A Regulatory Perspective on What is Needed for Evaluating Abuse Liability in Analgesic Clinical Trials

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The content of this talk does not necessarily reflect the views of the FDA, and is entirely based on my own observations and viewpoints.

What Are We Trying to Achieve?

- FDA's regulatory authority includes assuring that the product label is accurate and complete
- FDA's public health mandate requires that we take all actions within our authority to address the growing public health crisis of prescription opioid product abuse

The Regulatory Perspective

- The level and extent of the analysis is dependent on the nature of the new formulation and what is known about abuse of the drug substance.
- Current standards for labeling claims of abuse-deterrence:
  - There are four levels of possible claims:
    - In vitro physical or chemical formulation manipulation
    - In vivo PK assessment of the results of physical or chemical manipulation
    - **Relative likeablility studies of manipulated product compared to intact product and, if relevant, older formulations of the drug substance**
    - Demonstration of reduced abuse in the community

The Regulatory Perspective

- Relative Likeability Studies
  - Demonstration that the product reduces drug liking in subjects with appropriate metric for assessing this factor
  - Appropriate for products with a sequestered antagonist
  - Study results would be allowed in the product label in the Clinical Pharmacology section
  - A disclaimer may be necessary

Studying Abuse Liability

- In order to set standards, provide accurate labeling, maintain a level playing field for industry, assure a reasonable risk-benefit balance and adequate safety information, and assure a strong scientific basis for our decisions, we need:
  - Definitions and a classification of degrees of abuse-liability that are broadly accepted
  - Standardized metrics and study design features
  - Data to support the translatability of study findings to the clinical setting

Why Standardized, Validated Metrics and Standardized Study Design Features?

- Regulatory Concerns:
  - Study results for "likeability" or other measures of a drug's abuse liability would be claims if added to the label
  - Claims provide an advantage in the market
  - Generally, these are implicit, if not explicit claims of superiority, e.g., safer, less likely to cause abuse, addiction, OD, death
  - Superiority claims require evidence from replicated adequate and well-controlled trials

Why Standardized, Validated Metrics and Standardized Study Design Features?

- Safety/public health concerns:
  - Is the new product/formulation safer/less safe for patients?
  - Is the new product/formulation safer/less safe for non-patients?
  - Does the change impact efficacy and/or the overall risk-benefit balance
  - Risk management

Why Standardized, Validated Metrics and Standardized Study Design Features?

- Risk management: The metrics must be standardized and validated in order to:
  - Allow assessment of risk across products/formulations
  - Allow choice of risk management tools
  - Both in a fair and balanced manner in order to
    - Provide level regulatory playing field, e.g. what tools?
    - Assure that benefits outweigh risks
    - Provide a safe product for patients and non-patients
    - Assess burden of risk management strategy (REMS, FDAAA)

Why Standardized, Validated Metrics and Standardized Study Design Features?

- Labeling
  - Sound science to support:
    - Accurate and appropriate dosing information
    - Reasoned and balanced warnings
    - Strategies for assessing abuse
    - Strategies for managing abuse
  - When we don't have sound science we say so, but this is clearly less desirable

Why Standardized, Validated Metrics and Standardized Study Design Features?

- Examples:
  - New opioid formulation is less likeable than its predecessor or another product on the market, e.g., Embeda
  - Reformulated opioid with new route of administration, higher strength/potency, history of high level of abuse; is it less or more likely to be abused than competitors?
  - What is the potential for abuse of a novel analgesic product compared to approved products?

Metrics

- What is being measured, i.e., content validity
- What are the best measures?
  - Likeability; euphoria/dysphoria; pt global?
- What degree of change is meaningful?
- How does one metric compare to others?
  - Which one should be primary? Interference?
- How will the data generated translate into the clinical setting?
- What is the proper statistical analysis for the metric?

Study Design Features

- What is the patient population being studied, i.e., inclusion/exclusion criteria
  - Include psychiatric pts? Pts with history of abuse?
  - Just recreational users? Dependent pts? Addicts?
  - Implications for prescribing instructions in the label and claims
- How will confounding variables be handled, e.g., concomitant medications, adjunctive treatments such as CBT

Study Design Features

- Dropouts related to abuse
  - Reason
  - Follow-up after dropout
  - Analysis
  - Impact on primary and secondary outcome analyses
  - Imputation strategies for lost data
    - LOCF? BOCF? Other?

Study Design Features

- Adverse event collection
  - Focus on events specific to abuse liability
    - Addiction, overdose, withdrawal
  - Methodology for collection
    - Same as the other adverse events?
    - More specific strategy?

Study Design Features

- What additional data should be collected
  - Urine drug screens
    - How often?
    - What drugs?
  - Pill Counts
    - How often?
  - High-risk or aberrant behaviors
    - What metric or just as AEs?
    - Diversion/theft

Summary

- We have a regulatory mandate to assure a level playing field for industry
- Impossible to assure this without standardization of metrics and study design features related to abuse liability
- Standardization of metrics requires validation
- We have a public health mandate to assure that the benefits of a product outweigh its risks and that a complete safety profile is available in the label
- High quality safety and risk management also require standardization of metrics and study designs
- The academic addiction treatment/abuse liability assessment community should provide the data and insights necessary to support regulatory use of metrics or study design features related to the assessment of abuse liability of an analgesic drug product