Panel 1: Clinical Trial Site Perspectives

- **Michael R. Cohen**, RPh, MS, ScD (hon.), DPS (hon.), FASHP, President, Institute for Safe Medication Practices (ISMP)
- **Sapna R. Amin**, PharmD, BCOP, Manager, Investigational Pharmacy Services, MD Anderson Cancer Center, Houston, Texas
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- **Jamie N. Brown**, PharmD, FCCP, BCPS, BCACP, Investigational Drug Service Program Manager, Durham VA Health Care System
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Panel 1: Clinical Trial Site Perspectives

Michael R. Cohen, RPh, MS, ScD (hon), DPS (hon), FASHP
President, Institute for Safe Medication Practices (ISMP)
Moderator, Panel 1

Medication Error Reporting Program
Vaccine Error Reporting Program
Consumer Error Reporting Program

ISMP National Error Reporting Programs

July 12 2014 Volume 19 Issue 14

ISMP

Acute Care

ISMP Medication Safety Alert!®

Educating the Healthcare Community About Safe Medication Practices

With oral chemotherapy, we simply must do better!

PROBLEM: Many healthcare organizations have focused intensely on improving safety with parenteral chemotherapy but have done less to ensure safe practices with oral chemotherapy. Although oral chemotherapy is associated with ease of administration, an error with an oral agent can be just as deadly as an error with a parenteral formulation of chemotherapy. Just last month, Ruth Ann Collins (Figure 1), a 60-year-old woman with a history of brain cancer, died a slow and painful death after accidentally taking the equivalent of 3 cycles of oral lomustine therapy at one time (450 mg), believing the pharmacy had dispensed just a single dose (150 mg). She had previously been taking oral temozolomide (TEMODAR), which she received from the pharmacy as a single dose made up of several different strength capsules each month. However, a 3-cycle supply of lomustine (1 dose to be taken every 6 weeks pending blood tests) had been dispensed. Assuming the newly prescribed lomustine had also been dispensed as a single dose, Ruth took all the lomustine capsules provided by the pharmacy as a single dose. The overdose accelerated the deterioration of Ruth's physical condition and likely led to her untimely death.

Figure 1. A lomustine overdose caused by dispensing more than a single dose hastened the death of Ruth Ann Collins.

Prior to taking lomustine, Ruth had visited the university-based oncologist she had been seeing every 2 months since diagnosis. Ruth's brain tumor had increased in size despite several courses of IV irinotecan (CAMPTOSAR) and oral temozolomide. The oncologist recommended trying a single dose of lomustine 150 mg, followed by a reassessment in 6 weeks to evaluate the next steps. The oncologist at the university hospital contacted Ruth's local oncologist to discuss the recommended therapy. The local oncologist then sent a prescription for lomustine to Ruth's mail order pharmacy. The mail order pharmacy asked a specialty pharmacy to help fill the prescription, but it could not locate a supply of the drug, possibly due to a shortage of the 100 mg capsules. The mail order pharmacy was able to procure lomustine and sent a 3-dose supply of the drug to Ruth instead of a single dose. It is uncertain why the pharmacy sent 3 doses. Although most mail order pharmacies dispense a 3-month supply of many medications, the plan for Ruth was to try a single lomustine dose and then reassess the benefit of further doses. It is also uncertain if the woman's insurance played a role in the decision, since sending 3 cycles of therapy at once might be less costly.

The mail order pharmacy dispensed three prescription bottles. One bottle contained three 100 mg capsules; the second bottle contained three 40 mg capsules; and the third bottle contained three 10 mg capsules. The labels on the bottles provided instructions for taking a dose from each bottle for a "total of 150 mg daily once per month as directed." (See Figure 2 for the exact wording of directions on the bottle holding 40 mg cap-

continued on page 2—Oral chemotherapy >

Figure 2. One of three vials of lomustine containing three doses intended to be taken 6 weeks apart.

SAFETY briefs

B. Braun 1,000 mL potassium chloride premix. Last Friday and again this week, we received reports from hospital pharmacists who said their respective organizations received cartons from B. Braun with 5% dextrose and 0.45% sodium chloride printed on one side and 0.15% potassium chloride (20 mEq/in 5% dextrose and 0.45% sodium chloride on the opposite side of the carton (Figure 1). The carton actually contained 1,000 mL bags of 0.15% potassium chloride (20 mEq/in 5% dextrose and

Figure 1. Same carton, two different drug labels.

0.45% sodium chloride. We contacted B. Braun, and the company confirmed there had been a labeling error. The company told us they are preparing a customer letter and said they have also informed the US Food and Drug Administration (FDA) in writing. The individual containers inside the carton correctly reflect the potassium content and note: "20 mEq K"/liter" in red print within a box. A single lot number (J4B581) is affected. Until B. Braun takes further action, we thought it best to notify readers who might be using this product. Please be sure to check your current supply of this specific premixed potassium product. If you have cartons in stock, please take the time to tear off, or otherwise black out, the incorrect label.

Duplicate the drug name on commercial labels. A technician accidentally selected a vial of trastuzumab (HERCEPTIN) and a vial of rituximab (RITUXAN) when she needed 2 vials of rituximab for a chemotherapy infusion. Unknowingly, the technician mixed the two different drugs

continued on page 2—Safety Briefs >

- Early warning system
  - Issue nationwide hazard alerts and press releases
- Learning
  - Dissemination of information and tools
- Change
  - Product nomenclature, labeling, and packaging changes, device design, practice issues
- Standards and Guidelines
  - Advocates for national standards and guidelines

April 19, 2018 ■ Volume 23 Issue 8

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Investigational drugs: Product-related issues pose significant challenges (Part I)

An investigational drug is a chemical or biological substance that has been tested in the laboratory and approved by the US Food and Drug Administration (FDA) for testing in people during clinical trials. Investigational drugs can include both prescription and nonprescription medications, but some fall into the category of high-alert medications and have a narrow therapeutic index that requires careful testing to determine the most effective and safe doses. While the sponsoring company's attention is highly focused on the safety profile of the drug and its clinical effects on patients, those working on new drug development, product manufacturing, and protocols for clinical trials are rarely well versed in medication error-prevention principles. Additionally, limited regulatory oversight exists to guide, standardize, and govern investigational drug labeling, packaging, and nomenclature, making this a lower priority for many sponsoring companies compared to the efficacy and safety profile of the drug. These conditions can create a perfect storm for errors with investigational drugs that may cause serious harm to patients and lead to inaccurate outcome data about the drug.

According to healthcare practitioners who have reported hazards and errors with investigational drugs to ISMP, there are many troubling product-related safety concerns that currently exist. In **Part I**, we explore the risks associated with investigational drug nomenclature, labeling, and packaging in detail. In **Part II**, which will be published in our **May 3, 2018** newsletter, we will recommend strategies for clinical sites that participate in investigational drug studies, as well as manufacturers and FDA, to improve the safety of investigational drug nomenclature, labeling, and packaging.

Drug Nomenclature

Look-alike product identification. In the early phase of research, investigational drugs are most often identified using a number preceded by an abbreviation of the sponsoring company's name (e.g., AMG-123456 for a drug sponsored by Amgen Oncology)—much like a vehicle license plate. Many clinical sites that participate in investigational drug studies are involved in multiple studies by the same sponsor; thus, the sponsor's abbreviation preceding the identification number adds to investigational drug name similarity. After the sponsor's abbreviation, the numbers that are used to identify the different drugs may vary by just the last digit (e.g., BMS-123456, BMS-123457, BMS-123458), further contributing to name similarities. Some letter/number designations can be up to 25 characters long, or are described using multiple words. These longer identifiers are often truncated on computer screens. The license plate-type numbers may also overlap with an existing protocol number.

Product name changes are not reflected on labels and protocols. As the investigational drug moves into different phases of clinical trials, a product with a license plate-type number may be assigned a generic name. While the research team, packing slips, and other shipping documentation may refer to the drug by its new generic name, product labels may continue to reflect an older license plate-type number. It is even possible for the license plate-type number to change during the

continued on page 2—Investigational drugs >

SAFETY briefs

Product appearance too similar. A hospital pharmacist informed us about look-alike ampuls of verapamil 5 mg/2 mL and fenta**NYL** 100 mcg/2 mL from Hospira (**Figure 1**). They share the same unique light tan labels and tan and blue colored bands along the ampul neck. Although no medication errors have been reported to ISMP, we wanted practitioners to be aware of the risk. A representative from Hospira told us that a label revision is in the process for the verapamil product. The revised ampul label will express the concentration per USP <7> guidelines as "5 mg/2 mL (2.5 mg/mL)." Also, the drug name will be printed on the label in blue. Hopefully this will help reduce the potential for look-alike confusion.

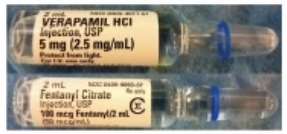

Figure 1. Similar appearance between verapamil and fenta**NYL** ampuls could contribute to mix-ups.

Potassium chloride concentrate unsafe in a syringe. We learned last week that at least one of the 503B outsourcers (Nephron) is distributing potassium chloride (KCl) concentrate to hospitals in a syringe (**Figure 1**). These were ordered by mistake by a hospital pharmacy technician and then reported to us. It's unknown if other outsourcing companies provide syringes of concentrated KCl as well. For safety reasons, we highly recommend not using these products. Perhaps the syringes are meant for use only in the pharmacy as an additive to be diluted in a minibag or large volume parenteral due to the shortage of commercially available premixed KCl infusion products. But the last manufacturer to distribute additive syringes of KCl concentrate

Figure 1. Potassium chloride concentrate injection (10 mEq/5 mL) in a 10 mL syringe.

continued on page 2—SAFETY briefs >

May 3, 2018 ■ Volume 23 Issue 9

ISMP

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Investigational drugs: Strategies for sponsors, FDA, and clinical sites to prevent product-related errors (Part II)

Limited regulatory guidance exists for investigational drug labeling, packaging, and nomenclature, exposing sites that participate in clinical trials to many troubling product-related safety risks. Many of these risks are unique to investigational drugs and are less likely to be encountered with US Food and Drug Administration (FDA)-approved medications used outside the research setting. Some of these safety concerns, which were described in detail in **Part I** in our April 19, 2018 newsletter, include:

- Look-alike license plate-type identification names during the early phase of research
- Generic name assigned in later phases not included on the label or in the protocol
- Unlabeled containers or bulky outer cartons
- Labels without a discernable drug name or identified by only a protocol number
- Labels without strength/concentration, formulation, lot number, expiration/retest date, and/or barcode
- Inaccurate expiration/retest dates
- Look-alike labels in small black and white font, sometimes with unsafe abbreviations and dose expressions
- Critical product information (e.g., name and strength) hidden below a peel-off label
- Labels expressed in multiple languages, each often found behind a peel-off label
- Products packaged in inappropriate sizes (e.g., single doses require many vials or serial dilutions/aliquots) or in containers typically not used for the intended route of administration (e.g., oral medications in vials)
- Identical tablet/capsule appearance for different strengths of the same drug
- Different quantities of capsules/tablets in sealed bottles than is stated on the label
- Variable or missing content in protocols, pharmacy manuals, drug information sheets, and investigator brochures

These conditions increase the risk of potentially harmful errors that may elude detection and lead to inaccurate data about the safety and effectiveness of investigational drugs.

REGULATORY STANDARDS AND PROFESSIONAL GUIDELINES

The US Code of Federal Regulations (CFR) requires the following warning on the immediate package of any investigational drug: "Caution: New Drug—Limited by Federal (or United States) law to investigational use."[1] The CFR also includes requirements for the handling of investigational controlled substances, informed consent, investigational new drug applications, responsibilities of sponsors and investigators, and institutional review board (IRB) involvement.[1,2] However, unlike commercially available FDA-approved medications, there is scant FDA guidance in place related to investigational drug labeling, packaging, and nomenclature to promote safety.

The American Society of Health-System Pharmacists (ASHP)[3] and the Hematology/Oncology Pharmacy Association (HOPA)[4] have both published best practices associated with investigational drugs. Among the many practice recommendations, these guidelines call upon clinical sites to establish storage, dispensing, and labeling requirements for investigational drugs; track expiration dates; employ barcode scanning; and implement

continued on page 2—Investigational drugs >

SAFETY briefs

Standardization of expiration dates needed. Does "19 MAR 18" on a product label mean that it expires on March 18, 2019, or March 19, 2018? It is difficult to understand how something so important as a product expiration date is not communicated clearly, in a standard way. While the US Code of Federal Regulations (CFR) (Part 211) sets forth the conditions under which an expiration date must be listed on labels, it does not specify how expiration dates must be expressed. In the absence of standard regulations, inconsistent expressions of expiration dates has led to confusion and misinterpretation of the date beyond which manufacturers cannot guarantee full potency and safety of the drug.

We just received a report of an unusual expiration date that is difficult to interpret on Hospira's PACLitaxel injection. On the outer carton "200131" is stamped, which is intended to convey an expiration date of January 31, 2020. However, nurses and pharmacists might easily be confused by these numbers. If all four digits were used for the year, with dashes in between the numbers, the date would be clear (2020-01-31).

Another confusing example can be seen on Teva products, which display the month the product will expire as a 2-letter abbreviation. In Figure 1, does "EXP. MA-2019" indicate that the product expires in March or May? If "JU" is used, does it stand for June or July? If the month is abbreviated at all, at least 3 letters should be used.

We also received a report about the format used to express lot numbers and expiration dates by Avella, a US Food and Drug Administration (FDA)-registered

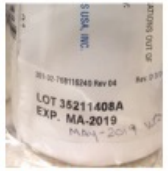


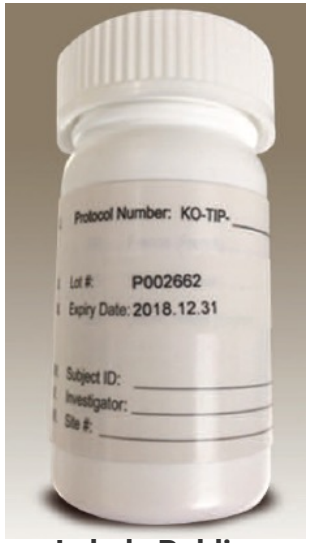
Figure 1. Is the product's expiration date the end of March or May 2019?

continued on page 2—SAFETY briefs >

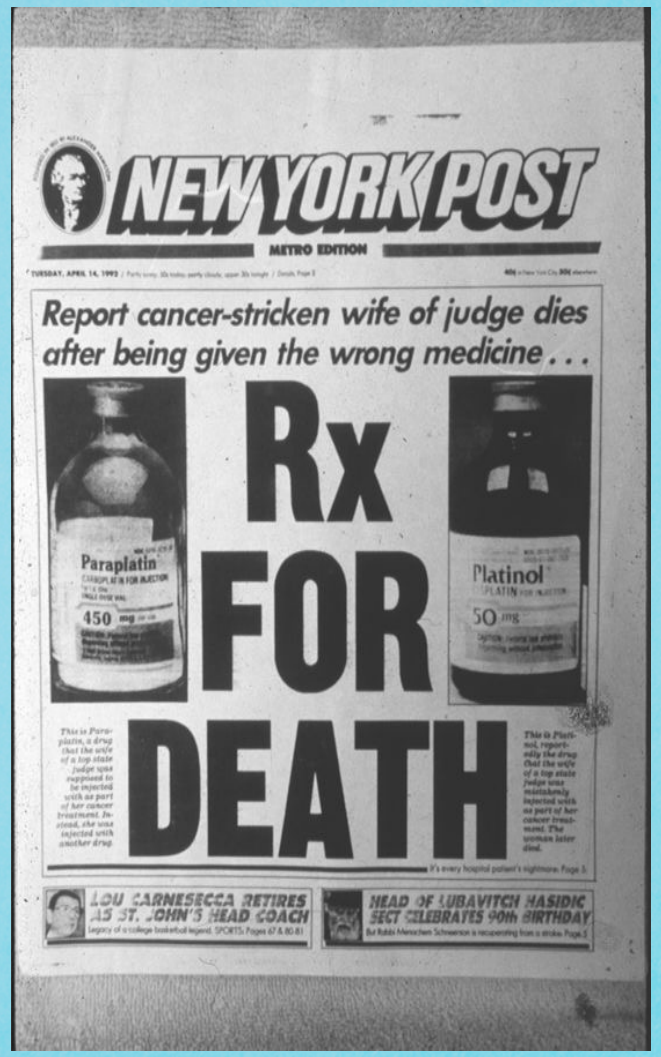
Investigational product related issues- ISMP-2018

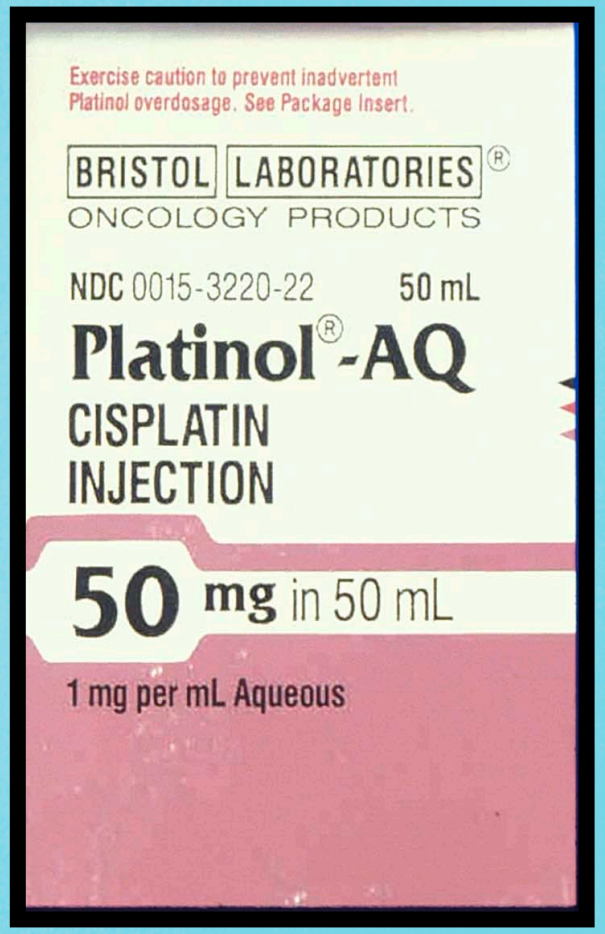
- License plate type product ID
- Changing product names not reflected on labels/protocols
- Unlabeled products
- Bulky “naked” boxes
- Missing, confusing or unnoticeable drug names
- Missing or hard to find strength
- Missing formulation
- International labels; multilanguage text
- Small font size; no differentiation of text
- Unsafe abbreviations and dose expressions
- Missing lot #’s and expiration dates
- No unit dose packaging for oral studies
- Multiple strengths of tablets-same color, size and shape

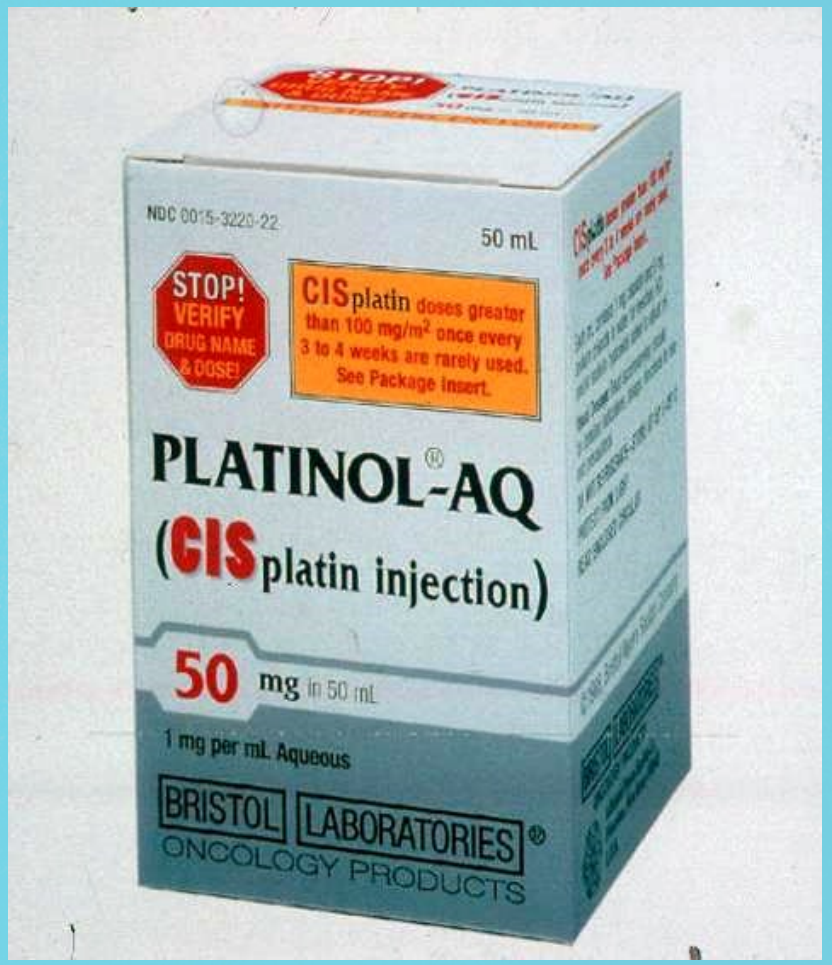
Some injectable investigational drugs that are light sensitive are packaged individually in bulky unlabeled white boxes that must be labeled by the clinical site prior to storage.



This investigational drug is identified by the protocol number only, although it has been assigned a generic name (tipifarnib). Also, the strength of the product (100 mg) can only be found below the peel-off label, although the drug is available in multiple strengths.


NEW YORK POST
METRO EDITION
Report cancer-stricken wife of judge dies after being given the wrong medicine . . .
Rx FOR DEATH
Paraplatin
450 mg
Platinol
50 mg
LOU CARNESECCA RETIRES AS ST. JOHN'S HEAD COACH
HEAD OF LUBAVITCH HASIDIC SECT CELEBRATES 90th BIRTHDAY


Exercise caution to prevent inadvertent Platinol overdosage. See Package Insert.
BRISTOL LABORATORIES
ONCOLOGY PRODUCTS
NDC 0015-3220-22 50 mL
Platinol®-AQ
CISPLATIN INJECTION
50 mg in 50 mL
1 mg per mL Aqueous


NDC 0015-3220-22
50 mL
STOP! VERIFY DRUG NAME & DOSE!
CISplatin doses greater than 100 mg/m² once every 3 to 4 weeks are rarely used. See Package Insert.
PLATINOL®-AQ
(CISplatin injection)
50 mg in 50 mL
1 mg per mL Aqueous
BRISTOL LABORATORIES
ONCOLOGY PRODUCTS

Speaker Disclaimer

All images and drug names are for illustration purposes only

Potential Medication Error Risks with Investigational New Drug Container Labels

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Manager, Investigational Pharmacy Services

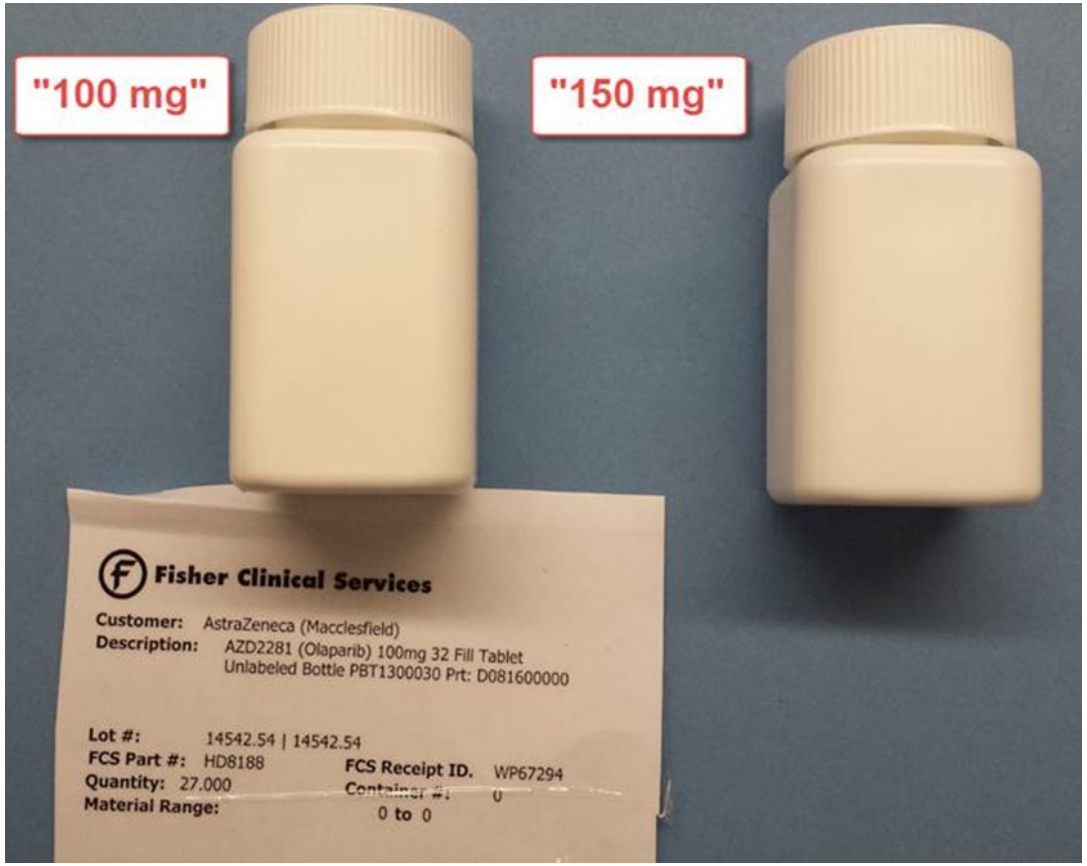
MD Anderson Cancer Center

Houston, Texas

Overview

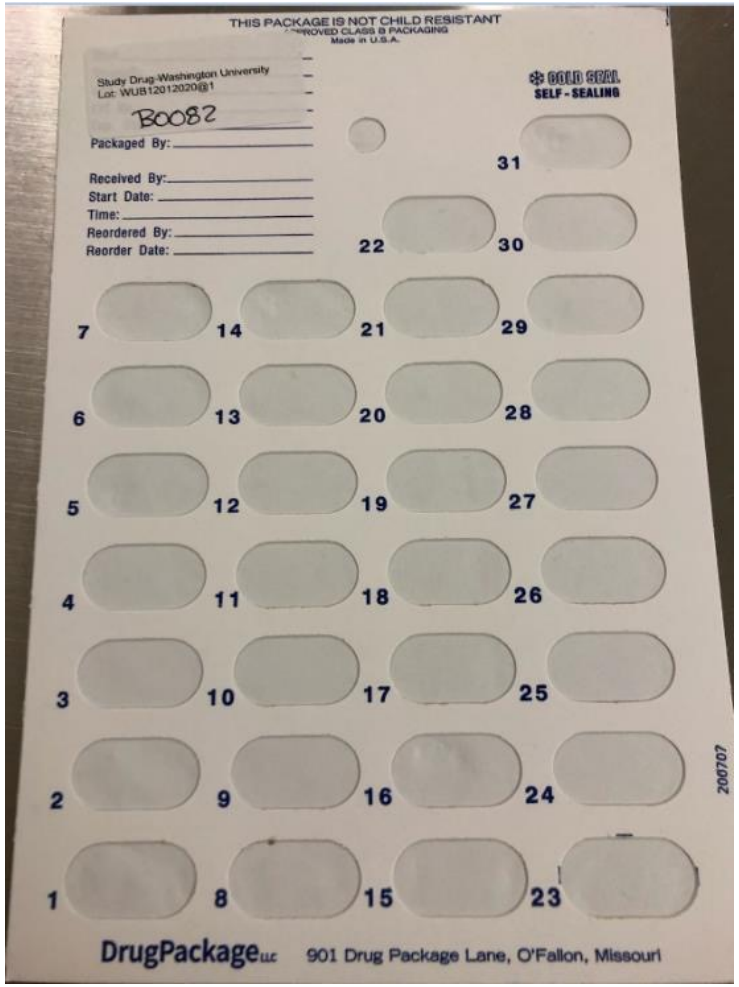
- Labeling Concern Examples
- Labeling overview and awareness timeline
- Pharmacy Practice Recommendations
    - Hematology Oncology Pharmacy Association (HOPA)
        - Investigational Best Practice Standards
    - Institute for Safe Medication Practices (ISMP)
        - Two part article
    - Association of Dedicated Cancer Centers (ADCC)
        - Investigational Sub-group Recommendations
    - American System Health System Pharmacy
- Summary

Labeling Concerns



DISCLAIMER: All images and drug names are for illustration purposes only.

Labeling Concerns



DISCLAIMER: All images and drug names are for illustration purposes only.

Labeling Requirement Overview

Table 1. Representative Region-Specific Labeling Requirements.[a]

	US		Japan		Canada		EU + Annex 13		India		EU Annex VI	
Minimum labeling criteria	2°	1°	2°	1°	2°	1°	2°	1°	2°	1°	2°	1°
Contact name							R	R	R	R	R	R
Contact address							R				R	
Contact telephone							R				R	
Name: shipper, importer, manufacturer									R	R		
Address: shipper, importer, manufacturer									R	R		
Drug name			R	R	R	R	R	R	R	R	R	R
Strength / potency / dosage							R	R	R	R	R	R
Dosage form							R	R	R	R	R	R
Route of administration							R	R	R	R	R	R
Quantity of dosage units							R	R	R	R	R	R
Batch/lot	R	R	R	R	R	R	R	R	R	R	R	R
Trial reference code					R	R	R	R	R	R	R	R
Subject number							R	R	R	R	R	R
Investigator name / number							R		R	R	R	
Directions for use							R				R	
"Clinical trial use" phrase	R	R	R	R	R	R	R		R	R	R	
Storage conditions			R		R	R	R		R	R	R	
Expiry date / period of use					R	R	R		R	R	R	R
"Keep out of reach of children"							R		R	R	R	
Handling / special precautions			R	R	R	R			R	R		
Manufacture date									R	R		
Country-specific language			R	R	R	R	R	R	R	R	R	R

Abbreviations: R, required; 1°, label on the primary or immediate packaging; 2°, label on secondary or outer packaging.
[a]This table is provided for informational purposes and is not intended to provide legal advice. Each company is responsible for determining compliance with specific laws, regulations, and guidances.

Smith-Gick, J., N. Barnes, R. Barone, et al., "The Near-Term Viability and Benefits of eLabels for Patients, Clinical Sites, and Sponsors," *Therapeutic Innovation and Regulatory Science*, vol. 52(5), pp. 537-545, 2018.

Presented at the Potential Medication Error Risks With Investigational Drug Container Labels Public Meeting

Labeling Issues Awareness Timeline

- 2014 Fall: Hematology Oncology Pharmacy Association (HOPA):
  - Investigational Drug Service (IDS) Best Practice Standards
- 2017 November: Alliance of Dedicated Cancer Center IDS: Standard Operating Procedure Document (Unpublished internal guidance at member centers)
- 2018 April: American Society of Health System Pharmacists (ASHP) Guidelines for the Management of Investigational Drug Products
- 2018 April/May: Institute for Safe Medication Practices (ISMP) Newsletters Parts 1 and II
- 2021: National Comprehensive Cancer Network: Investigational Drug Service Working Group (2019 - Present)
  - Investigational Drug Services Standards recommendations (Draft- in publication submission process)

HOPA IDS Best Practice Standards Labeling Recommendations

- Best Practice Standard Recommendation:
  - Establish investigational medication labeling policies
    - Recommendation: Clinical research sites in the Unites States should follow all applicable state and federal guidelines for medication compounding, dispensing, and labeling, including United States Pharmacopeia (USP) 797 and the Joint Commission standards.
  - The IDS Should Establish Dispensing and Labeling Requirements for Oral Investigational Medications
    - Local Pharmacy State Board requirements for labeling prior to dispense
  - Best Practice Standards did not specify labeling example

Amin SR, et al. HOPA investigational drug service best practice standards [Internet]. Available from: https://www.hoparx.org/images/hopa/resource-library/professional-tools/HOPA16_IDS_Guidelines.pdf.

Alliance of Dedicated Cancer Center (ADCC) Investigational Drug Services (IDS) Subgroup

- To establish best practice standards and procedures for IDS that adhere to Code of Federal Regulations (CFR) and drug accountability requirements.
- The document drafted by the subcommittee was intended to provide guidance and standardization pertaining to the pharmacy's role and participation in Clinical Research Protocols.

- City of Hope Comprehensive Cancer Center
- Dana Farber Cancer Institute
- Fox Chase Cancer Center
- The James: Ohio State University Comprehensive Cancer Center
- MD Anderson Cancer Center
- Memorial Sloan Kettering Cancer Center
- Moffitt Cancer Center and Research Institute
- Roswell Park Cancer Institute
- Seattle Cancer Care Alliance
- USC Norris Comprehensive Cancer Center

ADCC Investigational Pharmacy Subgroup Recommendation

- Investigational Pharmacy Subgroup formed to address practice gaps identified:
  - Investigational Drug Minimum Labeling criteria established for acceptance of products * Mandatory
    - *Complete Name of Product (eg, nab-paclitaxel, or salt form when more than one exists)
    - *Dosage/Concentration
    - *Formulation
    - *Quantity
    - *Lot/Batch Number
    - *Storage Conditions
    - Name and Address of Manufacturer
    - Expiration Date (if available)
    - CFR Statement: Caution; new drug – limited by US or Federal law to investigation use

*Internal ADCC Pharmacy Recommendation Document. Unpublished

Institute for Safe Medication Practices (ISMP) Labeling Recommendations

- Drug labeling issue escalated to ISMP by ADCC participants
  - Result: Two part article
- Publication Part 1
  - Product Related Issues and Challenges
- Publication Part 2
  - Recommendations and mitigation strategies for clinical sites and manufacturers

Institute for Safe Medication Practices. Available from: www.ismp.org/resources/investigational-drugs-product-related-issues-pose-significant-challenges-part-i
Institute for Safe Medication Practices. Available from: www.ismp.org/resources/investigational-drugs-strategies-sponsors-fda-and-clinical-sites-prevent-product-related

ASHP Recommendation

- Investigational Drug Product Receipt: Sponsor Label Recommendations
  - Investigational drug product name
  - Investigational drug product strength or concentration unless this aspect of the trial is blinded
  - Investigational drug product quantity (e.g., number of tablets, volume)
  - Investigational drug product lot number and/or container or kit number
  - Expiration or retest date (period of use) of the investigational drug product
  - Sponsor or manufacturer name and address
  - Clinical research protocol number
  - Oral medication intended to be dispensed to a participant for self-administration at home
    - Must comply with the Federal Poison Prevention Packaging Act and be packaged in a child-resistant container

Kay SC, et al. ASHP guidelines for the management of investigational drug products. Am J Health Syst Pharm. 2018;75:561-73

Summary

- Lack of standardized immediate drug container labeling and nude vials/bottles pose risk to patient safety and drug handling
- Labeling varies amongst sponsor held IND trials versus Investigator Initiated trials
- Recommendations issued from various Pharmacy stakeholder groups for standardization
- Mitigation strategies implemented at clinical sites:
  - Minimum standards for drug acceptance at their institutions as a policy/procedure
  - Site work arounds to mitigate risks of inadequate labeling
    - Lack of uniform approaches for sites
    - Third party labeling vendors
- Need Pharmacy, Sponsor, and Regulatory collaboration for standardization guidance and heightened awareness of issue

Investigational Container Label Examples

Richard Needleman, RPh

Investigational Drug Services Pharmacist

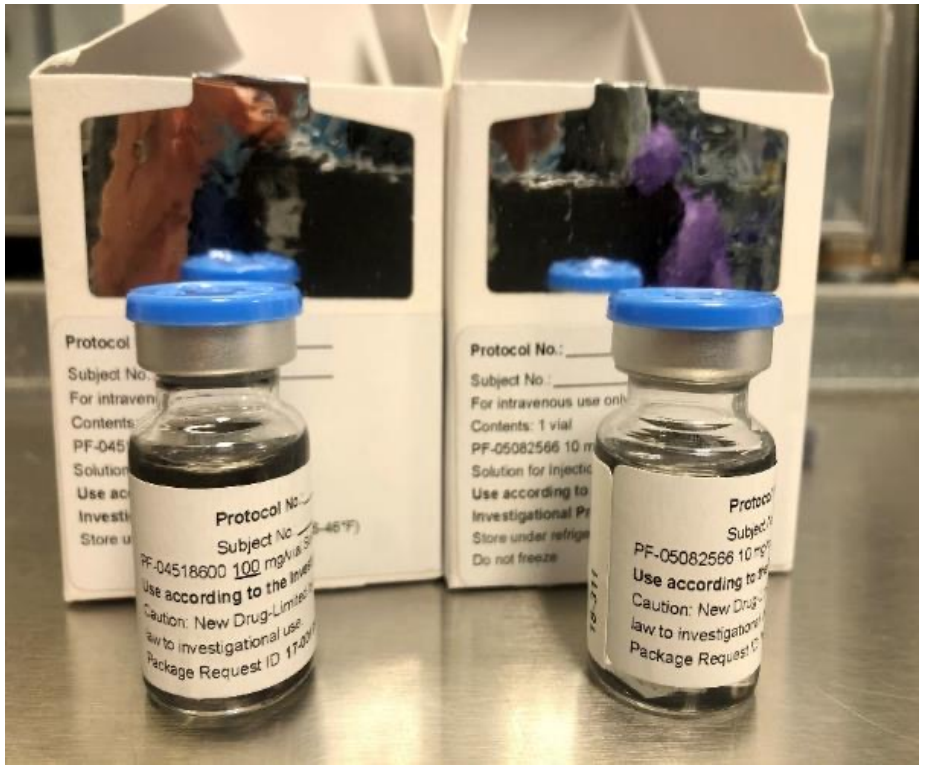
Fox Chase Cancer Center

Philadelphia PA

Labeling: what are the issues?

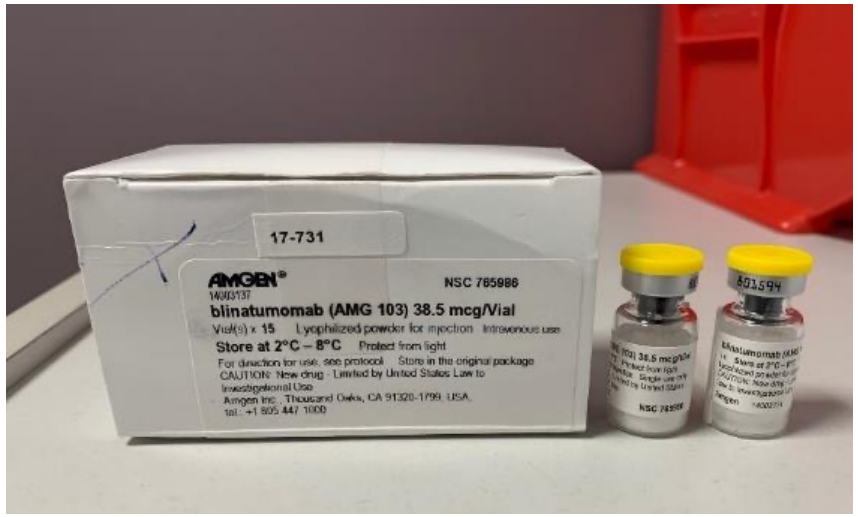
1. Label missing key information such as drug name, strength, dosage form, lot number.
2. Font size too small
3. Inconsistencies between the product label and the trail source documents (protocol, pharmacy manual, Investigator Brochure)
4. Multinational labels containing languages other than English

Drug names: what are the issues?



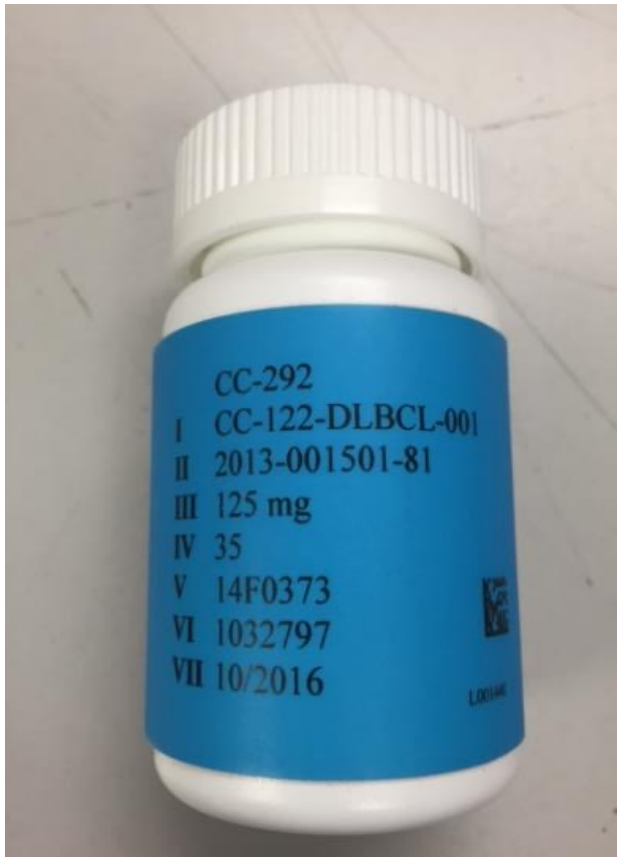
1. Drug name lacks differentiation from other drug/study info (protocol number very similar)
2. Drug name is nearly identical to another study drug (e.g., BMS-123456 and BMS-123458)
3. Drug name changed or did it? (PT2977 ➡ MK-6482 ➡ Belzutifan)

Drug names: what are the issues?



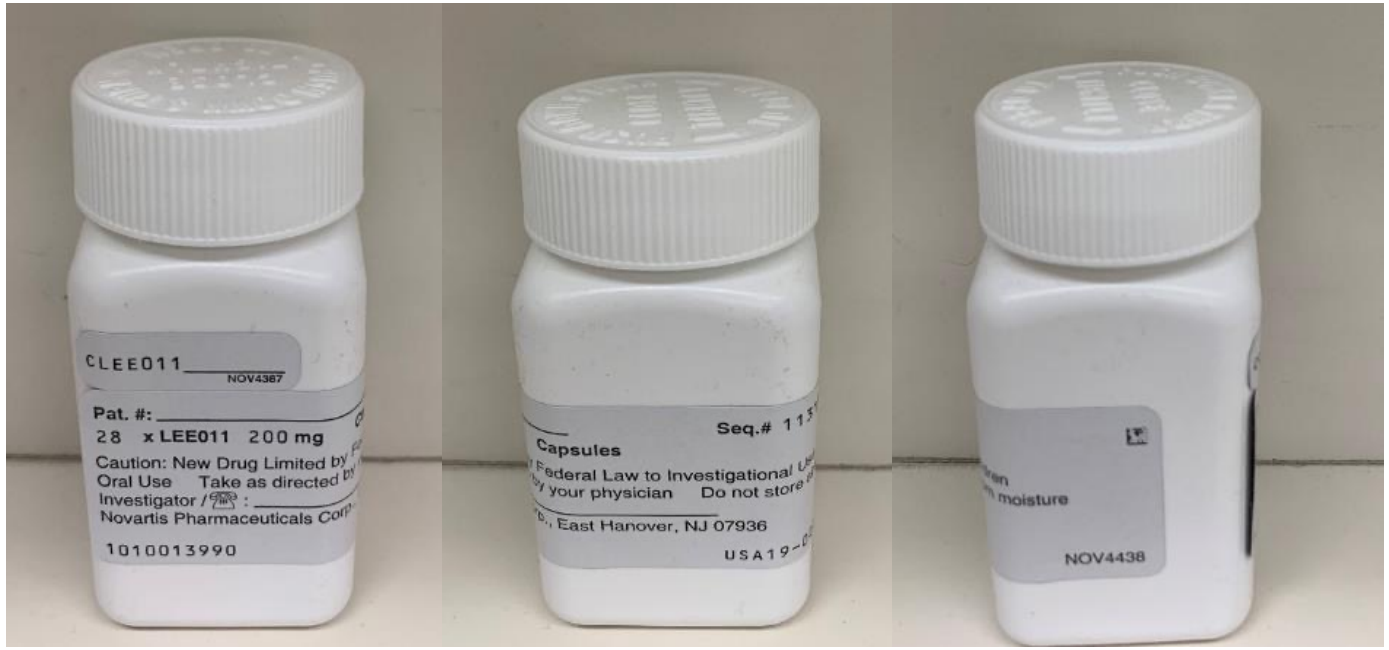
1. Use of a Key or Legend Label Format
2. Commercial vs. Investigational label issues.

Key or legend format label



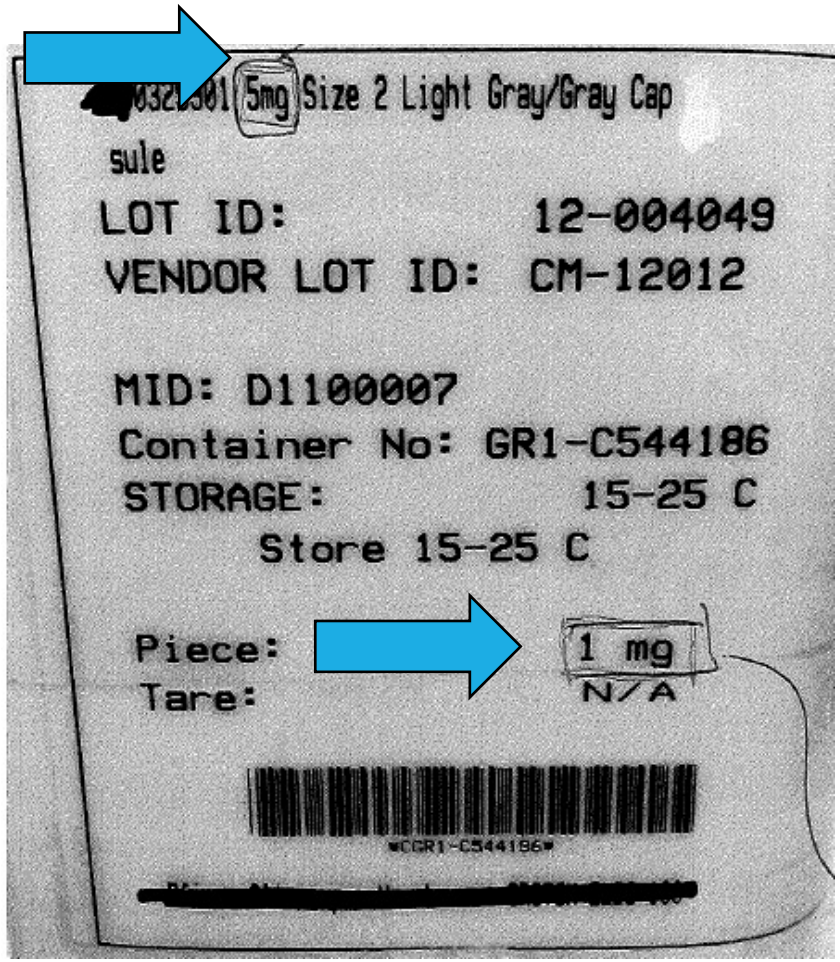
- What does each roman numeral represent?
- What is the drug name, dosage form, lot number, expiration date?

Drug Nomenclature



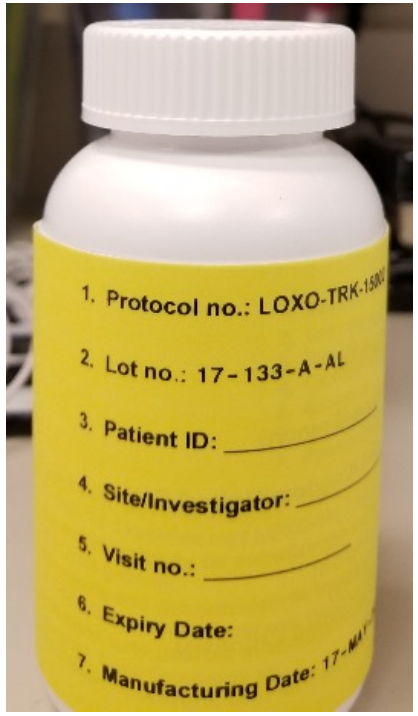
- "LICENSE PLATE" vs. GENERIC DRUG NAME
- Ribociclib received FDA approval March 13, 2017.
- Current bottle label format SHIPPED to site April 13, 2021
  - What is the lot number?
  - Expiration/Retest date?

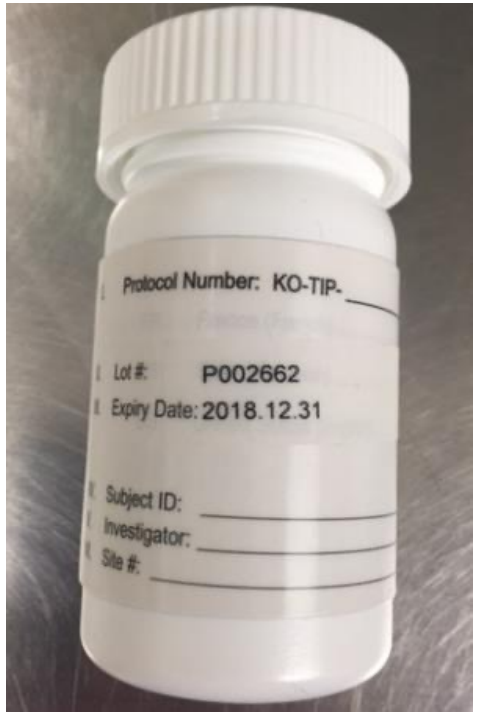
Label example (2 strengths?)



Which strength is in the container?

Labels Missing Critical Information



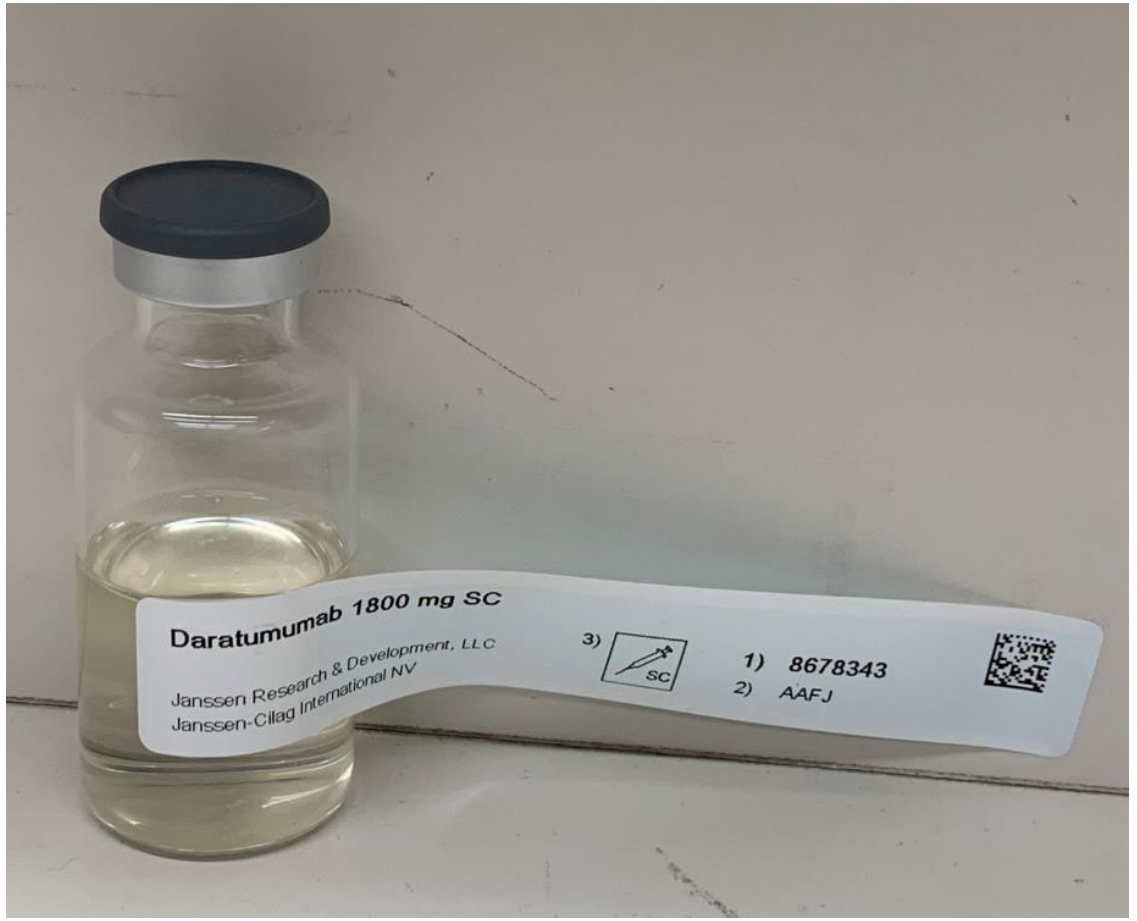


Missing Product Name/Identifier, Strength, and Dosage Form

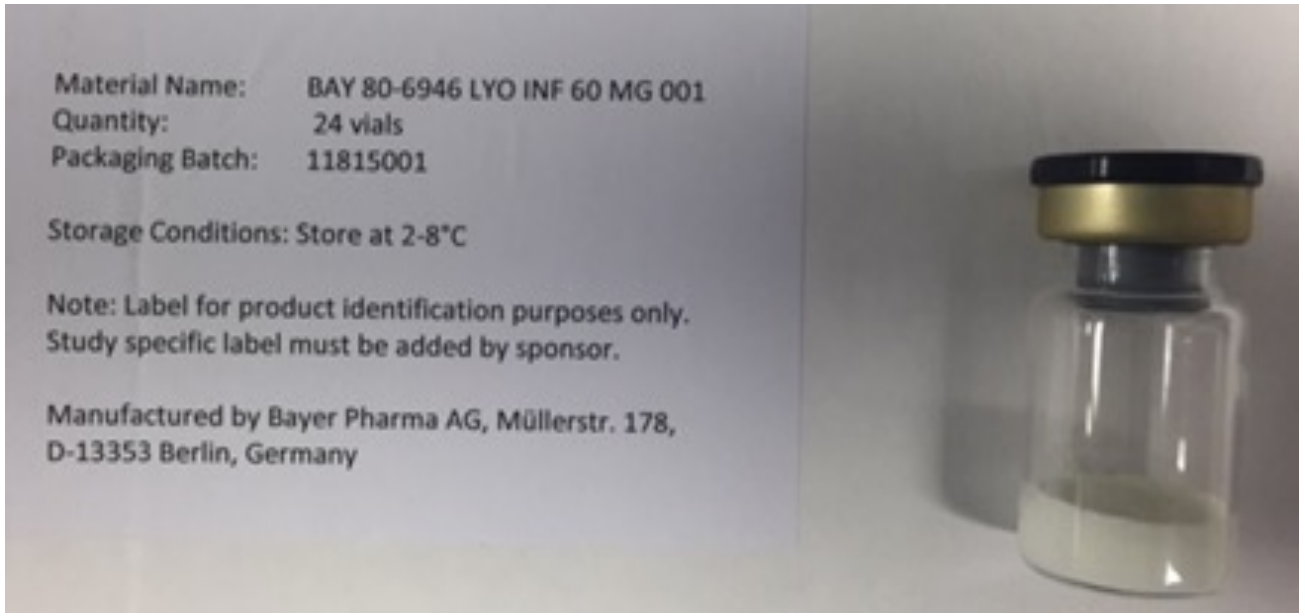
Missing Net Quantity

Critical Information Absence

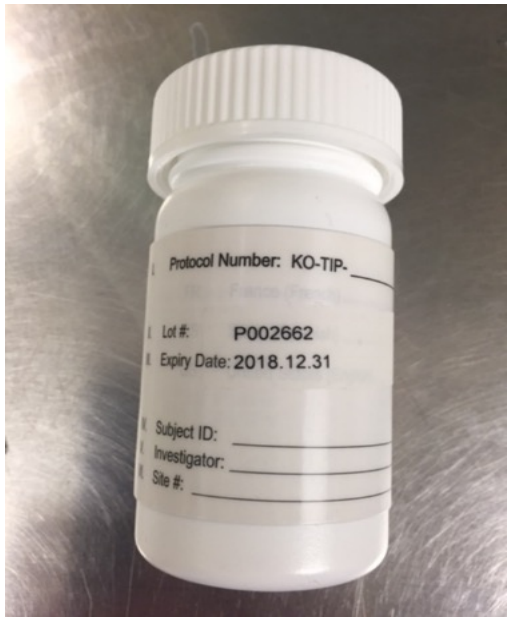
- Drug Concentration
- Lot
- Drug Volume
- Unapproved Abbreviation

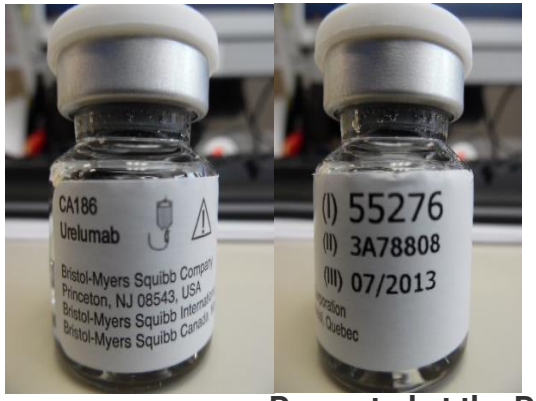


Naked vial


Material Name: BAY 80-6946 LYO INF 60 MG 001
Quantity: 24 vials
Packaging Batch: 11815001
Storage Conditions: Store at 2-8°C
Note: Label for product identification purposes only.
Study specific label must be added by sponsor.
Manufactured by Bayer Pharma AG, Müllerstr. 178,
D-13353 Berlin, Germany

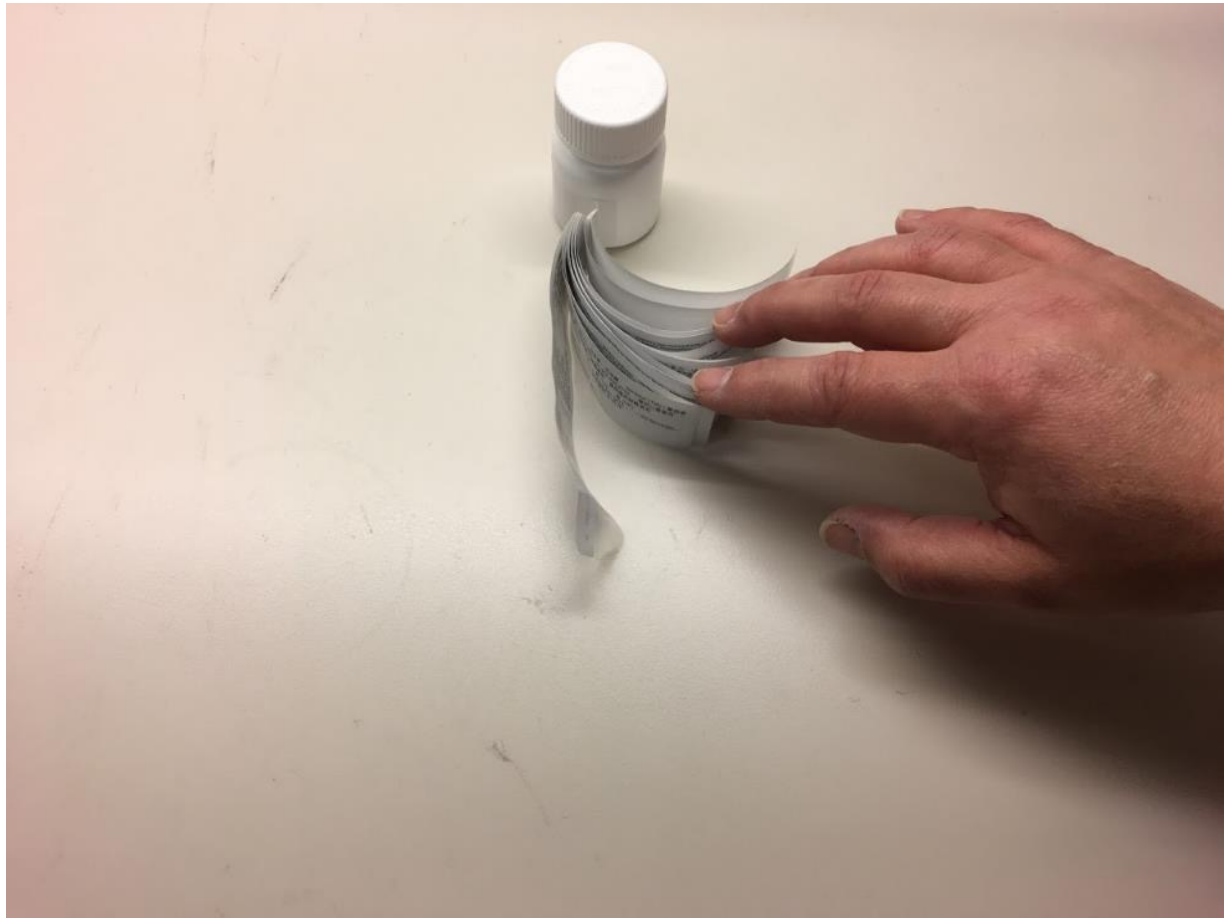
Label example (missing strength)





- "We just received drug in for a new study – no strength on the label
- The strength is lot# specific and we need to check a list of lot#s for the strength"

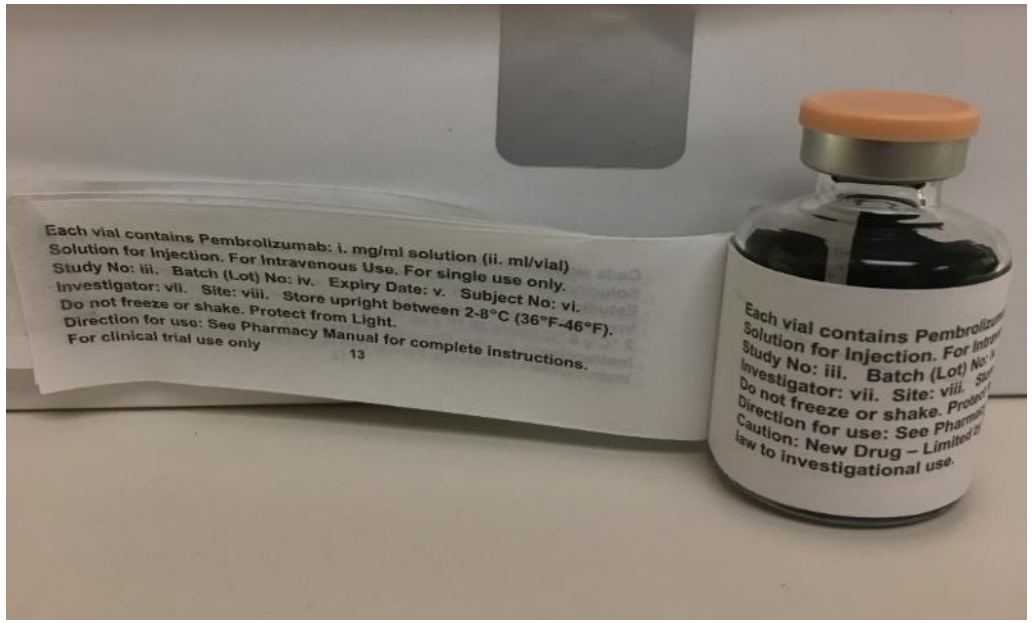
Multinational Labels



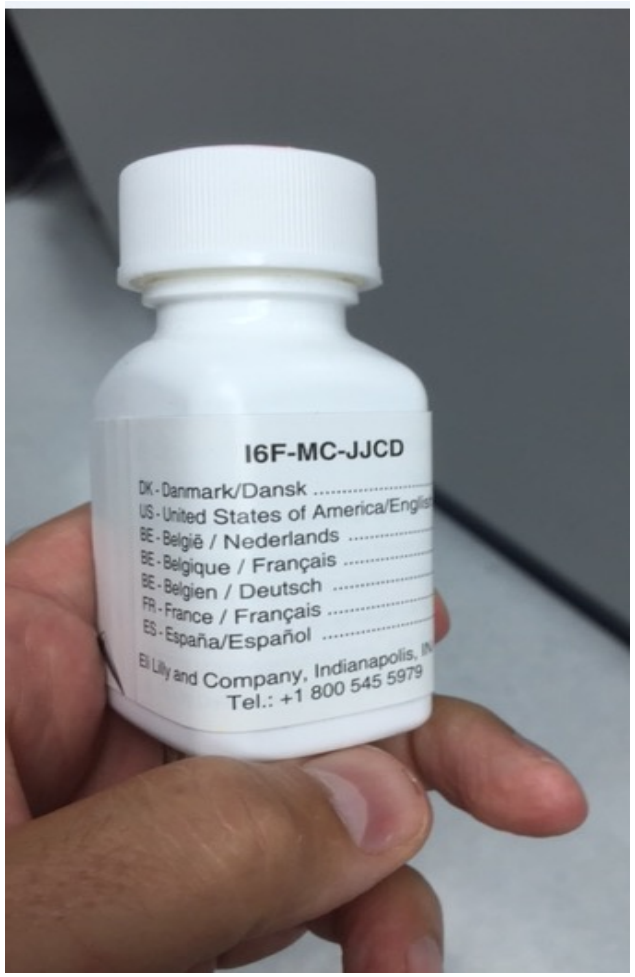
Presented at the Potential Medication Error Risks With Investigational Drug Container Labels Public Meeting

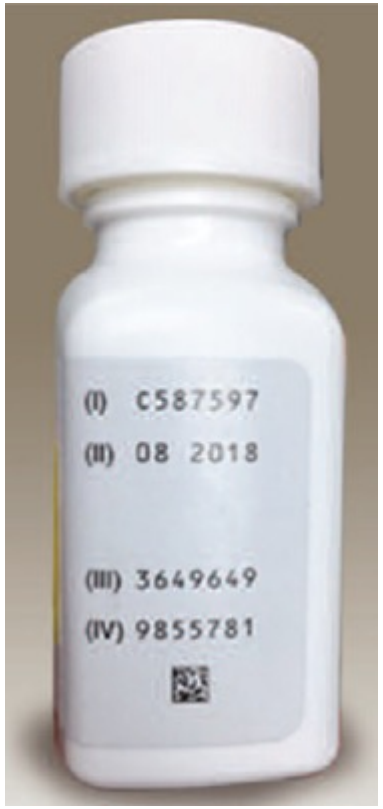
Multilabel Vial

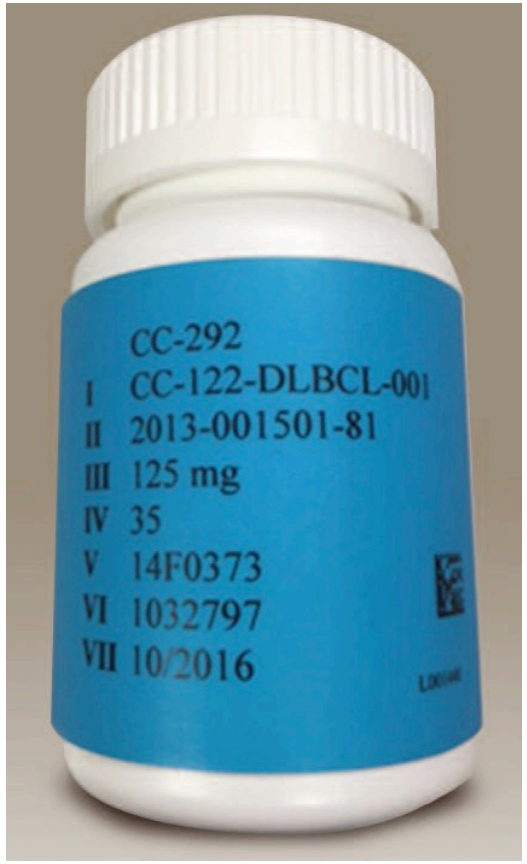
- Small font
- Too Much Information- Difficult to See Drug Name



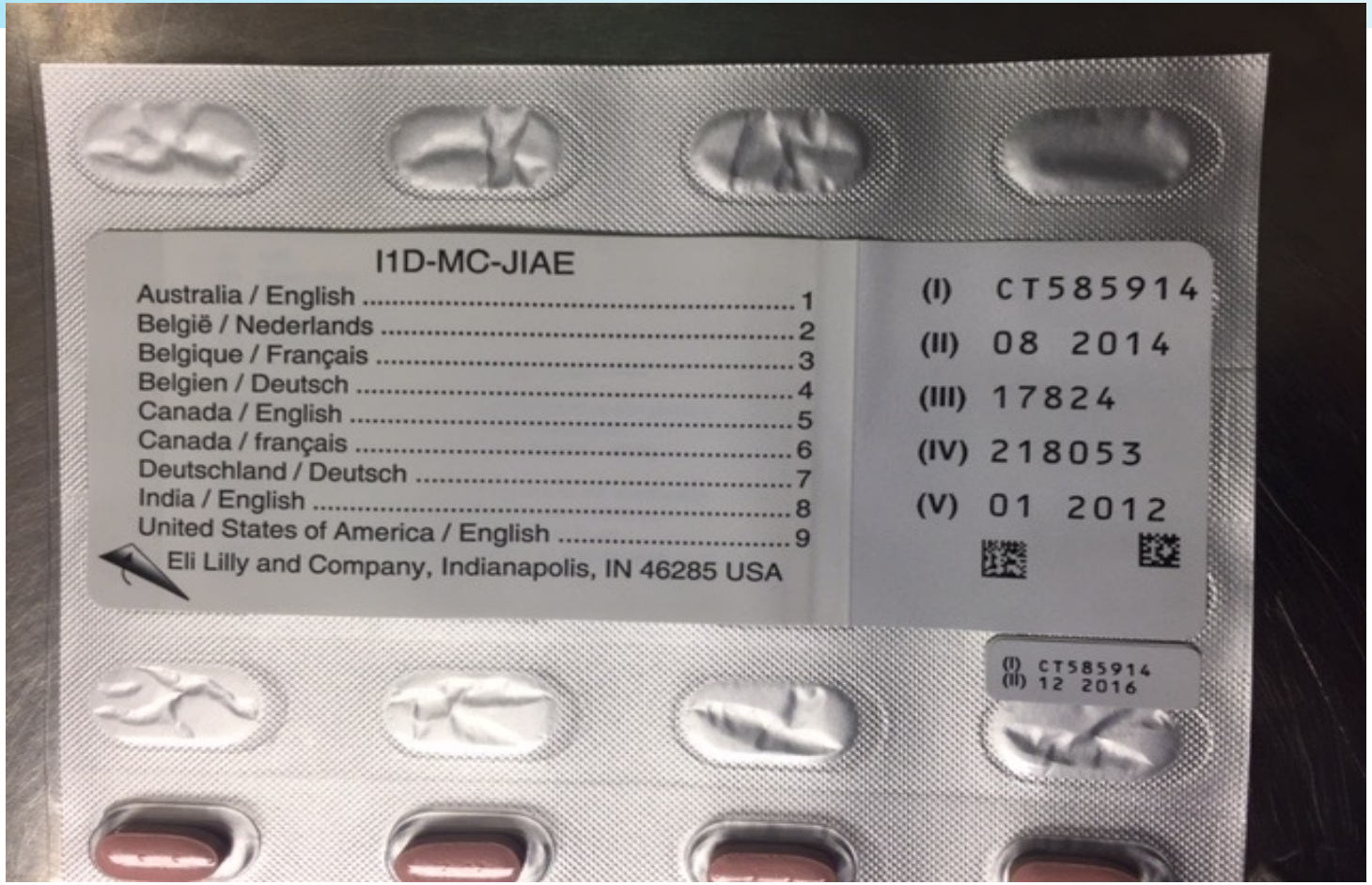
Use of Legends and Keys Instead of Field Names







Multinational Labels

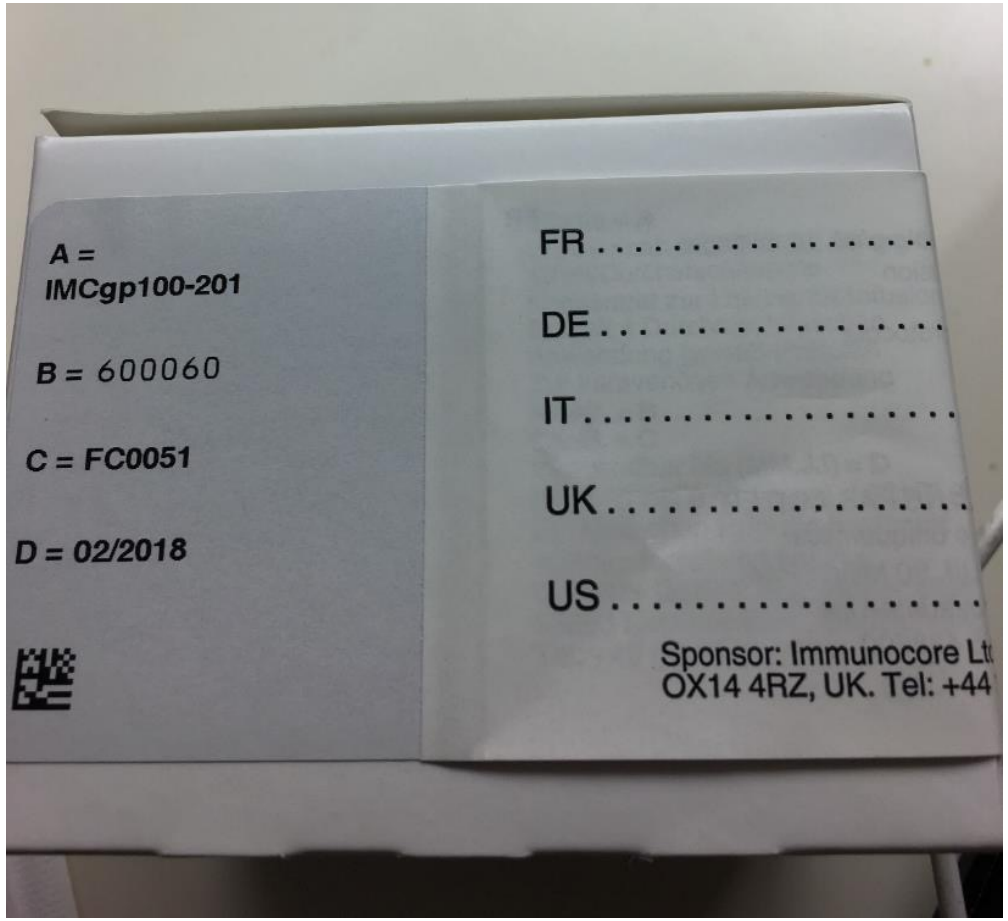


Outer Box Label

Protocol OR
Drug Name

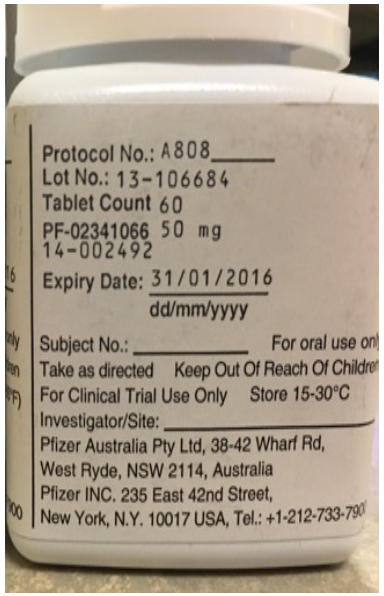
Drug Strength
Missing

Storage Conditions
Missing



Naked Box

Commercial vs. investigational product



Standardization Recommendation For Oral Label

Oral Investigational Agent Label Example

Font size:

- 8 is minimum, larger is preferred
- Agent Name in larger bold font is preferred

Minimum Required Information:

- Drug Name (with salt form when more than one exists)
- Strength
- Formulation (tablet, capsule, lozenge, etc)
- Quantity per container
- Lot or Batch Number
- Storage Requirements
- CFR Statement: Caution: new drug – limited by US or Federal law to investigational use
- Sponsor/Manufacturer information (Name and address)

Technology Requirement:

- Barcode
- Fast Track future technology

Optional Information:

- Clinical Trial Title
- Expiration/Retest Date (if available)
- Med Number (required for blinded studies)
- Investigator
- Patient Number
- Keep out of reach of children

Standardization Recommendation For Vial Label

Injectable Investigational Agent Label Example

Font size:

- 8 is minimum, larger is preferred
- Agent Name in larger bold font is preferred

Minimum Required Information:

- Drug Name (with salt form when more than one exists)
- Strength and Concentration
- Formulation (lyophilized powder, solution, suspension, etc)
- Quantity per container
- Lot or Batch Number
- Storage Requirements (additional information may be required)
- CFR Statement: Caution: new drug – limited by US or Federal law to investigational use
- Sponsor/Manufacturer information (Name and address)

Technology Requirement:

- Barcode
- Fast Track future technology

Optional Information:

- Clinical Trial Title
- Expiration/Retest Date (if available)
- Med Number (required for blinded studies)
- Investigator

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Investigational Drug Service Program Manager
Durham VA Health Care System

Han Feng, PharmD, BCPS
Supervisory Pharmacist, Medication Safety
National Institutes of Health

Literature Review – Cruz and Brown (2015)

- National survey of research pharmacists within the VA Healthcare System
- Assessed the perceived safety risks of investigational drugs
  - 81% indicated concern with medication safety risk
  - 42% stated that sponsors were not receptive to reports of safety concerns by pharmacists
- Top characteristics of packaging and labeling with identified safety concerns:
  - Lack of differentiation: 42.8%
  - No expiration date: 38.9%
  - Font size/color: 33.3%
  - Lack of barcodes: 33.3%

Cruz JL, Brown JN. Safety risks with investigational drugs: Pharmacy practices and perceptions in the Veterans Affairs health system. Ther Adv Drug Saf. 2015;6:103-9.

Literature Review – Dollinger et al. (2016)

- Assessed the impact of investigational drug labels on the risk of medication error
  - Utilized a simulation-based learning program
  - Enrolled pharmacists (n=15) and pharmacy technicians (n=32), residents (n=9), and students (n=7)
- Results
  - 12.5% (157/1260) error rate using the simulation-based tool
    - 17.1% error rate for high-risk labels
    - 7.8% error rate for low-risk labels
  - Most common errors were related to dose, trial name, and confusion risk
  - Error rate was not significantly affected by occupational category or experience in clinical trials
    - Indicates training and experience do not compensate for error risks with labels
  - High-risk labels resulted in significantly longer response times

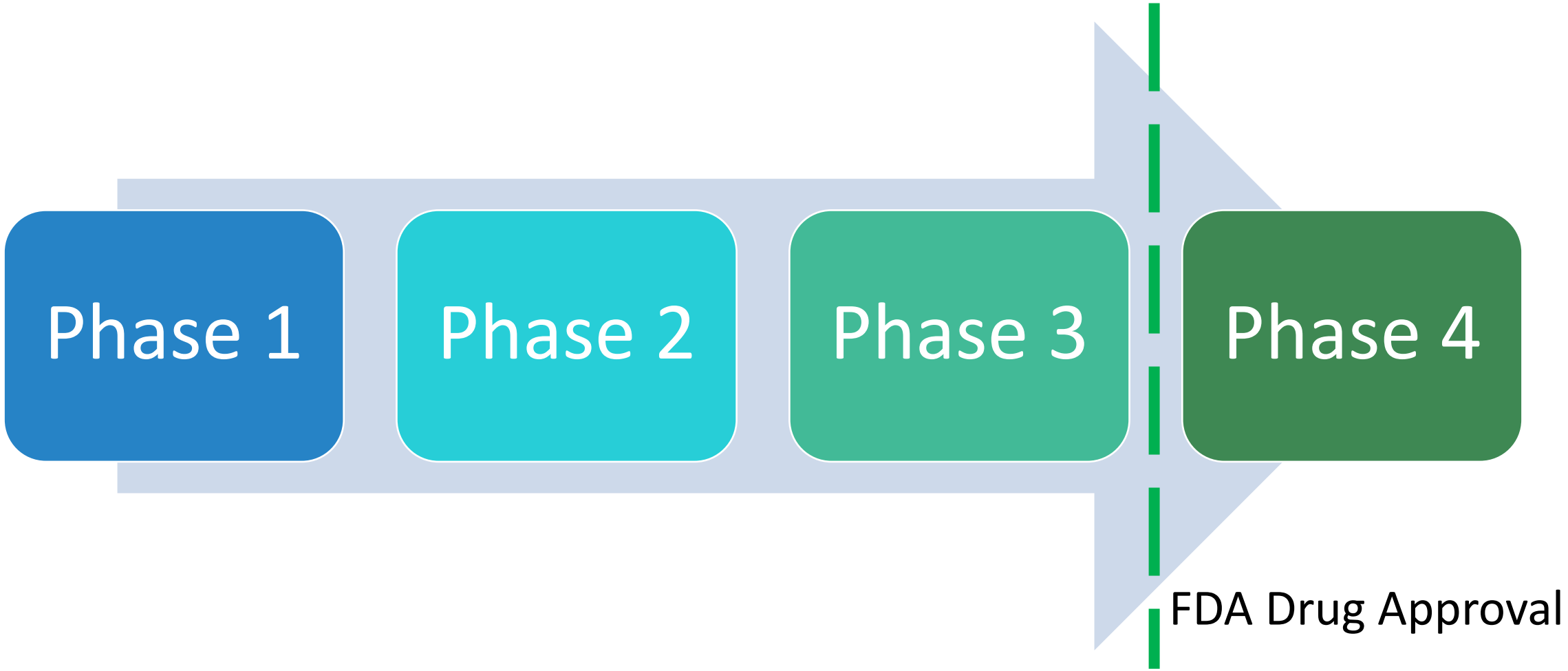
Dollinger C, et al. SIMulation of Medication Error induced by Clinical Trial drug labeling: the SIMME-CT study. Int J Qual Health Care. 2016;28:311-5..

Literature Review – Duhamel et al. (2019)

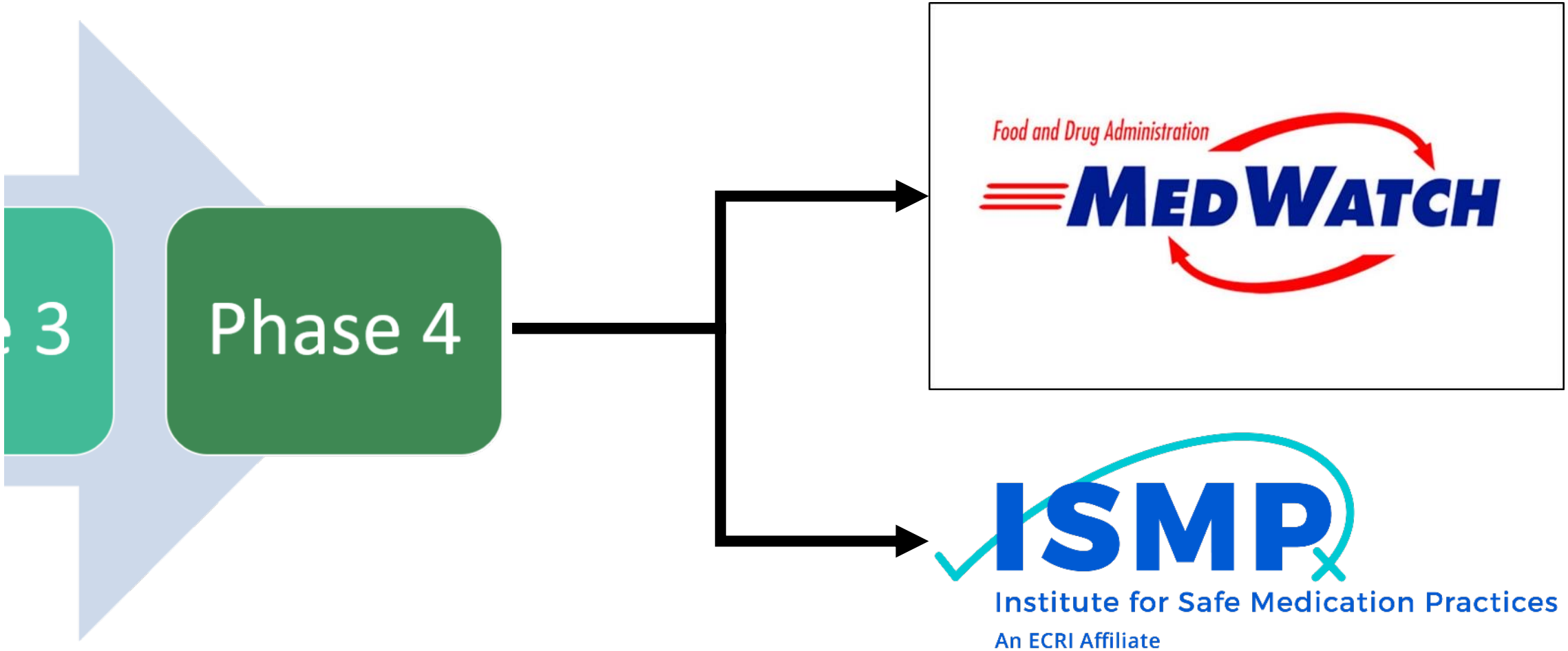
- Evaluated variability of investigational drug labels
  - 27 protocols (58 labels) were included
  - Utilized an 87-item checklist to assess content, format, and readability
- Results
  - Median of 14 (range: 1-69) pages of labels on bottles/packaging
    - Median of 10 languages (range: 2-50)
  - High discrepancy between labeling information contained in outer packaging compared to individual bottles/vials
  - Approximately half of the labels had kit numbers determined to be difficult to find by a panel of pharmacists
  - Expiration dates, when present, were supplied using different formats
    - DDMMMYYYY
    - MM/DD/YYYY

Duhamel A, et al. Investigational drug labeling variability. Clin Trials. 2019;16:204-213.

Phases of Clinical Research



Post-Marketing Surveillance & Safety

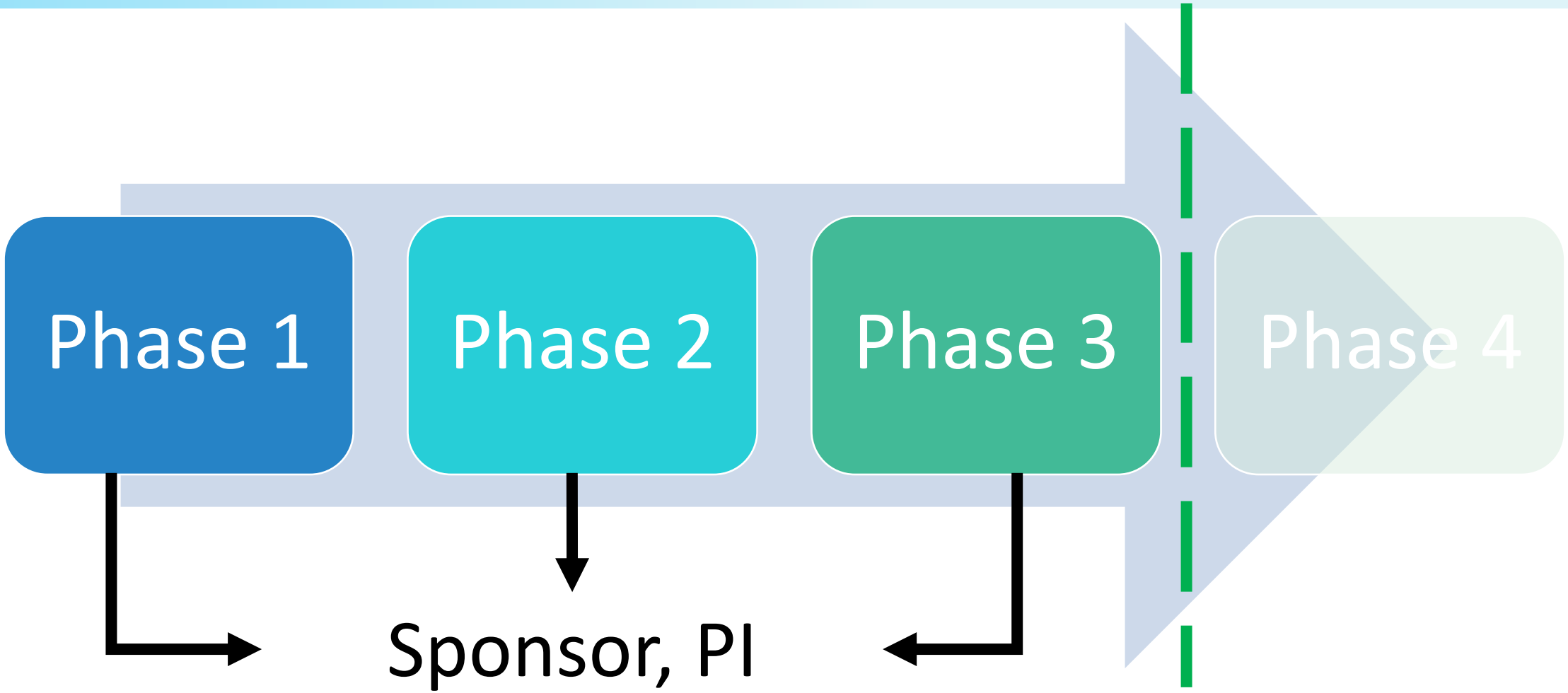


Safety Through Shared Learning

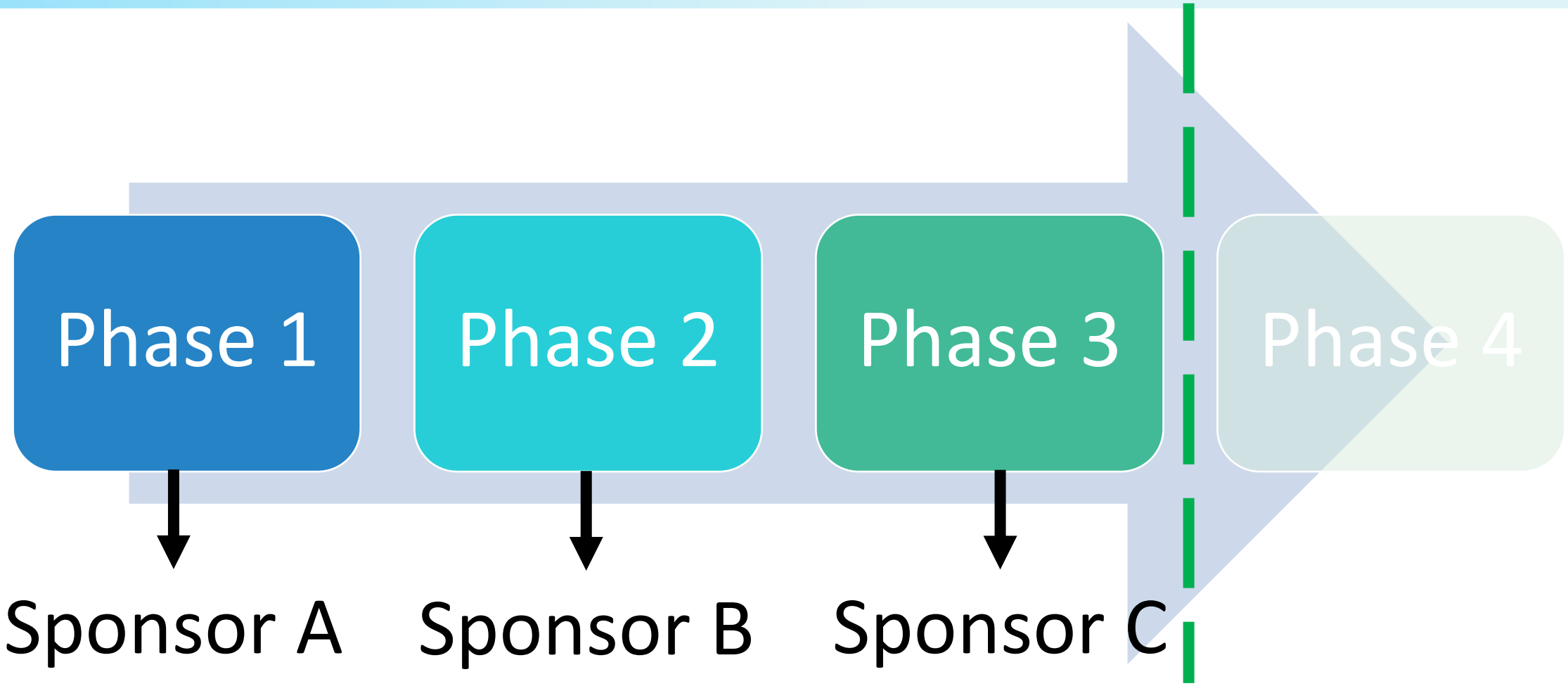
FDA Safety Communications

ISMP Medication Safety Alert!

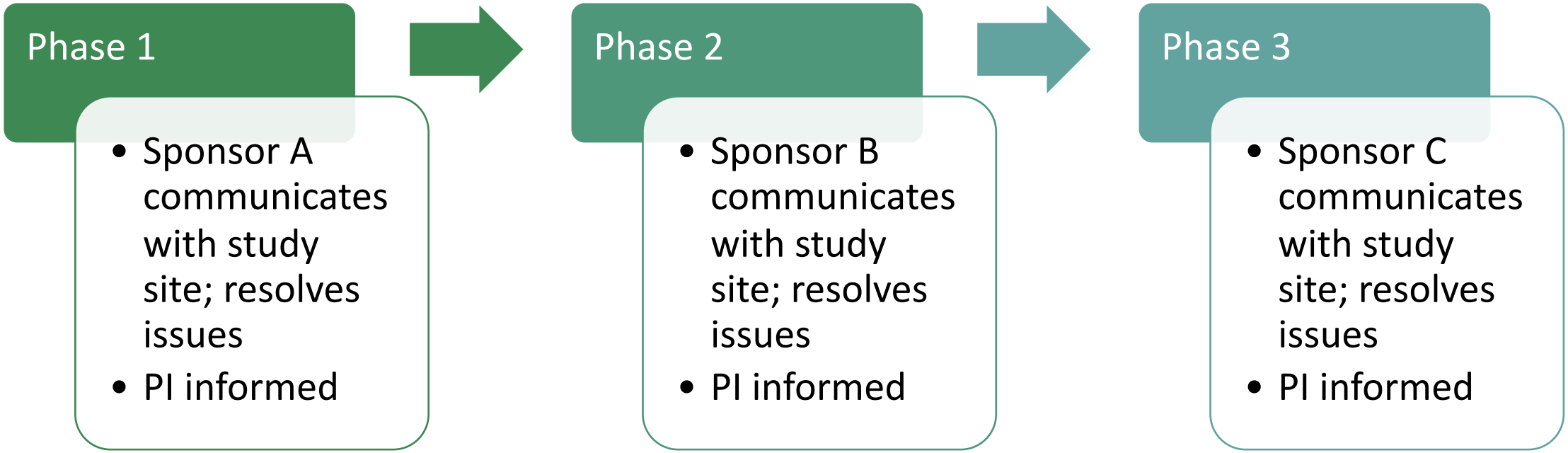
Reporting with Investigational Agents



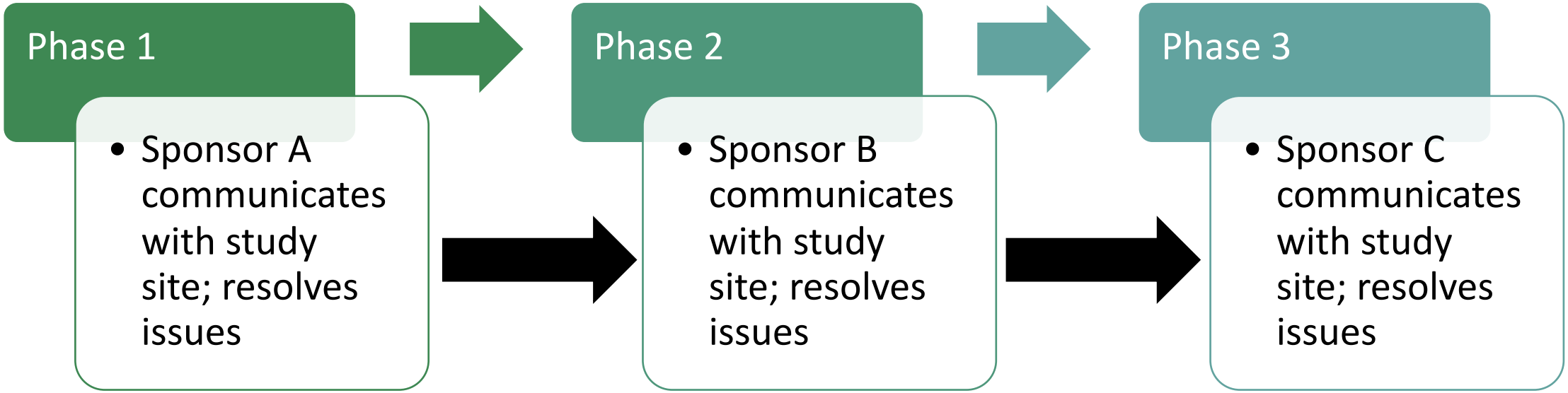
Multiple Phases, Multiple Sponsors



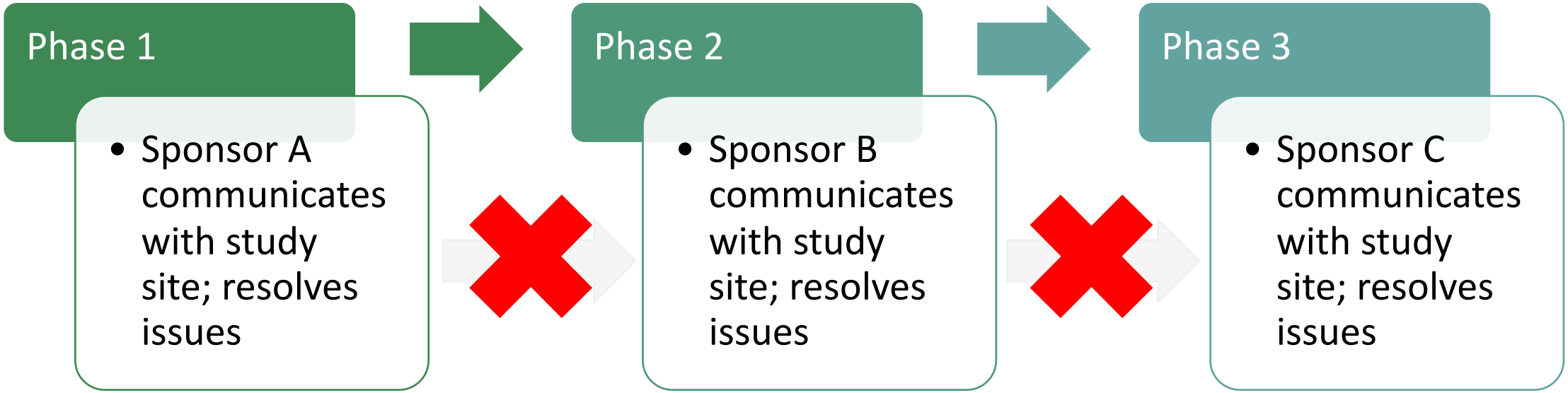
Improvement and Safety Information Siloed



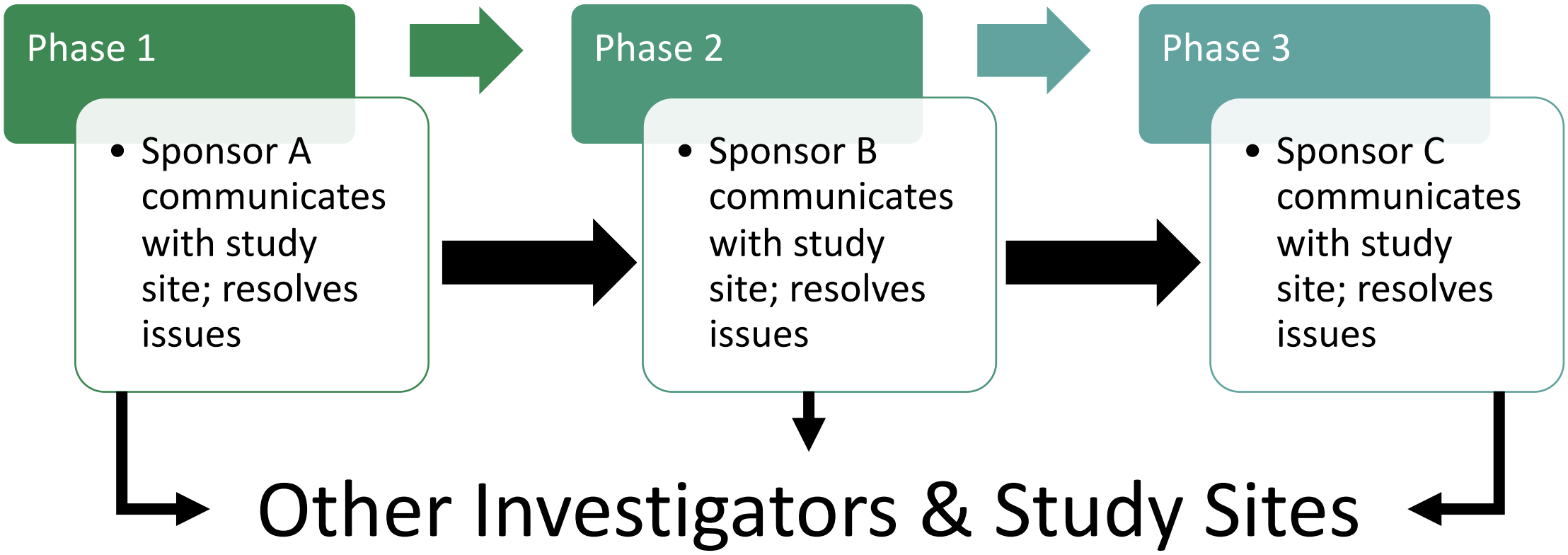
Knowledge Sharing to Prevent Errors



Errors May Resurface Through Phases



Knowledge Sharing to Prevent Errors



Panel 1 - Key Points

- ✓Investigational drug labeling needs to be consistent across sponsors, protocols, and formulations
- ✓Inconsistencies contribute to unsafe conditions and potential errors that could compromise research integrity or cause patient harm
- ✓Individual sites collaborate with sponsors to address safety challenges, but information & lessons learned may not be shared across phases or with other study sites
- ✓There is a need to report medication errors in a way that assures learning by all concerned