Preventing Medication Errors: Lessons Learned from Postmarket Safety Surveillance

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Objectives

- Describe general principles of medication error reporting and analysis
- Discuss assessment of reports to determine type of medication error, root cause, and contributing factors
- List examples of postmarket medication errors

Medication errors are a public health burden

- U.S. outpatient and inpatient preventable medication errors have an estimated **annual cost of nearly $21 billion**
  - Network for Excellence in Health Innovation. Dec 2011. Available from: http://www.nehi.net/bendthecurve/sup/documents/Medication_Errors_%20Brief.pdf

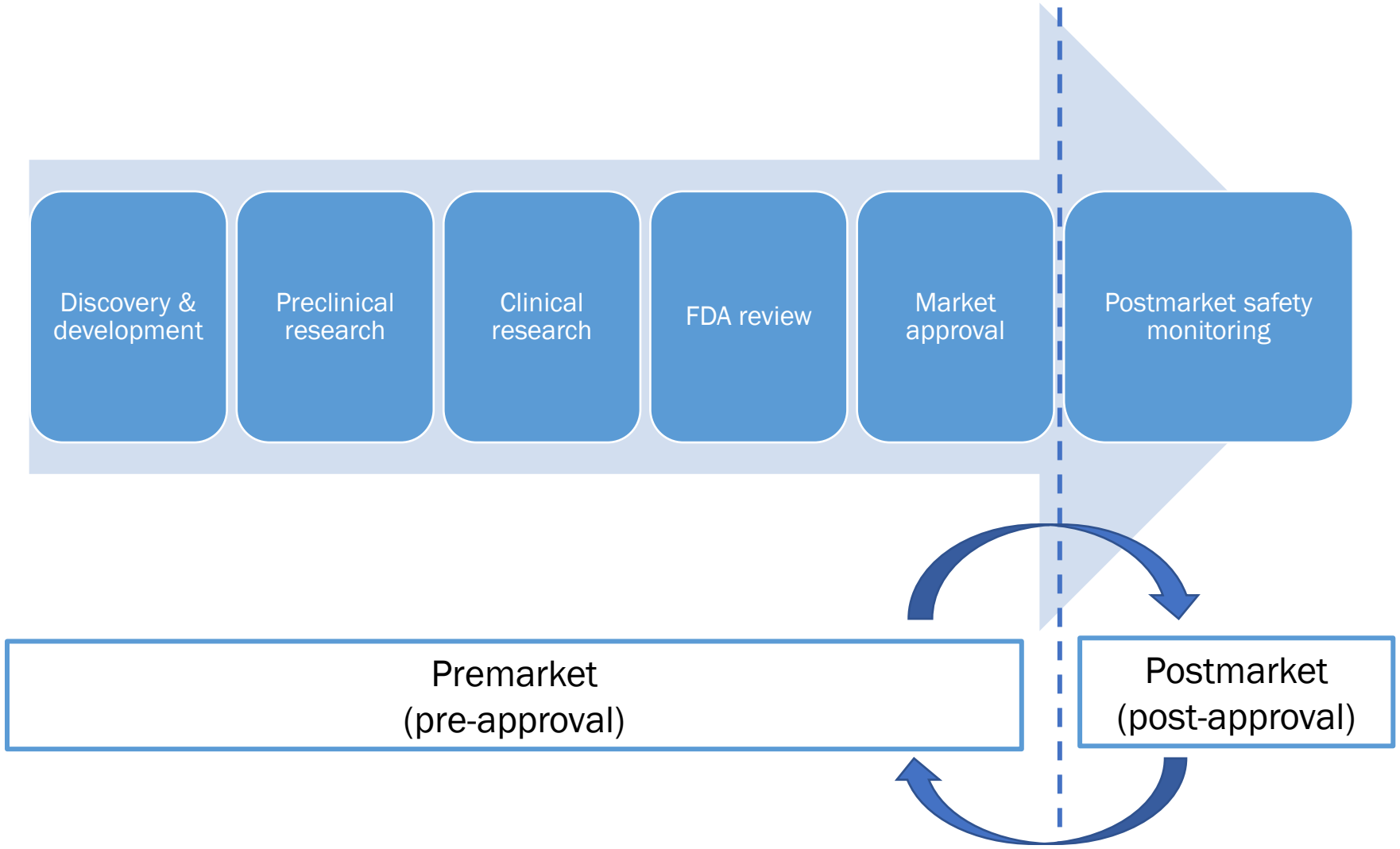
- Among adult outpatients…**52% (95% CI: 42–62%) of adverse drug reactions were preventable**. Among inpatients…45% (95% CI: 33–58%) of adverse drug reactions were preventable [errors].
  - Hakkarainen KM, et. al., Percentage of patients with preventable adverse drug reactions and preventability of adverse drug reactions – a meta-analysis. PLoS One. 2012.

DMEPA Review Activities

- Proprietary name
- Nonproprietary name suffix
- Product labeling
- Product packaging
- Human Factors/Product Design
- Postmarket surveillance

Reviews take into account current federal regulations, applicable Guidance for Industry, USP Standards, and **relevant postmarket experience.**

Medication errors and product life cycle

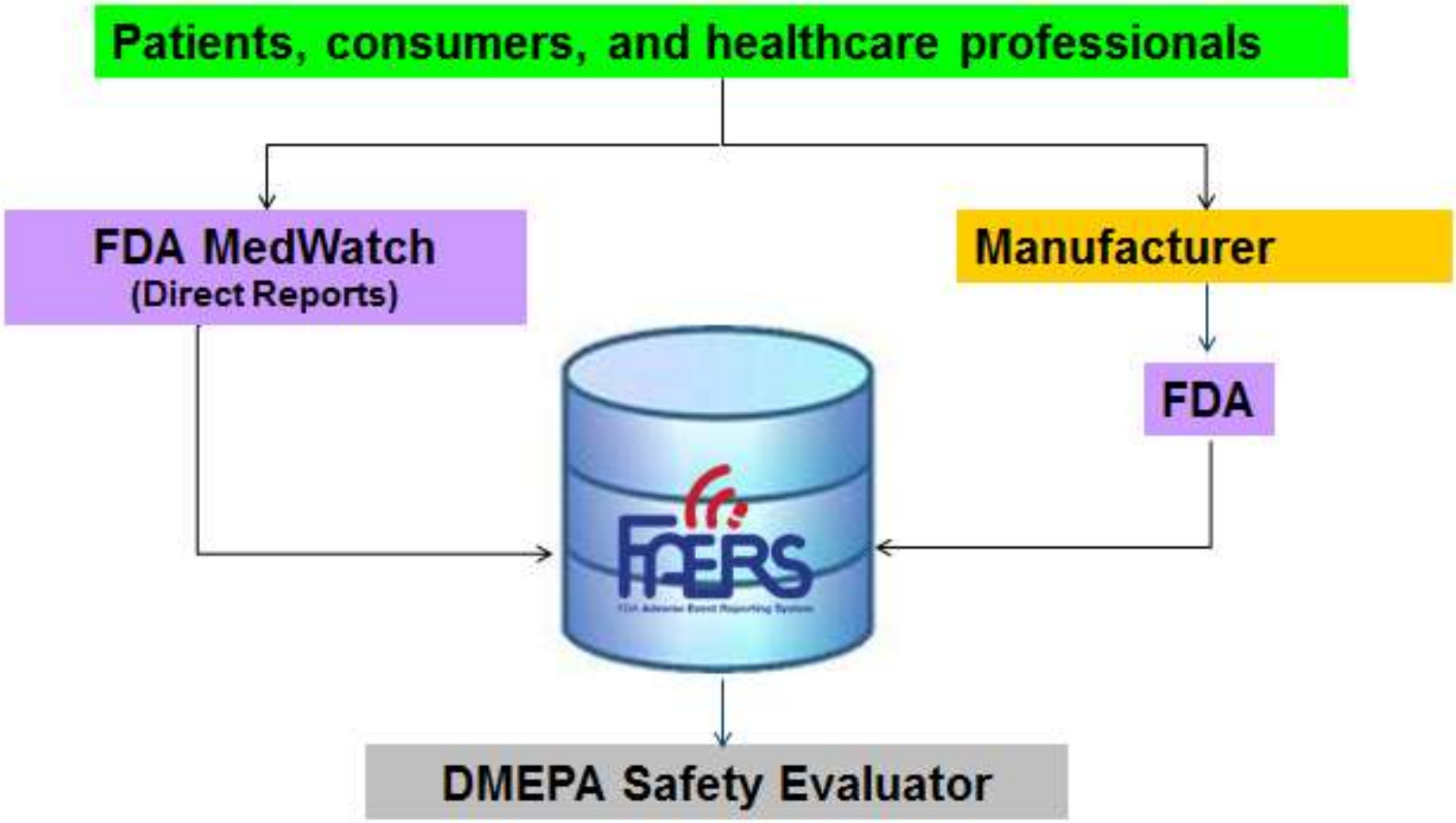


Why is postmarket surveillance needed?

- Limitations of premarket clinical trials
  - Trials are conducted under controlled conditions, and may not use the final approved name, labels, labeling, and packaging
  - Number of patients tested is too small to detect serious but rare problems, and some errors may fall into this category
  - Trials are often of short duration
- CDER has a robust program to identify potential errors and address them prior to approval. However, medication errors remain a significant burden on public health*
- Allows us to monitor error reports and address those causes of errors that may be related to a drug's name, label and labeling, or packaging (before a product is widely distributed).

*Preventing Mediation Errors: A $21 Billion Opportunity. Network for Excellence in Health Innovation (NEHI); 2011.
https://www.nehi.net/bendthecurve/sup/documents/Medication_Errors_%20Brief.pdf

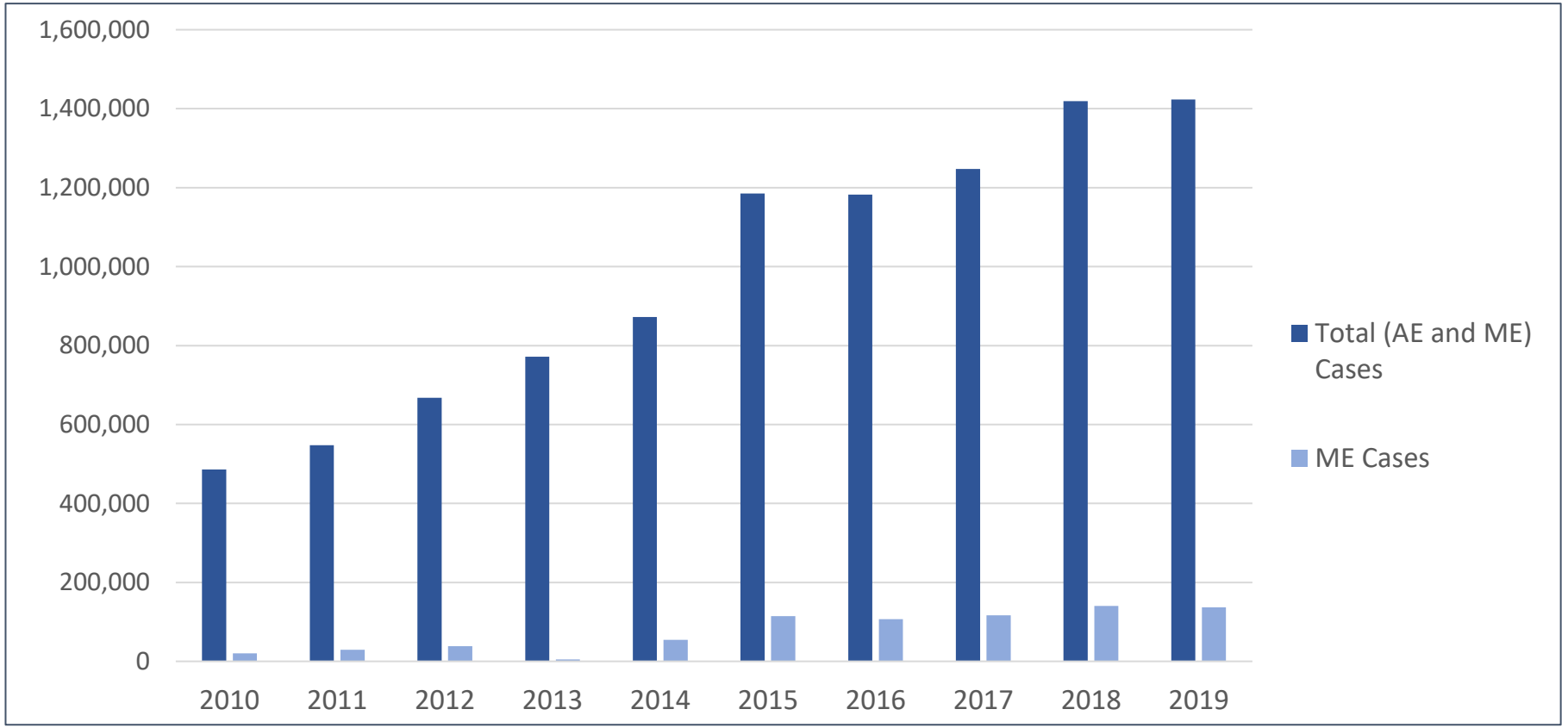
Postmarketing sources of information



Medication errors are underreported

- Extent of underreporting is unknown
  - Elliott, et.al., “estimated that **237 million medication errors occur** at some point in the medication process in England per year”
    - Prevalence and Economic Burden of Medication Errors in The NHS in England. 2018 (http://www.eepru.org.uk/wp-content/uploads/2018/02/eepru-report-medication-error-feb-2018.pdf)
  - Among adult outpatients…**52% (95% CI: 42–62%) of adverse drug reactions were preventable**. Among inpatients…45% (95% CI: 33–58%) of adverse drug reactions were preventable.
    - Hakkarainen KM, et. al., Percentage of patients with preventable adverse drug reactions and preventability of adverse drug reactions – a meta-analysis. PLoS One. 2012.
- No U.S. requirement to report medication errors to FAERS

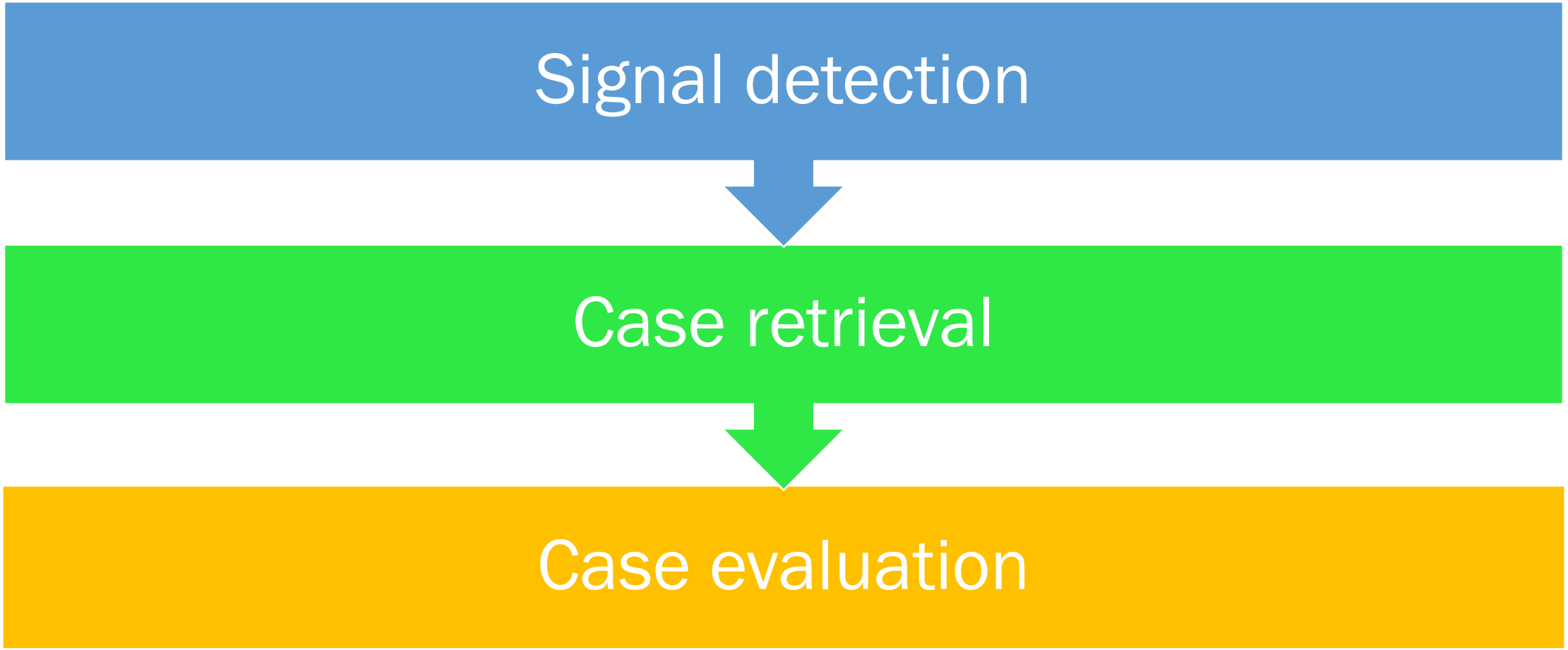
of adverse event and medication error cases submitted to FAERS is increasing



*FAERS = FDA Adverse Event Reporting System; AE=Adverse Event; ME=Medication Error
Chart includes both U.S. and foreign cases
Medication error case counts based on the MedDRA SMQ *Medication errors (narrow)*, V22.1

Considerations for postmarket medication error surveillance

Assessment of medication errors



Signal detection

- Goal: identify and address medication error risks before the product is widely distributed
- FDA uses the SMQ *Medication errors* as baseline for screening medication error cases
- Use early and targeted screenings based on approval date, report type, patient age (pediatric), error type, etc.
- Manual review of case narratives often needed

SMQ = Standard MedDRA Query
MedDRA = Medical Dictionary for Regulatory Activities

Medication error definition

- “A medication error is any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer”
  - National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP)

FDA Medication Errors Related to CDER-Regulated Drug Products: https://www.fda.gov/drugs/drug-safety-and-availability/medication-errors-related-cder-regulated-drug-products

Is it a medication error?

- A “preventable event” refers to events that are due to errors that could be avoided
- Events that happen during the manufacturing process aren’t medication errors, but can result in medication errors (e.g., device malfunction can result in a dose omission error)
- Intentional or deliberate use (e.g., abuse, misuse, off label use) of a drug product in a manner that is inconsistent with FDA-required labeling generally isn’t considered a medication error
- **If a suspected medication error:**
  - What is the type of error?
  - Where did the error originate (e.g., prescribing, dispensing)?
  - What are the contributing factors (e.g., look alike names, label confusion)?
  - Does it involve a potential for error (often described as a “complaint”), near miss or “actual” error?

NCC MERP Medication Error Taxonomy

- 70.1 Dose Omission
- 70.2 Improper Dose
- 70.3 Wrong Strength/Concentration
- 70.4 Wrong Drug
- 70.5 Wrong Dosage Form
- 70.6 Wrong Technique
- 70.7 Wrong Route of Administration
- 70.8 Wrong Rate
- 70.9 Wrong Duration
- 70.10 Wrong Time
- 70.11 Wrong Patient
- 70.12 Monitoring Error
- 70.13 Deteriorated Drug Error
- 70.14 Other

Available from: https://www.nccmerp.org/sites/default/files/taxonomy2001-07-31.pdf

Example

ISMP Acute Care ISMP Medication Safety Alert!

May 23, 2019 ■ Volume 24 Issue 10

SAFETY briefs

Potential for mix-ups between Prolia and Udenyca syringes. ISMP has received 8 reports this year about the potential for mix-ups between **PROLIA** (denosumab; Amgen), an osteoporosis drug, and **UDENYCA** (pegfilgrastim-cbqv; Coherus BioSciences), a biosimilar leukocyte growth factor associated with the reference peg-filgrastim product, **NEULASTA**. In one case, Prolia syringes were found stocked in place of Udenyca syringes at an outpatient infusion site. At another center, staff found Udenyca syringes stocked instead of Prolia syringes in an automated dispensing cabinet refrigerator. While we have not received any reports of patients receiving the wrong drug, the similarities between these two medications increases the risk of a mix-up.

While the brand names are listed clearly on the cartons, both medications have

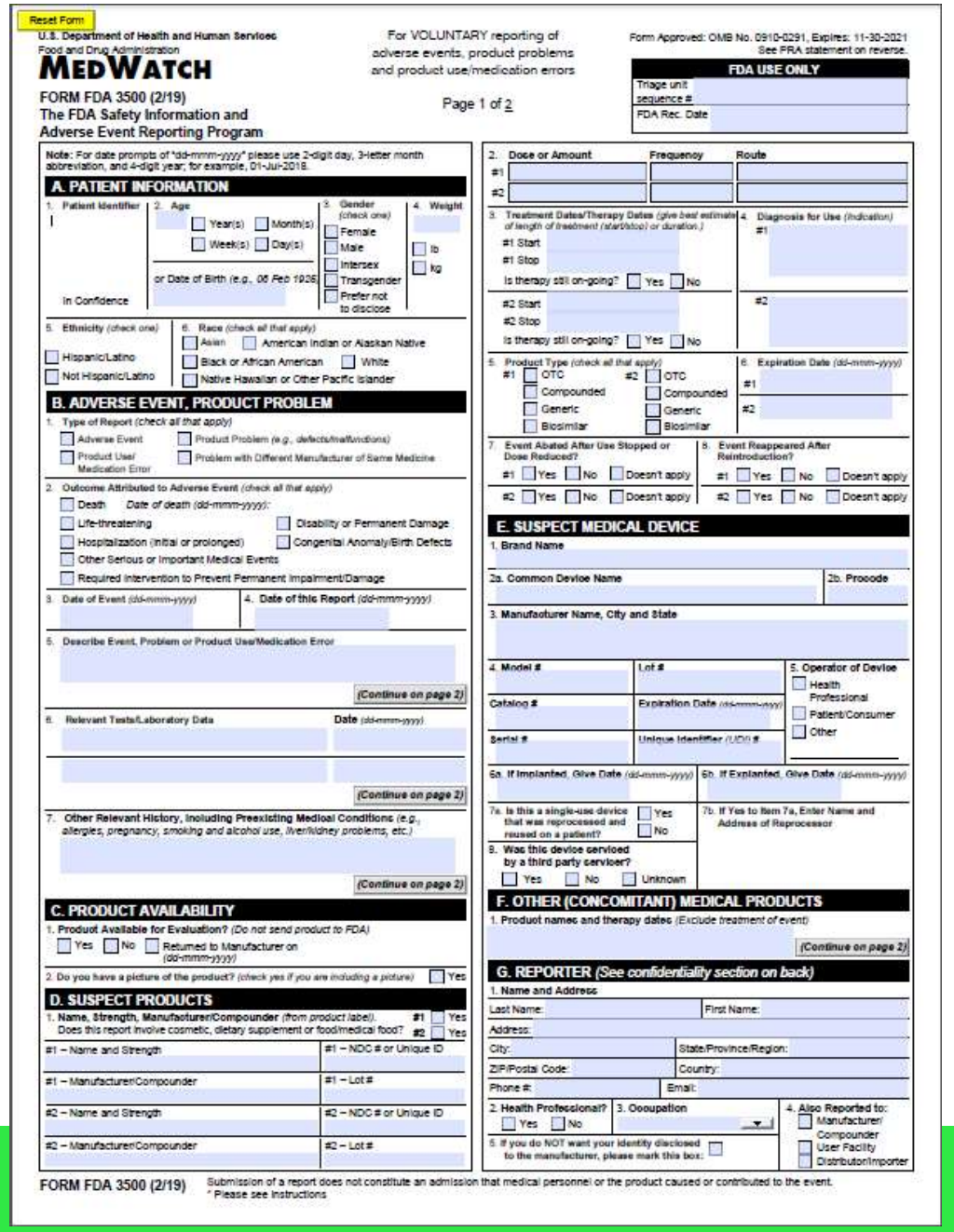
continued on page 2—SAFETY briefs >

- **Is it a medication error?**
- **What type of medication error?**
- **Contributing factors?**

Case retrieval

- Case retrieval requires careful considerations, expanded search terms, and narrative text searches
  - FDA uses the SMQ *Medication errors (narrow)* as the baseline search to retrieve FAERS medication error cases
  - May add product quality, device and or adverse event search terms
- Narrative text searches and manual review of case narratives often needed

E2B and other reporting forms lack structured fields to capture the type of error, causes/contributing factors, and other medication error information needed for assessment



Reset Form

U.S. Department of Health and Human Services
Food and Drug Administration

MEDWATCH

FORM FDA 3500 (2/19)
The FDA Safety Information and Adverse Event Reporting Program

For VOLUNTARY reporting of adverse events, product problems and product use/medication errors

Page 1 of 2

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

FDA USE ONLY
Triage unit
sequence #
FDA Rec. Date

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
In Confidence
2. Age — Year(s) Month(s) Week(s) Day(s) or Date of Birth (e.g., 06 Feb 1926)
3. Gender (check one) — Female, Male, Intersex, Transgender, Prefer not to disclose
4. Weight — lb, kg
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, PRODUCT PROBLEM

1. Type of Report (check all that apply) — Adverse Event, Product Problem (e.g., defects/malfunctions), Product Use/Medication Error, Problem with Different Manufacturer of Same Medicine
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, Problem or Product Use/Medication Error — (Continue on page 2)
6. Relevant Tests/Laboratory Data — Date (dd-mmm-yyyy) — (Continue on page 2)
7. Other Relevant History, Including Preexisting Medical Conditions (e.g., allergies, pregnancy, smoking and alcohol use, liver/kidney problems, etc.) — (Continue on page 2)

C. PRODUCT AVAILABILITY

1. Product Available for Evaluation? (Do not send product to FDA) — Yes, No, Returned to Manufacturer on (dd-mmm-yyyy)
2. Do you have a picture of the product? (check yes if you are including a picture) — Yes

D. SUSPECT PRODUCTS

1. Name, Strength, Manufacturer/Compounder (from product label). Does this report involve cosmetic, dietary supplement or food/medical food? #1 Yes, #2 Yes

#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 #

	Dose or Amount	Frequency	Route
#1			
#2			

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

E. SUSPECT MEDICAL DEVICE

1. Brand Name
2a. Common Device Name
2b. Procode
3. Manufacturer Name, City and State
4. Model #
Lot #
Catalog #
Expiration Date (dd-mmm-yyyy)
Serial #
Unique Identifier (UDI) #
5. Operator of Device — Health Professional, Patient/Consumer, Other
6a. If Implanted, Give Date (dd-mmm-yyyy)
6b. 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 to Item 7a, Enter Name and Address of Reprocessor
8. Was this device serviced by a third party servicer? Yes No Unknown

F. OTHER (CONCOMITANT) MEDICAL PRODUCTS

1. Product names and therapy dates (Exclude treatment of event) — (Continue on page 2)

G. REPORTER *(See confidentiality section on back)*

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
4. Also Reported to: Manufacturer/Compounder, User Facility, Distributor/Importer
5. If you do NOT want your identity disclosed to the manufacturer, please mark this box:

FORM FDA 3500 (2/19)

Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.
* Please see instructions

Example report narrative and coding

FAERS Case #	Narrative	MedDRA Code Submitted by Company
---	The patient is a 10 month old male with medical history of hematopoietic stem cell transplant for leukemia and resolved hypertension and concomitant medication included Trimethoprim sulfamethoxazole (sulfamethoxazole, trimethoprim) and citric acid via unknown route for unknown indication On an unknown date, the patient started cyclosporine for unknown indication and clonidine patch for hypertension (dose, frequency, route, unknown). The patient developed type IV renal tubular acidosis due to cyclosporin. On an unknown date, the patient presented to the emergency department with lethargy. He had been difficult to awaken since morning. His family denied fever, other symptoms suggestive of infection, or trauma and any possibility of unintentional toxic ingestion. The patient was admitted to the hospital for further monitoring. The combination of altered mental status and miosis raised concern for a toxicologic etiology, but no exposure could be identified. However, on hospital admission a nurse performing her assessment noted the unusual appearance of the dressing used to affix the nasogastric tube. The dressing was removed and found to be two 0.1-mg/day clonidine patches, which had been previously prescribed to treat hypertension. The family had mistaken the clonidine patches for a simple adhesive patch and placed them in the same bag they used to store nasogastric tube dressings. After their removal, the child was monitored and returned to his neurologic baseline within 24 hours. The exposure to clonidine was missed by the medication history that focused exclusively on medications taken orally. It was reported that clonidine exposure in this patient could have been suspected based on the constellation of central nervous system (CNS) depression and miosis. On examination, a Glasgow Coma Scale score was 10 (eye opening=2, verbal=3, motor=5), temperature was 98.6°F (37°C), heart rate was 102 beats/min, respiratory rate was 22 breaths/min, and blood pressure was 84/35 mm Hg. The head was without signs of trauma. Pupillary examination showed miosis (2mm-1mm) bilaterally. A nasogastric tube was affixed to the right cheek. No meningismus. The chest, cardiac, and abdominal examination results were all within normal limits. The neurologic examination was notable for lethargy but without other focal deficits. A complete blood cell count with a differential count revealed a white blood cell count of 5.6/microliter (0.01 multiplied by 109)(71% neutrophils), a hemoglobin level of 8.0 g/dL (80 g/L), and a platelet count of 129 multiplied by 103/microliter. Serum chemistry values (including calcium, magnesium, and phosphorous) were normal, bicarbonate level of 19 mEq/L (19 mmol/L). A urine toxicology screen was negative for opiates, cannabinoids, benzodiazepines, barbiturates, and cocaine. Findings from a non-contrast head computed tomographic scan, cerebrospinal fluid studies were within normal limits. Action taken with cyclosporine and clonidine was dose not changed and drug withdrawn respectively. The outcome of the events renal tubular acidosis was not resolved, medication error was unknown and for other events was resolved. Dechallenge and rechallenge were not applicable for cyclosporin. Dechallenge was positive and rechallenge was unknown for clonidine. The seriousness criteria for the events medication error, drug toxicity, miosis, mental status changes and lethargy was hospitalization, for renal tubular acidosis was medically significant and for CNS depression was hospitalisation and medically significant. Author comments: The family had mistaken the clonidine patches for a simple adhesive patch and placed them in the same bag they used to store nasogastric tube dressings. After their removal, the child was monitored and returned to his neurologic baseline within 24 hours. The exposure to clonidine was missed by the medication history that focused exclusively on medications taken orally.	Medication Error

MedDRA coding of medication error information is inconsistent or nonspecific

Case Scenario	Submitted MedDRA Code	FDA Recommended MedDRA Code
Patient at a general infusion center received DrugA instead of the prescribed DrugB	Wrong patient received medication	Wrong drug administered
She experienced difficulty pressing on the plunger, it was hard to push down and she could not push it down all the way	Accidental underdose	Device difficult to use
Patient died after receiving vecuronium instead of the intended midazolam	Incorrect dosage administered	Wrong drug administered

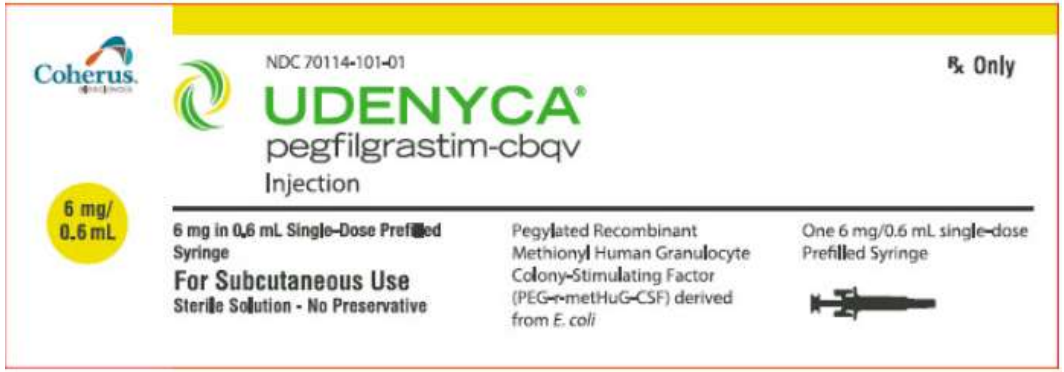
Case evaluation

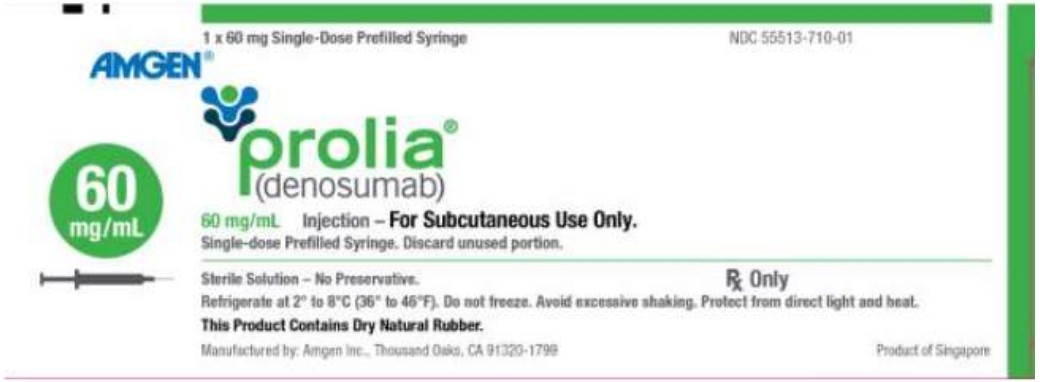
- Create case series and perform risk assessment
- Considerations:
  - Incomplete reports are difficult to interpret (“pen jammed” – is it malfunction or usability issue?)
  - Root cause and contributing factors
  - Stage in the medication use system where the error originated (e.g., prescribing, dispensing)
  - Setting of use
  - Reporter recommendations to prevent the error
  - Associated adverse events and outcomes
- Review labeling, packaging, design, and name if applicable
- Determine if regulatory action is warranted

Postmarket actions to mitigate risk of medication errors

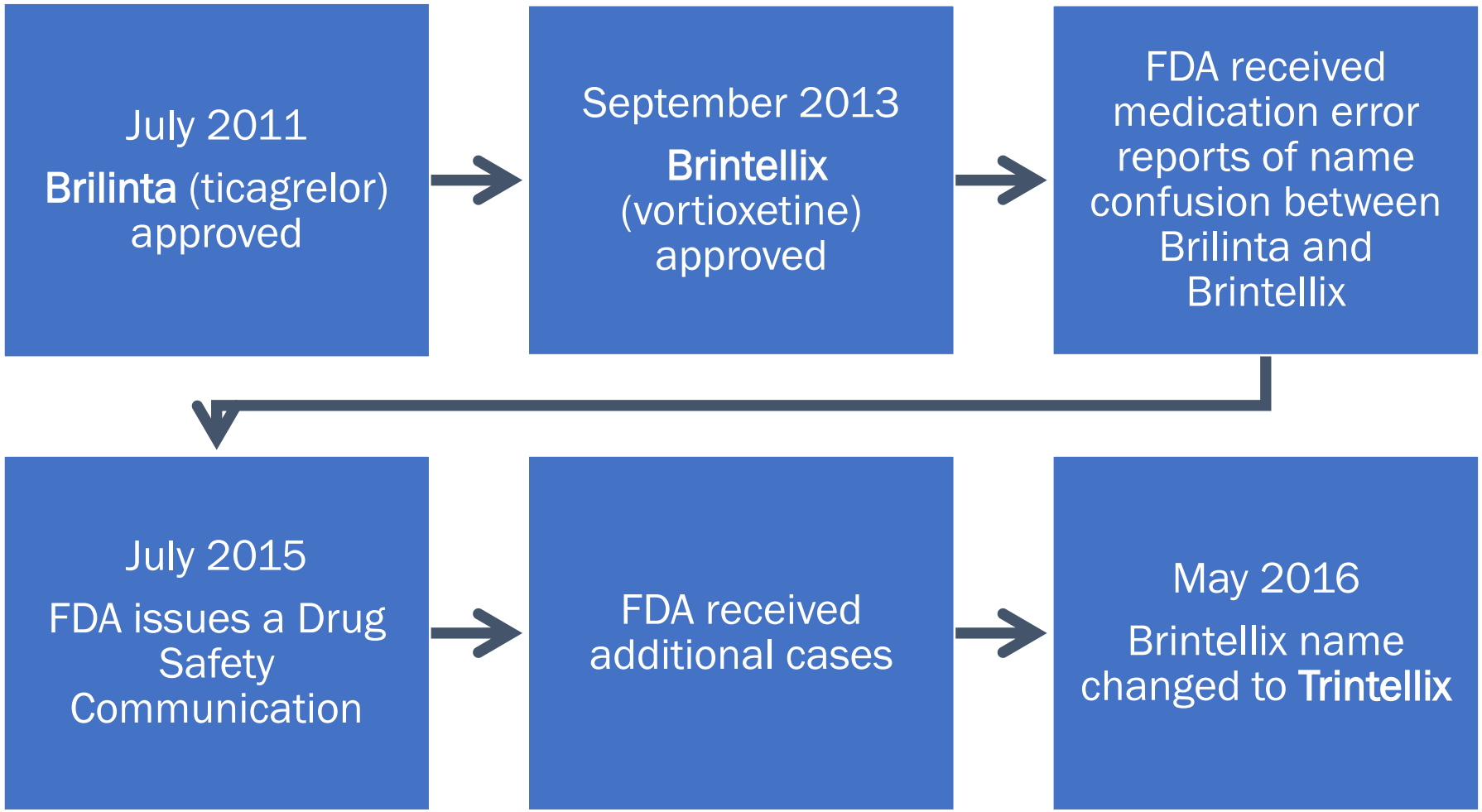
Potential postmarket actions

- Proprietary name changes
- Revise product labels and labeling
- Product packaging changes
- Product design revisions
- Issue safety communications

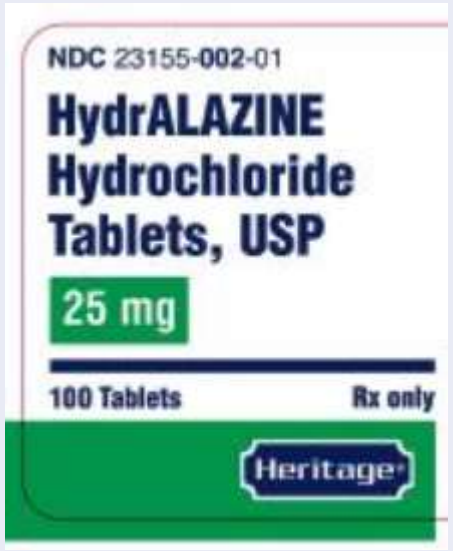




Proprietary name change



Container label revision

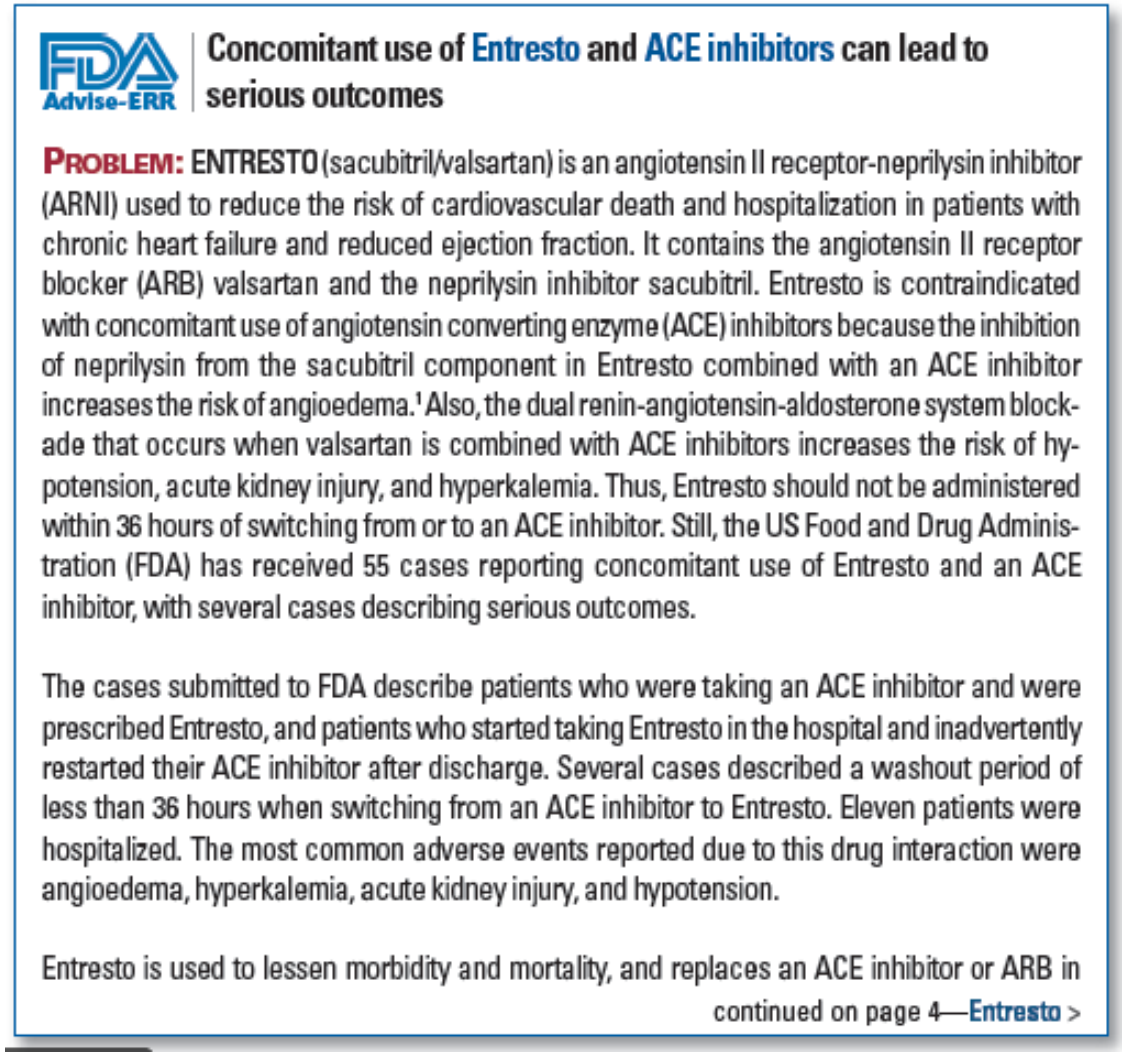
BEFORE	AFTER
	 

Packaging design change

BEFORE	AFTER
	

Communication

- Entresto (sacubitril-valsartan) was approved in 2015 and is contraindicated with use of ACEI
- FDA received multiple cases of concomitant use with adverse events (angioedema, hyperkalemia, AKI, hypotension)
- Published FDA Advise-ERR in ISMP newsletter



FDA Advise-ERR

Concomitant use of Entresto and ACE inhibitors can lead to serious outcomes

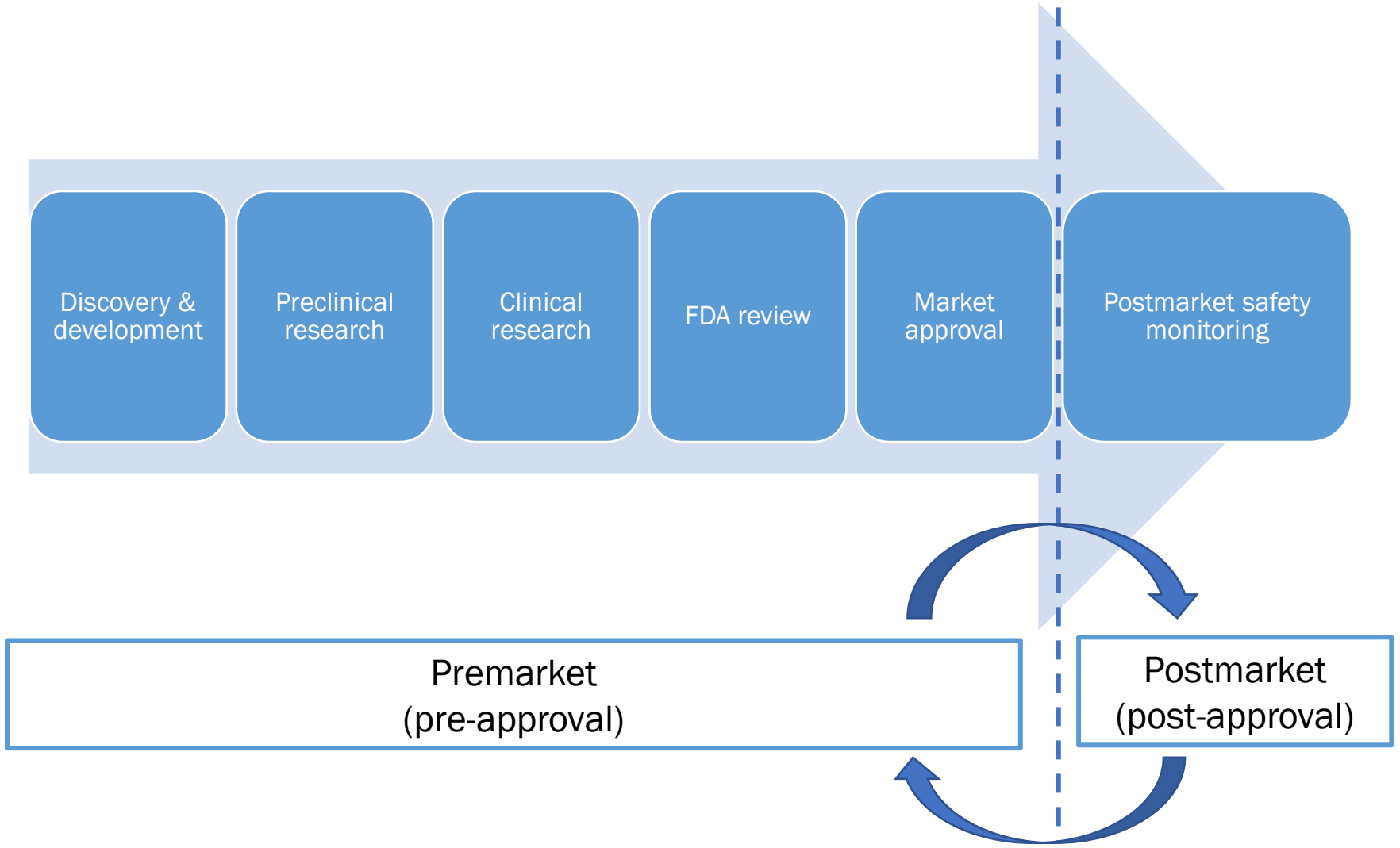
PROBLEM: ENTRESTO (sacubitril/valsartan) is an angiotensin II receptor-neprilysin inhibitor (ARNI) used to reduce the risk of cardiovascular death and hospitalization in patients with chronic heart failure and reduced ejection fraction. It contains the angiotensin II receptor blocker (ARB) valsartan and the neprilysin inhibitor sacubitril. Entresto is contraindicated with concomitant use of angiotensin converting enzyme (ACE) inhibitors because the inhibition of neprilysin from the sacubitril component in Entresto combined with an ACE inhibitor increases the risk of angioedema.[1] Also, the dual renin-angiotensin-aldosterone system blockade that occurs when valsartan is combined with ACE inhibitors increases the risk of hypotension, acute kidney injury, and hyperkalemia. Thus, Entresto should not be administered within 36 hours of switching from or to an ACE inhibitor. Still, the US Food and Drug Administration (FDA) has received 55 cases reporting concomitant use of Entresto and an ACE inhibitor, with several cases describing serious outcomes.

The cases submitted to FDA describe patients who were taking an ACE inhibitor and were prescribed Entresto, and patients who started taking Entresto in the hospital and inadvertently restarted their ACE inhibitor after discharge. Several cases described a washout period of less than 36 hours when switching from an ACE inhibitor to Entresto. Eleven patients were hospitalized. The most common adverse events reported due to this drug interaction were angioedema, hyperkalemia, acute kidney injury, and hypotension.

Entresto is used to lessen morbidity and mortality, and replaces an ACE inhibitor or ARB in

continued on page 4—Entresto >

Postmarket lessons inform premarket review



Summary

- Medication errors are a public health burden
- Postmarket surveillance can identify medication error reports and address causes related to a drug's name, label/labeling, or packaging
- When reviewing cases, consider the type of error, contributing factors, and potential mitigations
- Postmarketing experience also informs premarket review activities on how to prevent errors

Resources

Guidances for Industry	
• Best Practices in Developing Proprietary Names for Drugs (*Draft*) – May 2014	http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm398997.pdf
• Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (*Draft*) – April 2013	http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm349009.pdf
• Safety Considerations for Product Design to Minimize Medication Errors – April 2016	http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM331810.pdf
• Dosage Delivery Devices for Orally Ingested OTC Liquid Drug Products – May 2011	https://www.fda.gov/downloads/Drugs/Guidances/UCM188992.pdf
• Applying Human Factors and Usability Engineering to Medical Devices – February 2016	http://www.fda.gov/downloads/MedicalDevices/.../UCM259760.pdf
Regulations	
• 21 CFR 200s, 300s and 600s	http://www.ecfr.gov/cgi-bin/text-idx?SID=c8497935ae0f040dfcfe06c6251ba507&mc=true&tpl=/ecfrbrowse/Title21/21tab_02.tpl

Questions?