

Development and Evaluation of Abuse Deterrent Opioid Formulations, Part 1

FDA meeting on ADF
30 October 2014

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On behalf of the Branded Industry Working Group

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 - Collegium Pharmaceutical
 - Egalet Corporation
 - Endo Pharmaceutical Inc
 - Grunenthal
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Financial disclosure

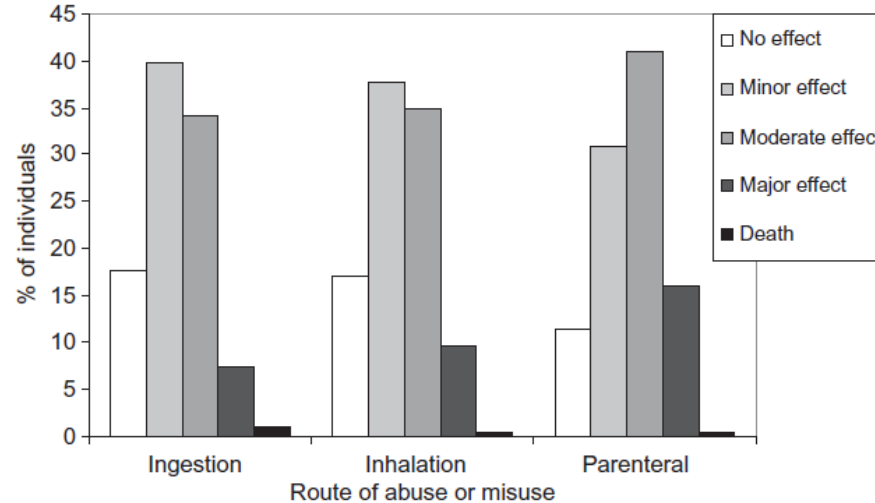
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Content

- Introduction
- Critical performance attributes
- Limitation of currently available abuse deterrent technologies and incremental improvements
- Evaluation of new abuse deterrent technologies

Introduction

- Oral abuse of prescription opioids is most prevalent¹
- Non-oral abuse is also common among opioid abusers and patterns of prescription opioid abuse vary between opioids and formulations^{1,2}
- Non-oral abuse of opioids (intranasal or intravenous) is associated with more severe adverse outcomes than oral abuse¹



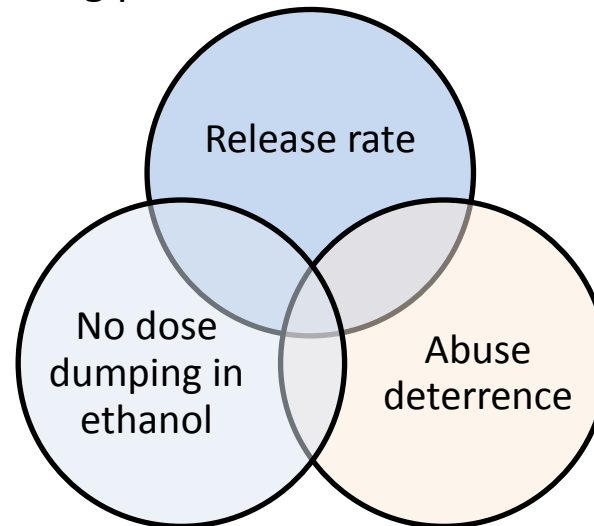
Notes: Data courtesy of Richard Dart and Elise Bailey; RADARS® System Poison Center Data, 2007-2008; Rocky Mountain Poison & Drug Center, Denver Health, Denver, Colorado.

1. Katz N et al, 2011 *Am J Drug Alcohol Abuse*; 37(4):205-17
2. Butler SF et al. 2011 *Harm Reduct J*; 8 (29): 1-17.

Abuse deterrent products

- Abuse deterrent formulation (ADF) products must have all of the attributes of the non-ADF dosage form
 - Available approved and consistent raw materials
 - Chemical and physical stability
 - Robust and efficient manufacturing process

Extended release
formulation



- Goal of abuse deterrent products:
 - To limit access or attractiveness of the highly desired active ingredient for abusers while assuring these products release the medication as designed to insure efficacy and safety for patients.

FDA question

- Please comment on what performance attributes should be considered “critical” in assessing whether and to what extent a formulation effectively deters abuse.... How can these performance attributes be quantified and linked to their impact on abuse deterrence? Please comment on the amount of time delay that should be considered significant and the basis for your recommendation.

Identification of critical performance attributes

- Evaluation of abuse deterrence should reflect abusers' behaviors.
 - A larger bolus dose and faster delivery mode is often the desired goal
 - Abusers who manipulate the formulations likely prefer fast and easy methods of tampering for oral and non-oral administration
- Critical ADF performance is understood as the impact on the ability to prepare the product for abuse and/or reduction of the drug liking when administered by one or more routes.
- Useful metrics for determining critical attributes:
 - **Time** required to manipulate
 - **Work** effort required
 - number of steps, difficulty of manipulation, availability and types of tools and reagents needed
 - **Reduction** in drug liking
 - amount of drug extracted, rate of onset and bioavailability after tampering, release of an aversive agent or antagonist

Example of critical performance attributes assessment

- In vitro assessment by experienced drug abusers can provide preliminary information about critical attributes for the specific ADF approaches¹⁻³
 - 10 min is the average estimate of the maximum time abusers were willing to spend tampering with medication but there was a great variability in the results¹⁻³
 - Amount of time and work abusers are willing to spend to manipulate with the formulation might depend on their motivation and experience, novelty of the technology

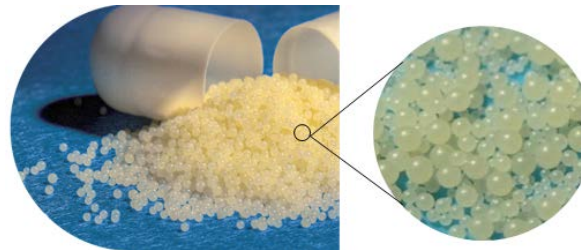
The physical and chemical methods used in sponsor designed in vitro studies should simulate prevalent procedures used by drug abusers, and anticipate more sophisticated "adaptive" procedures that the sponsor and FDA feel reasonably simulate practices that may emerge within the abuse community

FDA question

- Please comment on the limitations of currently available ADF technologies and what next-generation technologies or products might be able to overcome these limitations and provide improved protection against abuse and misuse. Comment on:
 - Development of iterative improvements in ADF technologies for solid oral dose forms of opioids
 - Development of ADF technologies for non-solid oral dosage forms

Abuse deterrent technologies

- FDA Draft Guidance for Industry: Abuse Deterrent Opioids- Evaluation and Labeling¹ has identified 6 approaches to abuse deterrence
 - Physical/Chemical barrier
 - Agonist/Antagonist combinations
 - Aversion
 - Delivery System
 - Pro-drug
 - Combinations



Review of currently available medications with abuse deterrent features

- Currently available ADF technologies
 - Physical/Chemical barrier
 - Polyethylene oxide matrix (e.g., OxyContin*, Opana ER)
 - Agonist/Antagonist combinations
 - Combination with available naloxone (e.g., Targiniq ER*, Suboxone)
 - Bead formulation with sequestered naltrexone (e.g., Embeda*)
 - Aversion / Combination
 - Combination with nasal irritants (e.g., Oxecta)

* products with ADF label according to the FDA Draft Guidance for Industry: Abuse Deterrent Opioids- Evaluation and Labeling (January 2013)

Advantages and limitations of available medications with abuse deterrent features

- Advantages of ADFs
 - Generally reduced abuse potential after non-oral administration (intranasal and intravenous)¹⁻⁵
 - Some show reduced abuse potential after oral administration (chewed or intact)⁵⁻⁷
 - Preliminary epidemiological data suggest that introduction of the reformulated products is associated with decrease in rates of abuse, diversion and death⁸⁻¹²
- Limitations of currently available ADF technologies
 - Potential for technologies to be overcome by manipulation to varying degrees for alternative routes of administration
 - Administration of multiple doses orally is still possible
 - Patients may potentially experience unintended consequences

1. Setnik et al. 2013 *Pain Res Manag*; 18(4): e55-62
2. Webster LR et al. 2011 *Drugs R D*; 11(3): 259-75
3. Colucci SV et al. 2014 *Clin Drug Investig*; 34(6):421-9
4. Schoedel KA et al. 2012 *J Opioid Manag*; 8(5):315-27

5. Taginiq ER label referenced 10/27/2014
6. Stauffer J et al. 2009 *Clin Drug Investig*; 29(12): 777-90
7. Setnik B et al. 2013 *Pain Med*; 14(8): 1173-86
8. Butler SF et al. 2013 *J Pain*; 14(4): 351-8

9. Coplan PM et al. 2013 *Pharmacoepidemiol Drug Saf*; 22(12): 1274-82
10. Havens JR et al. 2014 *Drug Alcohol Depend*; 139: 9-17
11. Sessler NE et al. 2014 *Pharmacoepidemiol Drug Saf*; Jun 11
12. Severtson SG et al. 2013 *J Pain*; 14(10): 1122-30

Review of ADF technologies under development

- Both oral and non-oral ADF technologies are under development
 - Physical/Chemical barrier
 - Viscoelastic fluid matrix
 - Hydrophobic matrix beads
 - Injection molding technology
 - Aversion / Combination
 - Combination with emetic agents
 - Delivery System
 - Depot injectable and sustained release implants
 - Controlled packaging (films and solutions)
 - Deactivating systems (transdermal patches)
 - Pro-drug/new molecular entities
 - In vivo release of active moiety governed by enzymatic conversion or other endogenous process
 - New chemical entity with inherent abuse deterrent characteristics

Incremental improvements in ADF technologies for solid oral dose forms

- Incremental improvements should address the limitations of current ADF technologies for example by
 - Increasingly complex physical barrier systems (e.g., use of new polymers with unique properties or new manufacturing processes)
 - Use of other antagonists or aversive agents
 - Combination of existing approaches
- Technologies under development might offer incremental improvement

Incremental advances in abuse deterrence should be supported and further discussion between stakeholders is required to define incremental improvement

FDA question

- Please comment on how FDA should adapt and expand its testing methodologies as new abuse deterrent technologies become available. Are there any specific emerging technologies that might require new types of testing?

Current evaluation of ADFs

- FDA Draft Guidance for Industry: Abuse Deterrent Opioids- Evaluation and Labeling identifies four types of studies to comprehensively evaluate ADFs
 - Pre-marketing:
 - Laboratory-based in vitro manipulation and extraction studies (Category 1)
 - Pharmacokinetic studies (Category 2)
 - Clinical abuse potential studies (Category 3)
 - Post-marketing (Category 4)
- ADF labeling (Tier 1 to 4) reflects the level of evidence collected to demonstrate the ADF characteristics
 - To obtain any tier ADF label data from Categories 1, 2 and 3 are generally required
 - Category 2 or 3 data (or both) may be needed to ensure that Tier 1 label is not misleading

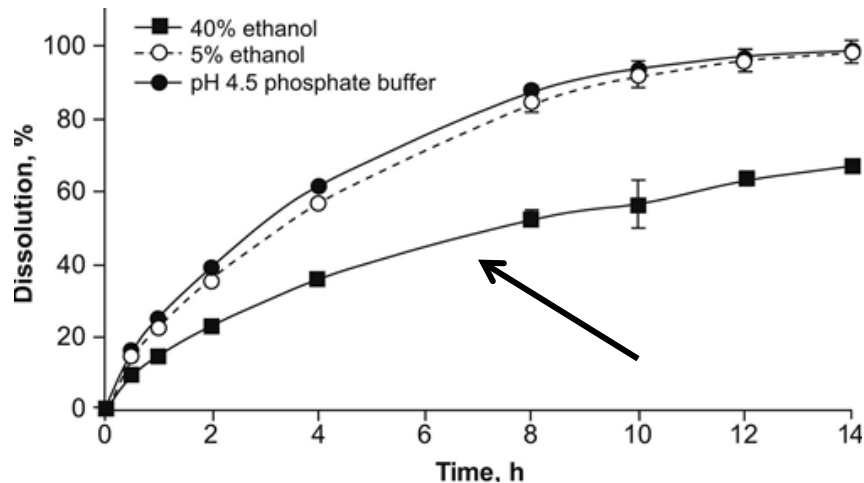
Evaluation of abuse deterrent formulations

Study type	Advantages	Limitations
Category 1, in vitro studies	<ul style="list-style-type: none">• Tailored and product specific testing	<ul style="list-style-type: none">• In vitro/ in vivo abuse deterrence correlation is not well established¹<ul style="list-style-type: none">• Differences observed in in vitro tests might not correlate with clinically important abuse deterrence (false negative findings)• Effects unrelated to opioid exposure might impact subject's experience

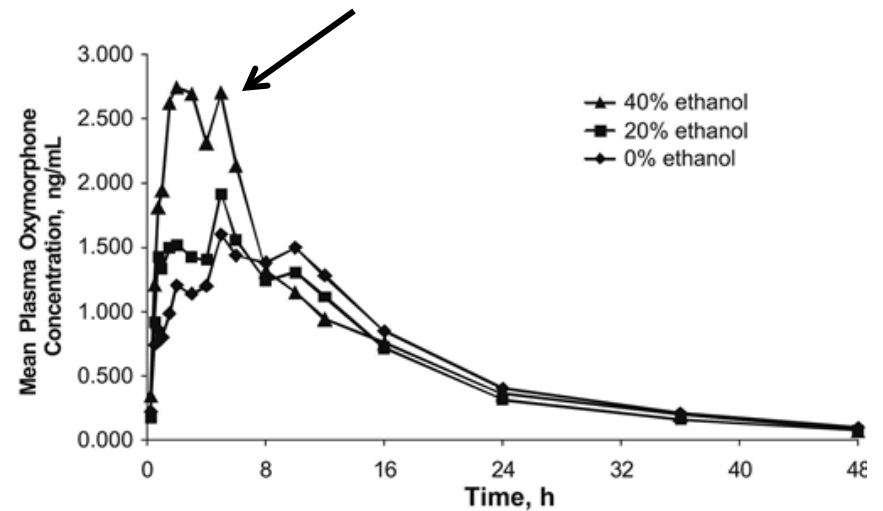
1. Fiske WD et al. 2012. J Pain. ; 13(1):90-9.

In vitro study results might not always predict in vivo abuse deterrence

Dissolution data (Category 1 study)



Pharmacokinetic data (Category 2 study)



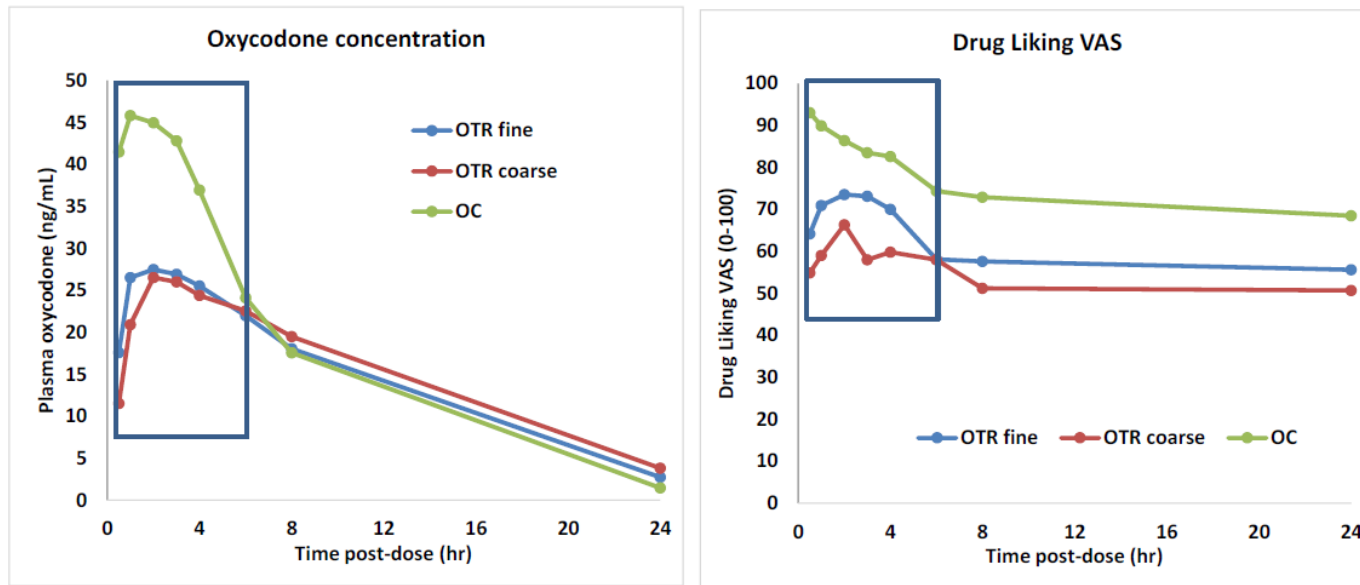
Evaluation of abuse deterrent formulations

Study type	Advantages	Limitations
Category 2, PK studies	<ul style="list-style-type: none"> Characterizes bioavailability of manipulated formulation administered via specific route 	<ul style="list-style-type: none"> Relationship between PK and abuse potential study results is not well established¹⁻⁵ <ul style="list-style-type: none"> Effects unrelated to opioid exposure might impact subject's experience Drug manipulation method can impact study outcomes Conducting such studies might not always be feasible

1. Shram M. 2013, oral presentation at ADF Science Meeting, North Bethesda, MD
2. Walsh S. 2013, oral presentation at ADF Science Meeting, North Bethesda, MD
3. Harris SC et al. 2014. *J Clin Pharmacol.*; 54(4):468-77
4. Harris et al, poster presented at PainWeek 2014, Las Vegas, NV
5. Sellers et al, poster presented at the American Academy of Pain Medicine meeting 2009, Honolulu, HI

Opioid exposure might not always predict subjective effects¹

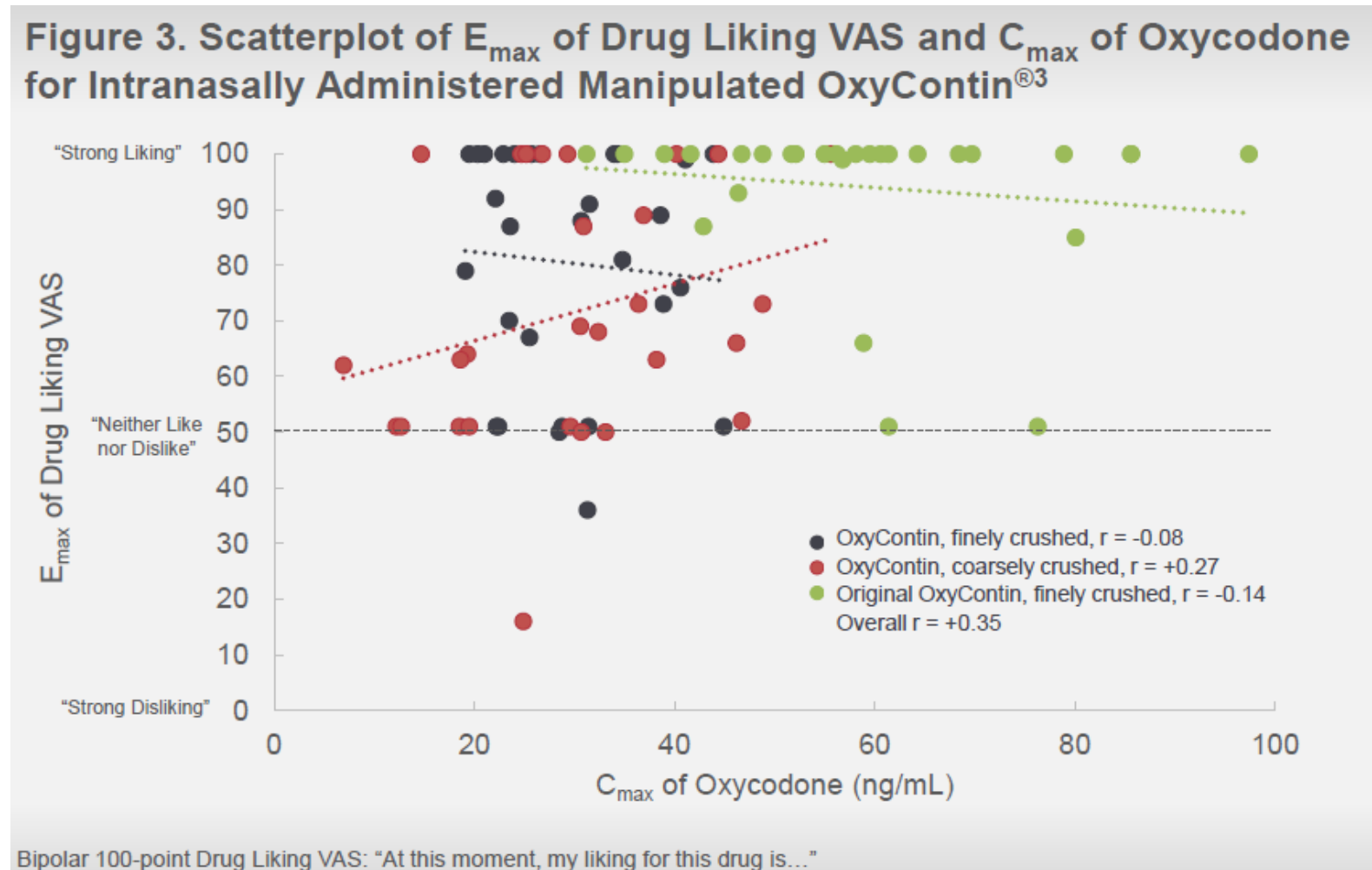
Reformulated OxyContin (OTR) evaluation after intranasal administration in comparison to the original OxyContin formulation (OC)



Effects unrelated to drug exposure can impact experience (at the moment and overall)

Courtesy of Purdue Pharma; Perrino et al., 2012 CPDD; Harris et al., submitted

PK/PD (subjective effects) correlations are generally modest¹



Evaluation of abuse deterrent formulations

Study type	Advantages	Limitations
Category 3, clinical abuse potential studies	<ul style="list-style-type: none"> Examines the interaction between manipulated drug product and subjective response of drug abusers 	<ul style="list-style-type: none"> Drug manipulation method can impact the study outcome Conducting such studies might not always be feasible
Category 4, Post-marketing studies	<ul style="list-style-type: none"> Ultimate demonstration of the ADF effectiveness 	<ul style="list-style-type: none"> Data sources directly measuring abuse are limited Formulation specific exposure can be difficult to determine For new market entrants it could take years or if not decades to collect sufficient data demonstrating epidemiological impact

Evaluation of testing methodologies for new ADF technologies

- In general, evaluation of new products should be based on the totality of Category 1, 2 and 3 data which are necessary to demonstrate the abuse deterrent qualities of these products
- Current flexible ADF assessment framework can accommodate new technologies under development
 - Pro-drug, rate limiting absorption
 - Injectable depot and sustained implant drug delivery
- Testing methods should be product specific and adjusted to accommodate new technologies
 - Sponsors must understand the strengths and weakness of their products
 - Manipulation method likely implemented by abusers should be used for Category 2 and 3 assessments

Evaluation of testing methodologies for products referencing current ADF

- In general, evaluation of new products referencing current ADF should be based on the totality of Category 1, 2 and 3 data which are necessary to confirm the abuse deterrent qualities of the new product.
- ANDA ADF submissions should demonstrate non-inferiority to the approved ADF referenced product and provide the necessary data and information to allow thorough and comprehensive risk-benefit assessment by FDA.
- As general guidance, applicants of new ADFs should not be able to “carve out” sub-sections of an approved ADF label in case of referencing to the approved product.
 - The application must meet all performance attributes and routes of abuse covered by the referenced product.

Conclusions

- Critical abuse deterrence performance metrics include time and work effort required to manipulate formulation and reduction in drug liking.
- Incremental advances in abuse deterrence are important as this field is evolving; further discussion between stakeholders is required to define incremental improvement
- The adaption and expansion of testing methodologies should be product specific. In general, evaluation of abuse deterrence for new ADF products should be based on data from Categories 1-3 studies to ensure rigorous testing and appropriate interpretation.