Tufts Health Care Institute Program on Opioid Risk Management

Guidelines for the Development of Abuse-Deterrent Opioid Formulations

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Analgesic Clinical Trials): Measuring Abuse Liability

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Analgesic Clinical trials

- Key elements that need to be included in the FDA guidance
  - 1. Studies required for all “abuse-deterrent” opioid formulations
  - 2. Studies required to support each specific claim related to abuse deterrence
  - 3. Additional element needed in guidance
  - 4. Additional element needed in guidance
  - 5. Additional element needed in guidance

Clinical Studies required for approval of all “abuse-deterrent” opioid formulations

1. For NMEs (prodrug)
   - Clinical studies for NMEs will not differ from the usual pathway of development of drugs to treat pain.
   - FDA guidance for pharmacokinetic assessment, phase 2 dose ranging studies should be considered with attention to adequate dose finding.
   - Pharmacogenomic studies to identify poor metabolizers to active moiety
   - Two adequate and well-controlled phase 3 trials that demonstrate the effectiveness of the agent in the intended target patient population suffering from pain. Guidance on clinical trial design can be obtained from the Guidance for Analgesic Drug Products (when it becomes available) but should be designed primarily to demonstrate the effect of the drug on pain as a primary outcome.
   - Additional safety data (including open label extensions) to generate a database of 1500 exposures (minimum) and 300 for 6 months and 100 for 1 year for drugs expected to be used in chronic treatment should provide adequate assurance of safety in most cases.

Clinical Studies required for approval of all “abuse-deterrent” opioid formulations

2. For “Tamper-resistant” ADF, opioids with aversive ingredients

   Because these products represent reformulation of drugs for which the Agency has already made the finding of efficacy and safety, these findings may be ultimate referenced through a 505(b)(2) NDA submission, therefore the essential clinical trial data necessary to support approval may be less. This may include

   - Pharmacokinetics of the new formulation (including a pharmacokinetic comparison with the reference drug) and phase 2 exploratory study(ies)
   - One AWCS in phase 3 in the intended population to provide the minimum data requirements for efficacy. Guidance on clinical trial design can be obtained from the Guidance for Analgesic Drug Products (when it becomes available) but should be designed primarily to demonstrate the effect of the drug on pain as a primary outcome.
   - Additional safety data to provide assurance of safety on chronic administration up to one year in at least a subset of the total exposed population.
   - Additional studies may be needed to demonstrate lack of aversive symptoms at high doses due to aversive component

NOTE: A sponsor may chose not to pursue approval by this route and submit an NDA with full clinical and nonclinical data to support an NDA under 505(b)(1)

Clinical Studies required for approval of all "abuse-deterrent" opioid formulations

3. For products formulated with (sequestered) antagonist
   - Pharmacokinetic studies of the new combination drug to determine the bioavailability of antagonist by the intended route of administration prior to proceeding to phase 2 or 3
   - **Presumed**: If the antagonists is shown not to be bioavailable by the intended route of administration the remainder of the clinical development program may proceed as outlined in the previous section describing the clinical data necessary to support an application under 505(b)(2).
     - Studies to demonstrate lack of bioavailability of antagonist at high doses (PK study)
     - **or** upon chronic administration by intended route (chronic safety with ?PK sampling)
     - Studies to demonstrate no LOE or WD upon transition from reference formulation to reformulation
     - ?others
   - **Presumed**: In order to gain approval for a combination product containing an active antagonist the contribution of the antagonist must be demonstrated. This contribution of the antagonist as providing a deterrent to IV abuse may be demonstrated in nonclinical studies or by reference to the literature. Studies supporting the dose of antagonist chosen for the final formulation should be justified. (Need to have this spelled out in guidance)

Potential Claims

1. In general the frequency of abuse in clinical analgesic trials was considered too low to be able to generate a sufficient signal to support a claim,
2. Specialized studies may be constructed that might lead to implicit claims

   "Implicit claims may be generated by demonstrating significant reduction in diversion or abuse in carefully designed and replicated active controlled studies in specialized populations"

Potential label claims related to this breakout group

Implicit Claim A: Description of the study design and results. "There is no apparent contraindication to analgesic treatment with X in patients with [name high risk category]."

Example: In two active controlled trials of X in chronic opioid abusers with LBP there was a significantly lower incidence of diversion/abuse in patients treated with X (reformulation) compared to those treated with Y (original formulation). There is no contraindication to treatment with X in patients with chronic opioid addiction.

Scientific studies needed to support specific claims

CLAIM A "There is no apparent contraindication to analgesic treatment with X in patients with [name high risk category]

Study: (Replicate trials) This would be an optional feature intended only to support a labeling claim—Could be done in Phase 4

- Active controlled (with innovator against reformulation)
- Duration: 6 month minimum
- High risk population with high event rate for diversion or abuse (eg, oxycontin abusers with pain)/ severe psych exclusion, past addiction (?)
- Primary Outcome (tentative) measures: aberrant behavior checklist, diversion/misuse
- Pain control
- Other Measures: AE pattern, quantitative urine testing, Tampering, Measures of Liking, ODs, Other drug use indicators or innovative strategies
- Meaningful difference that would lead to claim

Potential label claims related to this breakout group

Claim B:

- CMC (description) An opiate antagonist (name) has been added to this formulation in an attempt to deter abuse by the intravenous route.
- **WARNING: this product should only be administered orally. It contains an opiate antagonists which, if administered intravenously [or intranasally] it may precipitate opiate withdrawal. --elaborate**
- Pharmacology section (PK studies showing bioavailability (or lack thereof) of antagonist by PO route), studies to demonstrate bioavailability by IN (crushed)
- Description of nonclinical studies to support dose of antagonist that would precipitate withdrawal

Scientific studies needed to support specific claims

Claim **B** *(for drugs with opioid antagonist):*

Biopharmaceutics: study of bioavailability of antagonist studies by intended route in humans balanced by studies of bioavailabity by common routes of abuse.

(note guidance needed to confirm when animal studies of bioavailability by alternate routes may be sufficiently robust and when nonclinical studies to support dose of antagonist that would precipitate withdrawal could be provided)