being interrupted by other urgent care needs, the nurse accidentally picked up the Recothrom syringe and administered the product intravenously. The patient coded but was successfully resuscitated, largely because the nurse quickly recognized and acknowledged the error, enabling the code team to provide appropriate and timely treatment.

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ISMP Medication Safety Alert! 2017;22(1):1-3.

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Packaging Doesn't Match Route/Intended Use

- KCl concentrate (2 mEq/mL) must be diluted before use
- Report of a 503B outsourcer distributing in prefilled syringes; hospital pharmacy technician ordered the syringes by mistake
- Could erroneously be administered IV to a patient directly from the syringe, which may prove fatal

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ISMP Medication Safety Alert! 2018;23(8):1-2.

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Packaging Doesn't Match Route/Intended Use

- Clear Care is a contact lens cleaning solution that contains hydrogen peroxide and must ONLY be used with the provided lens case that neutralizes the hydrogen peroxide
- Direct administration to the eye can cause severe burning and pain and possibly eye injuries (ISMP has received hundreds of reports)
- The shape of the bottle is similar to other contact lens solutions, which can be used to rinse your contacts for direct application

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ISMP Safe Medicine. 2021;19(1):2-4. ; *ISMP Medication Safety Alert!* 2017;22(2):3.
ISMP Medication Safety Alert! 2014;19(20):1-5. ; *ISMP Medication Safety Alert!* 2013;18(3):1-2.
ISMP Medication Safety Alert! 2012;17(9):3. ; *ISMP Medication Safety Alert!* 2010;15(11):1,3.

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Importance of Premarket Labeling and Packaging Safety Evaluations in Minimizing Postmarket Medication Errors

Packaging Doesn't Match Route/Intended Use

— Rotarix (rotavirus vaccine) injected instead of given orally

Figure 1. Merck product, RotaTeq, is available as a liquid in a squeeze applicator.

Figure 2. Rotarix oral applicator with diluent for reconstitution. The reconstituted vaccine is redrawn into the applicator.

Rotarix diluent in between other vaccines that ARE injected

ISMP Medication Safety Alert! 2014;19(3):1,3.

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Lack of All Needed Supplies

— Berinert was packaged as a kit containing:

- **Single-use Berinert vial**
- **10 mL vial of sterile water for injection**
- **Mix2Vial filter transfer set**
- **Alcohol swab**

— Requires a silicone-free syringe for reconstitution and administration of the drug, which was not originally supplied with the kit

ISMP Medication Safety Alert! 2021;26(4):4-5.

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Product Safety Evaluations

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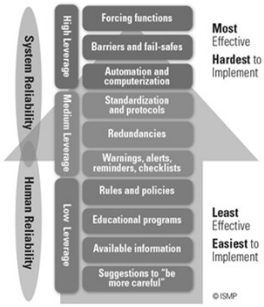
Importance of Premarket Labeling and Packaging Safety Evaluations in Minimizing Postmarket Medication Errors

ISMP's Hierarchy of Effectiveness of Risk-Reduction Strategies



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FDA Guidance for Industry and USP <7>


Guidance for Industry

Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

April 2013
Drug Safety


Safety Considerations for Product Design to Minimize Medication Errors

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

April 2016
Drug Safety


(7) LABELING

INTRODUCTION

DEFINITIONS

Labeling

Exceptions

LABELS AND LABELING FOR SELECTABLE PRODUCTS

www.fda.gov/regulatory-information/search-fda-guidance-documents/safety-considerations-container-labels-and-carton-labeling-design-minimize-medication-errors
www.fda.gov/regulatory-information/search-fda-guidance-documents/safety-considerations-product-design-minimize-medication-errors-guidance-industry

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Product Label/Package Evaluation

- Adherence to FDA Guidance, USP (General Chapter <7> Labeling), Code of Federal Regulations
- Overall appearance and readability of the labels, including when placed on actual container
- Placement and readability of critical information in a prominent position on the front of the label
  - **Brand/generic name, strength/concentration, route, essential warnings**
  - **Use of tall man lettering for FDA-approved generic pairs**
- Free from confusing terminology, abbreviations, symbols/icons, dose designations
- Minimized product logo and corporate dress

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Importance of Premarket Labeling and Packaging Safety Evaluations in Minimizing Postmarket Medication Errors

Product Label/Package Evaluation

- Lack of confusion with readable expiration dates, lot numbers
- Scannable barcode per unit dose
- Any potential for confusion with other products in company line
- Use of color or other design elements (e.g., reverse print, boxing) to differentiate products
- Label and packaging matches the provided, approved doses
- Packaging is appropriate for the route of administration
- Product includes any required special devices, and those devices match how the product should be administered

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Upcoming Workshop for Industry!

- Join us on **October 13** and **14, 2021**, for a live, virtual 2-day program: ***FDA, ISMP, and Industry Partners: Symbiosis for Medication Safety***
- Includes guest speakers from the US Food and Drug Administration (FDA) and USP
- Regulators and ISMP medication safety experts will provide a more in-depth understanding of how a company's products are impacted during dispensing and administration and the importance of safe product design
- For details and to register, visit: www.ismp.org/node/25772

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An ECRI Affiliate

Questions?

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