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Acute Care
ISMP Medication Safety Alert!®
Educating the Healthcare Community About Safe Medication Practices

More can be done to alleviate errors associated with pharmaceutical product labeling and packaging

Introduction

Visual similarities and confusing or absent presentation of important information on medication container labels, carton labels, and product packaging have frequently contributed to medication errors in the US. In the 1990s, early in the management of the former USP-ISMP Medication Errors Reporting Program (USP-ISMP MERP), up to a third of the reports and fatalities voluntarily submitted to the program cited labeling and packaging as contributing to the medication error.[1] Today, labeling- and packaging-related events continue to be one of the most frequent types of voluntary reports submitted to the ISMP National Medication Errors Reporting Program (ISMP MERP). These labeling- and packaging-related event reports continue despite significant advances in medical technology that could detect or prevent such errors (e.g., barcode scanning, clinical decision support [e.g., interactive warnings or cautionary statements that might be missed or absent on the label]); federal regulations related to the labeling and packaging of prescription drugs, biologics, and over-the-counter (OTC) products; US Food and Drug Administration (FDA) labeling and packaging Guidance for Industry documents; and USP standards associated with medication labeling and packaging. This is not surprising given that more than 20,000 prescription drugs and 300,000 OTC products, including thousands of generic products, are on the market today.[2,3]

Sources of Labeling- and Packaging-Related Errors

Common contributing factors identified in labeling- and packaging-related error reports submitted to ISMP are listed in **Table 1** (page 2). Most of these reports are associated with the immediate container label or carton label, rather than the official product labeling (i.e., package insert, patient package insert, Medication Guide) or packaging (e.g., container in which the medication is provided). The following are just a few examples of the many ways that labeling and packaging can contribute to a medication error:

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Remembering Ronald S. Litman, DO, ML

ISMP suffered a profound loss on April 21, 2021, when our remarkable colleague and ISMP Medical Director, Ronald S. Litman, DO, ML, passed away after a long struggle with acute myeloid leukemia. He was 62 years old. Ron was an internationally known pediatric anesthesiologist at Children's Hospital of Philadelphia (CHOP) and professor of anesthesiology and pediatrics at the Perelman School of Medicine at the University of Pennsylvania. In addition, he served as medical director for the Malignant Hyperthermia Association of the United States (MHAUS) and was a recent chairperson of the US Food and Drug Administration (FDA) Anesthetic and Analgesic Drug Products Advisory Committee. He was also editor of the textbook, *Basics of Pediatric Anesthesia*. Ron's intense interest in medication safety made him a valuable member of the ISMP team. He would always make himself available as an educator and lecturer. Just a week before his passing, Ron participated as a speaker for ISMP during a webinar on the use of smart pump data to improve perioperative medication safety. As a friend and a colleague, we will always cherish the memories of his kindness, quick wit, and genuine desire to make healthcare safer. We miss him dearly and offer our deepest condolences to his family.

SAFETY briefs

Compounding errors with bamlanivimab and etesevimab. Several compounding errors have been reported with Lilly's monoclonal antibody pair, bamlanivimab and etesevimab. In February, the US Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) for these products to be administered together (www.ismp.org/ext/699) as a single intravenous (IV) infusion. The EUA for use of bamlanivimab by itself has been withdrawn. The combination therapy is for treatment of mild to moderate coronavirus disease 2019 (COVID-19) in adults and pediatric patients (12 years and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) viral testing, and who are at high risk for progressing to severe COVID-19 and/or hospitalization. According to the EUA *Fact Sheet*, the infusion should be prepared using a polyvinyl chloride (PVC) or polyethylene (PE)-lined PVC sterile prefilled infusion bag containing 0.9% sodium chloride.

Bamlanivimab and etesevimab are available as solutions in separate vials and must be diluted and combined prior to administration. To prepare the dose, you need one vial of bamlanivimab (700 mg/20 mL) and two vials of etesevimab (700 mg/20 mL or 1,400 mg total). However, FDA is aware of three reports where two vials of bamlanivimab and only one vial of etesevimab were prepared for infusion. In addition, three other patients

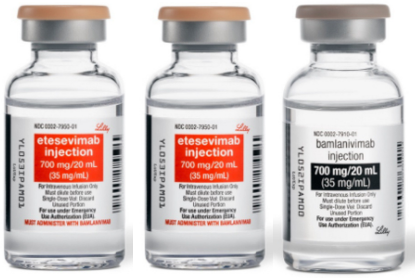

Figure 1. Proper dose requires two vials of etesevimab (red label, left and center) and one of bamlanivimab (black label, right).

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Table 1. Common Factors Associated with Labeling and Packaging Concerns (as reported to the ISMP MERP)

Aspect of Product Labeling/Packaging	Examples of Error-Prone Conditions
Readability	■ Clear or embossed labels without enough contrast to read the text ■ Small size text/font, label clutter, and poor legibility of labels ■ Manufacturer information competes in size and prominence with essential drug information
Product Name	■ Brand and/or generic names less prominent than the graphic design, corporate dress, or company logos ■ Brand name extensions in which the brand name is already in use and well known for a totally different product/ingredient (see the **Zantac reborn** *SAFETY* brief starting in the bottom right column)
Dose, Strength, and/or Amount in Container	■ Strength of injectables only expressed as a per mL concentration (e.g., mg per mL) rather than the total amount of drug per container volume ■ Dose/strength (or name) not visible on blister packs once separated ■ Different strengths of the same product not clearly differentiated ■ Dose, strength, and/or quantity expressed without a leading zero or with a trailing zero (e.g., .2 mg [incorrect way] instead of 0.2 mg [correct way]; 2.0 mg [incorrect way] instead of 2 mg [correct way]) ■ No space between the dose/strength and unit of measure (e.g., 10mg [incorrect way] instead of 10 mg [correct way]) ■ Commas not properly placed within numbers for large doses and strengths (e.g., 10000 [incorrect way] instead of 10,000 [correct way])
Route	■ Insufficient prominence given to the route of administration
Diluent	■ Product name more prominent than "Diluent" on the diluent container
Preparation	■ Unclear admixture and/or product preparation instructions ■ Expiration date and storage instructions after reconstitution are absent
Warning/Cautionary Statements	■ Absent warnings/cautionary statements about proper drug use, such as: □ Neuromuscular blocking agents: Warning, Paralyzing Agent □ Insulin Pens: Single Patient Use □ Drugs Requiring Dilution: Must Dilute Before Use □ Transdermal Patches: Must Remove Before MRI Procedure ■ Using negative (instead of affirmative) language for warning statements (e.g., Not for Intrathecal Use [incorrect way] instead of For Intravenous Use Only [correct way])
Differentiation	■ Container labels look similar to another product from the same or different manufacturer ■ Lack of differentiation between products that have similar names ■ Poor use or the absence of color to differentiate products ■ Transdermal patches are not easily identifiable on the skin
Expiration Dates/ Lot Numbers	■ Confusing expiration dates that do not follow the standard format of YYYY-MM-DD or YYYY-MM (or MMM if displaying the month in letters) ■ Expiration dates and lot numbers mistaken for each other when near each other and have a similar number sequence
Dosing Device	■ Dosing device not capable of measuring the recommended dose or with confusing measurement gradations ■ Oral dosing syringes with Luer connectors ■ Dosing devices that do not use only metric measurements
Barcode	■ Linear barcode not present or unscannable on the immediate container, blister packaging, overwrap (intravenous [IV] bags) ■ Multiple barcodes on the label, only one of which can be used to verify the product ■ Barcode located over perforation in packaging ■ Barcode presented in a horizontal position and curved around a vial (unscannable)
Abbreviations and Symbols	■ Error-prone abbreviations (e.g., U for units) or symbols used on the product label

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received the correct dose of bamlanivimab, but received only one vial (versus two) of etesevimab. The fact that each vial of both bamlanivimab and etesevimab contains 700 mg may contribute to the confusion, making it somewhat easy to pick up the wrong vial. Also, the vials are packaged separately, rather than in a carton holding one vial of bamlanivimab and two vials of etesevimab. Make sure staff are aware of this issue and use the correct number of vials (**Figure 1**, page 1). Consider banding vials together and utilize barcode scanning during compounding to ensure you are preparing the correct dose.

Although another pair of monoclonal antibodies, casirivimab and imdevimab (**REGEN-COV**), is available from Regeneron, both come in different vial sizes and in dose pack configurations that contain a sufficient number of vials to prepare one treatment dose. Lilly should similarly provide bamlanivimab and etesevimab in a single carton holding the proper number of vials for a single dose. It also might be safest to package etesevimab in one 1,400 mg vial rather than two 700 mg vials.

Incidentally, although Regen-Cov is available in dose packs, facilities may be removing the vials from the dose packs or have individual vials available. FDA received a report last week that a patient received three vials of casirivimab and five vials of imdevimab instead of the recommended four vials of each drug.

Zantac reborn. We were surprised to learn that the brand name **ZANTAC** has been recycled and is now used for famotidine (www.ismp.org/ext/688). The new over-the-counter (OTC) product is **ZANTAC 360°** (**Figure 1**, page 3). Ra**NITI**dine has been the active ingredient in Zantac since 1983. However, in 2020, the US Food and Drug Administration (FDA) requested a market withdrawal of all prescription and OTC ra**NITI**dine (www.ismp.org/ext/689) due to the presence of potentially carcinogenic levels of N-nitrosodimethylamine (NDMA). Still, Zantac is well known by practitioners (and consumers) as ra**NITI**dine, listed as ra**NITI**dine in drug information sources, and remains available outside the US, thus appearing in drug searches on the internet.

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1) packaging and/or labeling different medications or strengths of the same medication in a similar fashion; 2) labels with company names, logos, corporate dress (aspects of a product's packaging and labeling that distinguish it from the competition), or colors that are more prominent than the essential drug information; 3) error-prone abbreviations, dose designations, symbols, or other unsafe ways of expressing the name, concentration, dosage, quantity, or strength of the medication on labels; and 4) an error-prone design of labels from a human factors standpoint. Many of the contributing factors in **Table 1** (page 2) have been previously described in this newsletter.

Labeling and Packaging Safety Evaluations

One of the guiding principles associated with the FDA premarket regulatory review and subsequent drug approval is that the product's labeling and packaging should not mislead practitioners and consumers or be confused with any other medicinal product on the market. To that end, in November 2020, the American Society of Health-System Pharmacists (ASHP) House of Delegates adopted a policy to urge manufacturers, drug packagers and repackagers, outsourcing pharmacies, and the FDA to involve patients and practicing pharmacists, nurses, and physicians in decisions about drug labeling and packaging (and names) to help eliminate labeling and packaging characteristics that contribute to medication errors.[4]

Over the past two decades, the premarket safety evaluation of proposed labeling and packaging has grown somewhat but not as fast in contrast to trademark testing of brand names. Today, before seeking FDA approval of a new drug or changing the labeling or packaging, some pharmaceutical companies voluntarily use external companies to evaluate potential risks associated with proposed labeling and packaging. The Medication Safety Board (MSB) (www.medicationsafetyboard.com/), a wholly owned for-profit subsidiary of ISMP, is one of the independent companies that conducts these evaluations. Given ISMP's vast experience in analyzing medication errors, MSB offers a unique perspective as well as a variety of consulting services to support the pharmaceutical industry in designing safe labeling and packaging that minimizes the potential for medication errors. A strict editorial wall between MSB and the editors of this newsletter publication is maintained to avoid any conflict of interest.

Label evaluation and design work may include the immediate container label and the label on the outer or secondary packaging and can range from a single label to labels for an entire product line. A network of practicing healthcare providers who prescribe, dispense, and/or administer medications must be utilized, as needed, to help safety experts evaluate and identify any error-prone aspects of proposed labeling and packaging. Additional services such as conducting risk assessments using failure mode and effects analysis (FMEA), human factors testing in collaboration with human factors experts, and professional focus groups/advisory boards must also be utilized when applicable. Recommendations regarding the presentation of important and required labeling information and/or the packaging of the drug can then be made. Remediation of labeling and packaging issues identified during postmarket surveillance is also a service that must be provided.

It is important to remember that external evaluation of labeling and packaging is voluntary and that pharmaceutical companies are NOT required by regulation to test or evaluate, particularly with patients and practicing clinicians, their proposed labeling and packaging for error-prone aspects prior to seeking FDA approval. Thus, many pharmaceutical and biotech companies, including generic manufacturers, packagers/repackagers, and outsourcing pharmacies, have not adopted this practice. However, FDA encourages companies to evaluate their proposed labeling (and naming), including packaging and design, for error-prone aspects, and it should be noted that the FDA Division of Medication Error Prevention and Analysis (DMEPA) evaluates the labeling and packaging of products submitted for approval. DMEPA conducts this independent

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Zantac 360° as a brand name for famotidine is bound to cause confusion, as mix-ups due to recycling brand names have previously occurred. For example, two forms of **DULCOLAX** have been available, one containing the laxative bisacodyl and the other a stool softener containing docusate. A patient inadvertently took the stool softener in preparation for a colonoscopy. It is also unclear what the drug name modifier 360° means. One might think it means that the product offers 24-hour protection, but a dose of famotidine generally lasts 12 hours. Also, company advertising highlights that the product is the "new original strength Zantac 360° formulation." But Zantac as ra**NITI**dine was available in 150 or 300 mg tablets, not 10 or 20 mg tablets, as is the new famotidine product.

Figure 1. Zantac 360° is now a brand name for famotidine.

One of FDA's Guidance for Industry (www.ismp.org/ext/690) advises against using a brand name that is already associated with a marketed product. Another recent guidance (www.ismp.org/ext/691) recommends avoiding numbers within the proprietary name, as both Roman and Arabic numbers have been mistaken for the strength, quantity, duration, or controlled substance class of prescription drug products. We are not sure why the manufacturer of Zantac 360° and FDA chose not to take heed of the learnings from past errors, but we hope this unconventional naming does not signal the start of a new, unsafe medication naming trend.

To mitigate errors with this new product, review physician order entry systems, electronic health records, and pharmacy systems to ensure the degree symbol displays correctly. Include the brand AND generic name in all computer menus, if possible. Use visual flags in computer systems or on pharmacy shelves to draw attention to this product and possible name confusion with previous ra**NITI**dine products. Also educate staff about the new brand name product for famotidine, Zantac 360°, and the possibility of confusion with previously available Zantac products containing ra**NITI**dine.

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evaluation of the labeling and packaging, even if the company conducts its own safety evaluation of the product labeling and packaging and submits the supporting documentation to FDA.

Recommendations

Managing the risks associated with similar or confusing drug labeling and packaging is an industry-wide obligation. Healthcare professionals can certainly implement some risk-mitigation strategies that address certain contributing factors associated with error-prone product labeling and packaging, such as purchasing products from different manufacturers to help differentiate products or affixing auxiliary warning labels to products. However, this can be likened to putting a Band-Aid on a gaping wound. A safer and more robust preventative solution begins with pharmaceutical companies that evaluate their proposed product labeling and packaging, utilizing patients and practitioners as needed, before product launch; with a standards organization (USP) that continues to require safe labeling and packaging practices; and with a regulatory organization (FDA) that enforces adherence to the standards and also utilizes patients and practitioners as needed in the review of labeling and packaging before approval.

ISMP believes FDA should work with industry leaders to develop a more robust, standard, and proactive evaluation process for labeling and packaging to be employed during product development and prior to product launch or a label change. The evaluation should employ consistent and standardized methods to determine the safety and acceptability of the proposed label and packaging. ISMP also recommends that ALL pharmaceutical companies, packagers and repackagers, and outsourcing pharmacies proactively use an independent source or internal process to evaluate proposed labeling and packaging for safety concerns, involving consumers and practicing healthcare clinicians as needed. This is critical to identify and remedy any potential issues that may lead to serious errors. This proactive approach can reduce labeling and packaging similarities or confusion that may cause serious errors, and it could save the pharmaceutical company from the additional expense of revising error-prone label and packaging after launch.

Furthermore, FDA and USP should require that companies develop a risk management program that includes the timely evaluation and correction of an error-prone label or package if postmarketing surveillance (including error reports) shows harmful or potentially harmful confusion or error risk with an existing label or package. Better premarket evaluation of labels and packaging, using patients and practicing clinicians, along with postmarketing monitoring and remediation of serious or potentially serious confusion occurs, should reduce the risk of labeling- and packaging-related medication errors.

References

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Special Announcements

Free ISMP webinar on NEW perioperative assessment

We are inviting all US hospitals that offer perioperative services and freestanding ambulatory surgery centers (ASCs) to join us on **May 25, 2021**, for a **FREE** webinar, ***ISMP Medication Safety Self Assessment® for Perioperative Settings: How to Obtain the Most Valuable, Accurate, and Useful Results***. During this webinar, you will learn about our NEW perioperative self-assessment tool (which will be **launched on May 18, 2021**, www.ismp.org/node/18027) and how to utilize it to evaluate the safety of medication use in the perioperative setting. We will outline the steps to complete the self assessment and submit your findings to ISMP anonymously, discuss ways to promote interdisciplinary staff engagement, and describe how to use the assessment reports you will receive for improvement. For details and to register, visit: www.ismp.org/node/23830.

Free FDA webinar series

The US Food and Drug Administration's (FDA) Division of Drug Information is presenting the next in a series of **FREE** educational webinars, ***FDA Drug Topics: Safety Labeling Changes for Leukotriene Receptor Antagonists and Decisions Behind a Boxed Warning***, on **May 18, 2021**. Continuing education (CE) credit is available. For details, visit: www.ismp.org/ext/30. To register for the program, visit: www.ismp.org/ext/31.

Investigational drug labeling meeting

The US Food and Drug Administration (FDA) will be holding a Public Meeting on **May 18-19, 2021**, on medication error risks with **investigational drug container labels**. FDA is soliciting input from stakeholders (e.g., sponsors, investigators, clinical sites, entities that supply or label investigational drugs, study participants) about the risk of errors related to investigational drug container labels and practices that might minimize the risk of errors. For the meeting agenda, visit: www.ismp.org/ext/666. Also see our two-part newsletter series on challenges posed by investigational drug container labels (www.ismp.org/node/1048; www.ismp.org/node/1068).

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to access the online assessment, an Excel file containing demographic questions and assessment items, and the assessment workbook (including directions)

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