Advancement in the In-Vitro Evaluation of Abuse-Deterrent Formulations for Opioid Analgesics: Research and Assessment Perspectives

SBIA 2021: Advancing Generic Drug Development: Translating Science to Approval

Day 1 : Session 2:: **Considerations in Assessing Generic Drug Products of Oral Dosage Forms**

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Office of Pharmaceutical Quality| Office of Testing and Research

Pharmaceutical Quality

A quality product of any kind consistently meets the expectations of the user.

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A quality product of any kind consistently meets the expectations of the user.

Drugs are no different.

Patients expect safe and effective medicine with every dose they take.

Pharmaceutical quality is

consistently meeting standards that ensure every dose is safe and effective, free of contamination and defects.

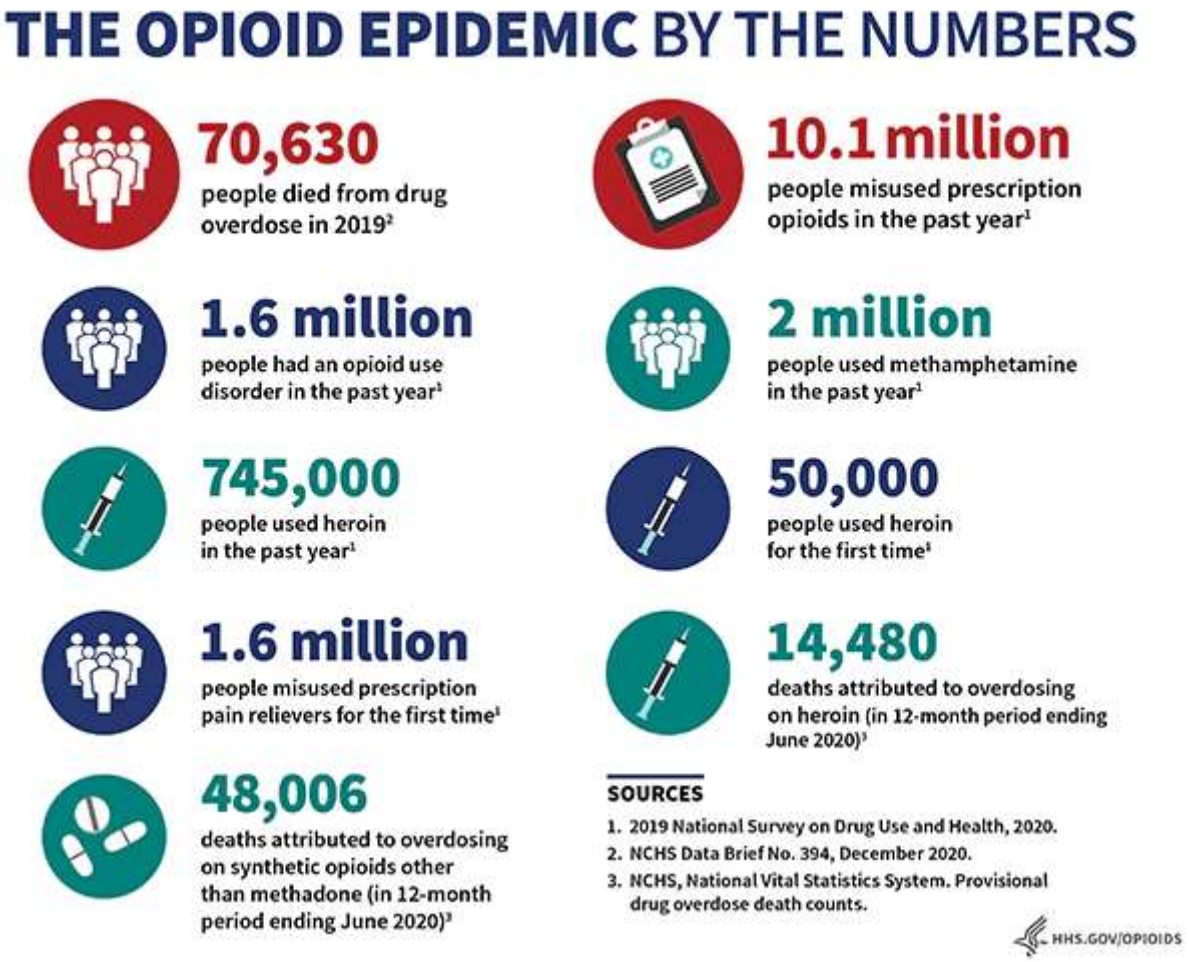
It is what gives patients confidence
in their *next* dose of medicine.

Objectives

- Describe FDA's research effort in evaluating abuse deterrent formulations
- Provide key considerations in assessment of in-vitro abuse-deterrent studies
- Provide examples of common deficiencies in in-vitro methods to evaluate abuse deterrent properties

U.S. Opioid Epidemic

- For decades, abuse of prescription opioids is a consistent problem in the US
- US department of health and human services (HHS) declared the opioid crisis a national public health emergency



FDA and Opioid Research

- One of the areas FDA has focused on to help address the opioid crisis is:

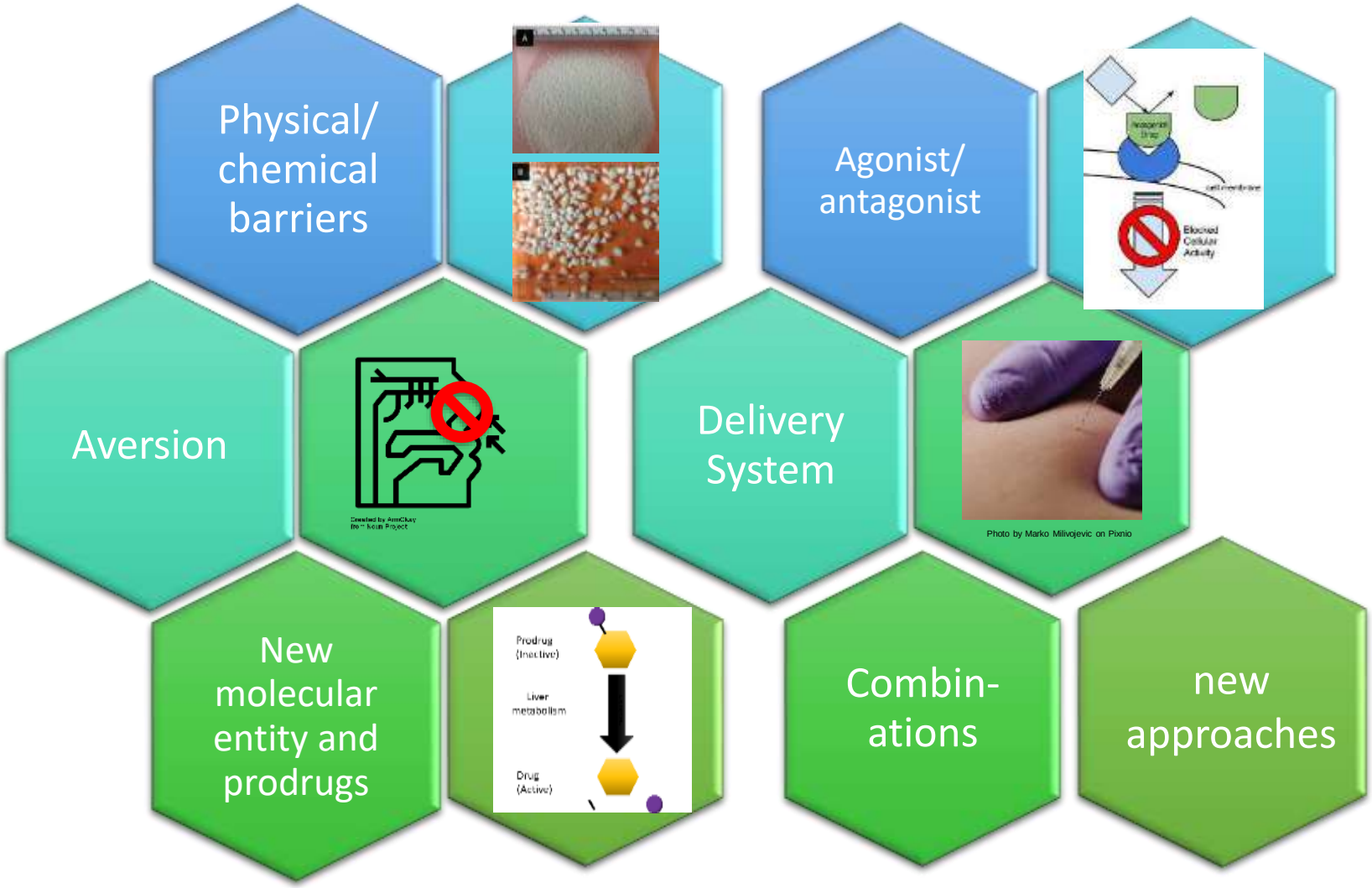
Supporting cutting-edge research

help expedite the development of more-effective abuse deterrent formulations of opioid drugs, and non-opioid alternatives for the treatment of pain.

Abuse Deterrent Formulations (ADF)

- Formulations that have the potential to make abuse of these products **more difficult or less rewarding**
- Are meant to **deter** abuse, even if they do not fully **prevent** abuse

Abuse-Deterrent (AD) Designs



Guidance for Industry: Abuse-deterrent opioids – evaluation and labeling

Regulatory Considerations on ADF

FDA

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← Drug Safety and Availability

Abuse-Deterrent Opioid Analgesics

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The FDA is encouraging the development of prescription opioids with abuse-deterrent formulations (ADFs) to help combat the opioid crisis. The agency recognizes that abuse-deterrent opioids are not abuse- or addiction-proof but are a step toward products that may help reduce abuse. The FDA fully supports efforts to better understand the impact of these products in the real-world setting and convened a public workshop on July 10-11, 2017, to discuss the current data and methods for evaluating ADF products postmarketing and what can be done to improve national data and methods moving forward.

The FDA also supports the development of innovative formulations that have the potential to make abuse of these products more difficult or less rewarding. This does not mean a product is impossible to abuse or that abuse-deterrent properties necessarily prevent addiction, overdose, and death. Notably, currently marketed technologies do not effectively deter one of the most common forms of opioid abuse -- swallowing the tablet or capsule. Because opioid medications must in the end be able to deliver the opioid to the patient, there may always be some potential for addiction and abuse of these products.

What does abuse-deterrent really mean?

Abuse-deterrent formulations target the known or expected routes of abuse, such as crushing in order

https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/abuse-deterrent-opioid-analgesics

Two Guidances (Final):

- "Guidance for Industry: Abuse-Deterrent Opioids – Evaluation and Labeling", 2015 (e.g., Category 1 studies)
- "General Principles for Evaluating the Abuse Deterrence of Generic Solid Oral Opioid Drug Products", 2017

Eight Product Specific Guidances

- Recommendations for bioequivalence studies, in-vivo abuse deterrence studies, and in-vitro abuse deterrence studies

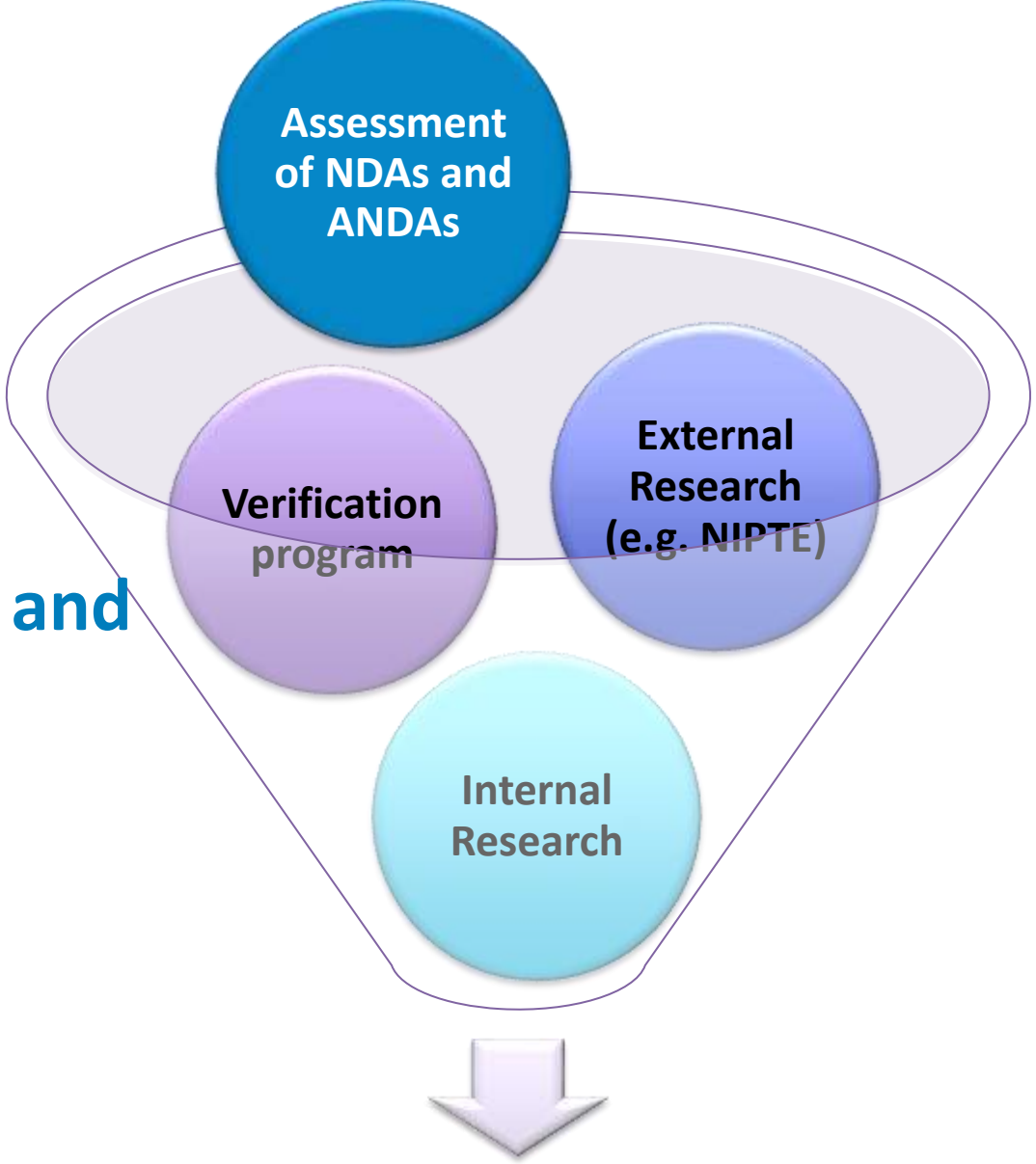
Opioid Products with AD Properties Described in the Label (Section 9.2)

Brand	API	Dosage Form	AD Design	AD Route	Product Specific Guidance	Generic
Embeda*	Morphine/Naltrexone	ER Capsule	Agonist / Antagonist	Oral, Nasal	07/2018	--
OxyContin	Oxycodone HCl	ER Tablet	Physical	IV, Nasal	07/2018	--
Targiniq ER*	Oxycodone HCl/Naloxone	ER Tablet	Agonist / Antagonist	IV, Nasal	11/2020	--
Hysingla ER	Hydrocodone Bitartrate	ER Tablet	Physical	IV, Oral, Nasal	07/2018	Yes
MorphaBond*	Morphine Sulfate	ER Tablet	Physical	IV, Nasal	09/2018	--
Xtampza ER	Oxycodone	ER Capsule	Physical	IV, Nasal, Oral	09/2018	--
Troxyca ER*	Oxycodone HCl/Naltrexone	ER Capsule	Agonist / Antagonist	Nasal, Oral	--	--
Arymo ER*	Morphine Sulfate	ER Tablet	Physical	IV	09/2018	--
Vantrela ER*	Hydrocodone Bitartrate	ER Tablet	Physical	IV, Nasal, Oral	--	--
RoxyBond*	Oxycodone HCl	IR Tablet	Physical	IV, Nasal	09/2018	--

ER: Extended release; IR: Immediate release; IV: Intravenous
*Discontinued

As of July 2021

The Products of Research, Testing and Assessment Experience



- General Guidances
- Product Specific Guidances
- Approval of Generic ADF Product

NDA: New Drug Application
ANDA: Abbreviated New Drug Application
NIPTE: National Institute for Pharmaceutical Technology & Education

Challenge Question 1:

Which of the following is NOT an abuse deterrent design:

a) Pill bottle lock

b) Aversion

c) Physical barrier

Internal Research

ABUSE DETERRENT FORMULATIONS (ADF)

ADF Internal Research Areas

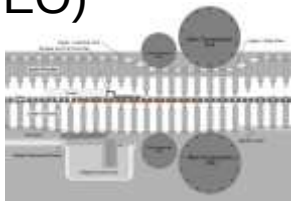
1. Reference Listed Drug (RLD) Characterization
2. Surrogate AD Properties and Shelf Life
3. New Technique/Procedure/Method
4. Standardization
5. Materials and Process Impact on AD Properties
6. Threshold Identification
7. Safety of ADF Materials
8. After-Market Risk/Benefit Assessment
9. Naloxone Product Quality

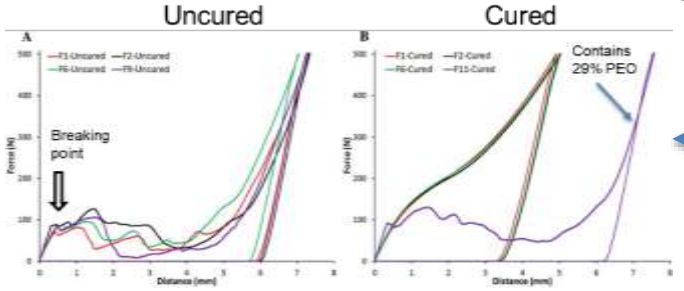
Impact of Materials and Process on AD Properties

- **The design feature of an ADF is a result of manufacturing process, material attributes or a combination of both.**
- **It is important to understand the relationship between the process or material and the AD properties.**

DIRECT COMPRESSION

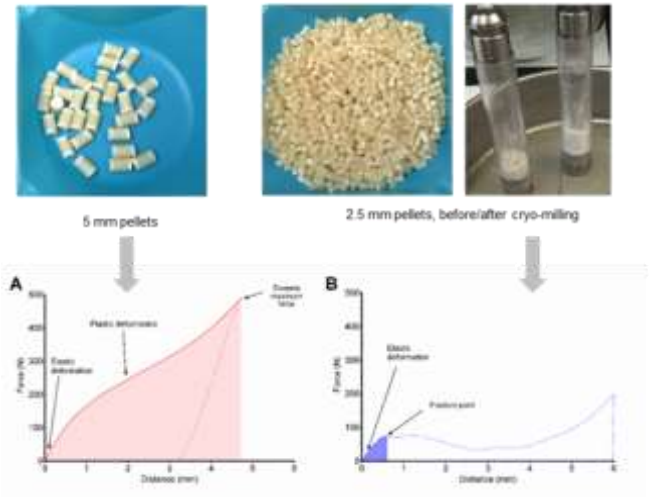
Material: Polyethylene oxide(PEO) various grades and percent
Process: Curing at various temperatures and time





Hardness Profiles

HOT MELT EXTRUSION



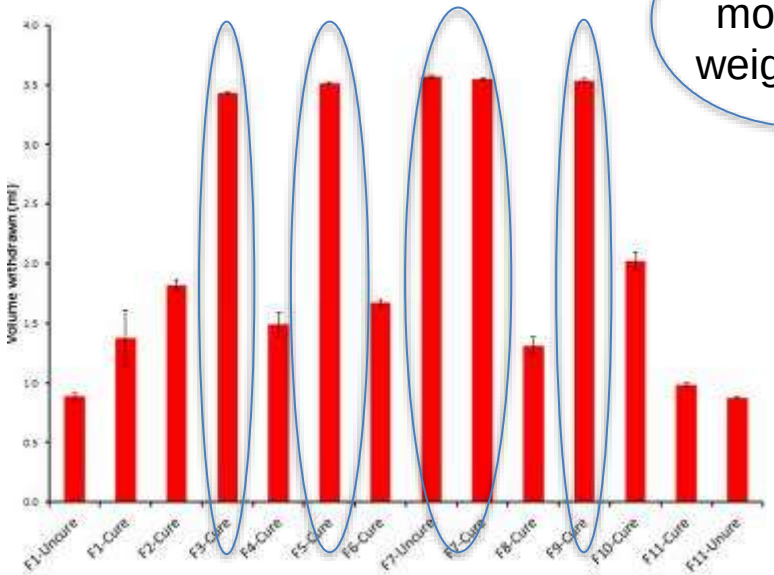
1 Rahman Z, et al. Int J Pharm. 2016;502(1-2):138-50
2 Rahman Z, et al. Int J Pharm.(2017) 2017;517(1-2):303-11

Xu X., et al. AAPS PharmSciTech. 2019;20(6):230

Surrogate AD Property: Syringeability and Injectability

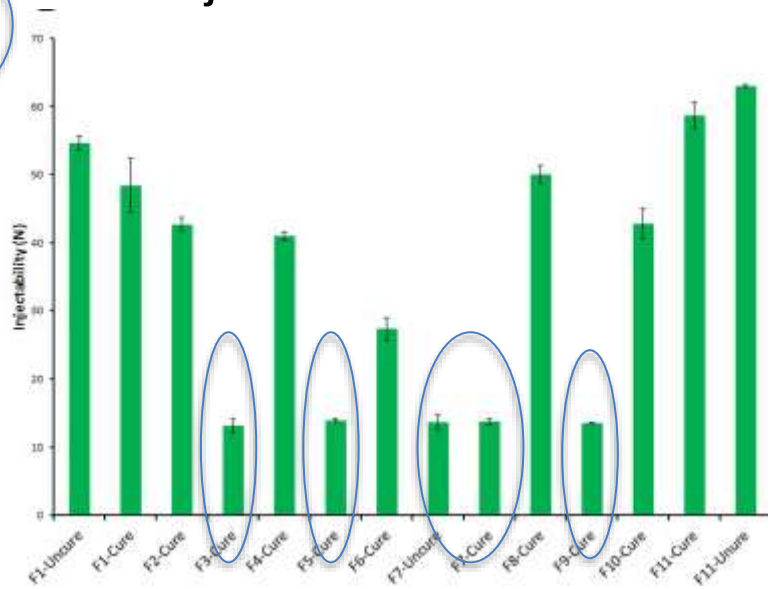
- Viscosity is the key material attribute affecting syringeability and injectability

Volume withdrawn



Low molecular weight PEO

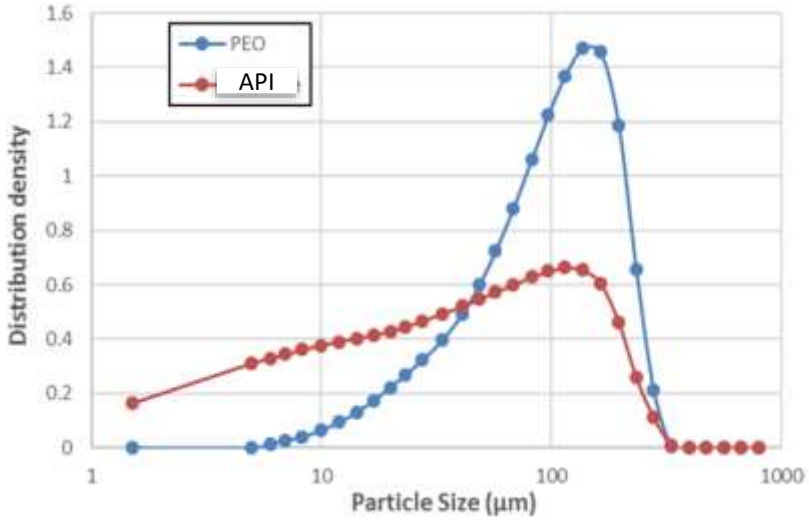
Injectable force



Rahman Z, et al. Int J Pharm. 2016;502(1-2):138-50

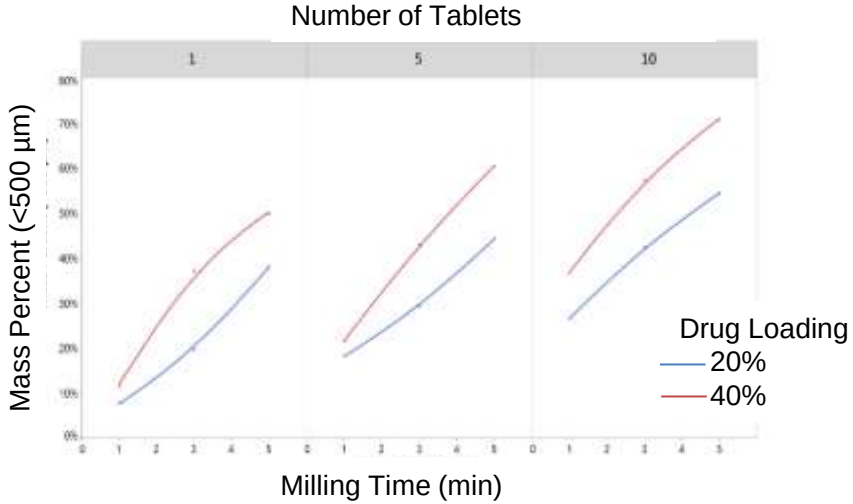
Standardization: Impact of Milling (Physical Manipulation) on the Evaluation of ADF

- Physical manipulation is a critical step in in-vitro and in-vivo AD evaluation
- Manipulation conditions and, thus, efficiency can impact the following AD evaluation

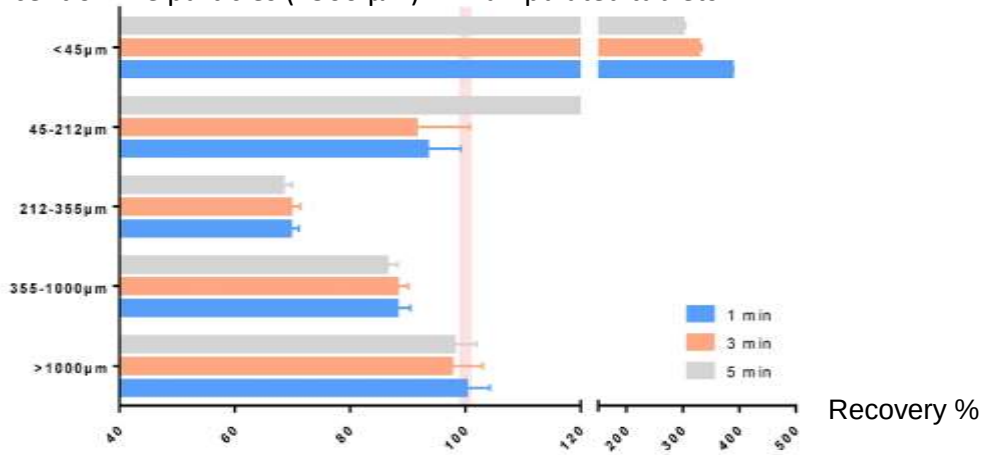


Particle size distribution of opioid surrogate(red line) and PEO (blue line)

Feng X et al. Poster AAPS 2019



Effect of drug loading, number of tablets and milling time on the mass percent of fine particles (<500 µm) in manipulated tablets.



Drug recovery from various particle size fractions of manipulated DC tablets. (Drug loading=20%, number of tablets=10, milling time=1,3 or 5 min, n=3).

Selected Publications

- Xu X, Gupta A, Al-Ghabeish M, Calderon SN, Khan MA. Risk based in vitro performance assessment of extended release abuse deterrent formulations. Int J Pharm. 2016;500(1-2):255-67.
- Rahman Z, Yang Y, Korang-Yeboah M, Siddiqui A, Xu X, Ashraf M, et al. Assessing impact of formulation and process variables on in-vitro performance of directly compressed abuse deterrent formulations. Int J Pharm. 2016;502(1-2):138-50.
- Rahman Z, Zidan AS, Korang-Yeboah M, Yang Y, Siddiqui A, Shakleya D, et al. Effects of excipients and curing process on the abuse deterrent properties of directly compressed tablets. Int J Pharm. 2017;517(1-2):303-11.
- Xu X, Siddiqui A, Srinivasan C, Mohammad A, Rahman Z, Korang-Yeboah M, et al. Evaluation of Abuse-Deterrent Characteristics of Tablets Prepared via Hot-Melt Extrusion. AAPS PharmSciTech. 2019;20(6):230.
- Externbrink A, Sharan S, Sun D, Jiang W, Keire D, Xu X. An in vitro approach for evaluating the oral abuse deterrence of solid oral extended-release opioids with properties intended to deter abuse via chewing. Int J Pharm. 2019;561:305-13.
- Hsu H, Yang Y, Pavuluri V, Abraham C, Naraharisetti S, Ashraf M, Al-Ghabeish M. Effect of Formulation Variables on the Nasal Permeability and Stability of Naloxone Intranasal Formulations. AAPS PharmSciTech (2019) 20:232.
- Feng X, Zidan A, Kamal NS, Xu X, Sun D, Walenga R, et al. Assessing Drug Release from Manipulated Abuse Deterrent Formulations. AAPS PharmSciTech. 2020;21(2):40.

Assessment

ABUSE DETERRENT FORMULATIONS (ADF)

Assessment of In-Vitro AD Studies: Critical Considerations

❑ Product quality attributes

Generic drug product is not required to be Q1/Q2 and the evaluation is performance based

AD Design, Material, Manufacturing Process (Risk assessment)

❑ Strengths to be evaluated

All strength or compositional proportionality and justification for bracketing design

❑ Evaluating ALL potential routes of abuse

To ensure the generic drug is no less abuse deterrent than the RLD with respect to all potential routes of abuse and minimize the risk of shifting abuse to other, potentially more dangerous, routes

RLD: Reference Listed Drug
Guidance for Industry: General principles for evaluating the abuse deterrence of generic solid oral opioid drug products

General Scheme of Comparative In-Vitro Studies

Comparative In-Vitro Studies

- Physical Manipulation
- Extractability

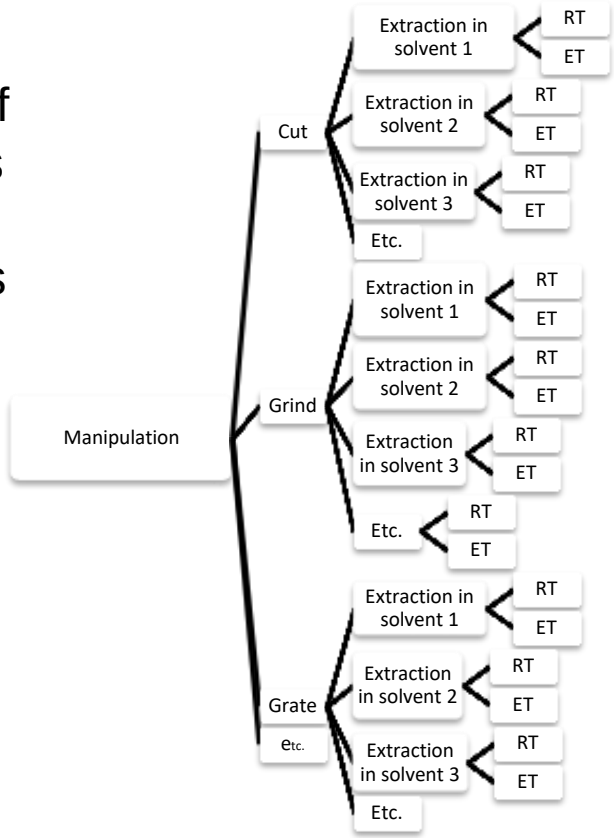
Route of abuse

Oral	Parenteral	Nasal	Inhalation
Comparative extractability	Small volume extractability Syringeability	Manipulation and fine particles (Tier 1)	Manipulation and smoking test

Guidance for Industry: General principles for evaluating the abuse deterrence of generic solid oral opioid drug products

Risk-Based Evaluation: Reduced Burden on Testing

Number of tests goes into thousands



RT: room temperature
ET: elevated temperature

Key considerations

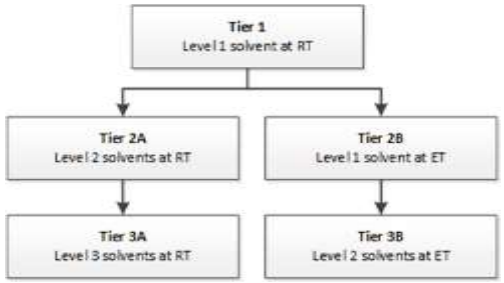
- Most effective manipulation and sample selection

The two extreme (**at least**) forms of a drug product should be selected

- Tier-based approach to testing

A **tier** refers to manipulations of similar complexity, difficulty and effort

Subsequent tiers with increasing complexity, difficulty, and effort

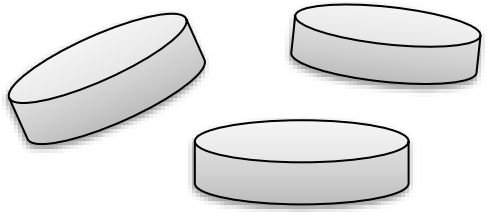


Examples of Deficiencies: Number of Units and Drug Content

- "…Specifying and justifying the **total number of units used** in a manipulation run …"
- "… determine the drug content in manipulated drug products and quantify the **drug loss** in samples prior to evaluating extractability."
- Recommendations on number of units and drug content that is based on current agency knowledge of that specific product

Examples of Deficiencies: Intermediate Manipulation and Product Design

- "..Conducting all in-vitro abuse deterrence studies comparing T and R products using an **intermediate manipulation** method..."
- When the AD feature is related to the **drug product design**, adding an intermediate manipulated sample that retains the design could be suitable in the comparative studies.



Intact
Extractability <10%

Intermediate
Extractability 10-50 %

Most effective manipulation
Extractability > 50%

Common Deficiencies: Replicates and Statistical Analysis

- "For your comparative studies, … the T product should be shown to be **statistically non-inferior** (NI) to R product. To do this, perform the statistical hypothesis test …"
- "… The [x ,y and z] tests were performed on [one or two] samples. Please explain how you selected **sample size** as a statistically meaningful sample or repeat these tests…"
- Recommendations statistical analysis (Sec VIII) to conclude that **T product is no less abuse deterrent than R product**.

Guidance for Industry: General principles for evaluating the abuse deterrence of generic solid oral opioid drug products

- **Challenge question 2:**

Which statistical test should be used to compare T vs R:

a) Paired t-test

b) Non-inferiority test

c) Regression analysis

Summary

- FDA has conducted comprehensive research in crucial areas of ADF
- ADF research has supported the assessment of in-vitro AD studies
- Common deficiencies in the AD in-vitro evaluation can be avoided with well-designed methods
- AD properties can be defeated with varying degree of difficulty; and hence iterative improvements on the existing AD technology and more innovative designs are needed

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