Emerging Technologies for Improving Patient Adherence: an FDA Viewpoint

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Disclosure Statement

I have no financial relationships with proprietary entities that produce health care goods and services

The opinions and information in this presentation are my own and do not necessarily reflect the views and policies of the FDA

Outline

- Medication Adherence—Why it Matters
  - Opioids crisis– the flip side of the adherence coin
- Tools available and under development
- FDA Actions to support development in this area

Medication Adherence: Why It Matters to the FDA

- For public health, medication adherence as important as drug development
  - FDA is focused on supporting development of innovative new therapies to treatment disease
  - Ongoing work to develop therapies for chronic conditions—statins, BP meds, anti-retrovirals
  - Promise of those therapies is realized only when they are used!

Medication Non-Adherence (MNA): Stats

- ~50% of US adults have chronic diseases
- Chronic disease accounts for 70% of mortality
  - Cardiovascular disease leading cause of death
- In the United States, it is estimated MNA causes approximately 125,000 deaths and at least 10% of hospitalizations (2012)*
- Recent annual cost estimate ~$528 Billion**

*Meera Viswanathan et al, *Ann Intern Med.* 2012;157(11):785-795
**Watanabe, J.H. et al, *Ann Pharmacotherapy.* 2018; 52: 829-837

Medication Adherence: Many Reasons Why It's Challenging

- Cost
- Human*
  - Risk aversion
  - Identity as 'sick'
  - Avoiding dependency
  - Lack of perceivable benefit
  - Complex medical regimens and poly-pharmacy
- Structural
  - Limited time to focus on issue during appointments
  - Barriers on getting renewals
  - Reminder systems and reminder fatigue

*-- Rosenbaum, L, NEJM (2015) 372:183-187. Beyond Belief — how people feel about taking medications for heart disease"

Approaches to Improving Adherence and Detecting Non-Adherence

- Pillboxes, Blister Packs, Pill-counting
- Regimen simplification
- Behavioral Interventions
  - Reminder systems (in-person or indirect/electronic)
  - Direct administration (e.g., methadone)

- Innovative Approaches (more to come!)
  - Software approaches (e.g., reminder apps)
  - Tools to measure pill consumption
    - 'Smart' pill bottles
    - Sensors embedded in pills (e.g., Proteus)

FDA Role in Improving Medication Adherence

- Supporting innovation in the development of tools to measure and improve adherence
  Examples:
  - ‘Smart’ pills and ‘smart’ pill storage
  - Reminder systems (software)
- Providing guidance on development and potential labeling

Claims for Medicine Adherence

- Measuring patient adherence
  - ‘Tool’ claim
- Improving patient adherence
  - ‘Patient benefit’ claim
    - Higher bar needing demonstrated patient benefit
    - Challenging to demonstrate

Supporting Innovations: Abilify Mycite

ABILIFY MYCITE, a drug-device combination product comprised of aripiprazole tablets embedded with an Ingestible Event Marker (IEM) sensor intended to track drug ingestion

…The ability of ABILIFY MYCITE to improve patient compliance or modify aripiprazole dosage has not been established

Supporting Innovations: ProAir Digihaler

ProAir Digihaler contains a built-in electronic module which detects, records, and stores data on inhaler events for transmission to the mobile App. Use of the App is not required for administration of medication to the patient.

Supporting Innovation: Prescription Drug-Use-Related Software (PDURS)

December 2018: FDA established Docket for comment on potential regulatory oversight for PDURS

https://www.federalregister.gov/documents/2018/11/20/2018-25206/

“Proposed framework lessens FDA's regulatory requirements for prescription drug companion apps”

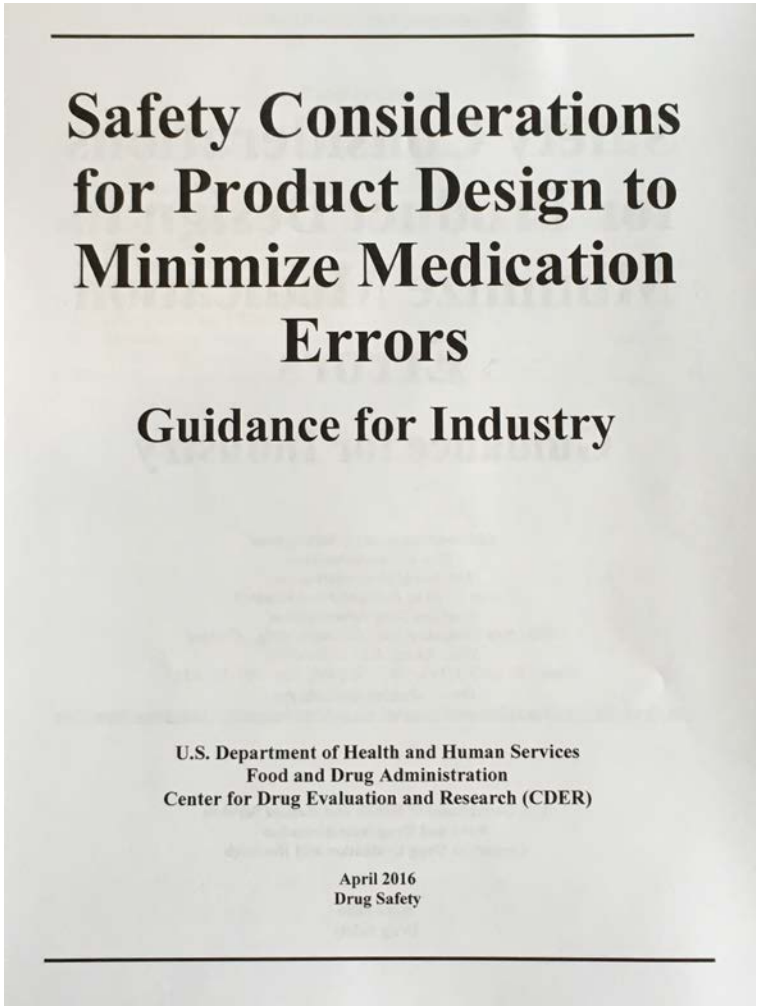
The agency's proposal would classify the majority of software released by pharmas as "promotional labeling" that would not require premarket review.”

November 19, 2018The FDA is seeking public comments for a proposed framework that would allow the majority of apps and software released by pharmas that accompany a drug treatment to avoid lengthy premarket review submissions.

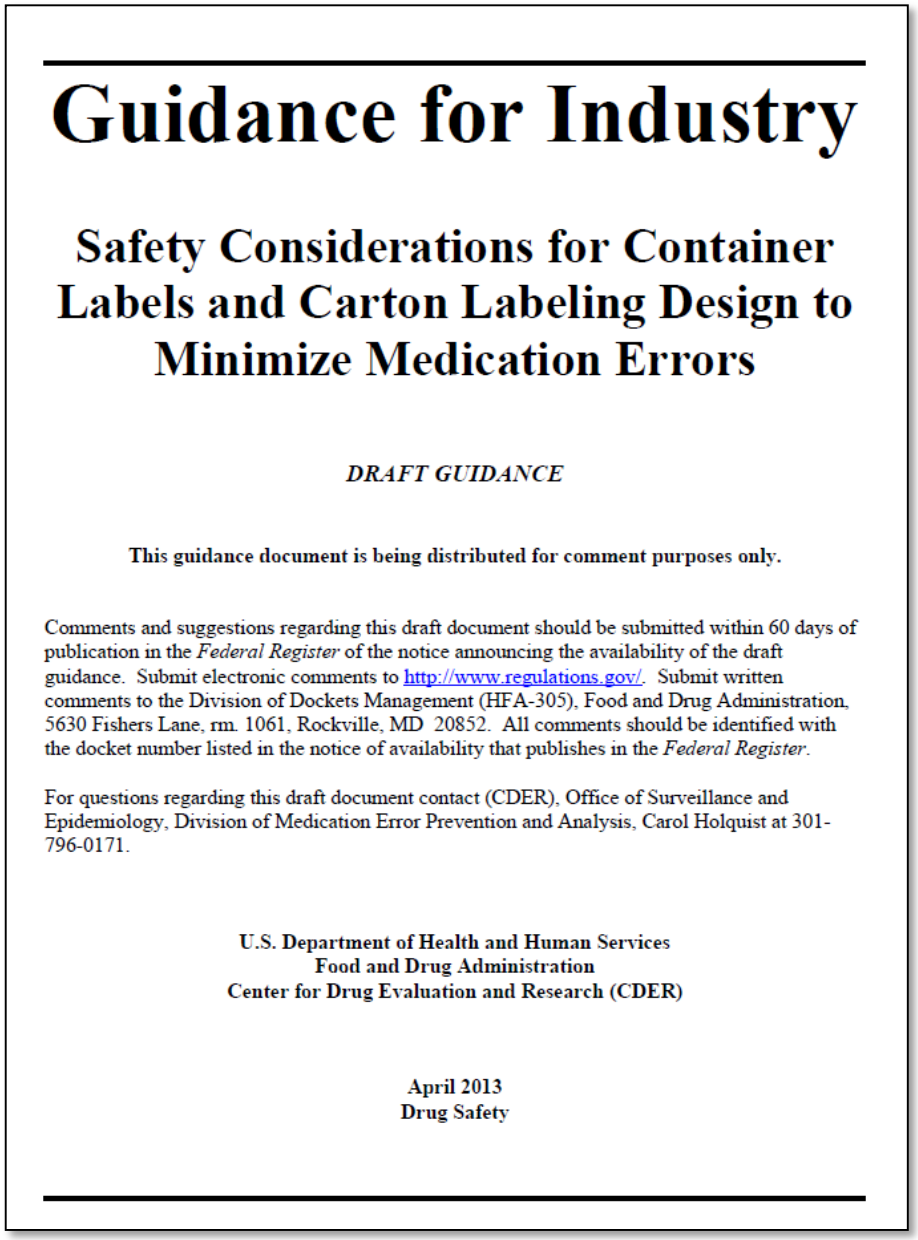
U.S. FOOD & DRUG ADMINISTRATION

Guidance on Development of Drug Products Addressing Adherence

Guidance on Packaging



- Designing in Safety
- Proactive Risk Assessment
  - Failure Modes and Effects Analysis
  - Simulated Use Testing



Guidance for Industry

Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

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

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

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

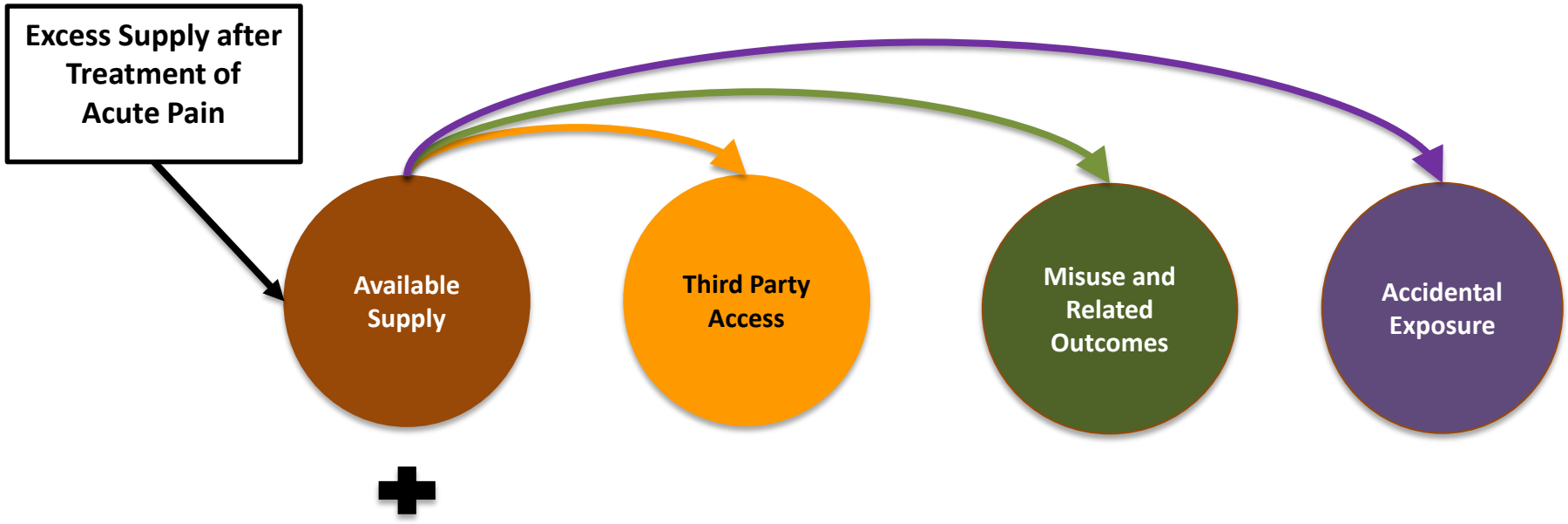
April 2013
Drug Safety

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

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

Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. 2013. Available from http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf

Medication 'Non'-Adherence: The Other Side of the Coin



- Non-Secure Storage
- Lack of Disposal

The Opioid Crisis: FDA's Priorities & Strategies

1. Decreasing Exposure & Prevent New Addiction

- Appropriate Dose/Duration Labeling
- Appropriate Packaging, Storage, and Disposal
- Health Care Provider Education

2. Supporting the Treatment of Those With Opioid Use Disorder

- Naloxone
- Medication Assisted Treatment (MAT)

3. Fostering the Development of Novel Pain Treatment Therapies

- Partnerships & Meetings
- Abuse Deterrent Formulations (ADFs)
- Pain Treatment Alternatives

4. Improving Enforcement & Assessing Benefit-Risk

- Improving Enforcement
- Assessing Benefit-Risk

FDA Authorities over Packaging Included in Recently Passed SUPPORT Act

- Substance Use-Disorder Prevention that Promotes Opioid Recovery and Treatment (SUPPORT) for Patients and Communities Act
- Many new provisions affecting FDA including tools to:
  - more efficiently stop illegal, illicit, unapproved, counterfeit and potentially dangerous drugs from entering the U.S. through the IMFs
  - reduce exposure to opioids as a way to lower the rate of new addiction
  - **require certain packaging, such as unit dose blister packs, for opioids and other drugs that pose a risk of abuse or overdose**
  - require that opioids be dispensed with a mail-back pouch or other safe disposal option
- Implementation ongoing

https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm624268.htm

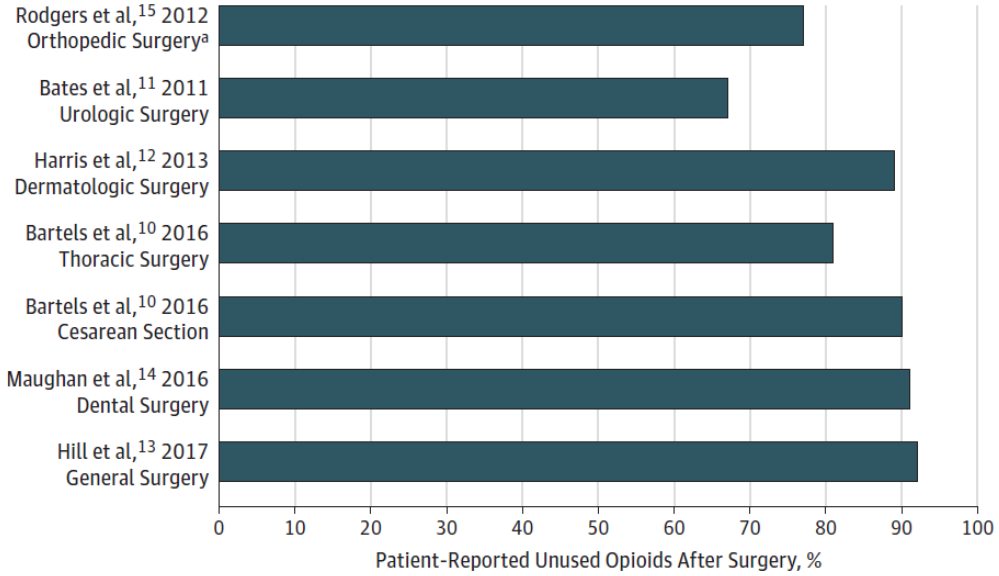
Opioid Analgesic Needs Vary by Condition/Procedure

Procedure	Mean/ (range) tablets filled	Mean/Median tablets consumed	~Days Used	~Leftover tablets
Outpatient Shoulder Surgery	60 (n.d.)*	37 (n.d.)*	9-10	23
Cesarean Delivery	40 (5-80)*	20*	4-5	20
Tooth Extraction	28 (n.d.)	13	2-3	15
Upper Extremity Surgery	30 (n.d.)	14 (Bone); 9 (Soft Tissue)	2-3	15
Laparoscopic Cholecystectomy	30 (0-100)	10-12	2-3	20
Laparoscopic Appendectomy	30 (n.d.)*	12*	2-3	18
Partial Mastectomy with Node Biopsy	23 (0-60)	6	1-2	17
Laparoscopic Inguinal Hernia Repair	33 (15-70)	9	1-2	24
Open Inguinal Hernia Repair	30 (15-120)	9	1-2	21
Partial Mastectomy	21 (0-50)	3	1	18
Dermatologic Surgery	9 (3-20)	4	1	5

1. Hill, et al., *Ann Surg*, 2017
2. Bateman, et al., *Obstet Gyn*, 2017
3. Maughan, et al., *Drug Alc Dep*, 2016
4. *Harris, et al., JAMA Dermatol. 2013*
5. *Bockman, et al. J Pain, 2017 (Abstract)*
6. *Kumar, et al. AJSM, 2017*

Target: Leftover Opioid Analgesics Reported in Post-surgical Populations

Figure. Prevalence of Unused Opioids Prescribed After Surgery



[a]percentage of patients reporting use of 15 tablets or fewer

- **Across many surgical procedures,**
  - **>50% of patients reported excess supply of opioid analgesics after treatment of acute pain**
  - **Most patients kept excess supply and stored supply in unsecured locations**

Figure Source: Bicket MC, Long JJ, Pronovost PJ, Alexander GC, Wu CL. Prescription Opioid Analgesics Commonl[illegible] After Surgery: A Systematic Review. JAMA Surg. 2017 Nov 1;152(11):1066-1071.

FDA Response: Potential Work on Packaging

- Exploring whether a defined, short-term supply of medication could be packaged in a manner that limits the number of pills dispensed (e.g., blister packs)
- Exploring packaging that could make it easier to track the number of doses that have been taken or reduce the risk for third-party access, such as teens ingesting pills they found in a medicine cabinet
- Work to improve storage and encourage prompt disposal to reduce the available supply of unused opioids

Summary

- Promise of new drug development is only realized when the drugs are used as directed
- Many factors contribute to decreased medication adherence
- Recognizing importance of innovation in this area, FDA working to support innovative products addressing adherence
- Opioids represent one part of the spectrum of medication adherence and FDA is exploring packaging solutions as a part of work to confront the opioids abuse crisis

Thank You