Structuring the Submission of Abuse Deterrence Data and Formulating the ADF Label

Naama Levy-Cooperman, PhD
Director and Principal
Altreos Research Partners Inc.
INC Consultant

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Disclosures

- Consultant to pharmaceutical and biotech companies

Outline

- Brief summary of FDA announcement
  - Safety labeling changes & post-marketing study requirements for ER/LA opioids
- Introduction
- Labeling
  - Background
  - Tier I to Tier IV
- Structure of Tier-Analysis

FDA ER/LA Labeling and Post-Marketing Requirements

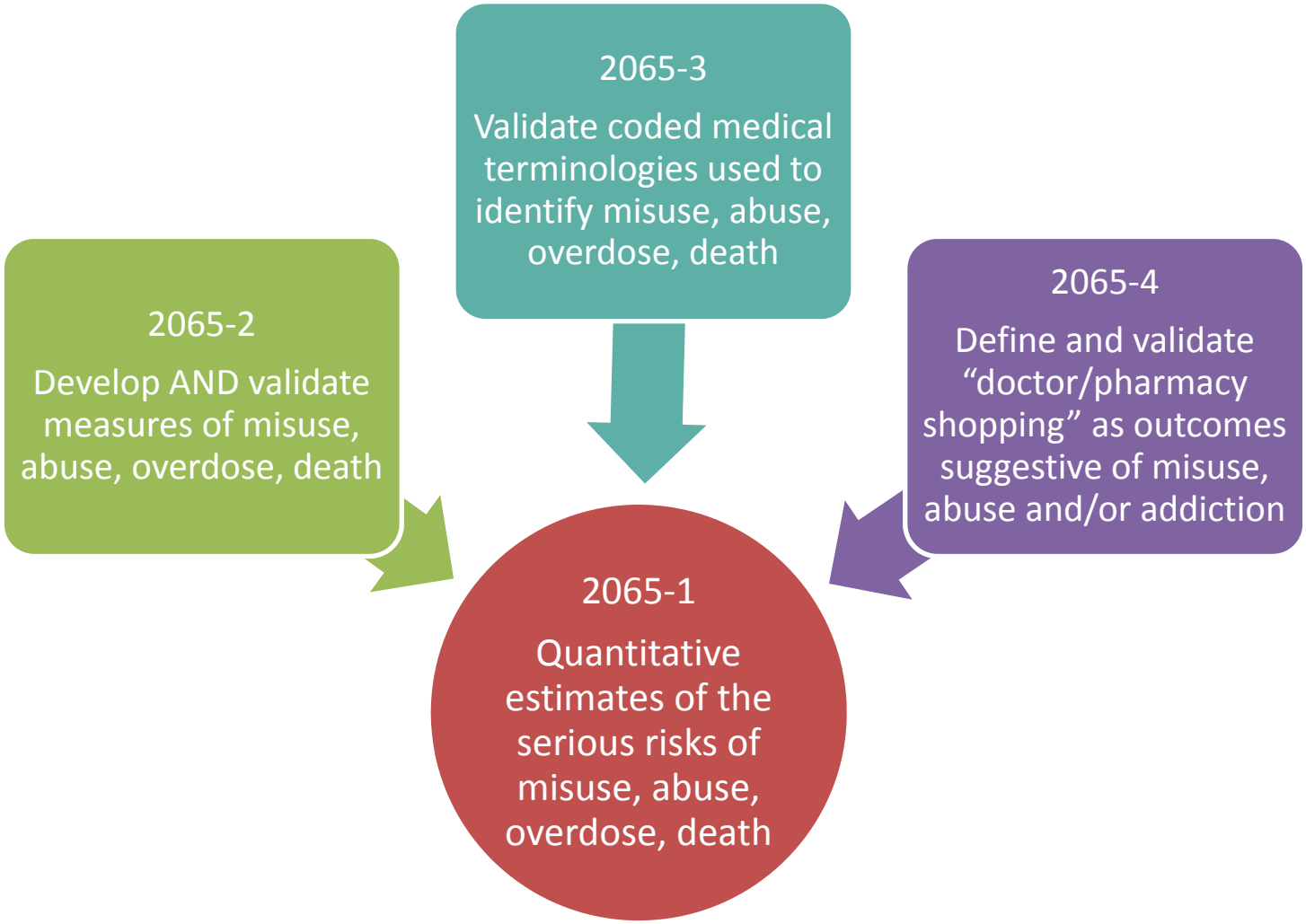
- September 10, 2013 – FDA releases class-wide safety labeling changes and new post-market study requirements for all ER/LA opioid analgesics
  - **Safety labeling changes**
    - Indication changes:

      Old: indicated for the management of moderate to severe pain when continuous, around-the clock analgesic is needed for an extended period of time.

      New: For pain severe enough to require daily, around the clock, long-term opioid treatment and **for which alternative treatments are ineffective, not tolerated, or otherwise inadequate to provide sufficient management of pain.**

      …not indicated as an as-needed analgesic
  - **Post-marketing**
    - Conduct one or more studies to provide quantitative estimates of the serious risks of misuse, abuse, addiction, overdose, and death
    - ……only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess the known serious risk of hyperalgesia …..

Required Post-marketing Studies

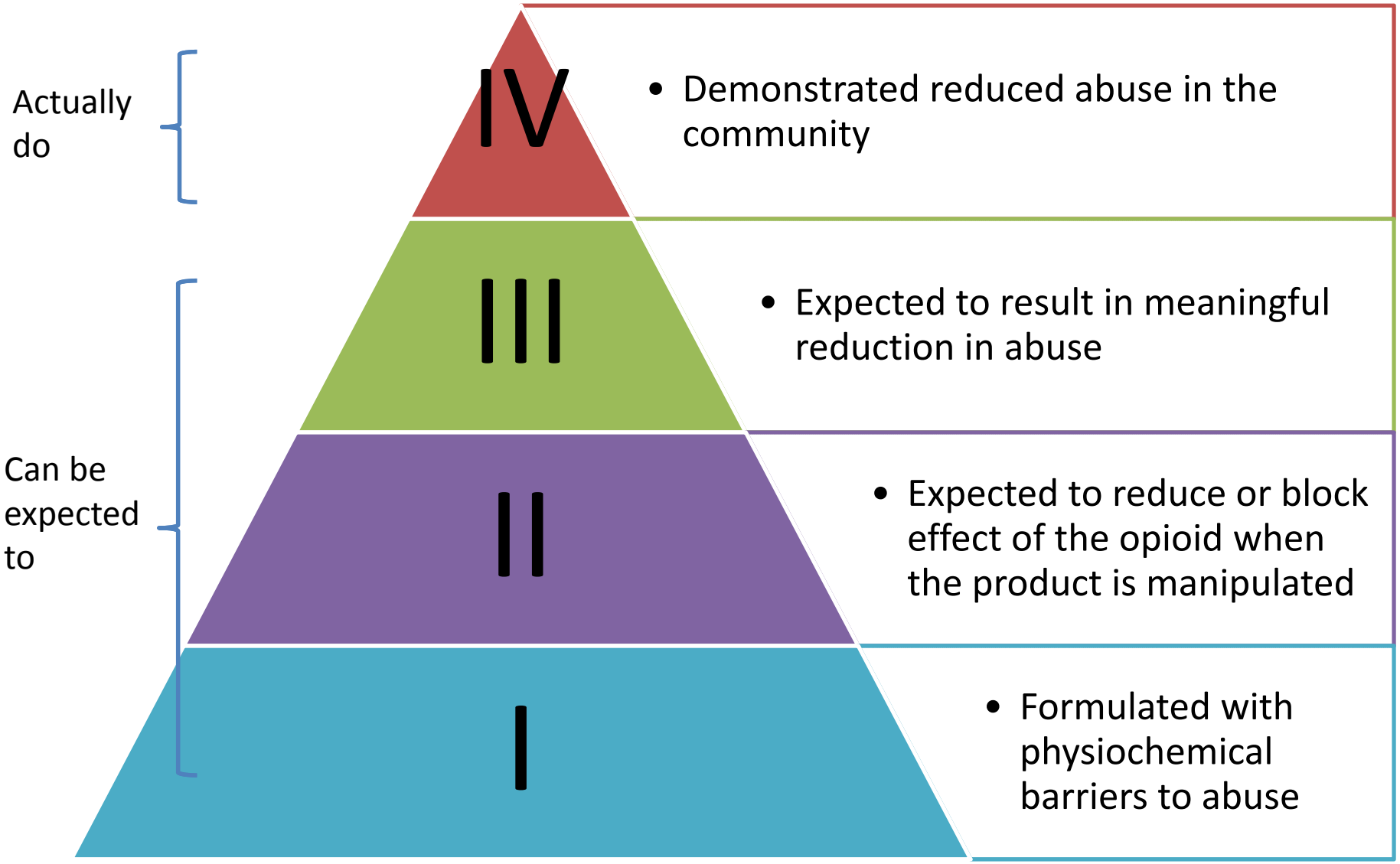


Introduction

- ADF Draft Guidance:

*"When the data predict or show that a product's potentially abuse-deterrent properties **can be expected to**, **or actually do**, result in a significant reduction in that product's abuse potential, these data, together with an accurate characterization of **what the data mean**, should be included in product labeling."*

Four Tiers of Labeling Claims



Labeling

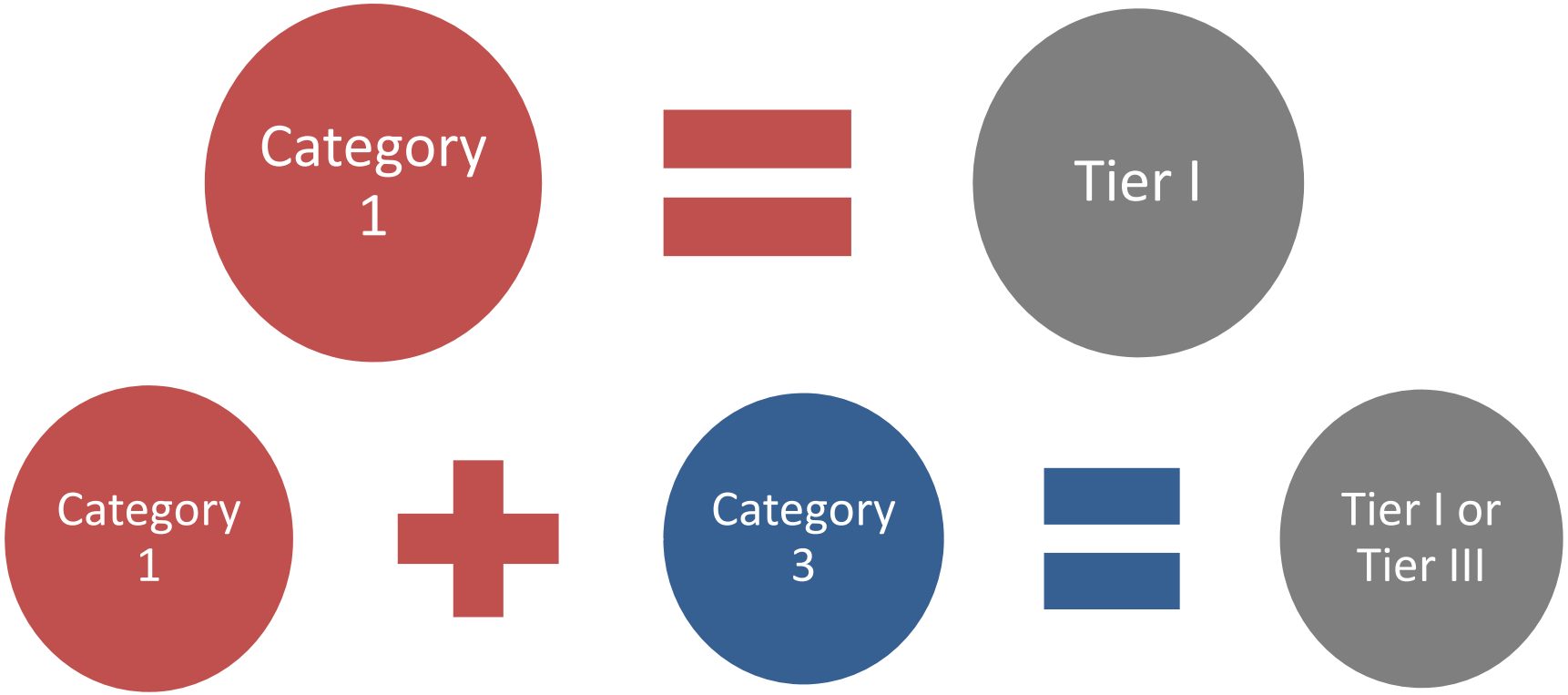
- For ADFs, label is more important than scheduling
  - Primary interface with **prescribers, patient community,** and **public**
  - Safety & indication
  - Can allow market distinction
  - Risk management tool
- Guidance outlines requirements for and example Tier I to IV claims
- Statements summarizing preclinical or clinical data can be included within label
  - Category 1 to 3 data summaries within label
- Labels can be modified post-approval with appropriate supporting data

Labeling

- Guidance suggests that data from all 3 categories of study are expected for any of the the first 3 tiers
- No guidance on magnitude of effect sufficient to support each type of claim
- To date, Tier I and Tier II claims have not made it into a label
  - OxyContin® – Tier III Section 9.2
  - Embeda® - Implicit claim, section 12 (Clinical Pharmacology)
  - Oxecta® - Implicit claim, Section 9.2

Example: Tier I Claim

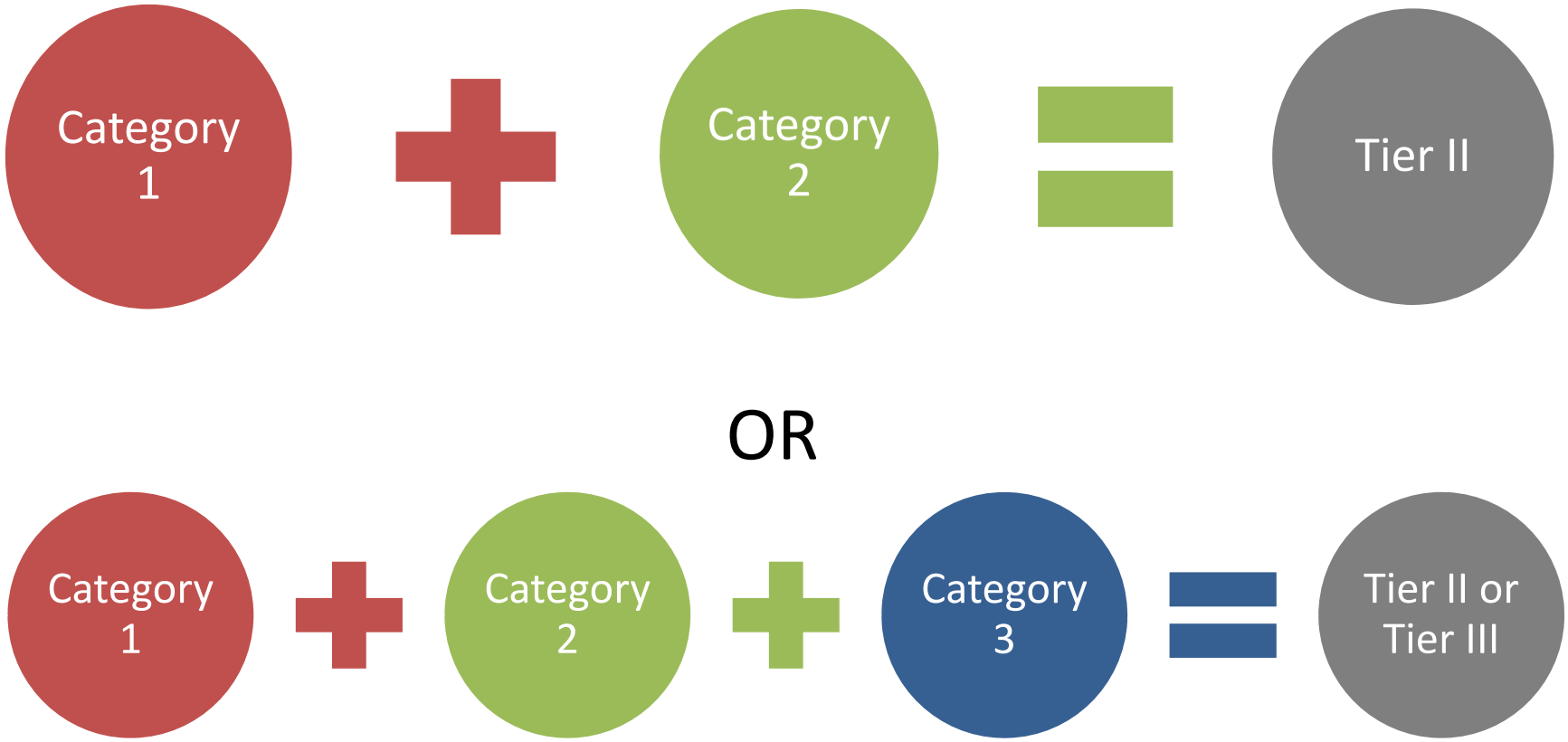
- Product with physiochemical barrier to abuse



- According to guidance, data from Category 1 not sufficient for any claim
- Category 2 only relevant if tampering with product (crushed etc.) results in complete maintenance of ER properties

Example: Tier II Label

- Combination agonist/antagonist product



Example: Tier I/II Label

- Prodrug

- Category 3 data not necessary if product is not active until metabolized in GI tract after oral ingestion

Can Tier III claim be achieved?

- Need “meaningful reduction”
- What is meaningful in terms of “drug liking” scores (i.e., the ever-elusive CID?)
- Options:
  - Non-inferiority approach- “at least not worse than”
  - OxyContin® as the active comparator in abuse liability study?

OxyContin®

- Purdue Pharma conducted the following studies:
  - In vitro tests (Category 1)
  - PK & PD studies (Category 2 & 3)
  - Epidemiological studies (Category 4)
- Precedent set: only achieved Tier III label
- Possibility of Tier IV following completion of long-term post-marketing studies?

Where does a Tier IV claim fit in?

- OxyContin® unique situation - epidemiological data was collected and submitted…Tier III label claim
- "The postmarketing data support the conclusions reached using the in vitro, PK, and clinical data, **but do not yet demonstrate, a reduction in OCR abuse following replacement of OC with OCR in the marketplace.**" (Office Director Memo Abuse - Deterrent Properties of Purdue's Reformulated OxyContin [oxycodone hydrochloride] Extended-Release Tablets)
- Post marketing epidemiologic studies of single products for the purpose of a Tier 4 label are scientifically very problematic
- Is the tier IV claim possible for other products?

Label Development

- Factual, based on supporting evidence

"This information should be communicated as **clearly** and **transparently** as possible."

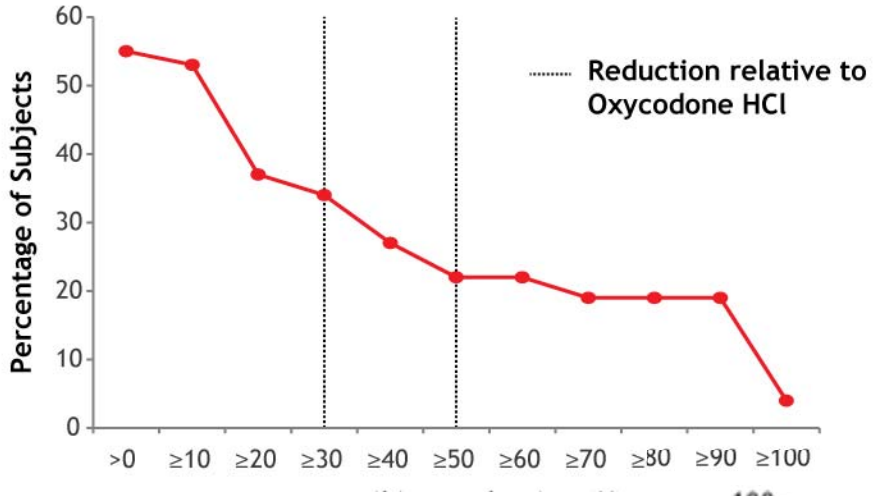
"Must contain a summary of the essential scientific information needed for the safe and effective use of the drug."

"…accurate characterization of **what the data mean."**

- Tier labeling examples are clear as outlined in guidance
- Are the summary of studies providing the best information?
  - Summarize study data *vs* road map to abuse
  - Can the audience interpret the data?

Label Data

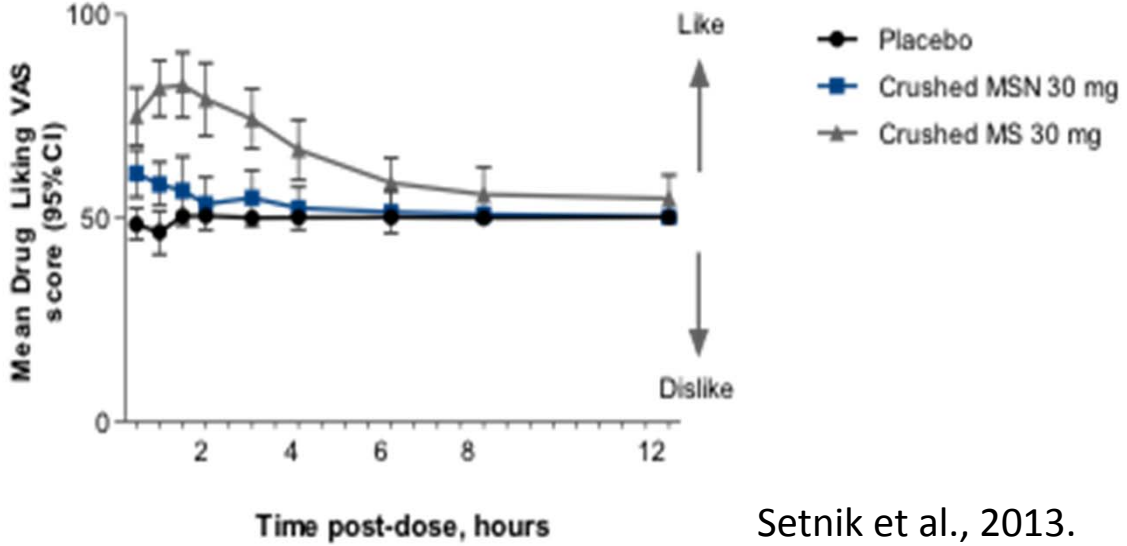
Relative to Powdered Oxycdone HCl Following Intranasal Administration



Responder Analysis Data

VS.

Time Course Data



Setnik et al., 2013.

Tier Analysis - Regulatory Submission

- Abbreviated evaluation ⟶ Tier Analysis
  - Approach acceptable for known entities (i.e., drugs with substantially similar pharmacology to marketed products or reformulation of marketed product)
  - Expecting same schedule
- Pro-drugs / NCEs
  - 8-factor analysis to build argument for differential scheduling
  - E.g., **NKTR-181: New Mu Opioid Analgesic Molecule for Chronic Pain Intended to Deter Abuse and Reduce CNS Side Effects by Reducing the Rate and Extent of Entry into the CNS** **(Webster et al., Poster presented at CPDD 2013)**

Elements of Tier Analysis

- Laboratory-based In Vitro Manipulation and Extraction Studies (Category 1)
  - Can include pre-clinical data (if relevant)
- Pharmacokinetic Studies (Category 2)
- Clinical Abuse Potential Studies (Category 3)
  - Summary of clinical trial abuse-related AEs (if relevant)
- Post-marketing Studies (Category 4)
- Summary
- Proposed labeling language

Summary

- Tiered labeling approach provides clear guidelines on the 4 categories of study required to support claims
- Some ambiguity on whether certain tiers can be achieved (i.e., Tier III and IV)
  - Could approved ADFs be added as comparators in HAL studies?
- To date studies including Category 1, 2 and 3 data of tampered ADF products have been consistent with post-marketing expectations (N=1)
- Until additional products approved, only standard is OxyContin®
- Information (including data) included in the label should be interpretable by end user