

Introduction to FDA's draft guidance on the *General Principles for Evaluation of Abuse Deterrence of Generic Solid Oral Opioid Drug Products*

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Disclaimer

- Guidance changes are not final until next revision or finalization
- But we will raise issues where we are considering changes to encourage discussion by the panel

Need for the Generics Guidance

- Generic products are a critical part of the health care system (86% of prescriptions in 2015)
- As new abuse deterrent technologies appear in brand products, there should be a pathway for them to appear in generic products
- Generic products should not be available unless they match the performance of the RLD

Context of the Generics Guidance

- Studies in the NDA map the performance of the RLD and set label claims
 - **Identify Critical Attributes**
- Studies in the ANDA ensure performance is no worse than the RLD
 - **Match Critical Attributes**

Key Aspects of the Generics Guidance

Key Aspects

- Scope of testing
- Step-wise approach
- Use of control
- Agonist/Antagonist combinations
- Aversive agents
- Role of in vitro testing
- Role of in vivo testing
- Policy

Public Comments

- 78 total comments
- This presentation will summarize comments on each aspect

Key Aspect: Scope

- When RLD has **any** AD labeling, ANDA provides data for **all** routes of abuse in the guidance
- Parenteral
 - Extraction from intact or manipulated and injectability
- Oral
 - Extraction from intact or manipulated
 - Ingestion of chewed or manipulated
- Nasal
 - Insufflation of manipulated
 - Aversive agents
- Respiratory
 - Sublimation of free base

Key Aspect: **Scope**

Comments

- In light of the statement "FDA considers totality of evidence", what is the impact of failing any of the tests? Request to specify minimum, number of tests to assure consistency. Totality of evidence must be clarified. Lack of clarity in “totality of evidence” disincentivizes development of generics for ADFs.
 - *FDA: guidance represents the baseline data set, totality of the evidence allows for decision making based on clinical significance of noted difference between T and R.*
 - *Other complex generics (drug-devices for inhalation, glatiramer acetate) also use a weight of evidence approach*

Key Aspect: **Step Wise Approach**

- Step-wise testing from simple to complex manipulations
 - Selection of solvents for extractions
- Stop comparisons when RLD abuse deterrence is defeated
- Not prescriptive about test conditions
 - Use of a negative control and results from testing the RLD and proposed generic to justify conditions

Step Wise Illustration

- Level of complexity
 1. Water (Level 1 solvent) at room temperature
 2. Water (Level 1 solvent) at elevated temperature
 3. Household solvents (Level 2 solvents) at room temperature
 4. Household solvents (Level 2 solvents) at elevated temperature

Step Wise Illustration

Intact Tablet

1. Water (Level 1 solvent) at room temperature
 - Control releases in 30 minutes
 - Both T and R have normal ER release control
 - Compare T and R
2. Water (Level 1 solvent) at elevated temperature
 - Control releases fully in 10 minutes
 - R releases fully in 10 minutes
 - No comparison of T and R: T is acceptable

Step Wise Illustration

Intact Tablet

1. Water (Level 1 solvent) at room temperature
 - Control releases in 30 minutes
 - Both T and R have normal ER release control
 - Compare T and R
2. Water (Level 1 solvent) at elevated temperature
 - Control releases fully in 10 minutes
 - R releases fully in 90 minutes
 - Examine profiles: Compare T and R at 30 minutes

Step Wise Illustration

Cut, Grated or Milled Tablet

1. Water (Level 1 solvent) at room temperature
 - Control releases in 15 minutes
 - Both T and R maintain ER release control after cutting, grinding and milling
 - Compare T and R after cutting, grinding and milling
2. Water (Level 1 solvent) at elevated temperature
 - Control releases fully in 5 minutes
 - Milled R releases fully in 5 minutes
 - No comparison of T and R: T is acceptable

Key Aspect: **Step-wise approach**

Comments

- Given that the test and reference product might have different AD technology, in testing, should we not consider the manipulation methods more relevant to the T rather than R?
 - *FDA: on a comparative tier worst case for T should be included*
- Please clarify the various permissible solvents for each category with criteria or provide greater clarity under which situations further testing would be required and when the testing as outlined in the guidance would be acceptable.

Key Aspect: **Use of Control**

Comments

- Why is C recommended while it is already established that R has AD properties?
- How should the comparator be selected? Can a generic non AD marketed in another country be used as C? What would be an appropriate C? IR with a smaller dose, another ER version, is a different salt form acceptable?
- Can pure API be used as the C if there is not an obvious/available C product?

Approved Opioids with Abuse-Deterrent Properties



NDA	API	Brand	Approval	Dosage Form	Possible controls
206627	Hydrocodone	Hysingla ER	11/20/14	ER Tablet	IR Hydrocodone combination tablet
208090	Oxycodone	Xtampza ER	04/26/16	ER Capsule	IR oxycodone capsule
022272	Oxycodone	OxyContin	04/05/10	ER Tablet	IR oxycodone tablet
206544	Morphine	MorphaBond	10/02/15	ER Tablet	IR morphine tablet; Non ADF ER tablet
207621	Oxycodone/ Naltrexone	Troxyca ER	08/19/16	ER Capsule	IR oxycodone capsule
205777	Oxycodone/ Naloxone	Targiniq ER	07/23/14	ER Tablet	IR oxycodone tablet
022321	Morphine/ Naltrexone	Embeda	08/13/09	ER Capsule	Non-ADF ER capsule

Key Aspect: Use of Control

- Controls appear available
 - Using an IR tablet as a control for a capsule RLD is also feasible
- No current need for non-US or manufactured formulations

Key Aspect: **Agonist/Antagonist combinations**

- Clarify how these should be tested
 - *All active ingredients (e.g. Oxycodone/Naltrexone) are measured in the BE PK studies*
 - *Draft guidance recommend measuring all active ingredients in all in vitro tests*
 - *Potential revision to indicate that we will look at differential separation and maintain the ratio that is linked to abuse deterrence*
 - *PK studies to confirm oral absorption of sequestered actives after manipulation will be recommended in product specific guidance if needed*

Key Aspect: **Role of in vitro Testing**

Comments

- Statistical acceptance criteria
- Selection of specific solvents
- Particle characterization
 - *Revision will clarify when to report the size distribution and what metric (50% or 90% fraction) to use for cut offs that are in the guidance*

Key Aspect: Role of in vitro Testing

Comments

- In vitro and PK studies do not provide sufficient evidence to demonstrate that T product is no less abuse-deterrent than R product. Need to conduct abuse liability studies.
 - *As for other generics, our approach is to use in vitro methodologies and bioequivalence where ever possible to evaluate equivalence of generics and innovator products*
 - *We request comments on mechanisms of abuse deterrence that are not captured by the current draft guidance*

Key Aspect: Aversive Agents

Comments

- As the amount of certain aversive agent is increased, the aversive effect might be reduced. Therefore the aversive agents should be Q1/Q2 with the reference. A clinical study is the only means to assure the sameness of aversive effect.
- An abuse deterrent opioid product may contain multiple aversive agents and it is not possible to say how much of the aversive effect is due to which agent.
- A combination of excipients may produce an aversive effect while none of the excipients alone is considered to be an aversive agent.
 - *During NDA review the contribution of each ingredient to the aversive effect should be identified*
- Revisions under consideration
 - *Bioavailability of an aversive agent*
 - *Destruction of aversive agents by manipulation*

Key Aspect: **Role of in vivo testing**

Comments on nasal abuse

- Population for PK comparison
 - *Considering change from healthy subjects to experienced nasal abusers*
- Statistical test for PK comparisons
 - *Considering revision to CI approach similar to BE*
- PK metrics
 - *Specific pAUC under evaluation*

Key Aspect: Policy

Comments

- ANDA pathway should be permitted for generics with novel abuse deterrent technologies.
 - *Generally novel AD technology is acceptable for ANDA so long as product meets guidance and all other ANDA requirements.*
- Provide clarity on the required testing and assessments for IR ADF generic products.
 - *IR ADF is challenging because IR need to release drug quickly for normal use, but general framework will apply if an IR NDA gains ADF labeling*

Future Steps

- ANDA guidance comments under review
- Docket (FDA-2016-N-2896) Open until Dec 1
- Regulatory science continues
 - Research support is in GDUFA regulatory science plan
- Use product-specific recommendations where appropriate
- There are OGD mechanisms for pre-ANDA input
 - Control Correspondence
 - Pre-ANDA meeting request for alternative approaches

Conclusions

- Review standards for generic opioids support FDA policy goals
- They encourage progressive development of improvements in abuse deterrent properties
- Incorporation of improvements in abuse deterrent properties into future generic products is needed to ensure access to these advances