Overview of the Abuse Deterrent Formulation Science Meeting Outcomes with Focus on Clinical Assessments

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Objectives

• Provide an overview of Panel Recommendations from Pharmacokinetic (Category 2) & Clinical Abuse Potential Studies (Category 3)
  – Open recommendations for further discussion
• Relationship between PK and PD of abuse potential is weak and highly variable, at least for individual subjects
  – Effects unrelated to opioid exposure impact subjective experience
• Pharmacokinetic parameters such as $C_{\text{max}}$, $T_{\text{max}}$ and AUC will nearly always need to be evaluated in the context of pharmacodynamic outcomes
  – Particularly for intranasal studies
  – Possible exception of oral study where PK of tampered is identical to PK of intact (for simple physical barrier formulation)
• Pharmacokinetic data alone can answer questions about BE/BA, food effects, alcohol interactions
Use of same (or intermediate dose) in Qualification appears to have advantages over use of a lower dose:

- Lower dose may result in plateau effects, increased dropouts, and select for a less relevant population.
- Subject eligibility criteria should attempt to strike balance between Type I and Type II errors (e.g., balance enrichment with generalizability).
Blinding and Manipulation

- Lack of public data on appropriate manipulation techniques
  - When comparing data to existing ADFs (present and future) how do we know manipulation techniques were “equivalent”?

- Blinding should be undertaken, but should not obliterate the features of the formulation you are trying to assess
  - No adjustment for weight or particle size (most “naturalistic”)
  - “Intermediate placebo” or two placebos
  - Use of true “double dummy” with weight and/or particle size matching

- (Encapsulation may be acceptable for oral studies but should generally be last resort:
  - Use of alternative vehicles (tomato juice? Apple sauce?) or placebo solution manipulations (flour/gelatin in placebo solution?)
Measures and Interpretation

• Primary measures of Drug Liking should be bipolar for most cases
  • Unipolar measures such as Good and Bad Effects may be important for interpretation

• Over-reliance on peak effect ($E_{\text{max}}$) may increase risk of false negative results
  • Derived endpoints evaluating time course profile important for interpretation ($TE_{\text{max}}$, partial AUEs)
  • Consider whole profile of effects and in particular end-of-day/next-day measures of Overall Liking and Take Drug Again
  • Value of open-ended feedback or development standardized follow-up questions? (Why take the drug again? Why not?)
Statistics: Interpretation and CID

- Insufficient data currently available to support pre-specifying $\delta_1$ “super superiority” margin (i.e., margin of reduction of test drug from positive control)
  - $\delta_1$ must be based on scientific/regulatory consensus:
    - Potential public health consequences of unsupported estimates of $\delta_1$
  - Sufficient data to pre-specify $\delta_2$ (PBO-Control) but probably not needed
    - Interpretation of clinical relevance should consider whole profile of effects → Convergence of data
    - Make use of anchors on bipolar scales → Strong liking/disliking vs. Neutral
    - Make better use of other arms within the study (e.g., PBO vs. Test; intact arm in oral study, oral arm in IN study) or add additional comparisons → preferable to adding multiple doses
    - (Start to consider how we may develop non-inferiority/equivalence margins in comparison to existing ADFs?)
Statistics

• Recommendations for statistical analysis relatively clear
  • Data may require non-parametric methods not mentioned in guidance

• Use of responder analysis to arbitrarily convert continuous Drug Liking variable into categorical variable
  • Potential loss of power
  • Interpretability, i.e., assumptions of clinically relevant margins x 2 (% of subjects and % decrease in Liking)

• Data presentations must consider the end-users of the labels (prescribers)
  • Data presentation should be familiar and easy to understand
Final Considerations

• Remember conceptual framework:
  • Flexible, adaptive approach → there will never be a one-size fits all, but we do need to provide some “off the rack options”
  • Consider public health implications of design choices (balance type I and II errors)
  • Consider the purpose of ADF studies (label) and end users (prescribers)