



Current Thinking on the Premarketing Evaluation of Abuse-Deterrent Opioid Formulations – Category 2 and 3

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Premarketing Assessment of Abuse Deterrent (AD) Formulations

- Three types of studies
 - Category 1. In vitro studies
 - Category 2. Pharmacokinetic studies
 - Category 3. Human abuse potential studies



Category 2 Pharmacokinetic Studies

- Provide data on the bioavailability of a manipulated AD formulation (ADF) relative to the intact ADF, and to that of a positive control(s) (IR or ER products or a manipulated form of an ER product known to be abused) when taken orally or intranasally
 - Is there a difference in the PK profile between the intact and manipulated ADF when taken orally or intranasally?
 - How does the PK profile of the intact and manipulated formulation compare to that of the positive controls?
- Conducted on the to-be-marketed formulation
- Evaluate food and alcohol effect
- Influence the design of human abuse potential studies





Category 2 Pharmacokinetic Studies

- Open-label, randomized, single-dose, crossover design
- Healthy adult volunteers, opioid-blocked
- Pharmacokinetic Parameters
 - Peak plasma concentration (C_{max})
 - Time to peak plasma concentration (T_{max})
 - Area under the concentration versus time curve (AUC_{0-t} and AUC_{0-inf}), relevant partial areas under the curve, such as $AUC_{0-30 \text{ min}}$ or $AUC_{0-2 \text{ hr}}$



Category 3

Human Abuse Potential Studies

- Measure the abuse potential (“likeability”) of an intact and manipulated ADF, relative to positive control(s) (intact and manipulated approved ER product, and approved IR product or the API), through relevant routes of abuse
- Are predictive of the likelihood that the AD features of the formulation may reduce levels of abuse of the product, when compared to marketed and abused products, and when taken through relevant routes of abuse (oral crushing and chewing, IN, and in some instances IV)



Category 3

Human Abuse Potential Studies

- Randomized, placebo-controlled, single-dose, double-blind, crossover design
- Opioid-experienced, non-dependent volunteers who have abused opioids through the route of administration being studied
- Manipulation method and route of administration should be based on relevant routes of abuse for similar marketed products, and on study results from Category 1 and 2 studies
- Include a Qualification Phase

Category 3

Human Abuse Potential Studies

- Qualification Phase
 - Critical to identify subjects who can distinguish the effects of the opioid from placebo
 - Test drug usually is an IR version of the same opioid as present in the ADF
 - 
 Dose of IR test drug usually lower than dose of opioid in the treatment (test) phase
 - Pre-specification of an acceptable placebo response range

Category 3

Human Abuse Potential Studies

- Treatment Phase
 - Include the test ADF (intact and manipulated), ER approved product (intact and manipulated), and a positive control consisting of an IR, or API
 - Selected doses should be known to produce high levels of liking in opioid-experienced users
 - Manipulation of the product is based on Category 1 and 2 data for specific route of abuse
 - Include PK measures
 - Subjective endpoints - Bipolar or unipolar VAS scales (Drug Liking, Good Effects, High, Bad Effects, Overall Drug Liking, Take Drug Again)
 - Maximum effect (E_{max}), Time to maximum effect (T_{max}) and pharmacokinetic parameters (C_{max} , T_{max} , AUC_{0-t})





Category 3

Human Abuse Potential Studies



Statistical Analysis

- Descriptive statistics – Mean, median, standard error, interquartile range
- Primary and secondary analysis
 - Comparison of means (or medians) between the manipulated ADF and the positive control(s)
 - Percent reduction
 - Responder analysis



Challenges and Questions

- Science of abuse deterrence is relatively new and rapidly evolving
- The methodology and interpretation of human abuse potential studies require further discussion and research
- Specific questions, include:
 - What is the impact of the rate of rise, which may contribute to differential abuse potential among drugs, formulations, and routes of administration?
 - Is it possible to predict clinical abuse potential study results based on different pharmacokinetic profiles between formulations?



Challenges and Questions

- Methodology and interpretation of human abuse potential studies
- Several areas for discussion:
 - Subject selection. Based on individuals who can distinguish an IR opioid control from placebo in a qualification phase
 - Do the following influence subject selection?
 - Dose or doses of the test drug
 - Range of doses of the test drug
 - Setting or establishment of an appropriate placebo response



Challenges and Questions

- Methodology and interpretation of human abuse potential studies
- Several areas for discussion:
 - Maintaining blinding as a result of the manipulation
 - Crushing or grinding may result in a different volume or in a crushed powder of different particle size or the crushed material may not be going easily into a solution or into a suspension for oral use
 - How can we improve blinding?
 - Is it acceptable to encapsulate crushed product that can not be taken into a solution?



Challenges and Questions

- Methodology and interpretation of human abuse potential studies
- Several areas for discussion:
 - Food effect
 - If there is a food effect, should the studies be conducted under fed conditions, to achieve maximum levels of exposure and highest drug liking?
 - Measures
 - Does it make a difference if measures are taken in a unipolar or a bipolar scale(s)?
 - Interpretation of results
 - What constitutes a clinically significant difference in drug liking between the test drug and positive controls?
 - Statistical analysis
 - What is the best approach?