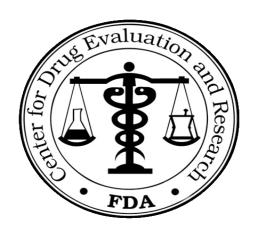
FDA Abuse Liability Review

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

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