Study Drug Monitoring and Diversion in Analgesic Clinical Trials

IMMPACT-XII Research Methods and Outcomes for Human Experimental and Clinical Studies involving Abuse Liability of Analgesic Medications

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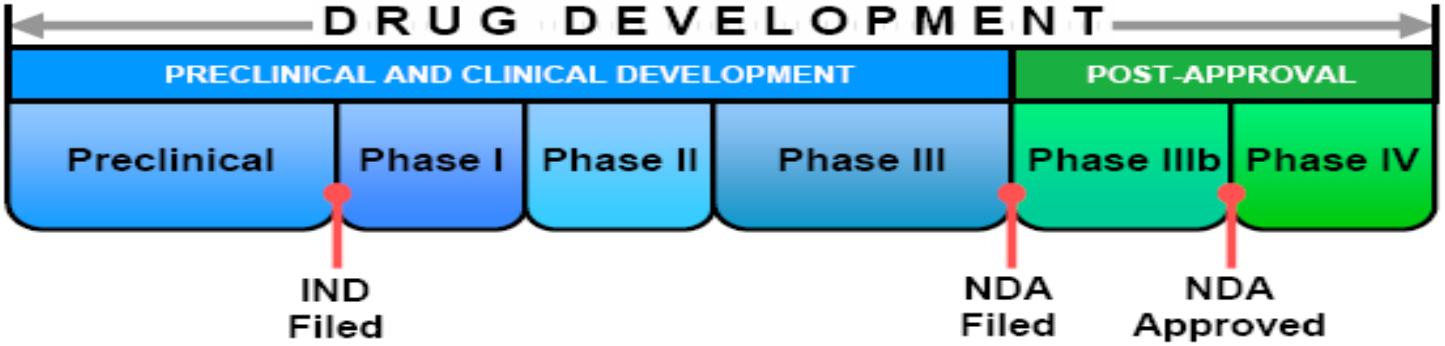
Risk Management Occurs Throughout Product's Lifecycle



Early Phase Risk Assessment

- Pre-clinical Animal Studies
- Abuse Liabilities Studies
- Existing Compounds Abuse Analysis

Ph 2, 3 Safety Studies & NDA Filing

- Risk Assessment – Clinical Trial Safety Data-base Assessment
- Risk Assessment – Epidemiological Assessment?
- Risk MAP Development
- FDA/ Regulatory Presentation and Interactions
- Labeling and Scheduling Studies

Ph IIIB, IV Studies

- Post-Marketing Surveillance
- Peri-Approval Studies – QOL, Long Exposure Studies etc.
- Existing Data Source Analysis
- High Risk Population Surveys
- Internet/ Media Monitoring
- Prescription Monitoring
- KIN & Field Studies
- Alcohol Co-Ingestion Studies

Current Approaches for Evaluating Abuse and Diversion in Clinical Trials

- Prospective evaluation
- Retrospective evaluation

Abuse and Diversion of Study Drug During Clinical Development

- Limited Information is currently available on the abuse and diversion of study medication ***during*** clinical development
- Despite the exclusionary criteria that normally employ to prevent the inclusion of drug abusers or diversion problems from participating in these trials, some abusers and or diverters are able to enter the studies; the most common reason is non-disclosure

Why conduct systematic evaluation in clinical studies?

- A systematic evaluation of medication handling irregularities is a first step in conducting a thorough and comprehensive Risk Management Program which may identify possible abuse or diversion of study drug (especially of new formulation or NCE) and aid in the accurate presentation of clinical results, improve post-marketing risk management of the product.
- Medication handling irregularities represent instances of site misconduct and a violation of GCP and must be reported to the FDA. Confirmed diversion is a felony and must be reported to the local authorities and the DEA.

Example 1
Aberrant Drug Behaviors in Opioid Clinical Trials

- Prospective evaluation from 3 opioid clinical trials ranging from 21-120 days in length; 2 trials were ongoing and 1 trial was completed
- A total of 798 patients evaluated
- Opioids used included: OxyContin® Tablets, Duragesic®, Vicodin®, Perocet®, extended –release hydromorphone and transdermal buprenorphine
- Patients were excluded with past or present alcohol or drug abuse or serious psychiatric disorders
- SAEs and possible abuse and diversion were reported to the FDA
- Events of significant loss or diversion were reported to the local authorities and DEA

Zalman et al. 2004 College on Problems of Drug Dependence

Systematic Assessment of Abuse or Diversion

Clinical Investigator

Case Report Form (3 questions)

Investigator Follow-up questionnaire

Evaluation and Investigation Risk Assessment specialist (Sponsor)

Log Cases in Repository and Retain Documents

Final Classification (*possible abuse, diversion, noncompliance, past or current substance abuse, or other*)

Prospective Assessment
CRF Questions included: *At anytime during the study…*

1. Was there any indication of abuse of alcohol or illicit drug by the subject ?
2. Was there any indication of abuse of study drug by the subject?
3. Was there any indication of diversion of this subject's study drug to someone other than the subject?

If any of these questions were positive a series of follow up questions were asked

Prospective Assessment
Investigator follow-up questionnaire…

- The subjects use of alcohol, illicit drugs, or study medication causing substance-related social or legal problems, or unacceptable risk or harm or medical problems, such as physical injury or overdose
- Evidence of tolerance or withdrawal, or compulsive behaviors related to alcohol or drug abuse
- The subject's use of study drug for any other effect other than analgesia
- The subject's experiencing signs and symptoms of excessive drug effect, such as intoxication or impairment

Prospective Assessment Investigator follow-up questionnaire… (cont'd)

- The subject's experiencing inadequate analgesia despite appropriate dosing during the course of the study
- The use of other drugs due to inadequate analgesia
- If opioid analgesia was continued at the conclusion of the subject's participation in the study

Types of Episodes
30 Cases of Medication Handling Investigation

- 5 packaging / return of clinical supplies or site staff conduct issues
- *25 patient Issues (N=798; 3.1%)*
  - 10 noncompliance issues (4 cases of unreturned study medication including rescue and 6 cases of consumption in excess of protocol prescribed dosages)
  - 7 reports of lost, stolen, or damaged study medication
  - 4 cases of inadequate analgesia
  - 3 previously unrealized abuse / dependence problems
  - 1 “economic” diversion due to medication costs

Patient Abuse Evaluation

25 Medication Handling Investigation – Patient Issues **(3.1%)**

16 cases categorized as not related to abuse

9 cases categorized as possible or probable abuse or diversion **(N = 798, 1.1 %)**

7 cases were categorized as possible abuse

- 4 lost or stolen or damaged prescriptions
- 2 noncompliance, did not return study drug
- 1 current drug abuse problem

2 cases were categorized as probable abuse

- 2 noncompliance, did not return study drug: Investigator presumed patient abuse or diversion

Systematic Assessment of Abuse or Diversion - Prospective Assessment

- Following investigation, it was determined that approximately 1% (9/798) of the patients demonstrated behaviors suggestive of abuse and diversion
- All medications handling discrepancies were reported to the FDA during routine ADE
- Of the 9 cases of possible of abuse or diversion, 2 cases were reported to the FDA as SAEs and 2 cases warranted local law enforcement authorities
- There were no cases as iatrogenic addiction

Follow up Evaluation at the Completion of Vicodin – BTDS Switching Trial

32 Medication Handling Irregularities (N=274)

25 Medication Handling Irregularities by subject

- 10 cases of noncompliance or medication accounting errors by subject
- 9 cases of lost or theft of study medication by subject (not abuse or diversion)
- 1 case of current drug abuse problem not involving study medication
- 5 cases of possible abuse or diversion of study medication

7 Irregularities at site

- 5 cases involving Vicodin tablets
- 1 case involving Vicodin tablets and unused BTDS patches
- 1 case involving Vicodin tablets and ibuprofen tablets

Wright et al. 2006 College on Problems of Drug Dependence

Systematic Assessment of Abuse or Diversion – Corrective Measures

- **Site**
  - A letter was sent to the site suggesting obtaining confirmation by the subject's physician of the clinical diagnosis and HC/APAP
  - Confirmation of previous use of HC/APAP by subject
  - A detailed medical history and physical exam at V1
  - Modification of the study medication packaging (20 count bottles were also made available)
  - New locked facilities were constructed with limited access if loss occurred at the site
- **Subject**
  - The investigator decided the subject's future study participation
  - Noncompliance: subject was typically re-instructed
  - Diversion: local authorities notified and DEA 106 forms completed
  - Possible abuse: subject may have been discontinued from the study

Example 2
Hydromorphone Extended–Release
Retrospective Analysis of Abuse or Diversion

- Retrospective review of pain patients enrolled in hydromorphone extended –release clinical program (5 clinical studies, N=1189)
- Opioids used included: HHER, HHIR and Durgesic®
- Drug accountability records of clinical trials participants
- Protocol deviation and violation information
- Discontinuation information
- Adverse Events information *(evaluation of the following: overdose, tolerance, dependence, abuse, addiction withdrawal euphoria, apnea, asphyxia, hypoventilation, hypoxia)*

Zalman et al. 2005 College on Problems of Drug Dependence

Possible Abuse in the Hydromorphone Extended–Release Clinical Program (1.1%)

- The majority of medication compliance events were one-time issues involving failure to return small unused medication or few episodes of lost medication. These “sub-threshold” issues can occur frequently in clinical trials depending on the complexity of medication handling instructions
- In 2-placebo controlled studies, 4 cases in the 381 subjects enrolled were determined to be possible abuse (1.0%)
- In 2-active controlled studies, 2 cases in the 344 subjects enrolled (0.58%) were determined to be possible abuse
- In a Phase 3b trial 7 cases in the 464 subjects enrolled (1.5%) were determined to be possible abuse (prospective evaluation)

Example 3
Aberrant Drug-Related Behaviors in Opioid Clinical Trials

- Retrospective review of patients enrolled in 5 Fentora® clinical studies (N=1160)
- CRFs were reviewed and events of abuse, overdose, and aberrant behaviors were identified
- Aberrant behaviors were categorized in those involving the use of Fentora or placebo

Passik et al. 2008 International Conference on Pain and Chemical Dependence

Aberrant Drug – Use Behavior Categories

- ***Events indicating Substance abuse or overdose***: Abuse/Dependence by PI, positive UDT, and overdose
- ***Aberrant Behavior possibly involving the use of the study drug***: Fear of addiction, report of theft of lost of study drug, overuse of study drug, unapproved use, MVA
- ***Aberrant Behavior not involving the use of the study drug***: Discharge of pain management practice, LTF, seeking prescriptions from other sources

Aberrant Drug-Related Behaviors Relation to Study Medication

- A total of 17% of patients displayed at least 1 aberrant behavior
- Overdose was possibly related to study medication in 8 patients
- 124 patients (11%) had aberrant behavior possibly involving the use of the study drug; overuse of study medication (58 patients) and medication theft (43 patients) were the most frequent events
- 68 patients (6%) had aberrant behavior not involving the use of the study drug: LTF (36 patients) and positive UDT (18 patients) were the most frequent events

General Conclusion and Future Considerations

- Evaluation of abuse/diversion in clinical trials allows for an "*initial understanding*" on the desirability for abuse of a drug.
- Need for ongoing assessment of abuse/diversion in large clinical trials.
- Further evaluation of factors that may influence the effect of abuse/diversion in clinical trials is required (i.e. patient population, use of advertisement in clinical trials, geographical location, etc.)
- Prospective evaluation on the occurrence of abuse /diversion in CDP compared to occurrence of post approval is required
- The development and use of *self report questionnaires* in large clinical trials may provide further insight on the potential for abuse and diversion of a product postmarketing