

Vision for Standardizing In Vitro Testing to Evaluate Abuse Deterrence of Opioid Products

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Outline

- Scope
- Current State
- Vision
- Bridging the Gap: What Else is Needed for New and Generic Drugs?
- Examples
- Summary

Scope

- Scope: Testing of solid oral opioid drug products
 - At initial approval, and
 - Throughout product life cycle
- Standardizing In Vitro Testing
 - Input from this meeting, published guidance, the docket to the draft guidance on evaluating generic opioids, and other sources may be used to develop a future guidance recommending common in-vitro methods to evaluate NDAs and ANDAs for these products

Current State



Current State

- Guidance: “Abuse-deterrent Opioids – Evaluation and Labeling” (April 2015)
- Draft Guidance: “General Principles for Evaluating the Abuse Deterrence of Generic Solid Oral Opioid Drug Products” (March 2016) (OGD guidance)
- FDA Lab Experience
- External Research and Development Experience
- Other

Current State

- NDA versus ANDAs: Some similarities and differences regarding the assessment of AD properties
 - Pharmaceutical Equivalence
 - Not required for 505(b)(2) NDA, n/a for 505(b)(1) NDA
 - ANDA must be pharmaceutically equivalent to the RLD
 - Bioequivalence
 - Required for ANDAs and (b2) NDAs
 - n/a for (b1) NDAs

Current State

- NDA versus ANDAs: Some similarities and differences regarding the assessment of AD properties
 - Labeling
 - ANDA must match RLD with limited exceptions
 - NDA premarket data must show a product's abuse-deterrent properties can be expected to result in a meaningful reduction in that product's abuse to merit labeling

Current State

- NDA versus ANDAs: Some similarities and differences regarding the assessment of AD properties
 - Technological approach to AD
 - For ANDAs, proposed generic should use the same AD technology category as the RLD (e.g., within physicochemical, aversive, etc.); the OGD guidance provides recommendations for evaluating abuse deterrence relative to RLDs within the same category of abuse-deterrent technologies.
 - For example same physical chemical approach to resist crushing should be used but a different polymer may be used

Current State

- Both NDA and ANDA should meet certain standards for AD performance which include
 - Where feasible, assessment using similar standardized approaches
 - AD properties for claimed route(s)
 - Should address abuse across all routes
 - AD performance is not tested for through expiry
 - No bridging to assure AD performance is maintained throughout product lifecycle

Current State: Abuse-deterrent Opioids Evaluation and Labeling (April 2015)



- **Guidance anticipates evolving landscape**
 - Physical Chemical Barriers
 - Agonist antagonist combinations
 - Aversion
 - Delivery System
 - New Molecular Entities (NME) and Prodrugs
 - Combinations
 - Novel approaches

Abuse-deterrent Opioids – Evaluation and Labeling (April 2015)



- Premarket Studies

- Category 1 (*in vitro* manipulation and extraction)

- Studies designed with specific physicochemical knowledge of the product and mechanism(s) used

- Studies consider abuser approaches and degree of effort required to defeat

- Includes heat and cold conditions

- Crushing, grinding, grating cutting, etc. manipulations

- Particle size Distribution (nasal)

Current State: General Principles for Evaluating the Abuse Deterrence of Generic Solid Oral Opioid Drug Products” (March 2016)



- **Summary**

- Decision tree / tiered approach
- Use of controls
- Compares results (T, R, and C) under discriminatory conditions where:
 - T is the test product in question,
 - R is the RLD or reference product, and
 - C is a control product for AD performance comparison

Vision

Vision

- Quantitatively Assess AD Properties in NDAs and ANDAs
 - Use standard methods based on OGD guidance that are relevant to methods of abuse
 - Provide AD performance criteria across all known routes of abuse
 - Better confidence that AD performance is maintained throughout shelf life and across product lifecycle for new drugs and generics
 - Is flexible enough to address product-specific issues and new AD technologies
- Integrate With Other Related Guidances
- Has Relevant Impact by Deterring Abuse

Vision

- Using “FP” to discuss “Failure Point” situations
- The FP may be considered to be the point where enough effort (as energy, knowledge, and time) has been applied to the AD product to defeat the AD mechanism so as to likely permit abuse against the AD claim
- FP determinations requires multiple considerations
 - If the AD approach is defeated (e.g., particle size reduction), is (or would) the result be “liked” if abused by various routes.
- Comparisons of FPs allow for an assessment of potential abuse scenarios when comparing products

Bridging the Gap towards the vision

Bridging the Gap

- Focused Scope: Solid oral AD opioid drug products
- Risk-based, Scientific Approach
 - Input from FDA, Industry, Academia, other stakeholders
 - Compare new drug product and appropriate comparator at failure point as well as at other points
 - Compare proposed generic drug products to RLD to assure generic does not fail when RLD demonstrates AD

Bridging the Gap

- Balanced in Practice
 - A mix of standardized approaches that are adaptable to product-specific situations
 - Assess under some standard conditions (TBD)
 - Assess the effort needed to reach failure (if so achieved or relevant)

What Else is Needed?

- Build on existing guidance documents
- Add failure point (FP) assessments
- Fullest testing during development to support AD claims at approval
- Determination of quality attributes that serve as relevant surrogates for AD performance over shelf life and which can support supplemental changes over the product's lifecycle.
- Statistical and sample size consideration
- Effective use of control and comparator products

Build on Existing Guidance

- Capture These Mechanisms of Abuse Deterrence
 - Physical / chemical barriers which reduce the ability to manipulate mechanically (e.g., crushing, extraction, etc.)
 - Agonist / antagonist combinations
 - Aversion substances
 - Prodrug
- Applied to These Approaches to Abuse
 - Oral
 - Insufflation
 - Injection
 - Smoking
- Tier based approach to evaluation

Examples

Product Manipulation

- Determine the (FP) to get a powder if at All Feasible
 - Determine mechanical approaches that find the FP
 - Crush, grind, mill, cut, grate, etc.
 - Effort necessary (time and energy) to get it
 - Is the material likely to be abused orally, by insufflation, injection, etc.
 - Pretreatment necessary (heat, cold, etc.)
 - FDA labs may also assess in some cases
 - If an aversive agent is used, is it easily separable?
 - If an antagonist is used, know the conditions that release it

Product Manipulation

- Determine the quality attribute(s) that can be tested at release and on stability to assure that AD performance is maintained throughout shelf-life and across the product's lifecycle.
- Determine those aspects of formulation, excipients, manufacturing, and container closure that are critical to assure that level of AD performance during the product's life cycle
 - ICH Q8(R2)-like approach
- FP approach may be combined with a tiered approach
- Conditions for aversive agents and antagonist need to be accounted for.

Extraction

- No Aversive Agent or Antagonist used
 - Determine FP extraction scenarios using listed solvents
 - Time, Temp, and other conditions necessary to reach the FP
- Aversive Agent or Antagonist is used
 - Determine FP scenarios using listed solvents and simple differential methods (future)
 - Time, Temp, and other conditions necessary to reach the FP

Extraction

- Determine the quality attribute(s) that can be tested at release and on stability to assure an acceptable FP is maintained.
- Determine those aspects of formulation, excipients, manufacturing, and container closure that are critical to assure that level of AD performance during the product's life cycle
 - ICH Q8(R2)-like approach*
- FP approach may be combined with a tiered or decision tree based approach

Extraction and ICH Q8(R2)

- ICH Q8(R2) provides guidance on how to utilize the knowledge gained through the application of scientific approaches and quality risk management to the development of a product, its manufacturing process and life cycle changes.
- ICH Q8(R2) concepts and approaches may be used to enhance AD product development and product life cycle support. For example:
 - *“Identifying potential critical quality attributes (CQAs) of the drug product, so that those product characteristics having an impact on product quality can be studied and controlled.”*
 - In this case the impact could be directed towards AD performance in an ICH-Q8(R2)-like manner

Smoking

- Determine the FP for smoking as feasible
 - Pretreatment if necessary (e.g., manipulation FP)
 - Temperature range and other conditions of failure
 - Combined manipulations to smoke
- Determine the quality attribute(s) that can be tested at release and on stability to assure an acceptable FP is maintained.
- As relevant, determine those aspects of formulation, excipients, manufacturing, and container closure that are critical to assure that level of AD performance during life cycle
 - ICH Q8(R2)-like approach



The Role of FDA Labs in the Evaluation of AD Properties for NDAs and ANDAs

- FDA labs:
 - May verify applicant data and assessment approaches
 - Intend to continue research into AD technologies, testing and assessment standards development

Statistical and Sample Size Considerations

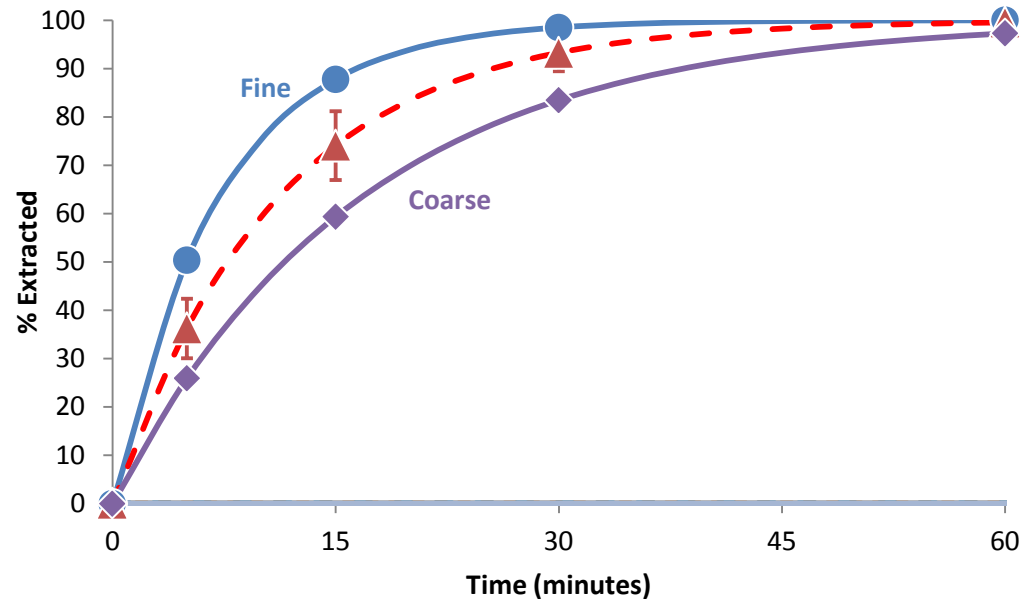
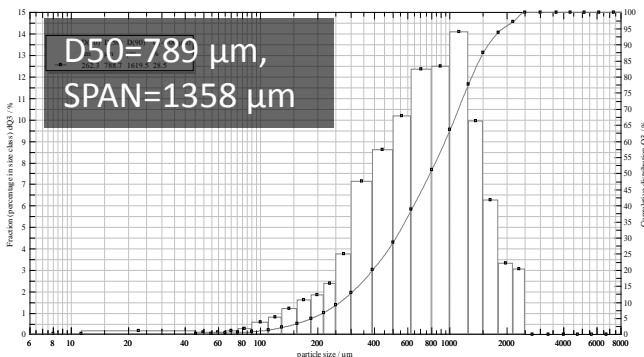


- Statistical relevance / power
 - The burden is on the applicant to justify sample size, statistical test, number of batches to assess AD properties and consistency of AD performance
 - Possibly standardize accept/reject criteria based on delta or confidence interval (CI)
 - Delta and CI should be relevant to AD outcomes
 - Annual Stability Issues
 - matrixing, bracketing, testing time points

Statistical Challenges

Points to consider:

- Sources of variability (sampling technique? number? method reproducibility?)
- Sampling procedure may greatly impact statistical analysis outcome



Effective Use of Comparator and Control Products

- Preferred: Use the corresponding IR product for an MR Product NDA, ANDA may use a control
- What if there is no corresponding IR Product for the NDA comparison? What is the comparator product?
 - Make a research formulation for this purpose?
 - Use a product approved elsewhere?
 - From an ICH country or anywhere?
 - Use the API?
 - Use an IR / MR Product for another drug?
 - Match formulation / mechanism type?



Effective Use of Comparator and Control Products

- What if the NDA is also for an IR product
 - Which IR product(s) will be used to compare to?
- Develop standard performance characteristics that may (eventually) take the place of control formulation as we learn more.

Summary

Summary

- There is a gap between the current state and the vision.
 - There needs to be assurance through testing that AD performance is maintained throughout shelf-life and over the product lifecycle (i.e., support supplemental changes) for new and generic drug products
 - It is useful to consider an ICH Q8(R2)-like approach to determining the product quality attributes that assure AD product performance as part of routine testing
 - The use of relevant statistics (e.g., sampling plans, etc.) to support evaluation of AD properties has multiple challenges

Summary

- In addition to AD standard performance characteristics for new and generic drug products (TBD); these products also need to be tested to failure across all abuse routes as part of the initial assessment.
- We can build on existing guidance.
- FDA Labs may verify some AD assessments and contribute to future guidance development, develop standardized techniques, and perform AD performance assessments for opioid drug products

Thank you !



