Branded Industry Perspective on Standardizing *In Vitro* Testing

FDA 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

Financial Disclosure

- Employee of Collegium Pharmaceutical, Inc.

Disclaimer

- The Branded Industry Working Group included representatives from the following 10 companies:
  - Acura Pharmaceuticals, Inc.
  - Collegium Pharmaceutical, Inc.
  - Depomed, Inc.
  - Egalet Corporation
  - Endo Pharmaceuticals Inc.
  - Grunenthal USA, Inc.
  - KemPharm, Inc.
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  - 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.

Outline of Presentation

- Review current status of guidance on *in vitro* testing and AD technology
- Benefits and drawbacks of standardization in relation to evolving science of abuse-deterrence
- Perspectives on standardization proposals in Innovator and Draft Generic guidances
- Conclusions and recommendations

Innovator and Draft Generic Guidances Include Paradigms for *In Vitro* Testing of ADFs

- April 2015 Final Guidance, "Abuse-Deterrent Opioids — Evaluation and Labeling" [Innovator Guidance]
- March 2016 Draft Guidance, "General Principles for Evaluating the Abuse Deterrence of Generic Solid Oral Opioid Drug Products" [Draft Generic Guidance]
- Both guidances outline testing in the following areas:
  - Mechanical manipulation
  - Extractability (intact and manipulated products)
  - Injectability/Syringeability
  - Assessment for nasal administration
  - Smoking studies

Innovator and Generic Guidances Differ in Approach

Innovator guidance

Flexible, adaptable approach to testing; stresses totality of evidence

- Iterative testing paradigm whereby formulation is tested under increasingly more rigorous conditions relative to appropriate comparator
- Provides examples of tools, solvents, but generally few specifics
- *In vitro* results used to design *in vivo* PK and human abuse potential studies

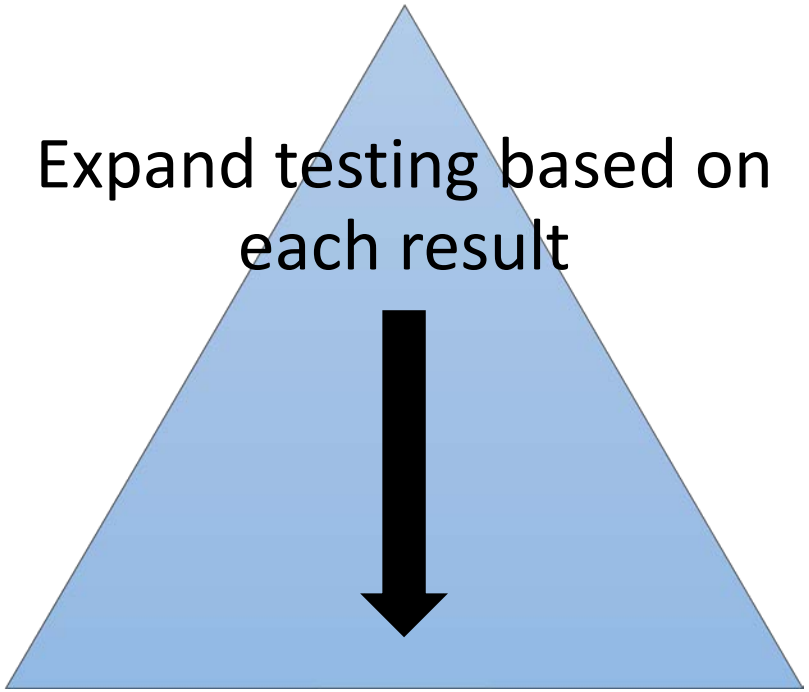
Draft Generic guidance

Rigid, linear approach to testing

- Tier-based testing paradigm; “discriminatory” conditions are established for product by comparison to a non-AD comparator
- Focused on testing of hard-to-crush tablets; other approaches not adequately covered
- Many specifics provided including tools, solvents, times

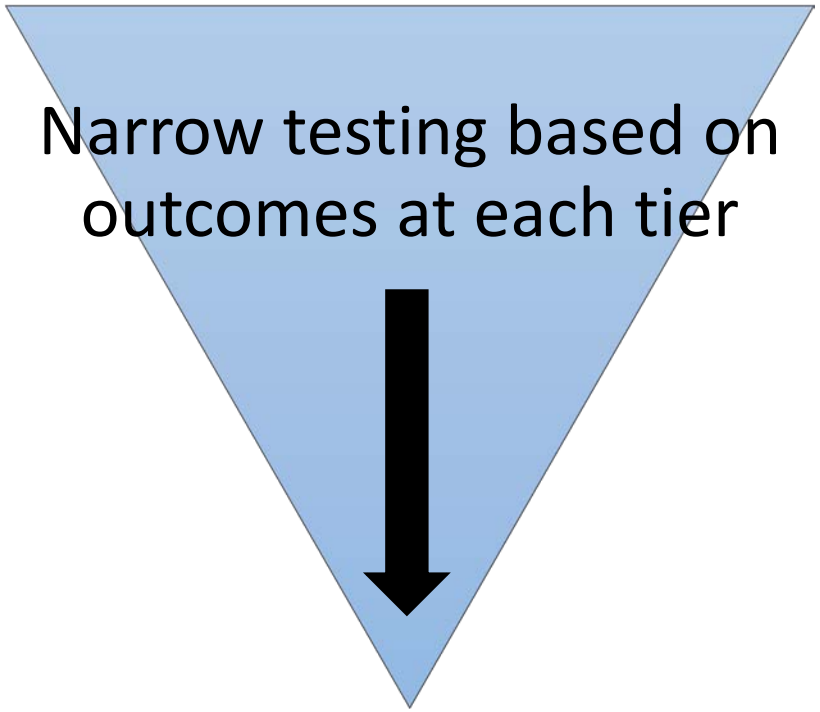
Iterative versus Tier-based Approach

Innovator guidance:
Iterative



Test new product to establish failure modes

Draft Generic guidance:
Tier-based



Match RLD in limited number of tests

Benefits and Drawbacks of Standardization

Potential benefits

- Clear expectations for sponsors (Innovator and generic)
- Facilitates review by Agency and Advisory Committees
- Improves interpretation of results
- Reduction of testing that does not provide meaningful data

Potential drawbacks

- Potential weaknesses of formulations not adequately explored
- Testing protocols quickly outdated with new product innovations
- Impractical to design studies to adequately characterize unknowns of future technologies
- Oversimplifies complexity of AD features; risk of future formulations with less rigorous AD properties

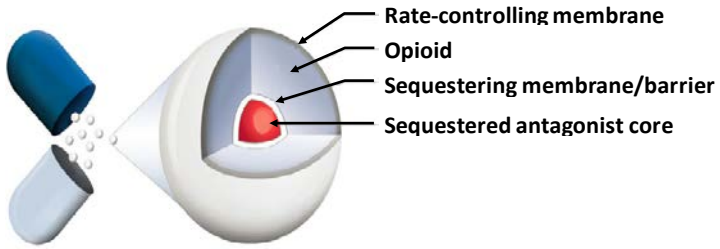
FDA-Approved Labeling Describing Abuse-Deterrent Properties Consistent with Innovator Guidance

ER Opioids		
Approach	**Product**	**Active Substance(s)**
Physical/Chemical Barriers	OxyContin	Oxycodone
	Hysingla ER	Hydrocodone
	MorphaBond	Morphine
	Xtampza ER	Oxycodone
Agonist/Antagonist	Targiniq ER	Oxycodone/Naloxone
	Embeda	Morphine/Naltrexone
	Troxyca ER	Oxycodone/Naltrexone

Approved Products Span a Diverse Range of Technologies

- Different approaches to AD (barrier versus antagonist)
- Physical forms – monolithic tablets and multiparticulates
- Inactive ingredients – gelling polymers, waxy materials, insoluble coatings
  - Range of solubility, melting points, physical properties

Hardened tablet



Pellets in a capsule
(sequestered antagonist core)

Waxy microspheres in a capsule

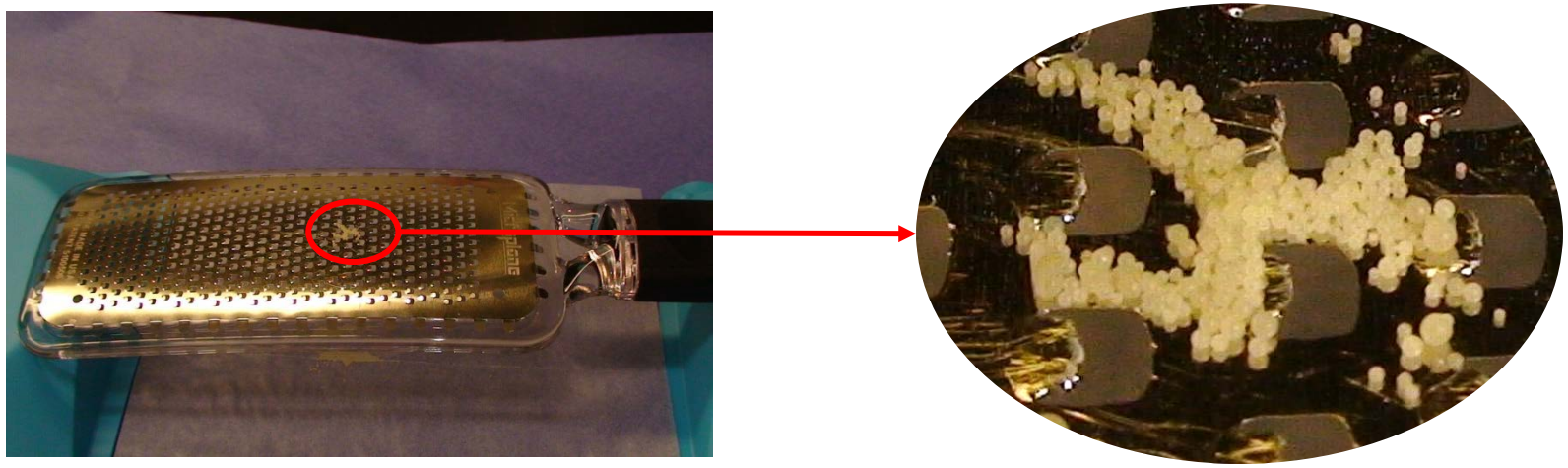
Products in Development Introduce Additional Complexity

- Range of approaches within physical/chemical barrier category
  - Capsules containing viscous liquid
  - Coated particles embedded in gelling matrix
  - Injection molded tablets
- Other approaches to abuse deterrence described in Innovator guidance
  - Aversive agents
  - Prodrugs
  - Combinations of approaches
- Future innovations ??

Overly specific testing protocols don't cover diversity in current ADF's; future ADFs will only add to this complexity

Limitations of Standardization: Mechanical Manipulation (Draft Generic Guidance)

Generic Guidance Paradigm	Issues Identified
• 3 tools included • All ways to “chop” formulations	• No tools to pulverize (e.g., hammer, pill crusher, mortar & pestle) • 2 of 3 manipulations (cutting, grating) not applicable to multiparticulates



Scale of kitchen grater relative to microsphere formulation

Limitations of Standardization: Mechanical Manipulation (Draft Generic Guidance)- 2

Generic Guidance Paradigm	Issues Identified
• Single tool manipulation only • Testing up to 5 minutes	• Hard-to-crush tablets in development that may require multi-tool procedures to crush • Some technologies sensitive to “over crushing”; times shorter than 5 minutes may be optimal

- Appropriate optimization of mechanical manipulation critical; manipulation employed in <u>all</u> subsequent *in vitro* and *in vivo* (Cat 2 and Cat 3) studies

Limitations of Standardization: Abuse by Insufflation (Draft Generic Guidance)

Generic Guidance Paradigm	Issues Identified
• Mill for 5 minutes (with and without thermal pre-treatment) • Alternative crushing applied if milling does not produce fine particles (less than 500 μm) • If <10% mass reduced to fine particles, not suitable for insufflation	• No requirement to use best method (assumes milling best method) • Possible to by-pass *in vivo* study with sub-optimal crushing • For generics, possible to conduct PK study with non-discriminatory method

Metric	Product A*	Product B*
	% particles <500 μm	
Milling (selected as discriminatory)	15%	15%
Alternative crushing method X	15%	70%

**Note: theoretical example*

Limitations of Standardization: Abuse by Injection (Draft Generic Guidance)

Generic Guidance Paradigm	Issues Identified
• Range of parameters provided • Discriminatory conditions established within range • Testing at discriminatory conditions only	• Selection of discriminatory conditions can influence testing • Does not require investigating full range of relevant parameter space • See theoretical example below

- Consider gelling tablet versus a non-ADF control crushed at RT; statistically less extraction found at 2 mL for gelling tablet
- 2 mL selected as “discriminatory”, by-passing testing at more rigorous volumes of 5 mL and 10 mL
  - In case of generic, condition established for R vs C may not be discriminatory for R vs T

Limitations of Standardization: Extractability (Draft Generic Guidance)

Generic Guidance Paradigm	Issues Identified
• Limited discussion of requirements for agonist/antagonist products • Determine ratio of % extraction of agonist and antagonist in limited number of solvents	• Ratio of agonist/antagonist not only relevant metric • Biphasic solvent testing relevant to separation of agonist/antagonist

Metric	Product A*	Product B*
Ratio extracted (% agonist/% antagonist)	0.4	0.4
% opioid agonist extracted	90%	20%

Ratio alone does not determine product desirability (drug liking) or other subjective measures

**Note: theoretical example*

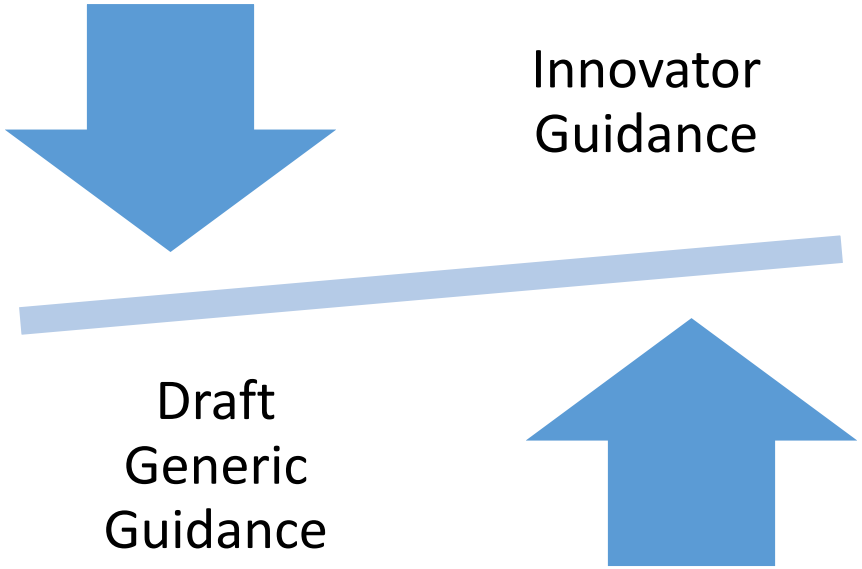
Limitations of Standardization: Additional Examples from Draft Generic Guidance

Type of Study	Generic Guidance Paradigm	Issues Identified
Abuse by Injection	• Extractability in small volumes of water • Syringeability through various sized needles	• No direct injection studies applying heating/melting for formulations that flow • Forcing through needles not applicable for formulations without gelling agents
Abuse by Ingestion (Extractability)	• Measure % opioid extracted	• No secondary procedures (filtration, dry off solvent, etc.) to determine if opioid concentrated/separated from inactive ingredients
Abuse by Ingestion (Dissolution)	• Specifies dissolution in 0.1N HCl to determine impact of manipulation	• For products with pH sensitive ingredients, 0.1N HCl may not be discriminatory

- Examples demonstrate difficulty in contemplating appropriate studies and parameters across an array of technologies

Standardization – Striking the Balance

- Establish balance between standardization and flexibility
  - Innovator guidance would benefit from additional specifics
  - Draft Generic guidance over specifies certain parameters; does not accommodate range of existing technologies or future innovations



Practical Approaches to Standardization – Recommendations

- May be possible to establish a "core" set of tests that evaluate certain AD features
  - Within core, parameters for each test can be standardized
  - Consider tailoring core to AD mechanism (e.g., different core tests for barrier and antagonist products)
  - Core should be supplemented with product specific tests (core is only the starting point)
- Monitoring of select AD properties on shelf-life should be driven by risk assessment and justified in pharmaceutical development report

Core *in vitro* tests

- Parameters (or ranges) specified for tests in each of following areas:
  1. Mechanical manipulation
  2. Extractability
  3. Injectability/Syringeability
  4. Particle size for Nasal Administration
  5. Vaporization
- Applicable tests determined based on mechanism of AD

Product Specific *in vitro* testing*

- Driven by product design, product specific knowledge
- Supplement core tests with additional parameters
- Examples – additional tools/combinations, pre-treatments, secondary extraction steps, etc.

Category 2 and 3 Studies*

- *In vitro* studies inform manipulations used in PK and human abuse potential studies

**For generics, requirements outlined in product specific guidance. Consider public health implications of disclosures*

Concluding Remarks

- Rationale and opportunity exists to incrementally increase level of standardization for *in vitro* testing
  - However, standardized tests must contemplate current and future range of ADF technologies
  - Several aspects of Draft Generic guidance lack flexibility
- Focused, concerted effort led by FDA needed to arrive at rational standardization recommendations
  - A Category 1 focus group with representatives from Industry, Academia and FDA has convened to explore and discuss potential of standardization (continue work of CCALC)
  - Additionally, an FDA working group on standardization may be beneficial
- As standardization is implemented, spirit of original guidance should not be lost
  - Iterative testing to establish robust abuse-deterrent properties
  - All sponsors should provide a totality of evidence supporting product abuse deterrence, including Category 1, 2 and 3 studies