

Premarket Data and Labeling Considerations for Packaging, Storage, and Disposal Options to Enhance Opioid Safety

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Accidental Exposure



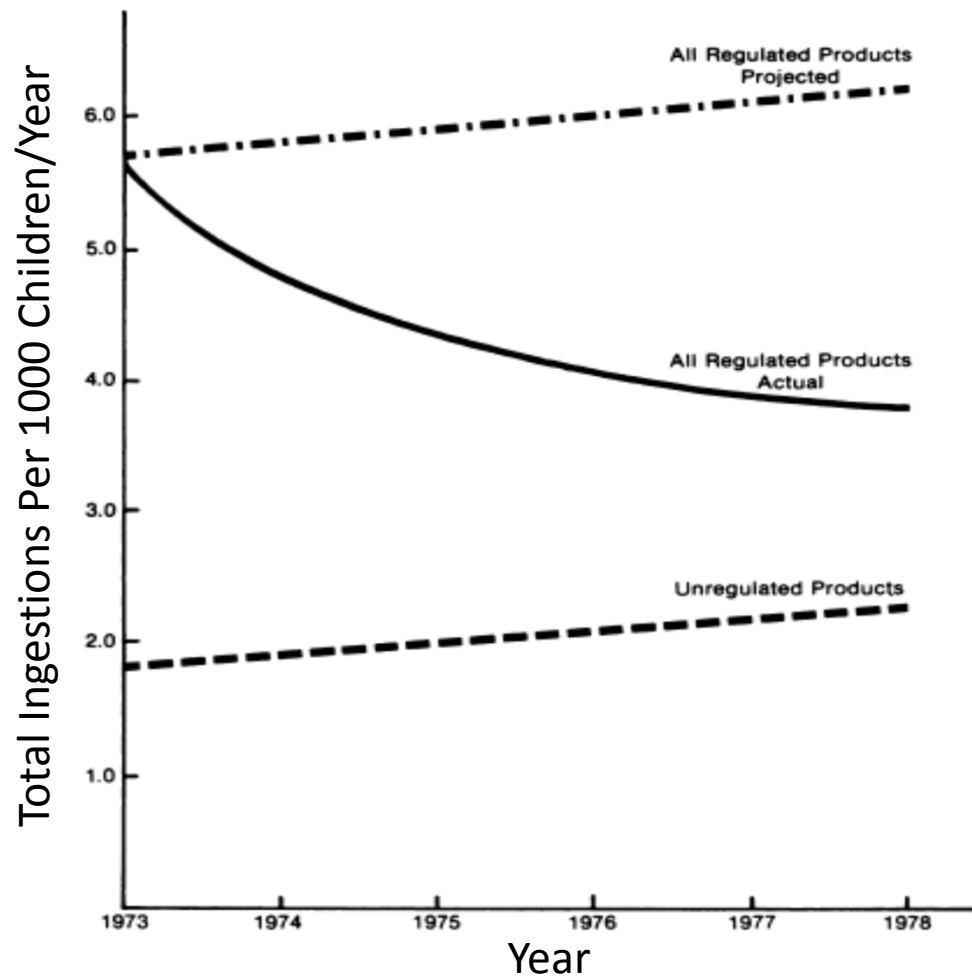
Accidental Exposure



Accidental Exposure

Poison Prevention Packaging Act (PPPA) enacted in 1970 and requires “special packaging” on a wide range of hazardous household products including most oral prescription drugs

“Although this study has shown that CRCs have significantly reduced deaths and injuries, accidental ingestions continue to occur... We must now consider what future measures might be most effective in reducing the continuing ingestions.”



Accidental Exposure

Make it more difficult for children to access the available supply



A packaging option designed to go straight to the patient's hands



Accidental Exposure

- Unit Dose Packaging Considerations
 - Passive Intervention (do not have to re-engage the child-resistant closure after removing a single dosage unit)
 - Each unit (e.g., tablet) has individual protection
 - How to demonstrate this offers a benefit over a CRC such as a medication vial cap?

Accidental Exposure

Pediatric Emergency Department Visits for Buprenorphine/Naloxone Ingestion — United States, 2008–2015

Daniel S. Budnitz, MD¹; Maribeth C. Lovegrove, MPH¹; Mathew R.P. Sapiano, PhD¹; Justin Mathew, PharmD²; Scott R. Kegler, PhD³; Andrew I. Geller, MD¹; Christian Hampp, PhD²

Expansion of buprenorphine treatment with naloxone is a key part of the national opioid epidemic (1). The number of pediatric emergency department visits for unintentional buprenorphine/naloxone ingestion increased, with the most common

93. The impact of repackaging from bottle to blister on paediatric intoxications with the levothyroxine brand Thyrax®

ARTICLE

Unit-Dose Packaging of Iron Supplements and Reduction of Iron Poisoning in Young Children

Milton Tenenbein, MD

Background: Iron poisoning is a major cause of unintentional poisoning death in young children. The US Food and Drug Administration proclaimed a regulation for unit-dose packaging of iron supplements in 1997.

Objective: To determine whether the requirement for unit-dose packaging of iron supplements decreases the incidence of iron ingestion and the incidence of deaths due to iron poisoning in children younger than 6 years.

Children younger than 6 years decreased from 2.99 per 1000 to 1.91 per 1000 (odds ratio, 1.29 [95% confidence interval, 1.27-1.32]; $P < .001$). The number of deaths decreased from 29 to 1 (odds ratio, 13.36 [95% confidence interval, 1.83-99.32]; $P = .03$).

Conclusions: These are the first data that show a decrease in the incidence of nonintentional ingestion of a specific drug by young children and a decrease in mor-

ssa E. van Riemsdijk, de Vries (CU), Utrecht, The

Unit-dose packaging of levothyroxine was changed by the manufacturer in order to improve protection against tampering such as light, air, and moisture. This change also increased child and parent inquiries to our Poisons Centre regarding the influence of this change on children.

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- Budnitz DS et al. *MMWR Morb Mortal Wkly Rep.* 2016; 65(41):1148-1149

- Tenenbein M. *Arch Pediatr Adolesc Med* 2005; 159(6):557-60

- (2017): 37th International Congress of the European Association of Poisons Centres and Clinical Toxicologists (EAPCCT) 16-19 May 2017, Basel, Switzerland, Clinical Toxicology



Accidental Exposure

- Premarket Data Considerations
 - Advance existing trial designs/testing protocols (e.g., leverage current CPSC human performance tests that were developed to measure child-resistance and adult-use effectiveness)
 - Comparative studies (enhanced CR packaging of one option over another) may require a head to head comparison trial between two packaging options
 - How to balance adult-use effectiveness?
 - Human Factors (HF) testing
- Labeling Considerations*
 - *The packaging has characteristics expected to lower the risk for accidental pediatric exposure of XXX. However, pediatric accidental exposure of XXX is still possible.*

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Misuse



Misuse



Misuse

- Medication use governed by complex behavioral interactions and beliefs
 - Example factors that can contribute to whether a patient misuses prescribed medication
 - Adverse events or fear of adverse events
 - Lower health literacy
 - Lack of understanding
 - Forgetfulness
 - Unwillingness to read information
 - Access
 - Cost



Misuse

Clinical Therapeutics/Volume 33, Number 1, 2011

Does Packaging with a Calendar Feature Improve Adherence to Self-Administered Medication for Long-Term Use? A Systematic Review

Barbara K. Zedler, MD¹; Priyanka Kakad, MS²; Susan Colilla, PhD, MPH^{1,3}; Lenn Murrelle, MSPH, PhD¹; and Nirav R. Shah, MD, MPH⁴

¹Venebio, LLC, Richmond, Virginia; ²Department of Pharmacotherapy and Outcomes Science, School of Pharmacy, Virginia Commonwealth University, Richmond, Virginia; ³Integrative Epidemiology, LLC, Cherry Hill, New Jersey; and ⁴Division of General Internal Medicine, New York University School of Medicine, New York, New York, and Geisinger Center for Health Research, Danville, Pennsylvania

ABSTRACT

Background: The therapeutic benefit of self-administered medications for long-term use is limited by an average 50% nonadherence rate. Patient forgetfulness is a common factor in unintentional nonadherence.

ical outcomes (seizures, blood pressure, psychiatric symptoms) or health care resource utilization. Substantial heterogeneity among trials precluded meta-analysis. In 3 studies, calendar packaging was part of a multicomponent adherence intervention. Six of 10



Misuse

- Existing data on adherence
 - Some methodological limitations
 - Inadequate randomization/blinding
 - Insufficient information regarding enrolled subjects and attrition rates
 - Short studies with limited sample sizes
 - Gaps in publishing of information
 - Risk of bias
 - Lack of further investigation into potential for harm



Misuse

Think broader than adherence

Could packaging, storage, or disposal options allow for...

- Patient reminders
- Limiting dosages only to those prescribed for
- Notifying prescribers of aberrant dosing patterns
- Destroying unused supply after completion of therapy
- Providing critical messages around safe use of prescription opioid

If yes, should premarket evaluation...

- Study individual effects?
- Assess combined effects?



Misuse

- Data Considerations
 - Adequacy of adherence alone as an outcome
 - Need for link to clinically relevant health outcome (proximal vs. distal outcome)?
 - Impact of critical information (e.g., warnings)
 - Correlating comprehension to behavioral outcomes
 - Patient preference or other qualitative survey methodologies
 - Comparative studies
 - Human Factors (HF) studies



Misuse

- Labeling Considerations
 - *The packaging has characteristics that improve patient compliance with labeled directions for use.*
 - *The packaging has characteristics that will destroy XXX after ## days of use, eliminating excess supply of XXX.*
 - *The packaging has characteristics expected to discourage the sharing of XXX.*

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Third Party Access



Third Party Access
Outpatient



Third Party Access
Inpatient

Image: Choose Help, <https://www.choosehelp.com/blogs/prescription-drug-abuse/teen-campaign-against-deadly-abuse-of-prescription-drugs.html>

Image: Academic Life in Emergency Medicine, <https://www.aliem.com/2015/03/art-of-syringe-labeling-in-the-ed/>

Third Party Access - Outpatient



CASE REPORT

WHEN THE OPIOID MEDICATIONS Go Missing: Confidentiality and Safety in Adolescents

by **MUHAMMAD HASSAN MAJEED, MD**

Dr. Majeed is an Attending Psychiatrist at Natchaug Hospital, Mansfield Center, Norwich, Connecticut.

Innov Clin Neurosci. 2017;14(5-6):25-27

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FINANCIAL DISCLOSURES: The author

ABSTRACT

Patients receiving end-of-life or

To provide easier access to healthcare, many state statutes are

“M, a 15-year-old girl, presented at the clinic...M revealed, after requesting confidentiality, that she was occasionally stealing opioid medications from her mother to use recreationally...The mother appeared to have no knowledge about M’s theft.”

Majeed MH. *Innov Clin Neurosci* 2017; 14(5-6): 25-27



Third Party Access - Outpatient

Could packaging, storage, or disposal options allow for...

- Patient notification of unauthorized access in real time
- Use of biometrics or other technology to limit access to patient
- GPS tracking of location
- Critical messages that may deter unauthorized access

If yes, should premarket evaluation...

- Study individual effects?
- Assess combined effects?



Third Party Access - Outpatient

- Data Considerations
 - Time to Defeat Studies
 - Time cutoffs?
 - Comparative studies
 - Qualitative studies and use of visual analog scales for subjective responses
 - Likelihood of attempting to thwart packaging/technology options
 - Population to study
 - Drug experienced, recreational users
 - Naïve users
 - Impact of critical information (e.g., warnings)
 - Correlating comprehension to behavioral outcomes
 - Qualitative research methods to inform the development of quantitative measures
 - Human Factors (HF) studies

Third Party Access - Outpatient



Labeling Considerations*

The packaging has characteristics expected to reduce use by persons other than the intended patient.

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Third Party Access - Inpatient

INFECTION CONTROL & HOSPITAL EPIDEMIOLOGY SEPTEMBER 2017, VOL. 38, NO. 9

ORIGINAL ARTICLE

Serratia marcescens Bacteremia: Nosocomial Cluster Following Narcotic Diversion

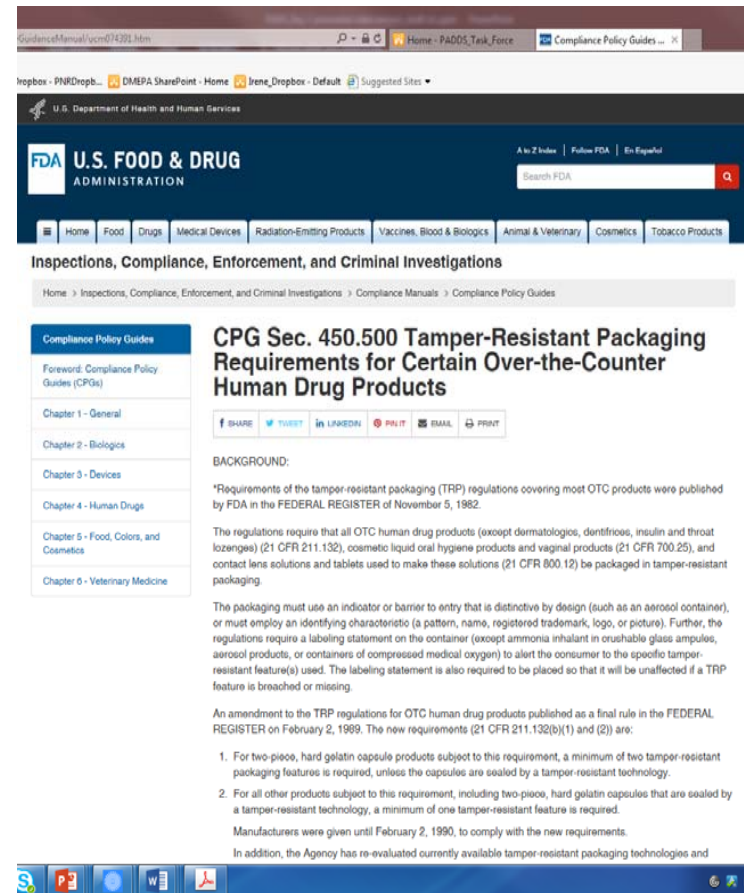
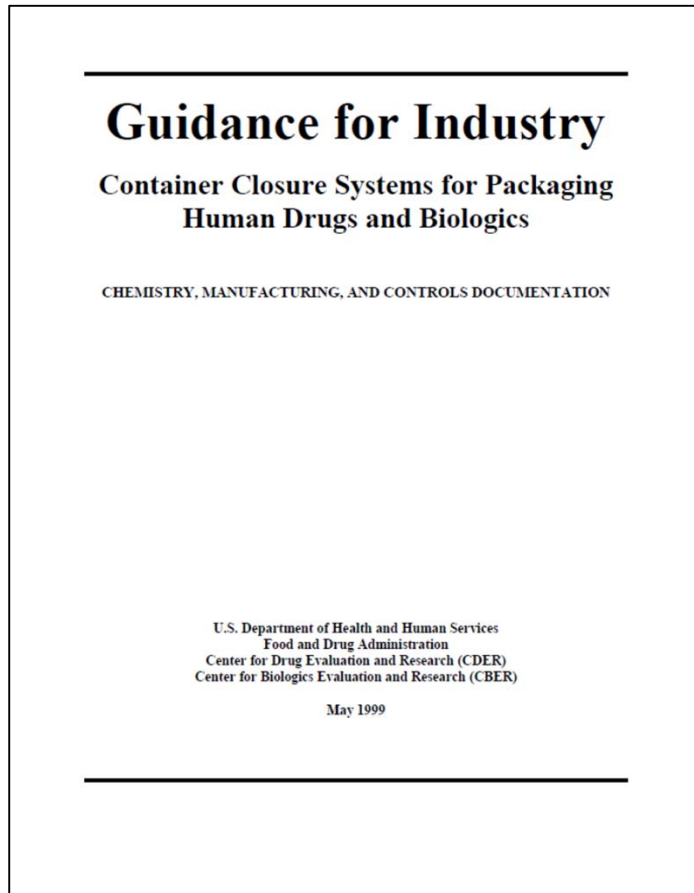
Leah M. Schuppener, DO;^{1,4} Aurora E. Pop-Vicas, MD, MPH;^{2,4} Erin G. Brooks, MD;¹ Megan N. Duster, MT;² Christopher J. Crnich, MD, PhD;^{2,4} Alana K. Sterkel, PhD;¹ Aaron P. Webb, PharmD, MS;³ Nasia Safdar, MD, PhD^{2,4}

OBJECTIVE. To describe the investigation and control of a cluster of *Serratia marcescens* bacteremia in a 505-bed tertiary-care center.

METHODS. Cluster cases were defined as all patients with *S. marcescens* bacteremia between March 2 and April 7, 2014, who were found to have identical or related blood isolates determined by molecular typing with pulsed-field gel electrophoresis. Cases were compared using bivariate analysis with controls admitted at the same time and to the same service as the cases, in a 4:1 ratio.



Third Party Access - Inpatient





Third Party Access - Inpatient

Data Considerations

- Dual Tamper Resistant Features
 - Detectability of entry
 - Time to entry
 - Qualitative studies and use of visual analog scales for subjective responses
- Comparative Studies
- Human Factors (HF) Studies

Labeling Considerations*

The packaging has tamper evident features expected to reduce use by persons other than the intended patient.

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Excess Supply



Excess Supply



Excess Supply

SPECIAL SERIES

Wide Variation and Excessive Dosage of Opioid Prescriptions for Common General Surgical Procedures

Maureen V. Hill, MD, Michelle L. McMahon, BS,† Ryland S. Stucke, MD,*
and Richard J. Barth Jr., MD**

Objective: To examine opioid prescribing patterns after general surgery procedures and to estimate an ideal number of pills to prescribe.

Background: Diversion of prescription opioids is a major contributor to the rising mortality from opioid overdoses. Data to inform surgeons on the optimal dose of opioids to prescribe after common general surgical procedures is lacking.

prescribing practice is due in part to the identification of pain as a “fifth vital sign” following the institution of rigorous pain assessment standards by the Joint Commission on Accreditation of Healthcare Organizations in 2001 and the curtailing of restrictions that previously limited opioid prescriptions to treat cancer related pain only.^{4,8,9}

The availability of prescription opioids has resulted in their



Excess Supply

- Example goals of packaging and disposal options
 - Drive prescribing behavior toward lower pre-packaged quantities (when appropriate)
 - Destroy unused product (which may impact third party access)



Excess Supply

- Data Considerations
 - Extraction Studies
 - Provider preference survey methodologies
 - Human Factors (HF) Studies
- Labeling Considerations*
 - *The packaging has characteristics that will destroy XXX after ## days of use, eliminating excess supply of XXX.*

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