Challenges and Data Needs in Assessing the Impact of Packaging, Storage, and Disposal Options after an Opioid Drug Product is Marketed

Tamra Meyer, PhD, MPH
Lead Epidemiologist
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research
US Food and Drug Administration

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Overview

- Framing
- Questions
- Relevant Populations
- Epidemiologic Study Designs
- Some Postmarketing Data Sources
- Capturing Exposures and Outcomes
- Main Messages

Framing: Evaluating Formulations with Abuse Deterrent Properties

Many of the Same Challenges

Public Meeting, July 10-11, 2017:

Data and Methods for Evaluating the Impact of Opioid Formulations with Properties Designed to Deter Abuse in the Postmarket Setting

https://www.fda.gov/Drugs/NewsEvents/ucm540845.htm

QUESTIONS ABOUT THE USE AND IMPACT OF PACKAGING, STORAGE, AND DISPOSAL SOLUTIONS IN THE POSTMARKET SETTING

Accidental Exposure

Misuse

Third Party Access

Excess Supply

Images: Asociación Española de Pediatría, http://enfamilia.aeped.es/temas-salud/intoxicaciones-por-medicamentos-en-ninos; Liga da Saúde, https://ligadasaude.blogspot.com/2012/09/idosos-podem-estar-usando-medicamentos.html; Choose Help, https://www.choosehelp.com/blogs/prescription-drug-abuse/teen-campaign-against-deadly-abuse-of-prescription-drugs.html; GeriPal, http://www.geripal.org/2013/08/inappropriate-management-of.html

DESCRIPTIVE QUESTIONS

WHO?

WHAT?

WHERE?

WHEN?

WHY?

HOW?

Images: Asociación Española de Pediatría, http://enfamilia.aeped.es/temas-salud/intoxicaciones-por-medicamentos-en-ninos; Liga da Saúde, https://ligadasaude.blogspot.com/2012/09/idosos-podem-estar-usando-medicamentos.html; http://www.worldpharmaceuticals.net/features/featuretime-to-act-challenging-packaging-conventions-4214752

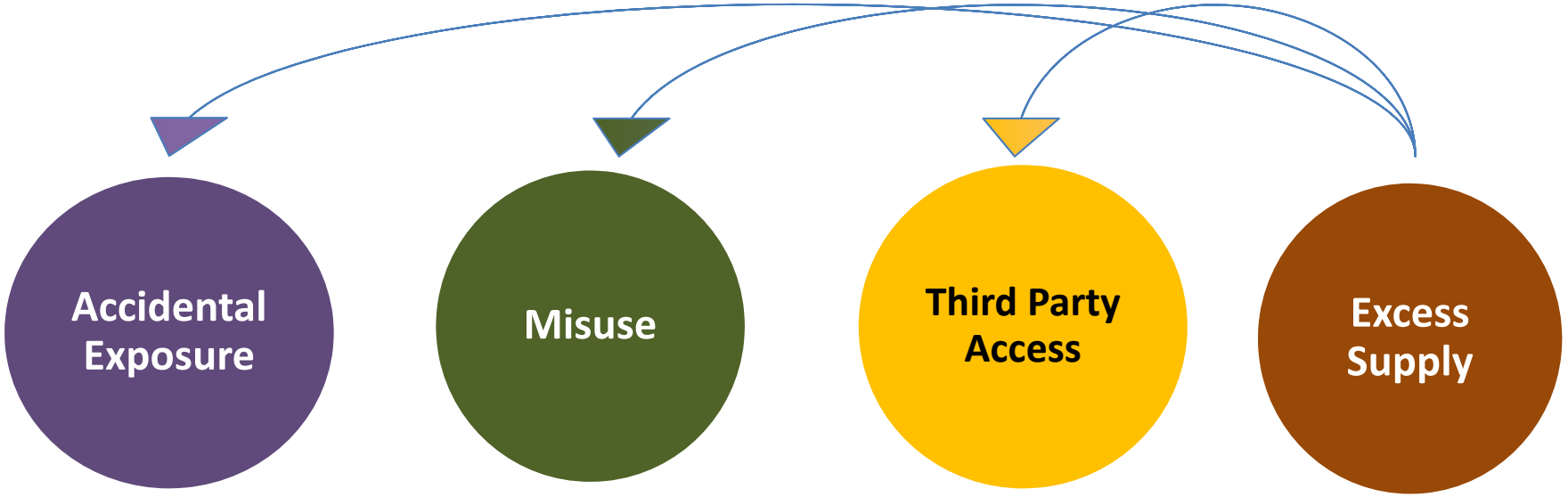
Effective in the Real World?

Compared to What??

- Accidental Exposure
- Misuse
- Third Party Access
- Excess Supply

Image: http://www.worldpharmaceuticals.net/features/featuretime-to-act-challenging-packaging-conventions-4214752

Relevant Populations



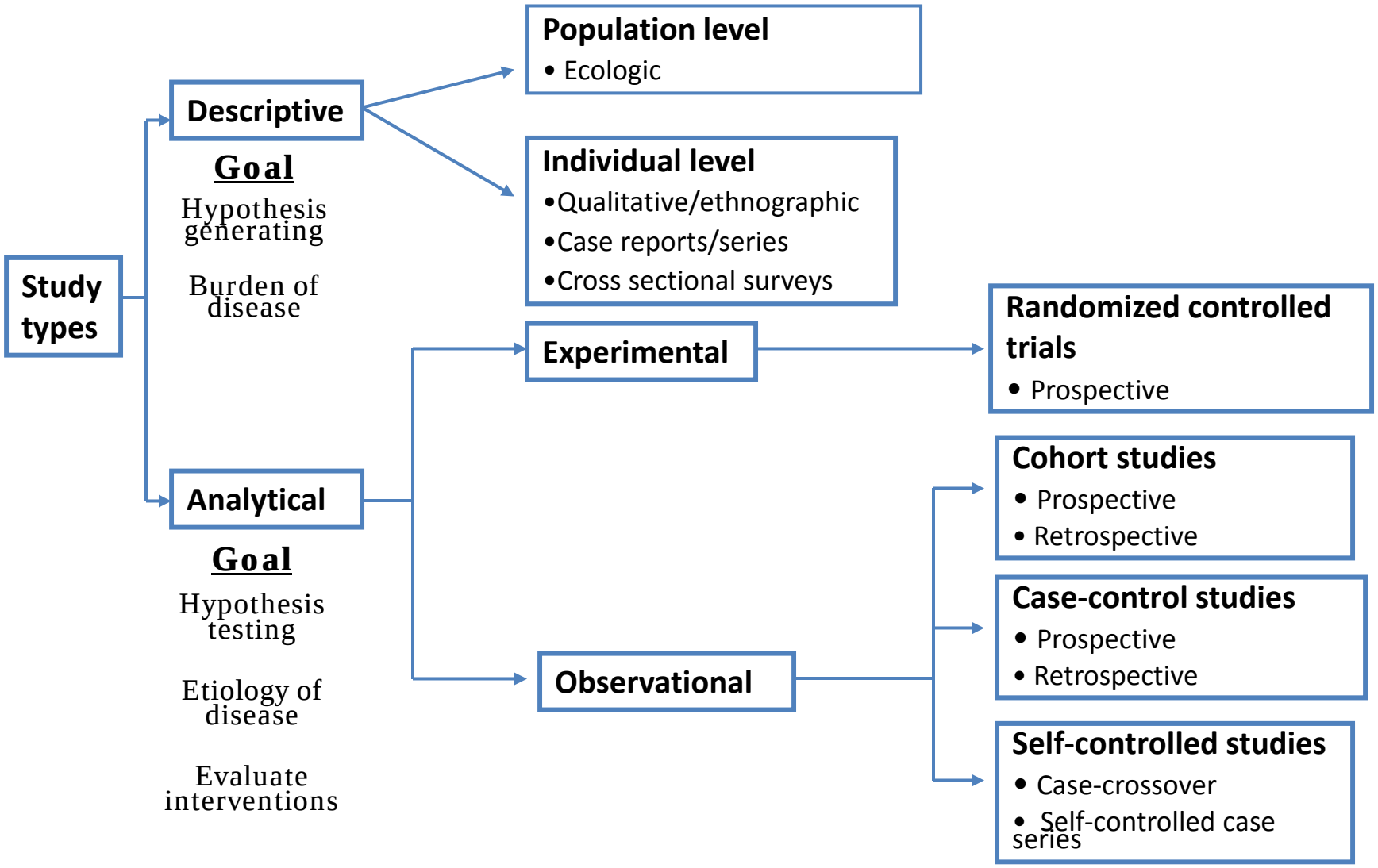
Non-Patients:
-Young children

Patients:
-Elderly
-Cognitive impairment
-Adolescents
-Naïve to opioids
-High risk of SUD
-Existing SUD

Non-Patients:
-Household members
-Adolescents
-Friends
-Visitors
-Healthcare workers
-"Black market"

SUD = substance use disorder

Epidemiologic Study Designs

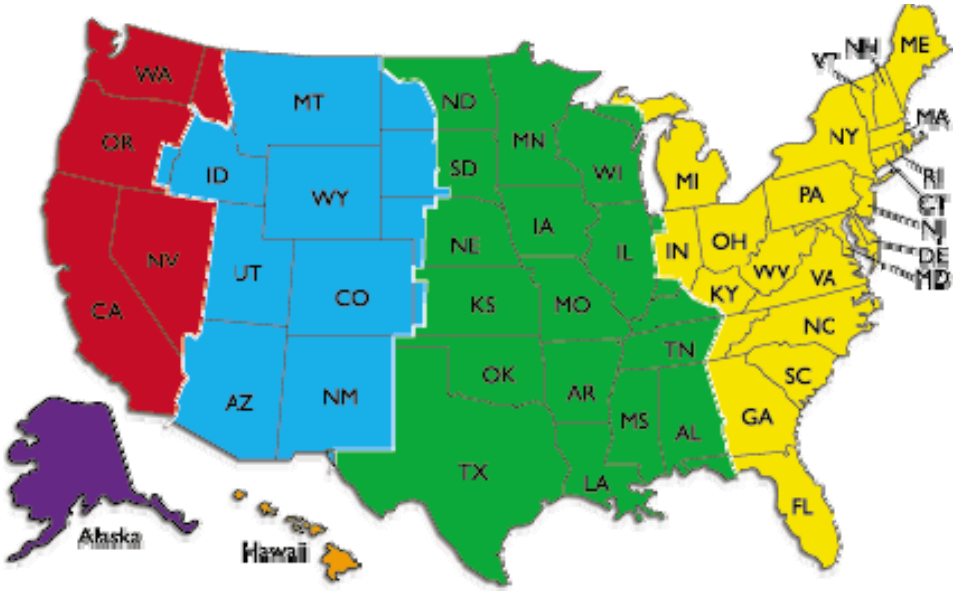


DESCRIPTIVE STUDIES
Qualitative, Quantitative, Ethnographic

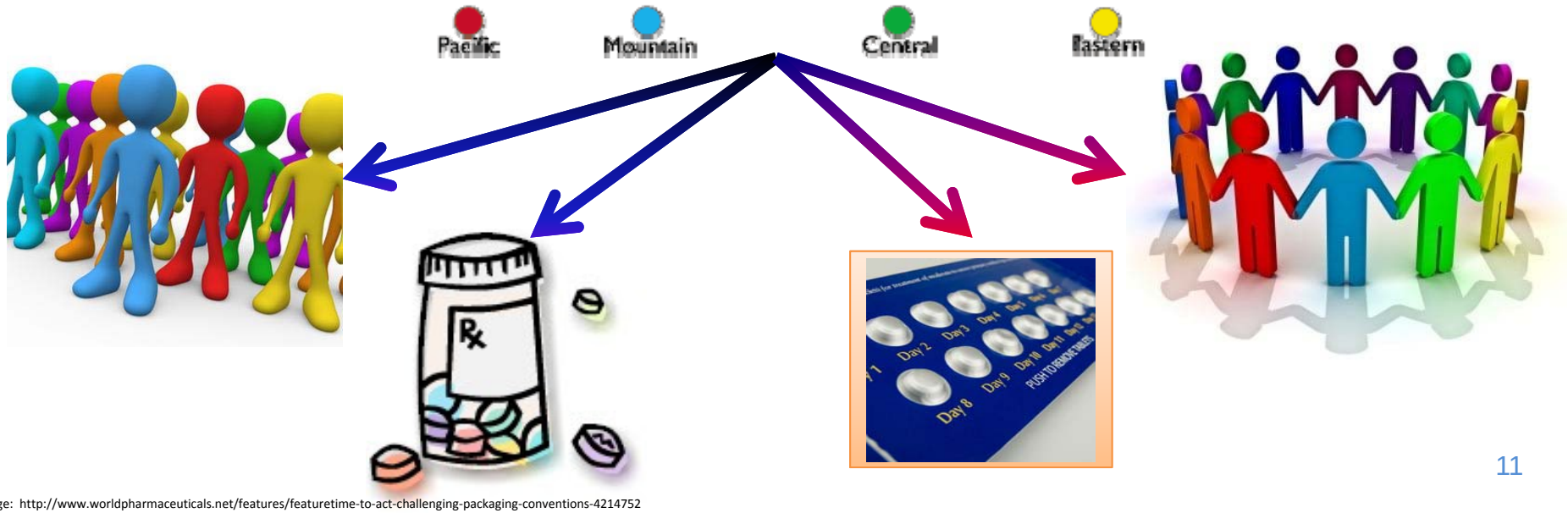
- **WHO** uses the packaging, storage, disposal options?
- **WHAT** options are being used?
- **WHERE** are they being used?
- **WHEN** are they being used?
- **WHY** are they being prescribed/added?
- **HOW** are they being used?
- Barriers to use and unintended consequences

Ecologic Studies

2008-2010



2011-2015



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Individual-Level Analytic Studies

CASE-CONTROL

TIME

COHORT

?

?

- Misuse
- Accidental Exposure
- Excess Supply
- Third Party Access

Image: http://www.worldpharmaceuticals.net/features/featuretime-to-act-challenging-packaging-conventions-4214752

Pragmatic Trials

Randomize Exposure to Option

Patient-level?

Misuse

Accidental Exposure

Excess Supply

Third Party Access

Household-level?

Image: http://www.worldpharmaceuticals.net/features/featuretime-to-act-challenging-packaging-conventions-4214752

Some Types of Data Used in the Postmarket Setting

Accidental Exposure

Misuse

Third Party Access

Excess Supply

- Electronic Health Data
- Other Utilization Data
- Surveys/Interviews
- Other Data Sources

Image: http://www.worldpharmaceuticals.net/features/featuretime-to-act-challenging-packaging-conventions-4214752; http://ecx.images-amazon.com/images/I/21I9aIgCBrL.jpg

Electronic Health Data

- Electronic health records
- Medical/prescription administrative claims
- Inpatient health records

Electronic Health Records

- **Type of prescription/packaging information**
  - Product name
  - Specific package order (?) or free-text notes on specific packaging directions for patient

  Reason for prescription/packaging
  - Diagnosis/procedure codes
  - Free-text notes
- **Outcomes**
  - Diagnosis/procedure codes
  - Vitals and lab results
  - Free-text notes
- **Caveats**
  - Possibly a single provider or group of providers; missing whole picture
  - Diagnosis/procedure codes for billing purposes
  - Free-text notes are hard to analyze
  - Actual product dispensed unknown

Image: https://www.columbiaeyeclinic.com/wp-content/uploads/2015/06/EMR-image.gif

Administrative Claims

?

- **Type of prescription/packaging information**
  - NDC code identifies drug & manufacturer packaging
- **Reason for prescription/packaging**
  - Diagnosis/procedure codes
- **Outcomes**
  - Diagnosis/procedure codes
- **Caveats**
  - Diagnosis/procedure codes for billing purposes
  - Actual product dispensed known, but don't know what was prescribed or how opioids ultimately used
  - Unclear whether will be "NDC" just for package added by pharmacist

Image: http://www.worldpharmaceuticals.net/features/featuretime-to-act-challenging-packaging-conventions-4214752; http://www.pharmaceutical-journal.com/pictures/380x217/2/6/4/1070264_community-pharmacy-store-front-16.jpg; ; http://ecx.images-amazon.com/images/I/21I9aIgCBrL.jpg

National Drug Code (NDC)

10-digits, 3-segments
Transformed to 11-digits (5-4-2, no dashes)

Mallinckrodt, Inc.

5mg/325mg oxycodone HCl/ acetaminophen tablets

500 tablets

0 4 0 6 – 0 5 1 2 – 0 5

Labeler Code (4-5 digits)

Manufacturing, repackaging, or distributing firm

Product Code (3-4 digits)

Active moieties, strength, dosage form, & formulation

Package Code (1-2 digits)

Package form & size

Inpatient Health Records

- **Records what happened during the hospitalization**
- **Information available varies according to the EHR system used and the hospital**
- **Type of prescription/packaging information**
  - NDC code identifies drug & manufacturer packaging
  - Other supply chain systems or automated dispensing cabinet data?
- **Outcomes**
  - Diagnosis/procedure codes
  - Vitals and lab results
  - Free-text notes within the EHR during hospitalization
- **Caveats**
  - Each hospital may have unique EHR or supply chain/automated dispensing data
  - Diagnosis/procedure codes are for billing purposes
  - Free-text difficult to analyze
  - Prior exposures, outcomes, and health conditions may not be in the hospital records

Other Utilization Data

- Pharmacy transaction records
  - Retail pharmacy dispensing
  - Prescription Drug Monitoring Programs (PDMP)
- Sales data
  - Distribution to retail pharmacies (back-door of the pharmacy)
  - End-user retail sales
    - Out the front door of the store (point of sale data)?
    - On-line sales?

Surveys/Interviews

- Big national surveys (e.g., National Survey on Drug Use and Health, Monitoring the Future, Youth Risk Behavior Surveillance System)
- Enriched populations (e.g., treatment center surveys, online drug discussion forums)
- Internet panel surveys using market research survey panels
- Provider, pharmacist, patient surveys

Selected National Health Surveys

Add questions about "options" to existing national health surveys?

National Survey on Drug Use and Health (NSDUH)	Household survey ≥ age 12 years Misuse of prescription opioids + reason Limited product-specific data
Monitoring the Future	School-based survey on adolescent drug abuse Limited product-specific data Longitudinal follow-up component
National Health and Nutrition Examination Survey	Interviews, physical exam, labs Longitudinal follow-up component Prescription drug use and whether interviewer saw medication container
Behavioral Risk Factor Surveillance System	Telephone survey of >400,000 adults per year Core, optional, and state-added questions Use of narcotics other than heroin
Youth Risk Behavior Surveillance System	School-based survey -- health risk behaviors National, state and district level data Pain medication use without prescription/differently than prescribed

Enriched Populations: Treatment Center Surveys

- Includes those entering or being assessed for substance use disorder treatment
  - Captures a hard-to-reach population of high-risk individuals
  - Can provide product-specific patterns of abuse
- Caveats
  - Drug may be separated from packaging or storage options
  - Packaging/storage not currently captured
  - Difficult to define underlying population
  - Generalizability of results is unclear

Internet Panel Surveys

- Survey administration company invites individuals to subscribe to online survey panel
- Members opt-in for specific surveys
- Existing surveys ask about intentional misuse and abuse
- Flexible surveys, can more easily add questions about packaging, storage, and disposal options
- Caveats
  - Generalizability of results is unclear (who participates?)
  - People may misremember or intentionally report incorrect responses

Provider, Pharmacist, Patient Surveys

Weeks Later

- May be the only way to capture some options and outcomes (e.g., intentional misuse)
- Caveats:
  - Usually small and generalizability may be poor
  - People may misremember or intentionally report incorrect responses

Other Data Sources

- Poison Control Centers
  - Product-specific information but does not currently capture separate packaging/storage information
  - Generalizability is unclear (who calls?)
  - Severe overdoses and immediate deaths unlikely to generate a call
- Mortality Data
  - Packaging, storage, and disposal options unlikely to be recorded
- Emerging Technologies?
  - Packaging that captures when the package is accessed or medication is consumed could help establish patterns of misuse

Capturing Exposures

(Opportunity for contact with the "option" by the patient or a third-party)

EHR

FDA

Claim

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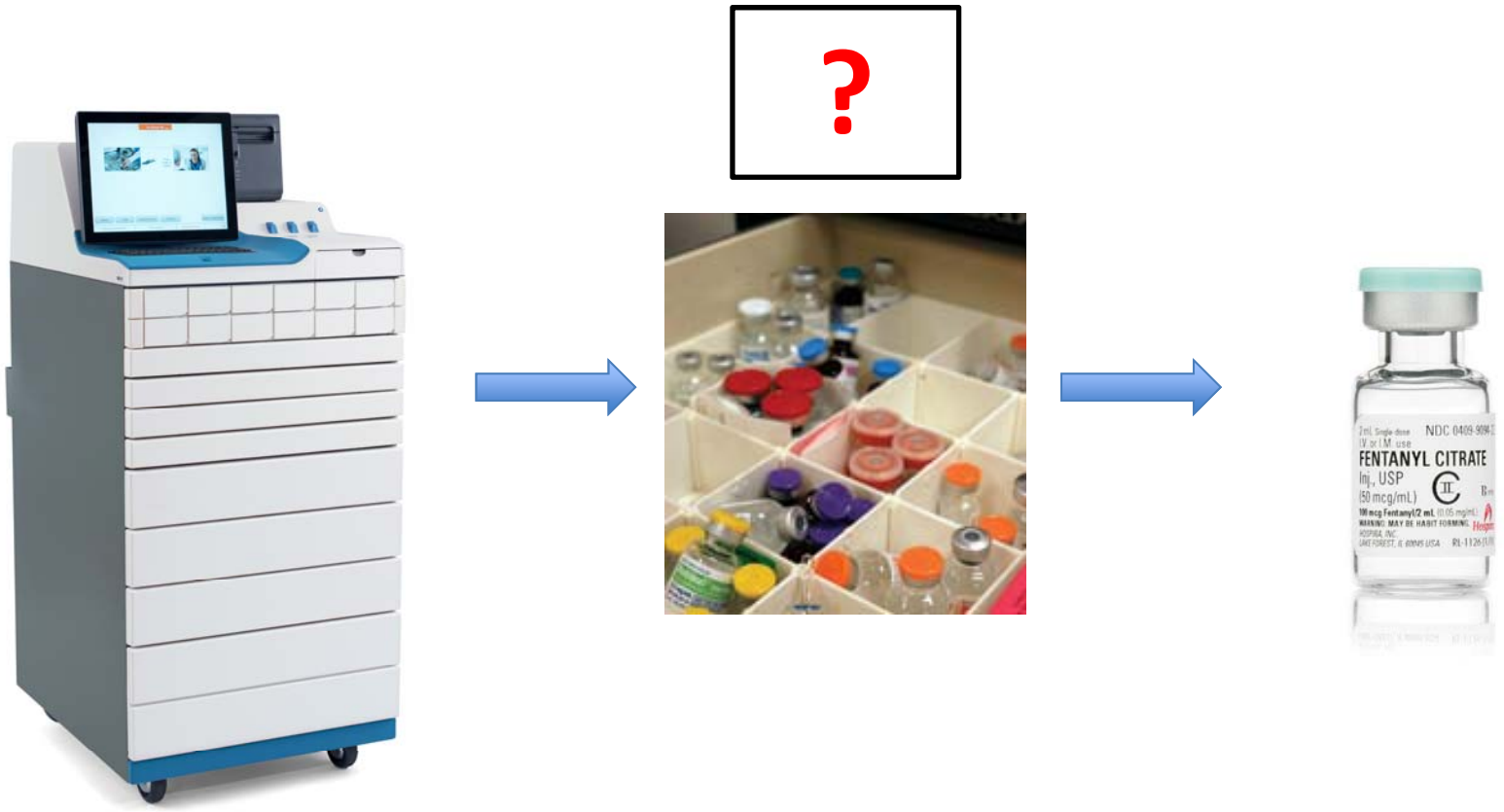
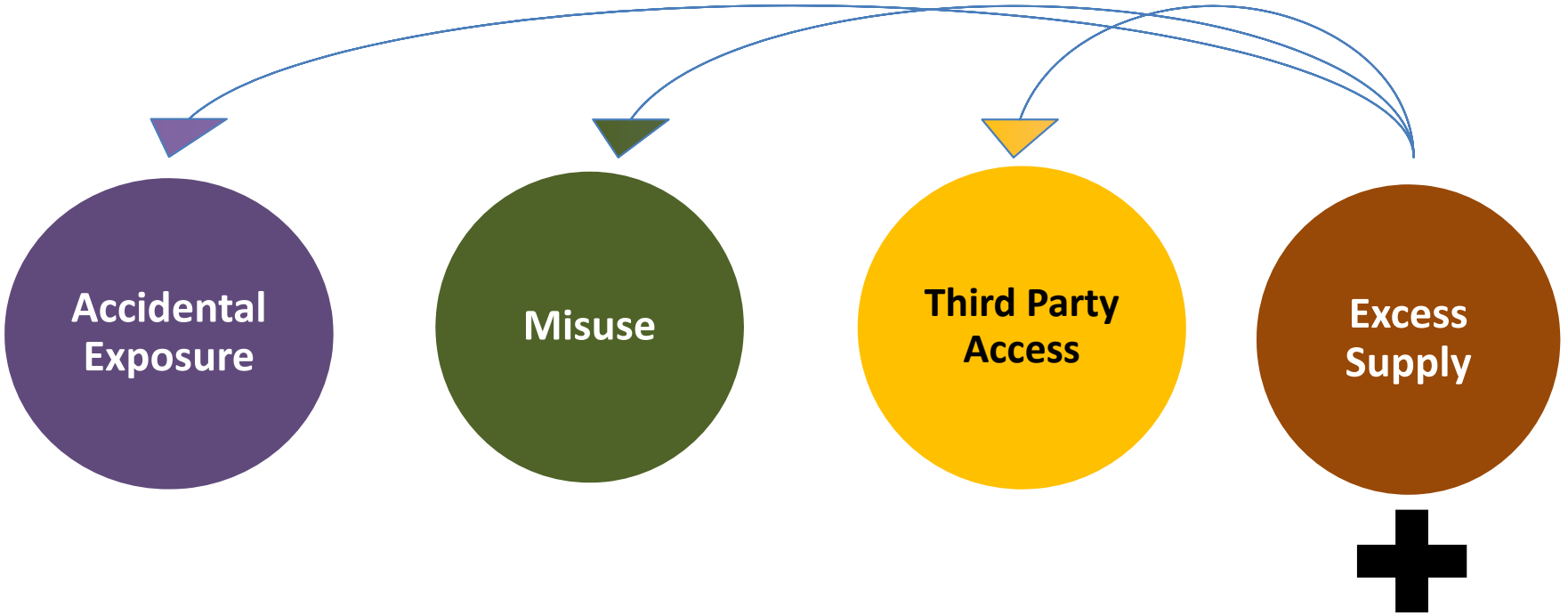
Images: : https://www.columbiaeyeclinic.com/wp-content/uploads/2015/06/EMR-image.gif; http://www.pharmaceutical-journal.com/pictures/380x217/2/6/4/1070264_community-pharmacy-store-front-16.jpg; http://www.worldpharmaceuticals.net/features/featuretime-to-act-challenging-packaging-conventions-4214752/; http://ecx.images-amazon.com/images/I/21I9algCBrL.jpg; http://enfamilia.aeped.es/temas-salud/intoxicaciones-por-medicamentos-en-ninos http://images.doba.com/products/1529/images_c159_image2_ctd_4900.jpg; http://www.betweenthekids.com/wp-content/uploads/2012/12/BottleCap.png; https://www.choosehelp.com/blogs/prescription-drug-abuse/teen-campaign-against-deadly-abuse-of-prescription-drugs.html; https://ligadasaude.blogspot.com/2012/09/idosos-podem-estar-usando-medicamentos.html

Third Party Access - Inpatient



Images: Rx-wiki, http://rx-wiki.org/index.php?title=File:AcuDose-RxLargeMainCabinetSideView-hires.jpg; Outpatient Surgery Magazine, http://www.outpatientsurgery.net/surgical-facility-administration/legal-and-regulatory/colorado-nurse-indicted-for-pain-med-theft--e-06-09-09 ; Opiate Addiction & Treatment Resource, http://www.opiateaddictionresource.com/media/images/fentanyl_iv

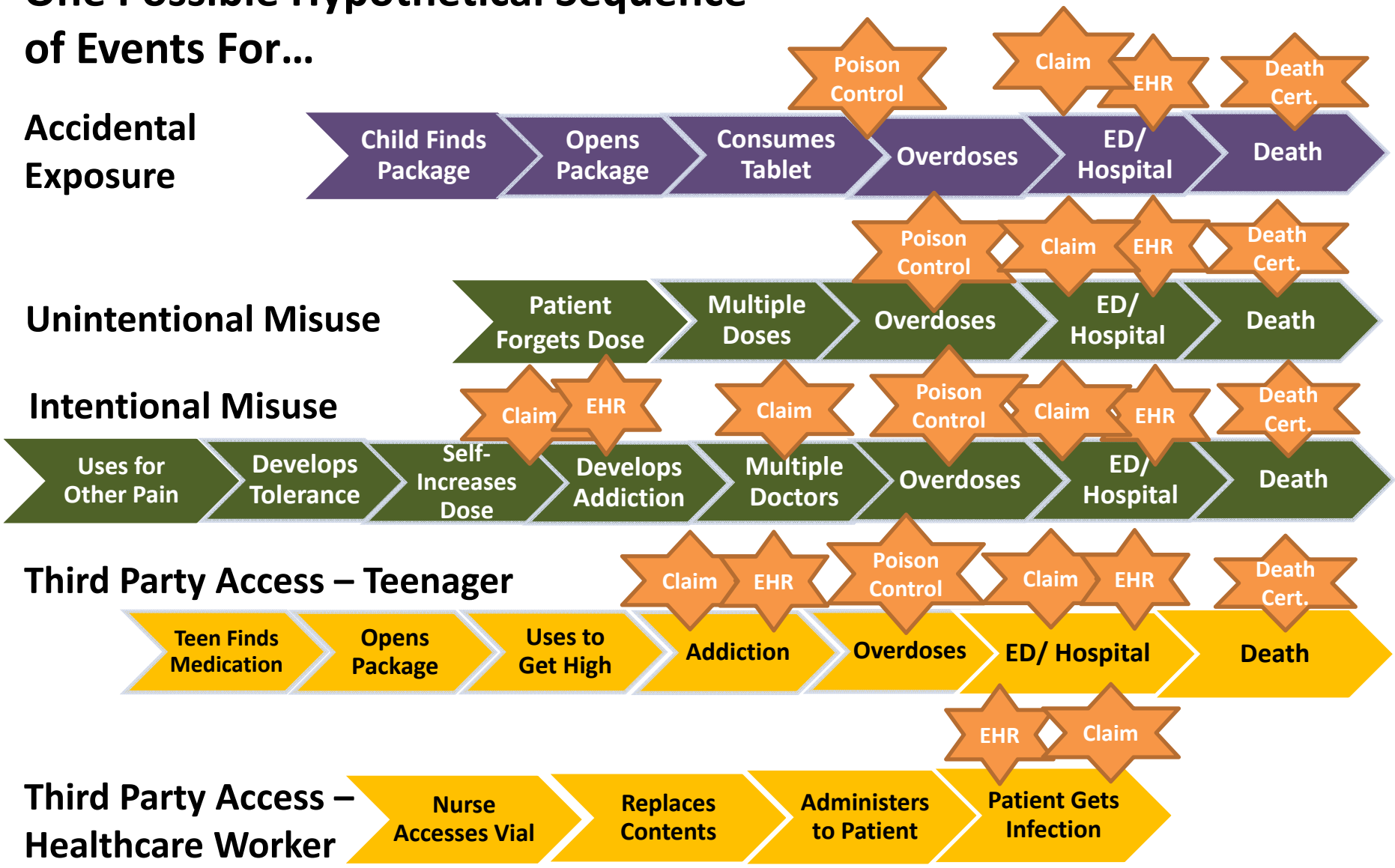
Excess Supply Feeds Other Problems



- Lack of Secure Storage
- Lack of Disposal

Capturing Outcomes

One Possible Hypothetical Sequence of Events For…



ED=emergency department;
EHR=electronic health record

Main Messages

- Designing studies to assess utilization and real-world effectiveness of the options may be challenging
  - Existing data systems may not capture exposure to the option, especially in the relevant population
  - Data sources may not exist to link exposure and outcome in the same person
  - Some of the problems that we're targeting are very difficult to measure (e.g., intentional misuse)
  - We may need more proximal outcomes or surrogates for outcomes to efficiently study these problems
  - May need to generate new data for proximal outcomes