

Branded Industry Perspective on the Generics ADF Guidance

**FDA Public Meeting on Pre-Market Evaluation of Abuse-Deterrent
Properties of Opioid Drug Products**

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On behalf of the Branded Industry Working Group

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Branded Industry Working Group

- The Branded Industry Working Group (BIWG) includes representatives from the following 10 companies:
 - Acura Pharmaceuticals, Inc.
 - Collegium Pharmaceutical, Inc.
 - Depomed, Inc.
 - Egalet Corporation
 - Endo Pharmaceuticals Inc.
 - Grunenthal USA, Inc.
 - KemPharm, Inc.
 - Pfizer, Inc.
 - Purdue Pharma, LP
 - Teva Pharmaceutical Industries, Inc.
- The remarks in this presentation do not necessarily represent the views of the individual or those of the individual's company, but represent only the best available consensus views of the Branded Industry Working Group as a whole

Financial Disclosure

- Employee and officer of Egalet Corporation

Overview

- Opioid crisis and public health imperative to respond
- Progress to date
- BIWG perspective on the generics ADF guidance
 - rationale for BIWG position
- Concluding remarks

Public Health Imperative

- Opioid epidemic requires action from multiple stakeholders to address this crisis
- FDA Opioid Action Plan (February 2016)¹
 - focused on both patients and the community at large
 - balance access to effective pain medications while reducing societal burden of opioid abuse and misuse
- Treating the problem
 - naloxone for OD
 - medication assisted therapy (MAT) for addiction
- A preventive approach to the problem
 - AD opioids are one component of multi-faceted approach to addressing the challenge of opioid abuse/addiction/OD/death

Progress to Date

- FDA Guidance for Industry: Abuse-Deterrent Opioids – Evaluation and Labeling (CDER, April 2015)¹
 - road map for the development and labeling of branded AD opioids
 - supports the “goal of creating safer opioid analgesics” through the development of opioids that are formulated to deter abuse
- Science of abuse deterrence is relatively new and the field is still evolving
- FDA takes a “flexible, adaptive approach to the evaluation and labeling of potentially abuse-deterrent products”
 - based on the ***totality of the evidence***
 - Advisory Committee meetings now convened for all opioid product candidates with potential abuse-deterrent properties
- To date, 7 ER/LA branded opioid products have been approved with abuse-deterrent label claims (consistent with the final Guidance for branded products)

Draft Generics ADF Guidance: BIWG Perspective

- Recognize the importance of a generics ADF guidance to ensure widespread access to safe and effective analgesics for appropriate patients who need them
- Could also help to accelerate the transition to AD opioids
 - eventual replacement of opioid products without AD properties
- Also recognize the imperative to ensure that a product “is no less abuse-deterrent than its reference listed drug (RLD) with respect to all potential routes of abuse”
 - so not to provide a path of least resistance for abusers to “preferentially seek out and abuse such easier-to-abuse generics”¹
- Given complexity of the science and range of existing and emerging AD technologies, current draft guidance does not adequately address what is needed to demonstrate comparable AD properties on a product specific basis relative to all potential routes of abuse
 - consider broader, more flexible and inclusive approach to generics ADF guidance to address full range of approved AD products and emerging technologies
 - product specific guidances for generic ADF opioids

State of the Science

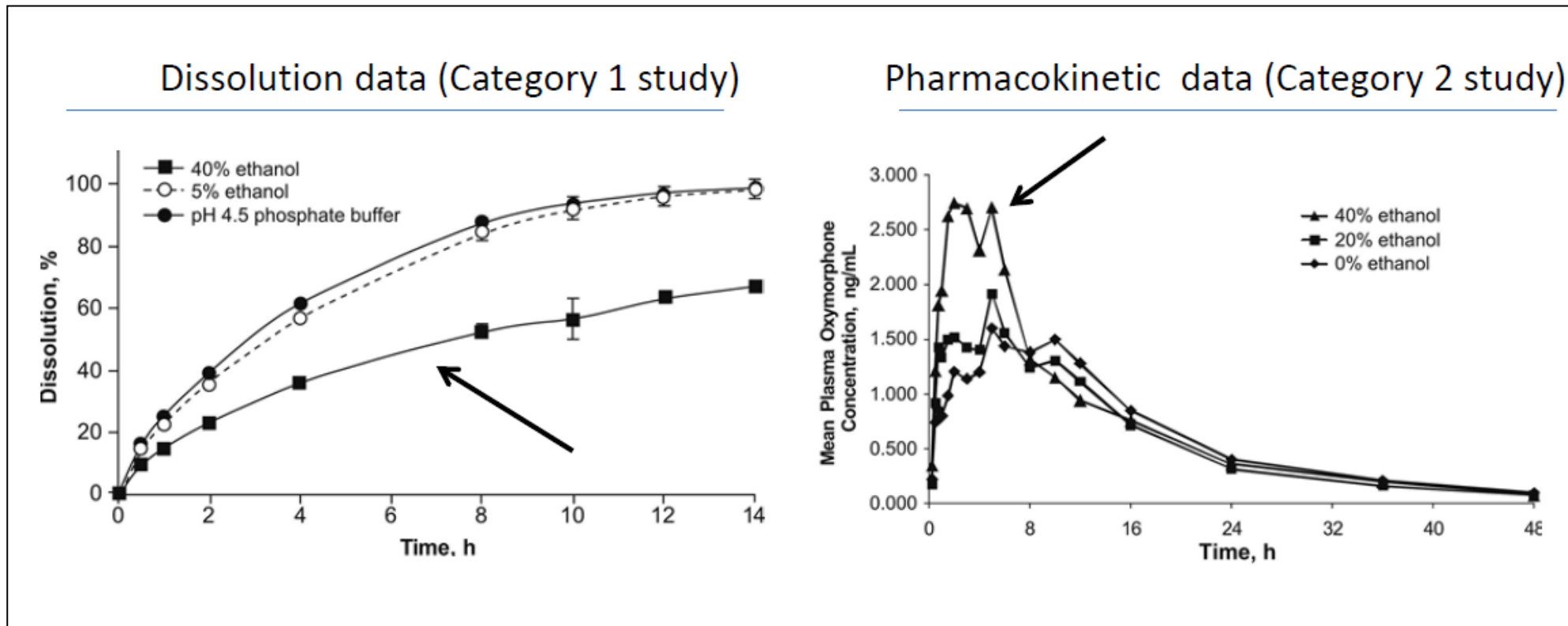
- 505(j) and “therapeutic equivalence”
 - demonstration of bioequivalence as the scientific bridge to safety and efficacy
 - based on years of data, evidence and confirmation of scientific principals
 - allows for product to be substitutable for the branded RLD
- Scientific bridge to demonstrate abuse-deterrent properties has not yet been established
- Ongoing efforts to standardize Category 1 testing
 - potential core set of Category 1 testing
 - further product/technology specific testing usually required to “take a product to defeat”
- Because of unknown/inconsistent correlations across different categories of AD testing, additional research needs identified in final AD Opioid Guidance (April 2015)
 - correlation between Category 2 pharmacokinetic (PK) data and Category 3 pharmacodynamic (PD) outcomes from clinical abuse potential studies

AD Opioid Development: Category 1 Studies

- Branded products have required an iterative approach based on proprietary technologies
 - standardized approach may not demonstrate full extent of AD properties of the RLD
 - iterative approach required to test a product to failure; involves extensive laboratory testing, with results informing further Category 1 experimental design
- Formulaic tier-based approach to Category 1 laboratory testing does not cover range of testing required based on experiences of BIWG
 - generics ADF guidance focused on physical/chemical barrier approach to abuse deterrence (hard-to-crush tablets with gelling properties)
 - for agonist/antagonist products, the impact of the antagonist on induction of withdrawal in the user cannot be demonstrated via category 1 study data
 - unidimensional; does not cover range of complexity, different approaches to AD, cumulative contribution of multiple factors for AD, nor uniqueness of current and emerging innovator technologies
 - identification of “discriminatory study conditions” is critical step but poorly defined
 - risk of approving generic AD products with non-equivalent abuse-deterrent properties
- Formulation + process = AD characteristics
 - not just based on formulation
 - important contributions from proprietary technologies and novel manufacturing processes
 - organoleptic properties
 - ***totality of the product***

IVIVC Models

- IVIVC models (based on multiple BA/BE clinical studies) in support of ANDA approvals
- An IVIVC correlation for abuse-deterrent properties has not been established
 - level of effort employed to defeat a product with *in vitro* testing another important factor

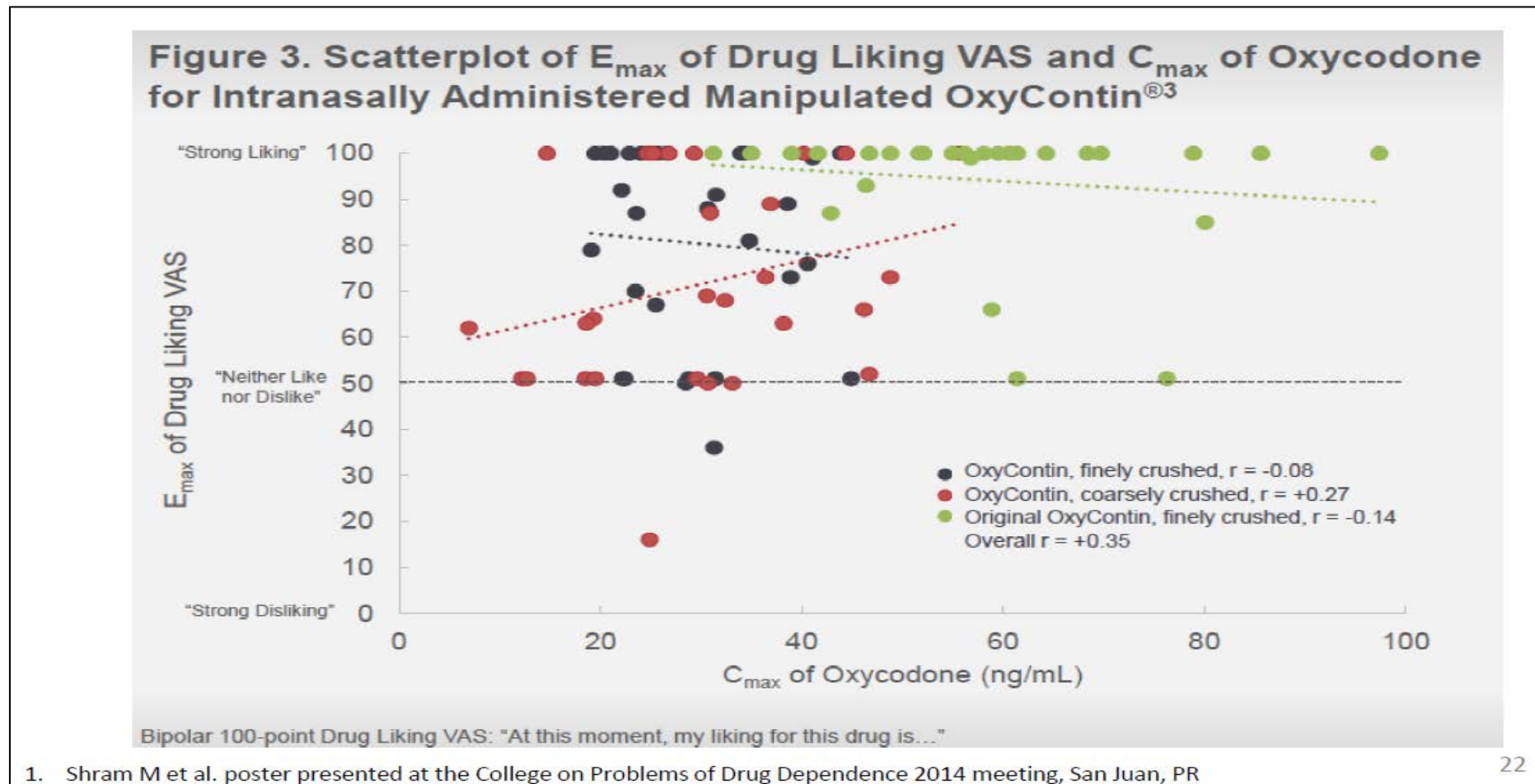


AD Opioid Development: Category 2 Studies

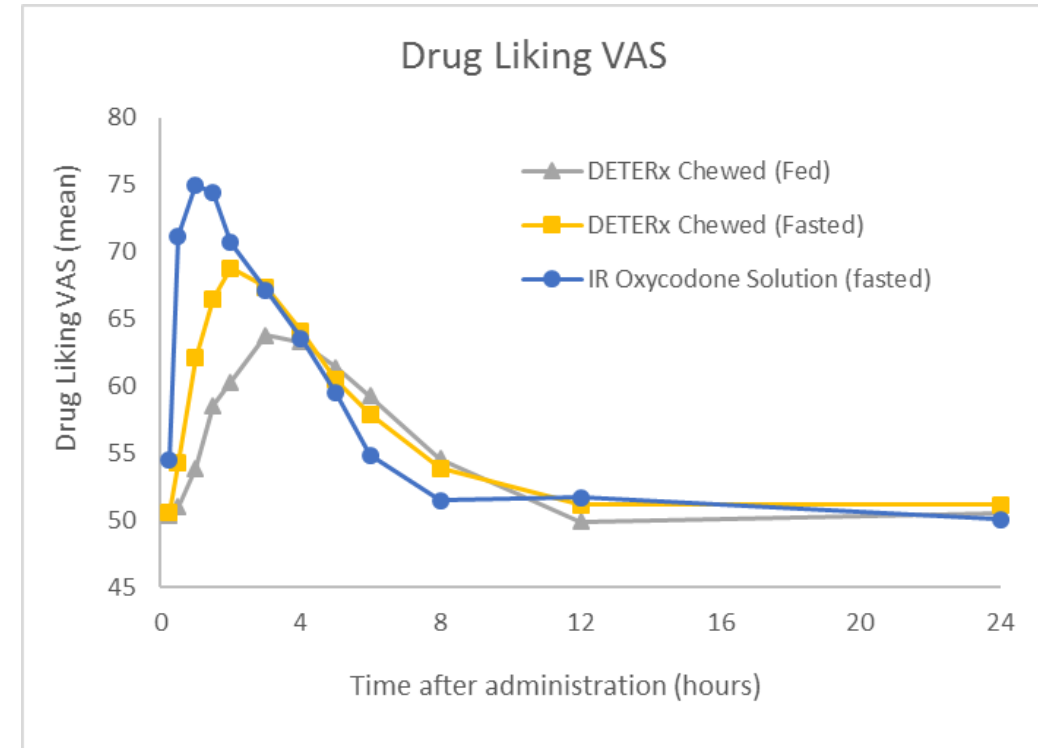
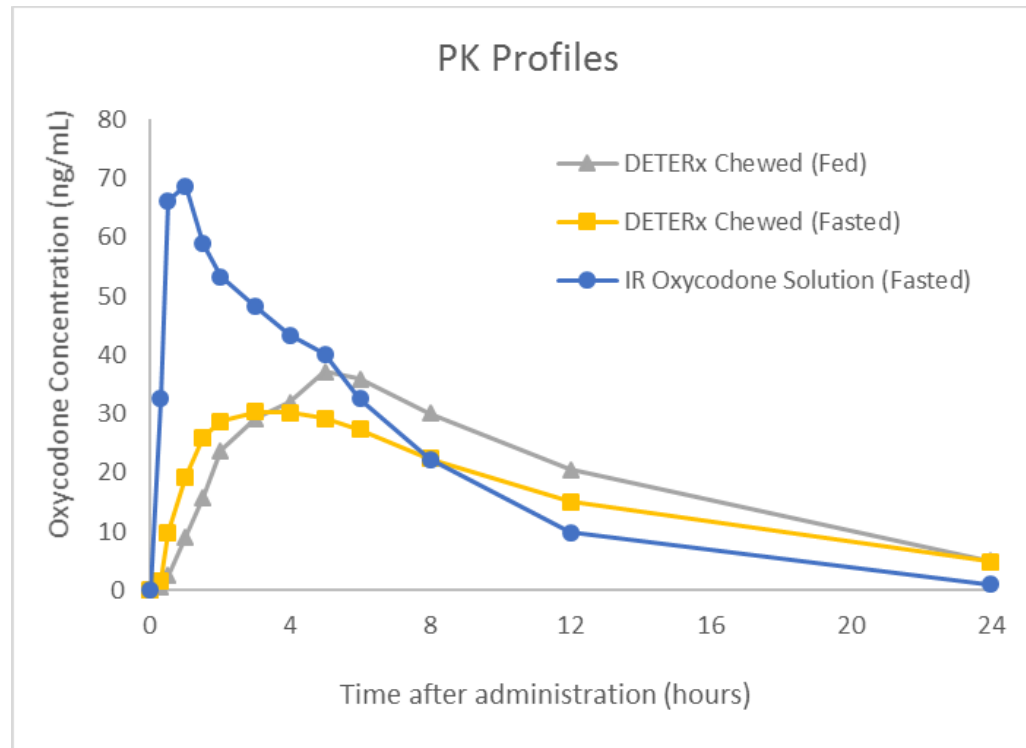
- IVIVC model as foundation for generic product approvals
 - demonstration of bioequivalence of intact product as bridge to safety and efficacy
- Important aspect of assessing abuse deterrence involves generating PK profile of manipulated product
 - comparison of generic to RLD in manipulated state
 - PK analyses beyond assessments for BE required (e.g., partial AUCs)
- AD properties represent unique ‘additional’ features of a product beyond a bioequivalent formulation; development programs run in parallel
 - demonstration of BE or phase 3 clinical program if pursuing 505(b)(2) pathway
 - conduct full battery of Category 1/2/3 AD studies
- Greater relevance when assessing all potential routes of abuse
 - lack of agonist/antagonist correlative data between antagonist blood concentration and impact on positive subjective measures; therefore Category 3 clinical data needed
 - Oral route – impact of chewing
 - Intranasal route
 - effect of particle size, weight, shape, and density as well as gelling properties
 - unique characteristics of other types of physical/chemical barrier technologies
 - metabolism of prodrug product via non-oral route

AD Opioid Development: Category 2/3 Studies

- Correlation between Category 2 PK data and Category 3 PD drug liking data complex and inconsistent based on BIWG experience
- Quantitative assessments not always predictive of qualitative outcomes



AD Opioid Development: Category 2/3 Studies



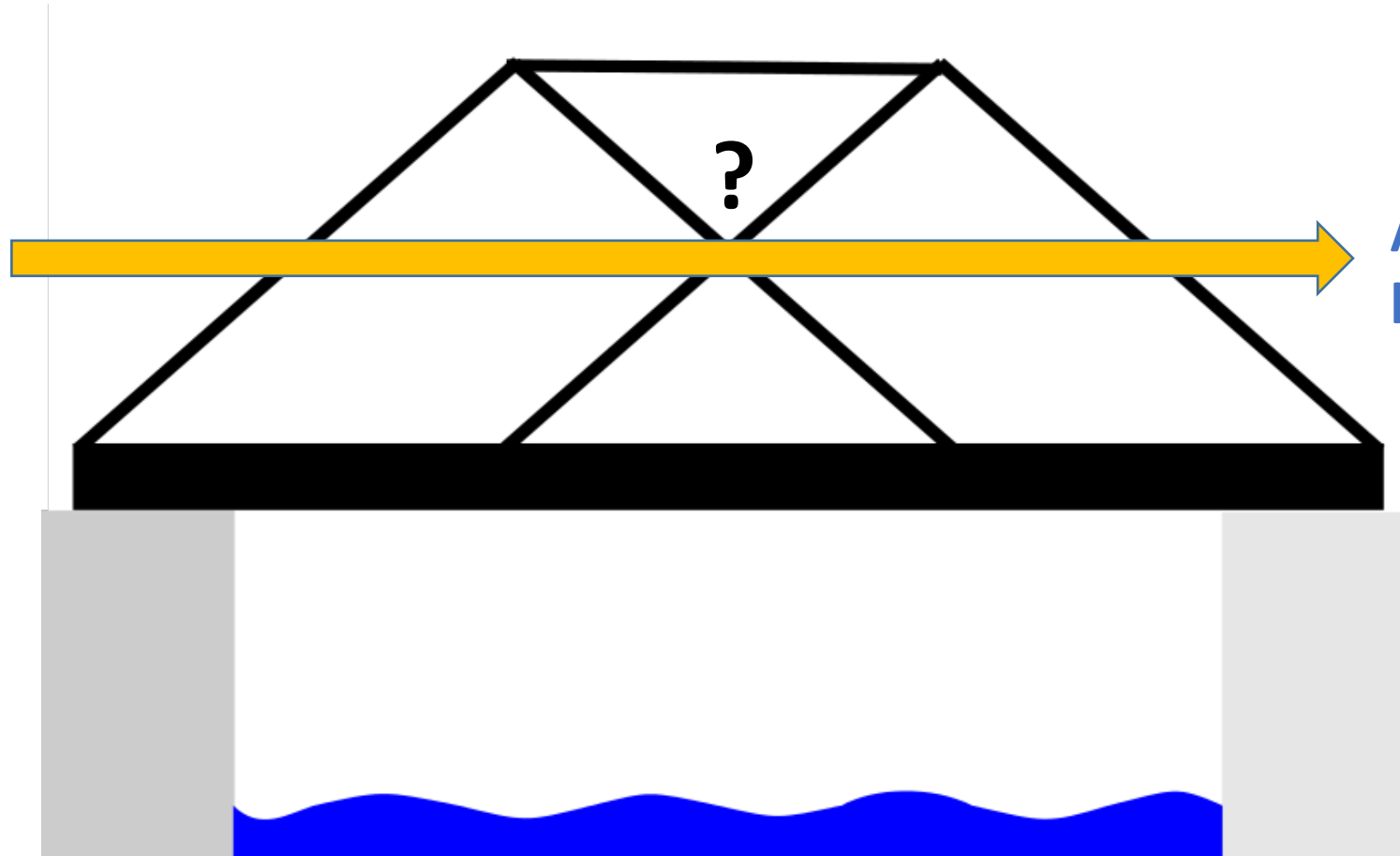
- Category 2 / Category 3 correlation example via oral route
 - although maximum plasma exposure (C_{max}) occurred following chewing in fed state, chewing in the fasted state produced greater drug liking

Cumulative Criticality of Abuse-Deterrent Attributes

- Each ADF has multiple attributes that may contribute to deterring abuse
- For example, for a particular AD product, the factors that may contribute to deterring nasal abuse may include...
 - Time and effort required to attempt to manipulate product and get into abusable form
 - Resistance to particle size reduction → yield of particles amenable to snorting
 - Mass of dosage form
 - Rate of hydration of gelling polymer
 - Extent of hydration of gelling polymer
 - Irritant properties of any components (even if not added as an irritant)
 - Presence of antagonist API upon manipulation
- Cannot separate the contribution of each particular attribute
- All contribute to the cumulative effect – deterring abuse

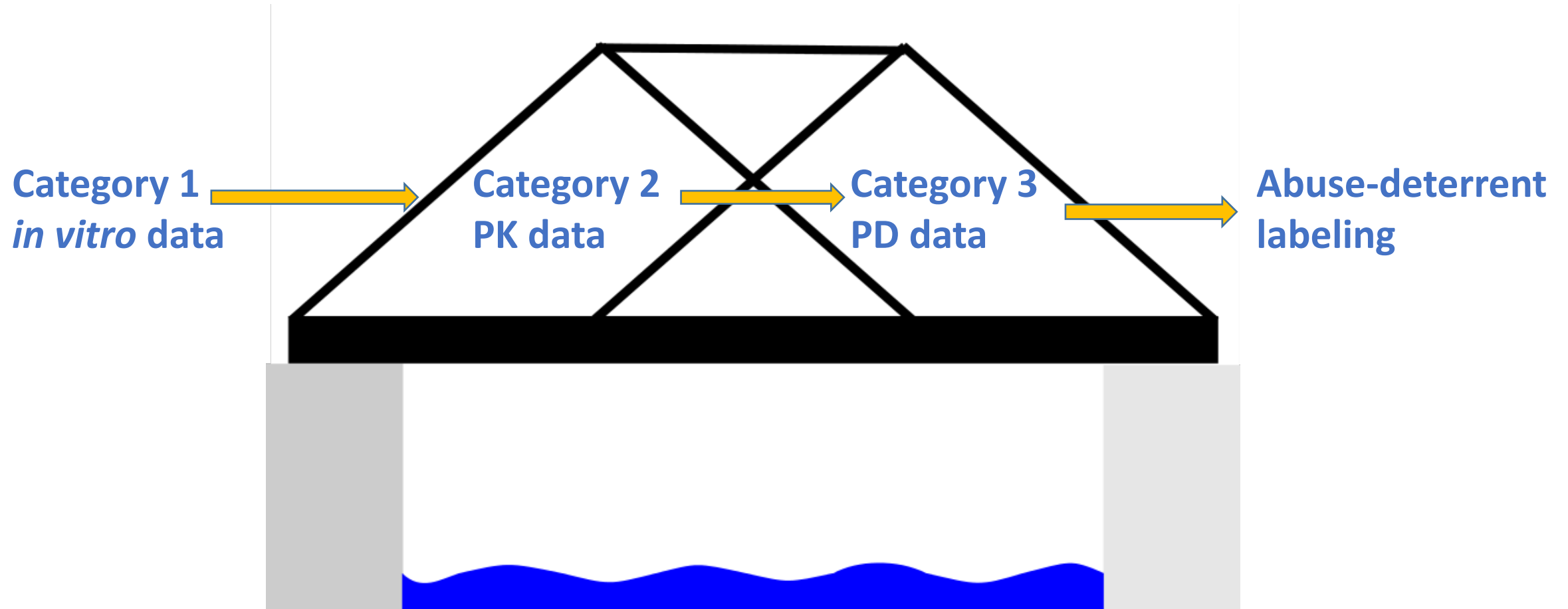
Scientific Bridge to Abuse Deterrence not Established

Category 1
in vitro data



Abuse-deterrent
labeling

Scientific Bridge to Abuse-Deterrent Labeling



Generics ADF Guidance: Product Specific Approach

- Regulatory requirements for various generic products for which additional clarity is needed
- Provide specific recommendations for testing based on unique features of the product, route of administration, etc.
- May require clinical data or other testing to demonstrate therapeutic equivalence if demonstration of bioequivalence is inadequate or not possible
- Examples
 - Topical dermatologic products^{1,2}
 - not intended for systemic absorption; cannot generate *in vitro* dissolution data or measure PK data
 - years of research to identify surrogate markers for efficacy
 - Fentanyl patch³
 - BE study required
 - other *in vivo* testing required to assess critical performance attributes (e.g., adhesion, irritation/sensitization safety study)
- In 2014, GIWG proposed that “FDA should develop the ADF requirements within each product specific BE guidance”⁴
 - guidance should clarify when generics should submit ANDA vs. 505(b)(2) application

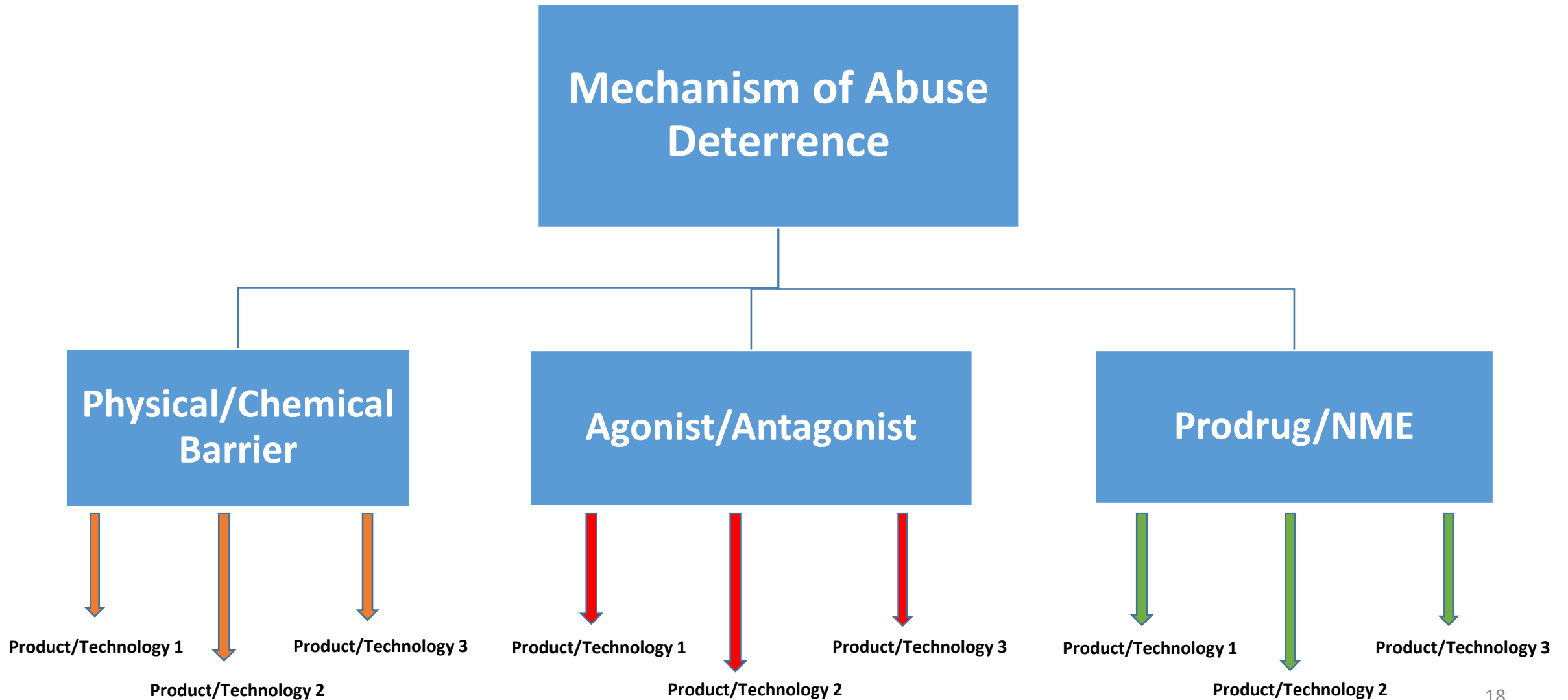
1. Nakar Y. *Pharm Research* 2010.

2. Shah VP et al. *Skin Pharmacol Appl Skin Physiol*. 1998.

3. FDA Draft Guidance on Fentanyl; Film, Extended Release, Transdermal; revised Oct 2016.

4. Recommendations from the Generic Industry Working Group for Regulations of Abuse-Deterrent Opioid Formulations; Development and Regulation of Abuse-Deterrent Opioid Medications, FDA Public Meeting; 30-31 Oct 2014.

Generics ADF Guidance: Mechanism-Based Approach



Concluding Remarks

- BIWG agrees with the goal of the generics ADF guidance and recognizes its importance in addressing the opioid crisis
- Common goal should be to advance the field in order to transition the market so that all opioids are in an abuse-deterrent formulation
- BIWG is committed to working with FDA and academia to advance the science of abuse-deterrent opioid development and identify path forward for generic AD opioids

Concluding Remarks (2)

Based on the state of the science, the following is the position of the BIWG on the generics ADF guidance:

- In its current form, does not adequately address what is required to demonstrate AD properties through all relevant routes of abuse
- Does not cover extent of Category 1 testing required, address complexity of different AD mechanisms, or the range of current and emerging technologies
- Category 1, 2 & 3 abuse-deterrent data still necessary to demonstrate that a generic product “is no less abuse-deterrent than its reference listed drug (RLD) with respect to all potential routes of abuse ”
 - Section 9.2 labeling should include the data generated for the generic product
- ***Totality of the evidence*** important without an established scientific bridge to link either *in vitro* or PK data to a reduction in drug liking and other important PD outcomes
- Two potential paths forward
 - broader approach to the generics ADF guidance that reflects the current state of the science and accounts for full range of established and emerging abuse-deterrent technologies
 - evolution of abuse-deterrent mechanism-based approach to development of product specific guidances that identify testing required for each product based on its unique technology and mechanism of abuse deterrence