FDA perspective on medication errors involving investigational drugs

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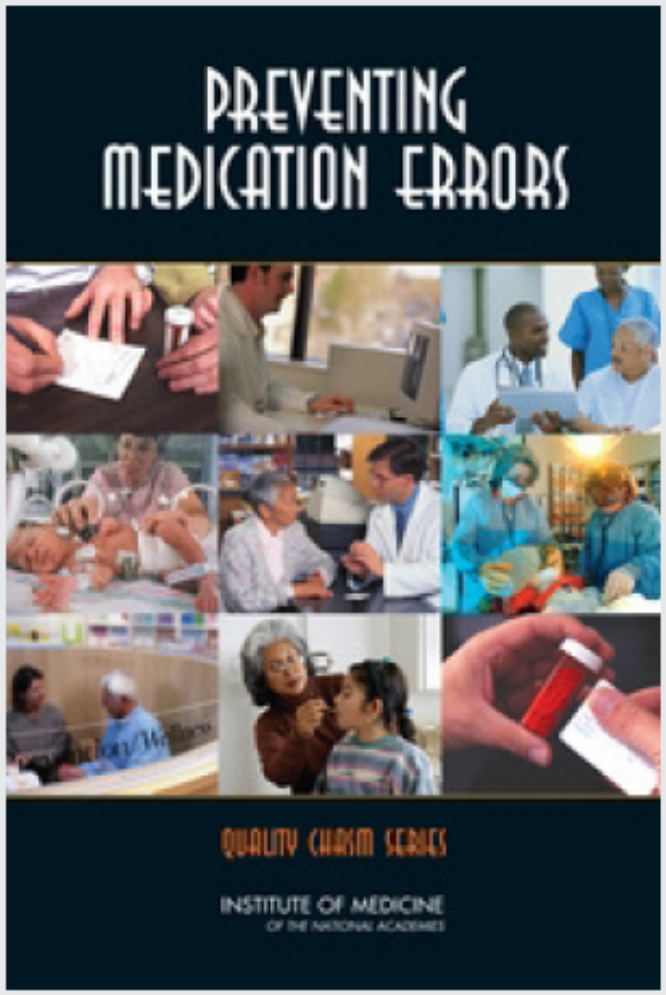
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
May 19, 2021

Topics

To provide FDA's perspective on medication errors and investigational drugs:

- Overview and role of the Division of Medication Error Prevention and Analysis (DMEPA)
- Published literature
- Contributing factors
- FDA label requirements
- Medication error reporting



Medication errors are a public health burden

- July 2006, the Institute of Medicine published a report, *Preventing Medication Errors*
  - Labeling and packaging issues are a cause of 33% of all medication errors, including 30% of fatalities
  - "Product naming, labeling, and packaging should be designed for the end user…"

Division of Medication Error Prevention and Analysis (DMEPA)

Overview of DMEPA

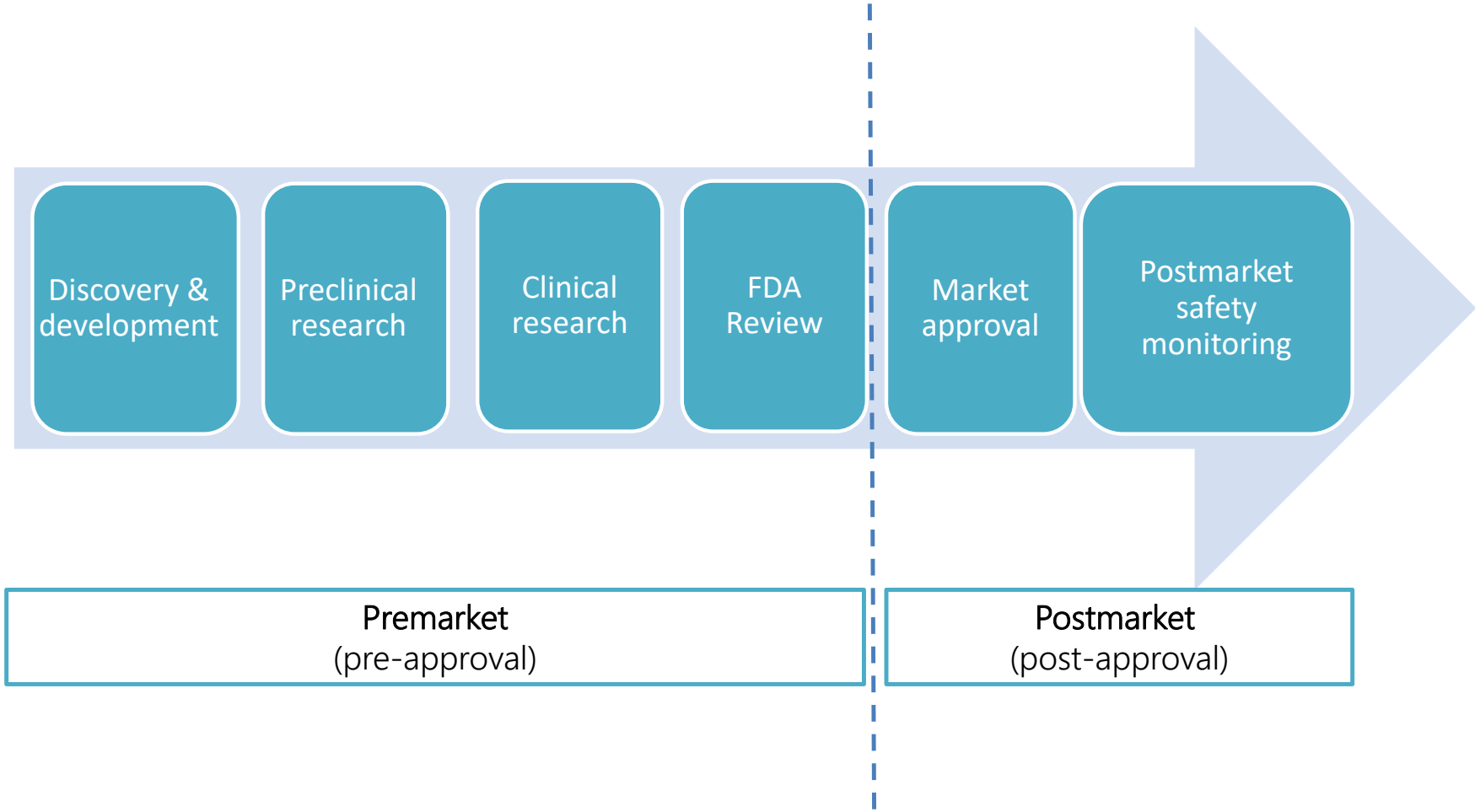
- Center for Drug Evaluation and Research (CDER) lead for medication error prevention and analysis for drug and therapeutic biological products
- Scientists and healthcare professionals with varied backgrounds, including engineers, pharmacists, nurses, and social scientists

Mission

To increase the safe use of drug products by minimizing use error that is related to the *naming, labeling, packaging, or design* of drug products

DMEPA: Medication Error Related Activities

Medication errors and product life cycle



Medication errors occur with investigational drugs
Published literature

- Recent literature highlight concerns related to unlabeled or poorly labeled investigational drug containers
  - labels can impact the ability of health care providers to readily locate and understand critical information for product use
  - labels affixed to containers were missing important information (e.g., expiration date, sponsor address, or storage conditions)
- Variable error rate estimates reported. A simulation study found an error rate of approximately 12%.
- ISMP has published case reports and a 2-part series on reported risks and mitigation strategies

Potential Medication Error Risks With Investigational Drug Container Labels, 86 Fed. Reg. 14457, Docket No. FDA-2021-N-0127 (16Mar2021). Available at: https://www.federalregister.gov/documents/2021/03/16/2021-05370/potential-medication-error-risks-with-investigational-drug-container-labels-public-meeting-request.

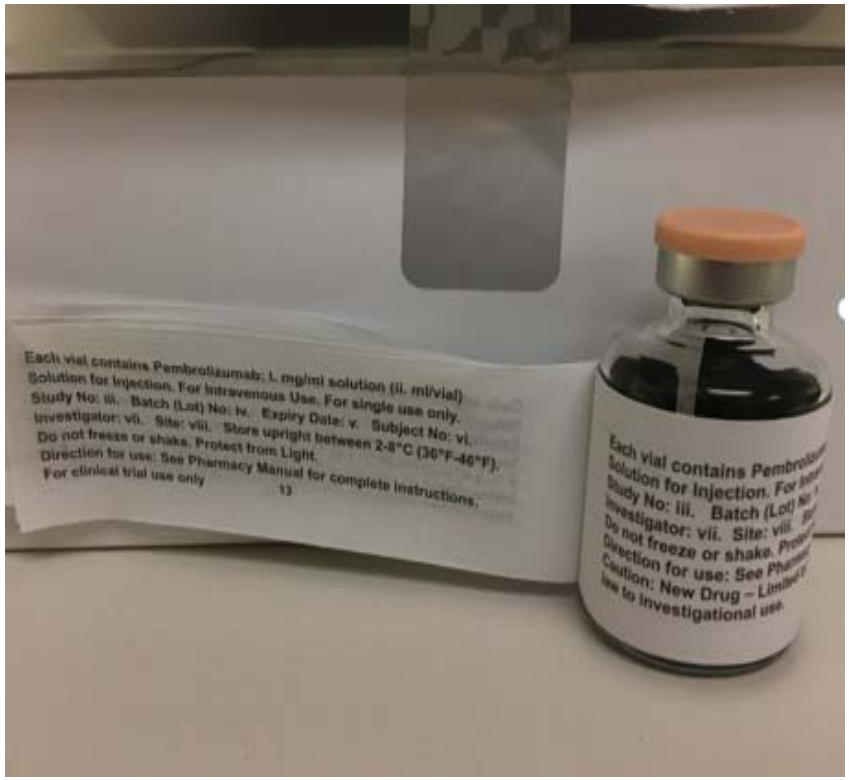
Medication errors occur with investigational drugs

Contributing factors

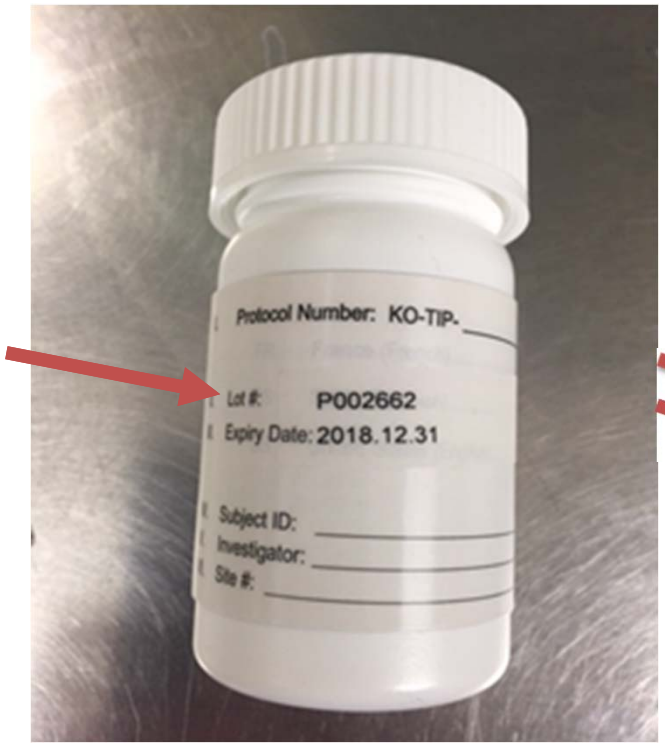
- Small font sizes (less than 8 point)
- Error-prone abbreviations
- Limited use of color/differentiation techniques
- Highly similar product or protocol identification numbers
- Variable formats for expiration dates, lot numbers
- Nomenclature inconsistencies/changes
- Unclear product strength and quantity
- The use of non-standard symbols and keys used to denote product information for trial conducted internationally

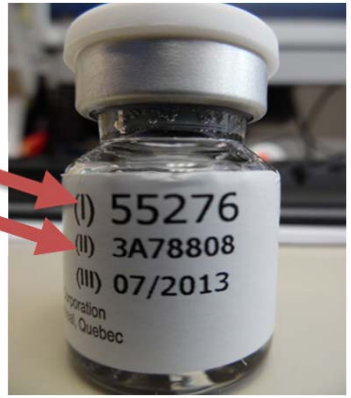
Contributing factor example
Small font size/Label clutter

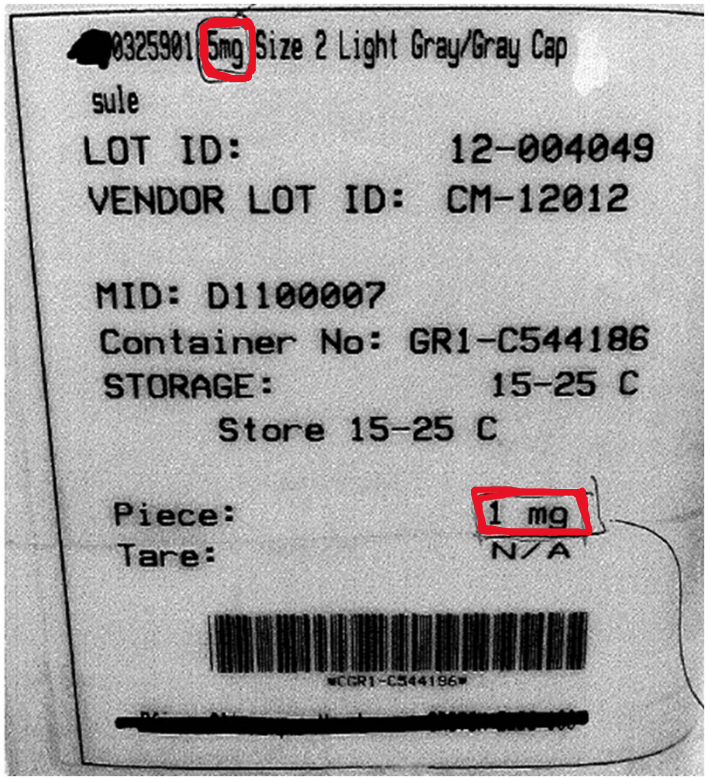
Protocol: ZZZ-ZZZZ-ZZZZ **Packaging Job #:** PPPPPPPPPPP
Lot Number: LLLLLLLLLLL Subject ID: _____
Investigator Name: _____ Solution for Intravenous Infusion.
PREPARE AND ADMINISTER AS DIRECTED IN THE PHARMACY MANUAL
Contents: 1 single use vial of DDDDDDD, 250mg/10mL (25mg/mL) Protect from light. Storage: Store at 2 °C – 8 °C (36 °F – 46 °F). Do not freeze. Store in upright position. CAUTION: New drug -Limited by Federal (or United States) law to investigational use. Keep out of reach of children. [redacted]
[redacted] San Francisco, CA 94158 United States [redacted]



Contributing factor example
Strength statement/ Lot number







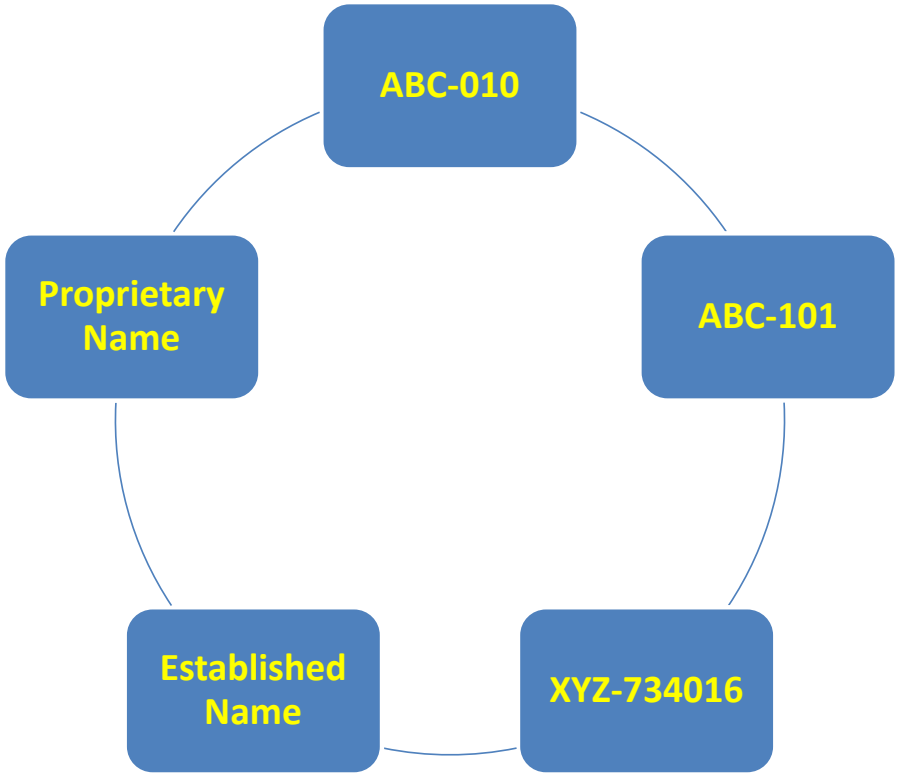
Contributing factor example

Protocol number/Product identifier

H2W-MC-ZYAA Lot: 800 mg KY1234567	KY12345673 BUD:
80 mg/mL, 10 mL Concentrate for solution for infusion. For intravenous use only. Storage conditions (-56°C to -40°C; -68.8°F to -40°F). Protect from direct heat and light Keep out of reach of children. CAUTION: New drug-Limited by Federal (or United States) law to investigational use. Sponsor Name, City, State, Zip Code USA	

H2W-MC-ZGAA Lot: 300 mg KY1298765	BUD:
30 mg/mL, 10 mL Concentrate for solution for infusion. For intravenous use only. Storage conditions (-56°C to -40°C; -68.8°F to -40°F). Protect from direct heat and light Keep out of reach of children. CAUTION: New drug-Limited by Federal (or United States) law to investigational use. Sponsor Name, City, State, Zip Code USA	

Contributing factor example
Nomenclature

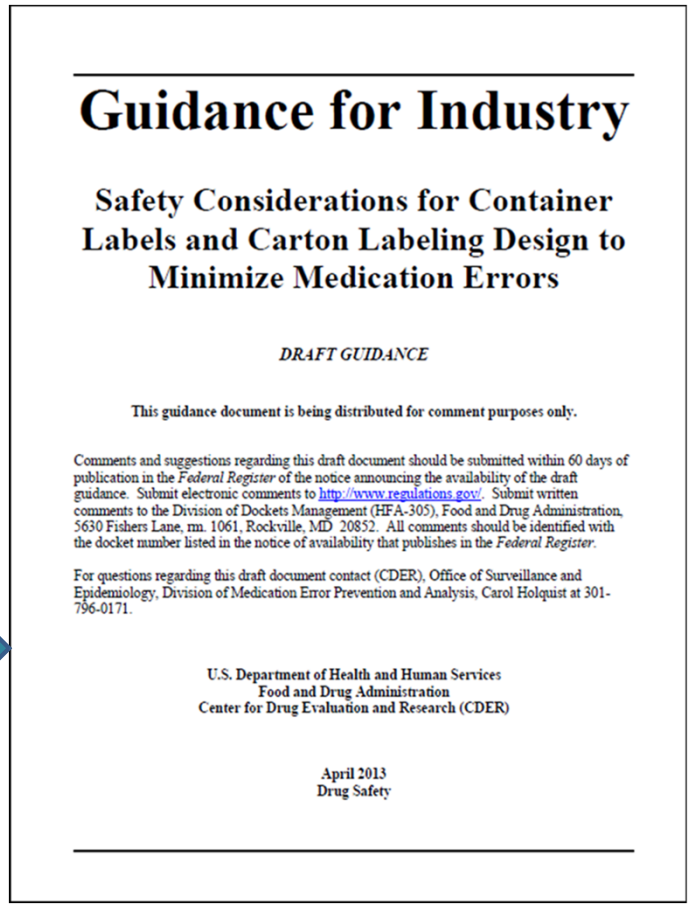


Container Labels and Carton Labeling to Minimize Medication Errors

- Product container labels and carton labeling should communicate information that is critical to the safe use of a medication throughout the medication use system.
- These methods should be applied **early** in the drug development process

Prescribing Procurement Preparation Dispensing Administration

Guidance available at: https://www.fda.gov/media/84903/download



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.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to http://www.regulations.gov/. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact (CDER), Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis, Carol Holquist at 301-796-0171.

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

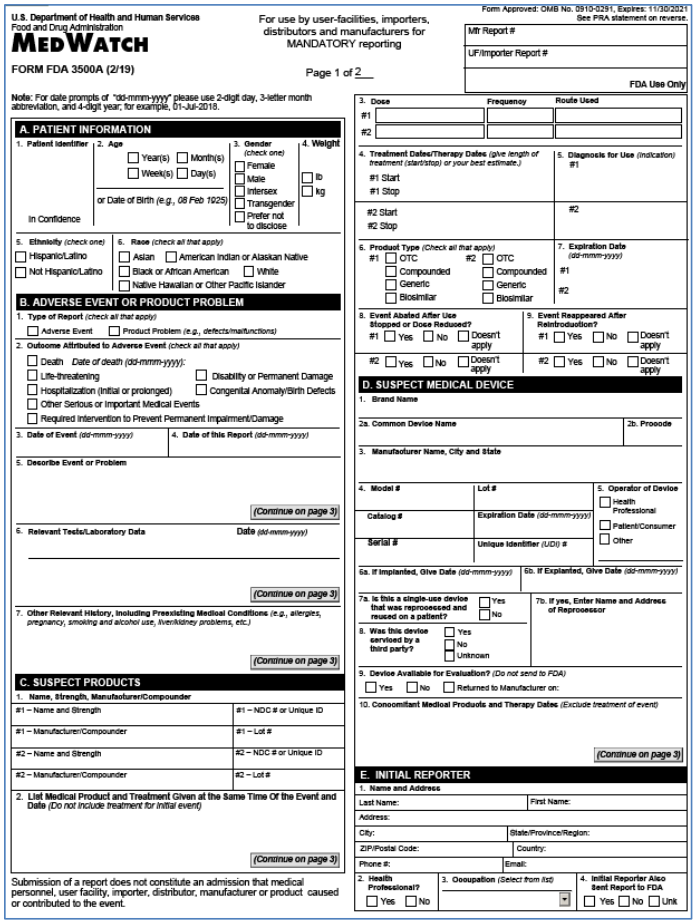
April 2013
Drug Safety

U.S. container label requirements for investigational new drug

- 21 CFR 312.6. Labeling of Investigational New Drug
  - Caution: New Drug—Limited by Federal (or United States) law to investigational use
  - The label or labeling of an investigational new drug shall not bear any statement that is false or misleading in any particular way and shall not represent that the investigational new drug is safe or effective for the purposes for which it is being investigated

Medication errors occur with investigational drugs

Case reports



U.S. Department of Health and Human Services
Food and Drug Administration
MEDWATCH
FORM FDA 3500A (2/19)

For use by user-facilities, importers, distributors and manufacturers for MANDATORY reporting

Form Approved: OMB No. 0910-0291, Expires: 11/30/2021
See PRA statement on reverse.

Page 1 of 2

Mfr Report #
UF/Importer Report #
FDA Use Only

Note: For date prompts of "dd-mmm-yyyy" please use 2-digit day, 3-letter month abbreviation, and 4-digit year, for example, 01-Jul-2018.

A. PATIENT INFORMATION

1. Patient Identifier
2. Age — Year(s) Month(s) Week(s) Day(s) or Date of Birth (e.g., 08 Feb 1925)
3. Gender (check one) — Female, Male, Intersex, Transgender, Prefer not to disclose
4. Weight — lb, kg
In Confidence
5. Ethnicity (check one) — Hispanic/Latino, Not Hispanic/Latino
6. Race (check all that apply) — Asian, American Indian or Alaskan Native, Black or African American, White, Native Hawaiian or Other Pacific Islander

B. ADVERSE EVENT OR PRODUCT PROBLEM

1. Type of Report (check all that apply) — Adverse Event, Product Problem (e.g., defects/malfunctions)
2. Outcome Attributed to Adverse Event (check all that apply) — Death Date of death (dd-mmm-yyyy); Life-threatening; Disability or Permanent Damage; Hospitalization (Initial or prolonged); Congenital Anomaly/Birth Defects; Other Serious or Important Medical Events; Required Intervention to Prevent Permanent Impairment/Damage
3. Date of Event (dd-mmm-yyyy)
4. Date of this Report (dd-mmm-yyyy)
5. Describe Event or Problem
(Continue on page 3)
6. Relevant Tests/Laboratory Data — Date (dd-mmm-yyyy)
(Continue on page 3)
7. Other Relevant History, Including Preexisting Medical Conditions (e.g., allergies, pregnancy, smoking and alcohol use, liver/kidney problems, etc.)
(Continue on page 3)

C. SUSPECT PRODUCTS

1. Name, Strength, Manufacturer/Compounder
#1 – Name and Strength | #1 – NDC # or Unique ID
#1 – Manufacturer/Compounder | #1 – Lot #
#2 – Name and Strength | #2 – NDC # or Unique ID
#2 – Manufacturer/Compounder | #2 – Lot #
2. List Medical Product and Treatment Given at the Same Time Of the Event and Date (Do not include treatment for initial event)
(Continue on page 3)

Submission of a report does not constitute an admission that medical personnel, user facility, importer, distributor, manufacturer or product caused or contributed to the event.

3. Dose — Frequency — Route Used
#1
#2
4. Treatment Dates/Therapy Dates (give length of treatment (start/stop) or your best estimate.)
#1 Start
#1 Stop
#2 Start
#2 Stop
5. Diagnosis for Use (Indication)
#1
#2
6. Product Type (Check all that apply)
#1 OTC, Compounded, Generic, Biosimilar
#2 OTC, Compounded, Generic, Biosimilar
7. Expiration Date (dd-mmm-yyyy)
#1
#2
8. Event Abated After Use Stopped or Dose Reduced? #1 Yes No Doesn't apply
9. Event Reappeared After Reintroduction? #1 Yes No Doesn't apply
#2 Yes No Doesn't apply
#2 Yes No Doesn't apply

D. SUSPECT MEDICAL DEVICE

1. Brand Name
2a. Common Device Name | 2b. Procode
3. Manufacturer Name, City and State
4. Model # | Lot # | Operator of Device: Health Professional, Patient/Consumer, Other
Catalog # | Expiration Date (dd-mmm-yyyy)
Serial # | Unique Identifier (UDI) #
5a. If Implanted, Give Date (dd-mmm-yyyy) | 5b. If Explanted, Give Date (dd-mmm-yyyy)
7a. Is this a single-use device that was reprocessed and reused on a patient? Yes No
7b. If yes, Enter Name and Address of Reprocessor
8. Was this device serviced by a third party? Yes No Unknown
9. Device Available for Evaluation? (Do not send to FDA) Yes No Returned to Manufacturer on:
10. Concomitant Medical Products and Therapy Dates (Exclude treatment of event)
(Continue on page 3)

E. INITIAL REPORTER

1. Name and Address
Last Name: | First Name:
Address:
City: | State/Province/Region:
ZIP/Postal Code: | Country:
Phone #: | Email:
2. Health Professional? Yes No
3. Occupation (Select from list)
4. Initial Reporter Also Sent Report to FDA Yes No Unk

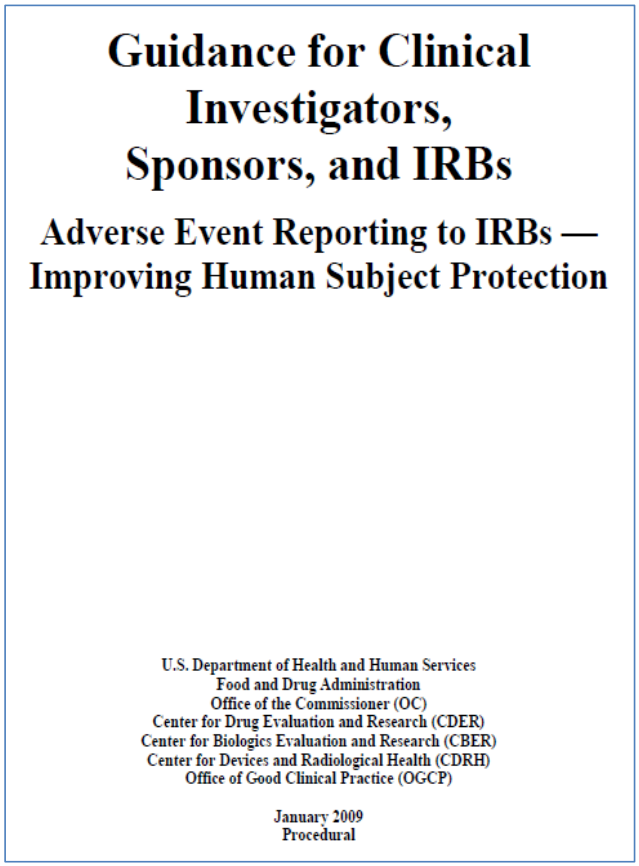
- Serious Adverse Event (SAE)
  - Study patient hospitalized with grade 4 anaphylaxis and febrile neutropenia secondary to accidental overdose
- Protocol Deviation
  - Patient was randomized to receive Drug A but inadvertently received Drug B (at the recommended dose for Drug A).

Investigational Drugs and Medication Errors

Reports contain limited information

- Serious Adverse Event (SAE)
  - Study patient hospitalized with grade 4 anaphylaxis and febrile neutropenia secondary to accidental overdose
    - Contributing factors?
- Protocol Deviation
  - Patient was randomized to receive Drug A but inadvertently received Drug B (at the recommended dose for Drug A).
    - Contributing factors?

Investigational Drugs and Medication Errors: Reporting



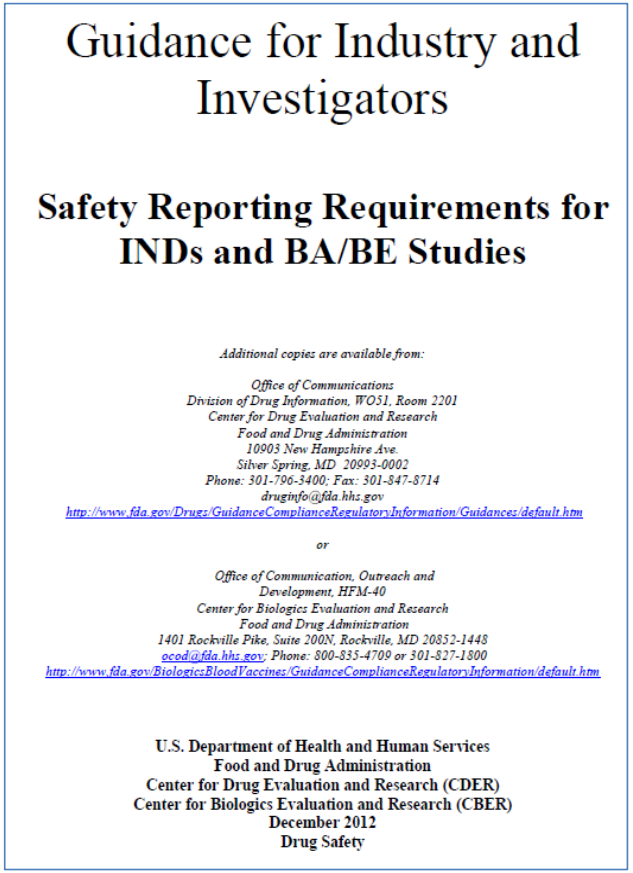
Guidance for Clinical Investigators, Sponsors, and IRBs

Adverse Event Reporting to IRBs — Improving Human Subject Protection

U.S. Department of Health and Human Services
Food and Drug Administration
Office of the Commissioner (OC)
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)
Office of Good Clinical Practice (OGCP)

January 2009
Procedural

Guidance available at:
https://www.fda.gov/media/72267/download



Guidance for Industry and Investigators

Safety Reporting Requirements for INDs and BA/BE Studies

Additional copies are available from:

Office of Communications
Division of Drug Information, WO51, Room 2201
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave.
Silver Spring, MD 20993-0002
Phone: 301-796-3400; Fax: 301-847-8714
druginfo@fda.hhs.gov
http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

or

Office of Communication, Outreach and Development, HFM-40
Center for Biologics Evaluation and Research
Food and Drug Administration
1401 Rockville Pike, Suite 200N, Rockville, MD 20852-1448
ocod@fda.hhs.gov; Phone: 800-835-4709 or 301-827-1800
http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/default.htm

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
December 2012
Drug Safety

Guidance available at:
https://www.fda.gov/media/79394/download

In Summary…

- The prevalence and impact of medication errors on clinical trials is unknown
- Poorly labeled containers are a contributing factor for medication errors.
- Design issues should be identified proactively and addressed early in drug development.
- Medication errors are inconsistently reported and contain limited information necessary for analysis
- Mitigating the risk of medication errors will help protect research participants from harm, and protect the integrity of trial data.

References

[1] Moon, JY, Lee Y, Han JM, et al. "Effects of pharmacist interventions on reducing prescribing errors of investigational drugs in oncology clinical trials." J. Clinical Pharm Practice. 2020, 26(I): 29-35.

[2] Duhamel, A., M. Thibault, D. Lebel, et al., "Investigational Drug Labeling Variability," Clinical Trials, vol. 16(2), pp. 204–213, 2019.

[3] Fell GL, O'Loughlin AA, Nandivada P, et al., "Methods to reduce medication errors in a clinical trial of an investigational parenteral medication." Contemporary Clinical Trials Communications. 2016, 4: 64-67.

[4] Dollinger, C., V. Schwiertz, L. Sarfati, et al., "SIMulation of Medication Error Induced by Clinical Trial Drug Labeling: The SIMME–CT Study." International Journal for Quality in Health Care, vol. 28(3), pp. 311–315, 2016.

[5] Cruz JL, Brown JN. Safety risks with investigational drugs: Pharmacy practices and perceptions in the Veterans Affairs health system. Ther Adv Drug Saf. 2015, 6(3): 103-109

[6] Federal Register Notice: Potential Medication Error Risks With Investigational Drug Container Labels; Public Meeting available at: https://www.govinfo.gov/content/pkg/FR-2021-03-16/pdf/2021-05370.pdf

Safety Considerations for Labels and Labeling to Minimize Medication Errors

Lubna Merchant

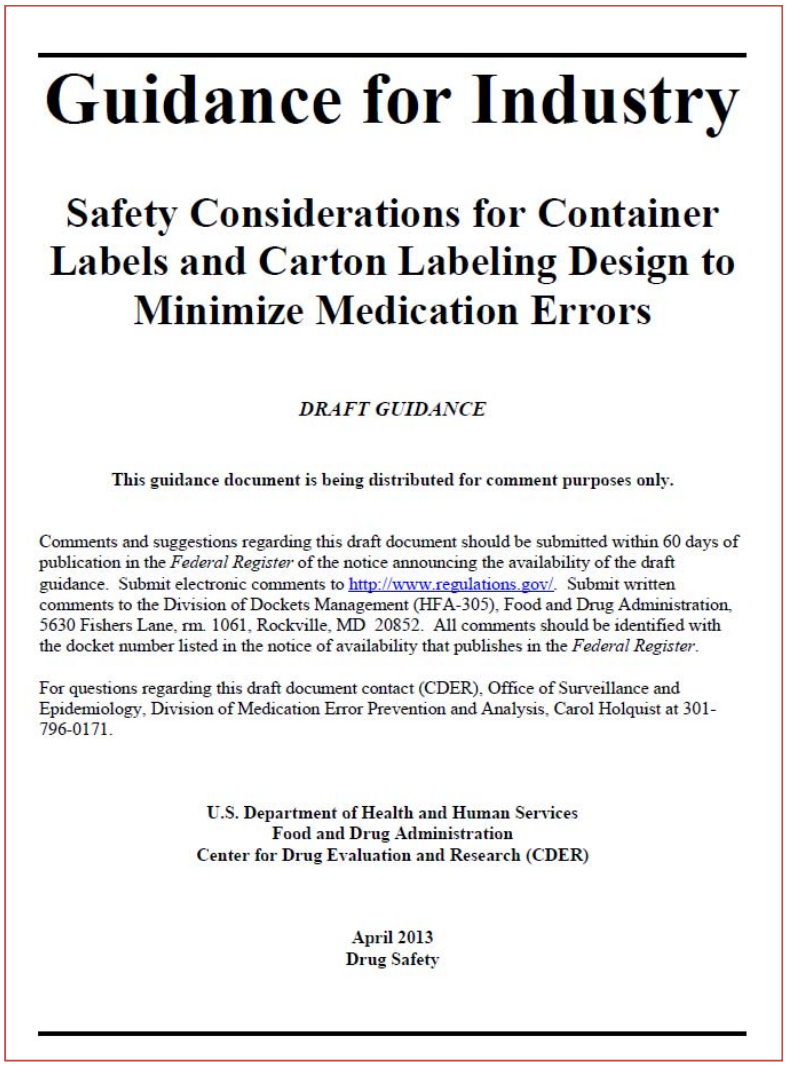
Deputy Director
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
May 19, 2021

How Drugs are Stored

Look-alike Labels and Labeling

Examples of Container Labels

Examples of Carton Labeling



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

April 2013
Drug Safety

Product container labels and carton labeling should communicate information that is critical to the safe use of a medication during:

- Initial prescription
- Procurement
- Preparation
- Dispensing
- Administration to the patient

Container Label Size

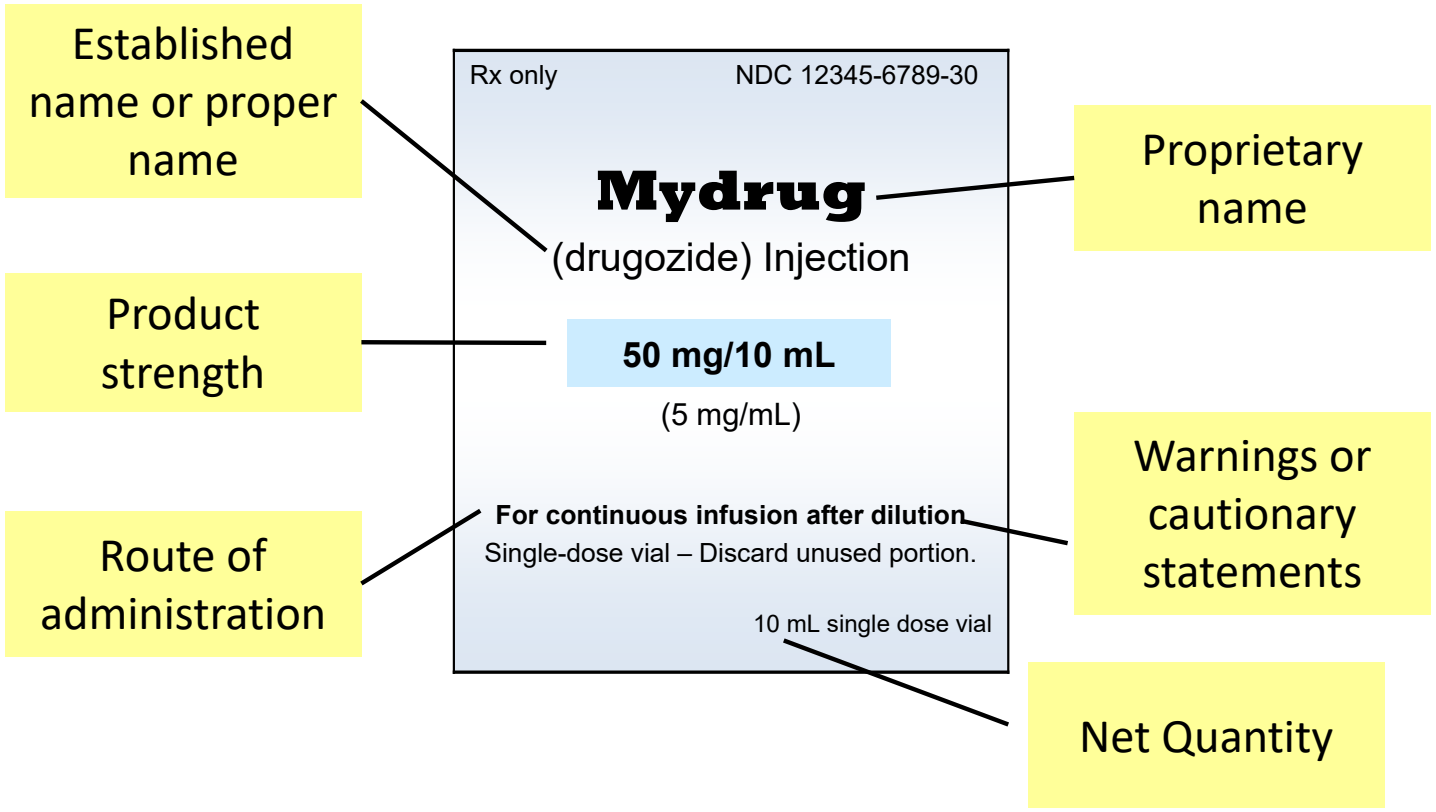
Create larger container labels or unique packaging to accommodate all critical information on the immediate product container label.

21 CFR 201.10(i) exempted small containers provided that the following required information are present:

- Proprietary name and established name (if any)
- Product strength
- Lot number
- Name of manufacturer, packer, or distributor

USP requires labels of official drug product to bear an expiration date

Principal Display Panel (PDP)



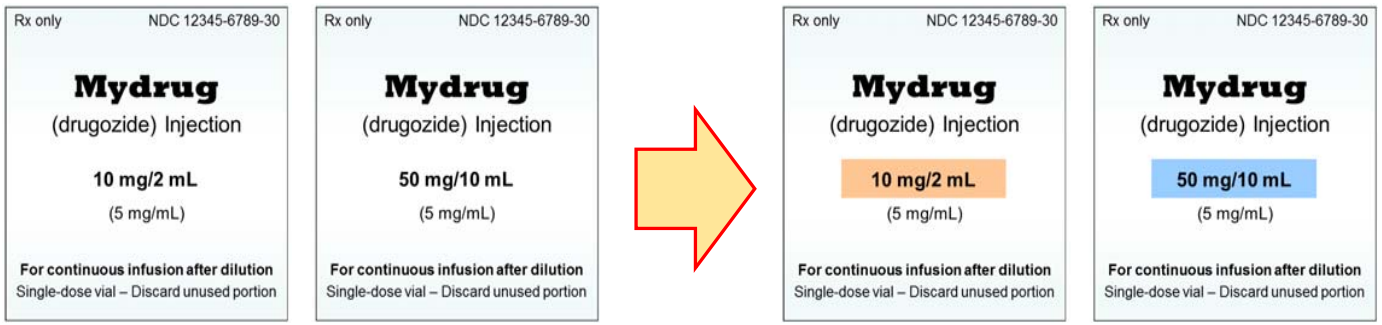
Information Crowding and Visual Clutter on Labels

- When labels are crowded, important information may be difficult to read or easily overlooked
- Therefore, we ensure that
  - lines or blocks of text are separated by sufficient white space
  - Text is not superimposed by images or logos
  - Less important information is located on back panels, side panels, or in prescribing information

Product Strength - Differentiation

- **Strength Differentiation:**
  - Ensure the product strength stands out on the container label and carton labeling

- **Techniques include:**
  - Boxing
  - Prominent typeface or type weight
  - Color differentiation

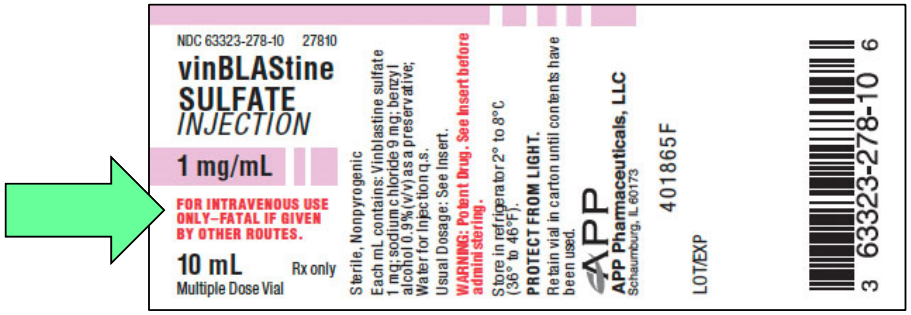


Strength and Net Quantity Statements Placement

Route of Administration

- Avoid use of abbreviations
- Use positive statements instead of negative statements
  - E.g., May overlook the word “not”
  - Affirmative statements help to ensure readers understand the intended route of administration, even if they do not read every word

NOT FOR INTRATHECAL USE



Lot Number

- Ensure that there are no other numbers located in close proximity to the lot number where it can be mistaken as the lot number
- Ensure the lot number won't be confused as expiration date

Figure 1. Which number is the lot number?

Figure 2. 2D15 is the lot number, nor expiration date

Institute for Safe Medication Practices. Safety Briefs: The lot number is where? ISMP Med Saf Alert Acute Care. July 2009;14(15):2-3.
Institute for Safe Medication Practices. Safety Briefs: Lot number, not expiration date. ISMP Med Saf Alert Acute Care. Nov 2014;19(23):2.

Expiration Dates

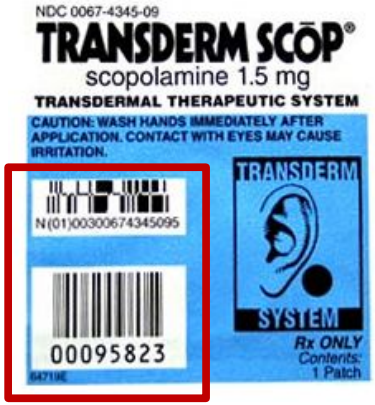
- Current practice
  - Expression of expiration dates varied
  - The use of abbreviations such as 2-letter months and 2-digit years (e.g., MA12) has led to confusion and misinterpretation. For e.g., MA could mean March or May, and the number 12 could represent the day, month, or year.

- Recommend
  - Minimum of 3-letter text for month,
  - 2-digit numerals for day/month, and
  - 4-digit numerals for the year
- When all-numeric dates are used:
  - YYYY-MM-DD (e.g., 2019-06-30)
  - YYYY-MM (e.g., 2019-06)
- When alphanumeric dates are used,
  - YYYY-MMM-DD (e.g., 2019-JUN-30)
  - YYYY-MMM (e.g., 2019-JUN)

Institute for Safe Medication Practices. Expression of expiration dates on labels needs to be standardized. ISMP Med Saf Alert Acute Care. June 2005;10(11):3.

Barcodes

- Ensure there is enough blank space surrounding barcode to allow barcode scanning per 21 CFR 201.25(c)(1)(i)
- Ensure there is a barcode on the container label and carton labeling (and product identifier when applicable).
- Ensure that the barcode is not placed in an area where it can be easily damaged because it appears at the point of label separation (e.g. perforation)



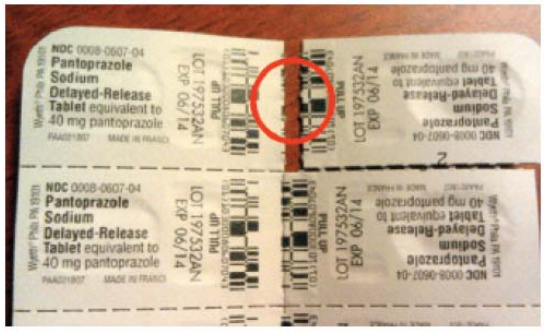


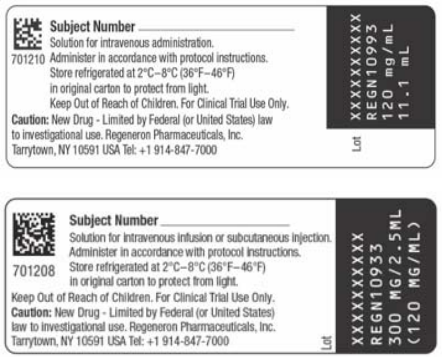
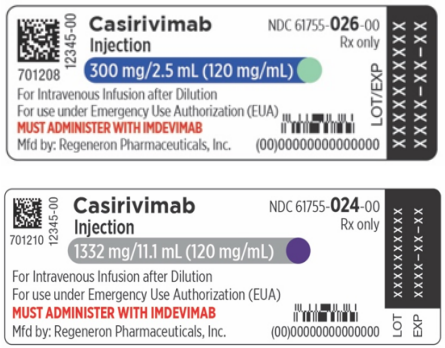
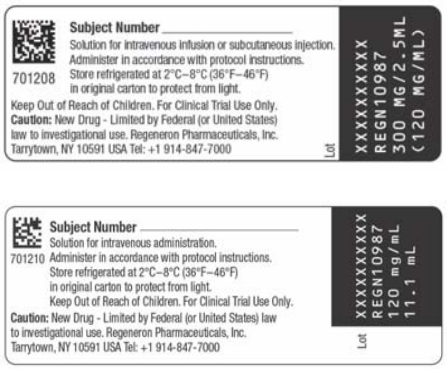
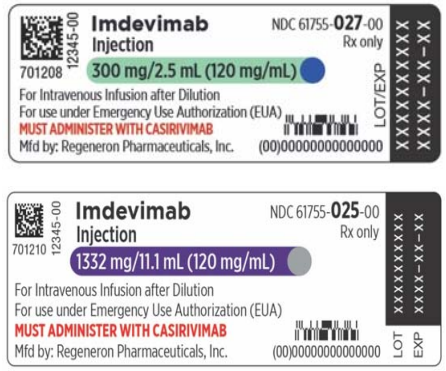
Figure 1. Barcode tears apart at perforation.

Institute for Safe Medication Practices. Safety Briefs: QC for barcodes. ISMP Med Saf Alert Acute Care. March 2013;18(5):1-2.

Veklury (Remdesivir)

	IND-Labeled Product	Approved Product
Injection	For Clinical Trial Use Only **Remdesivir (GS-5734™) Injection, 5 mg/mL** Contents: 21.2 mL. Store under refrigeration, 2 – 8 °C (36 – 46 °F). For intravenous use. See clinical study protocol for dosage and administration. Keep out of reach of children. **Caution: New Drug - Limited by Federal (USA) law to investigational use.** Sponsor: Gilead Sciences, Inc., 333 Lakeside Dr., Foster City, CA 94404, USA. Tel: +1 800 445 3235. GILEAD	**Veklury®** (remdesivir) injection 100 mg/20 mL (5 mg/mL) Single-Dose Vial: Discard Unused Portion Must be diluted prior to use. For Intravenous Infusion. 90287901 Rx only GILEAD Store refrigerated between 2 °C and 8 °C (36 °F and 46 °F) until required for use. See package insert for dosage and administration. KEEP OUT OF THE REACH OF CHILDREN Manufactured for: Gilead Sciences, Inc., Foster City, CA 94404 © 2020 Gilead Sciences, Inc. NDC 61958-**2902**-2
For Injection	For Clinical Trial Use Only **Remdesivir (GS-5734™) for Injection, 100 mg** Contents: Each Vial Contains Lyophilized Powder for Intravenous use. Store below 30 °C (86 °F). Directions: See Clinical study protocol for dosage and Administration. Keep out of reach of children. **Caution: New Drug - Limited by Federal (USA) law to investigational use.** Sponsor: Gilead Sciences, Inc., 333 Lakeside Drive, Foster City, CA 94404, USA. Tel.: +1 800 445 3235 GILEAD 	**Veklury®** (remdesivir) for injection 100 mg/vial Single-Dose Vial: Discard Unused Portion Must be reconstituted and further diluted prior to use. For Intravenous Infusion. 90286101 Rx only GILEAD Store below 30 °C (86 °F). After reconstitution, use vials immediately to prepare diluted solution. The diluted Veklury solution in the infusion bags can be stored up to 24 hours at room temperature (20 °C to 25 °C [68 °F to 77 °F]) prior to administration or 48 hours at refrigerated temperature (2 °C to 8 °C [36 °F to 46 °F]). KEEP OUT OF THE REACH OF CHILDREN Manufactured for: Gilead Sciences, Inc., Foster City, CA 94404 © 2020 Gilead Sciences, Inc. NDC 61958-**2901**-2 

Regen-Cov (Casirivimab/Imdevimab)

	IND-Labeled Product	EUA Label
Casirivimab		
Imdevimab		

Standard Global Best Practices

- The creation of a minimum set of best practices for the investigational drug container labeling and packaging aimed at reducing medication errors and the implementation of these recommendations would reduce medication errors at a global scale.
- Regulatory authorities can ensure product labels and packages are designed to minimize medication errors.
- This would benefit patients as well as pharmaceutical industry by decreasing regulatory burden on manufacturers that produce drugs for the global market.
- The recommendations could be similar to those set forth in guidances from various regulators and will promote safe labeling practices and the use of consistent safe labeling globally thereby improving medication safety worldwide.