FDA Abuse Liability Review

IMMPACT-XII - Outcome Measures for Human Experimental and Clinical Studies of the Abuse Liability of Analgesic Medications

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Pre-Market New Product Review

- Investigational New Drug (IND)
  - Process by which a sponsor advances to the next stage of drug development known as clinical trials
    - Animal Pharmacology and Toxicology Information
    - Manufacturing Information
    - Clinical Protocols and Investigator Information
- New Drug Application (NDA)
  - Formal application to the FDA for approval of a new drug

Human Abuse & Diversion Potential Data: In Drug Development

- Human Pharmacology Laboratory Study
- Controlled and Open Label Clinical Studies – Efficacy and Safety Studies (Phases 1 – 3)
- Populations Included
  - Patients, Healthy, Experienced Drug Users
- Safety Assessment
  - *Euphoria, mood elevation*
  - *Sedation, stimulation, hallucinations*
  - *Other relevant behavioral events*
- Evidence of actual abuse and diversion

Regulatory Results

- Drug Scheduling
- Product Labeling to include description of abuse potential of new products
- Obtain information that may relate to directions for use and precautions
- Assess relative risks of the product compared to other drug products with same indication
- Determine effectiveness and safe use of drug
- Providing new information suggestive of need for a REMS

Analysis of Data

- **Prospective evaluation**
  - Procedures and criteria are defined and the clinical investigator receives appropriate training in the identification and coding of the behaviors of interest
- **Retrospective analysis**
  - Dropouts, study discontinuations, misuse, abuse, addiction, aberrant behaviors, diversion, etc.
  - Compare different pain patient populations for qualitative and quantitative differences in occurrence of aberrant behaviors

High Risk Behaviors

- Evidence for occurrence in clinical trials
- Can be as high as 20% patient population
  - Abuse/dependence
  - Overdose
  - Overuse
  - Positive UDS
- Possible Signals
  - Lack of drug accountability
  - Lost to follow-up
  - Identified as administrative reasons
  - Not known

See various papers by S. Passik et al., 2006-9

Reasons for Subject Dropout/Discontinuations

- Lack of efficacy
- Adverse event
- Noncompliance to study protocol
  - Study visits
  - Study drug use
- Subject choice (convenience, other)
- PI choice

Diversion in Clinical Trials

- Patients withdrawn
  - Drug thefts related to patient actions
- Study centers reported thefts of study drug
  - Taken from locked cabinets and involved forced entry
  - Lost in transit between pharmacy and study center
- Tabulate drug thefts
  - Tabulate by number (%) of patients
  - Tabulate by number (%) of study centers

Diversion

- Difficult to study prospectively
- Site investigators need to be trained so that each site is reporting events consistently.
- Training needs to occur before the start of the trial.
- “Diversion” is often not well defined
- Patterns of diversion heterogeneous
  - Example: Drugs shared with family & friends

General Problem of Drug Safety

- Even after subject drops out or is discontinued, we want the detailed information of reasons for event
- All data on dropouts should be submitted for review
- Missing data can change interpretation of study results
- The protocol should define the terms of dropping out and discontinuations
  - Specific descriptions and reasons for the event need to be incorporated prospectively into the protocol
  - Site investigators need to be aware of signs and signals of abuse and diversion

Analyses of dropouts/discontinuations

There is no good solution for the analysis

- The rates of dropout and discontinuation between the test drug and placebo can be compared
  - If significantly different (much higher), validity of study results is questionable
- Often times, there is a lack of adequate documentation of reason for the dropout
  - Time to dropout or discontinuation
  - Need to follow-up on the dropout subject to the end of the trial time
- All reasons for dropouts are important

Analyses, continued

- Identify presence or lack of a treatment effect
- Some individuals might continue on the drug because it is abuseable, as opposed to being effective
- If dropout rate is too high, fileability of the NDA may be an issue
- If too much missing data, study results may not be interpretable

Additional Relevant Information

- Narratives of CRF's for all patients who drop out or discontinue
- Overall profile of these patients:
  - By reason for dropping out (e.g. AEs, treatment failures, lost to follow up, etc.) should be provided
- For more common events associated with dropouts, the incidence of these AEs should be provided

Data Needs

- Validated scales for different populations
- Approaches to assess abuse potential of new formulations
- Interpret retrospective data
- Use of positive controls