Tufts Health Care Institute Program on Opioid Risk Management

Guidelines for the Development of Abuse-Deterrent Opioid Formulations

November 9 – 10, 2006

Tufts Health Care Institute

Tufts University School of Medicine

Alcohol Interaction Studies Workshop Participants

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Overall Comments

- ADF include those based on technology, other components and PK
- Ethanol effects (efficacy, safety and abuse deterrent claim) on each active constituent of ADF may need to be assessed
- In any scientific White Paper or Citizen's Petition a section with details on manufacturing and in vitro testing consideration will be needed
- Topic complex and important with wide implications (e.g., affects other drugs); it may merit a separate conference leading to a guidance document strategy

Key elements that need to be included in the FDA guidance

1. Design of and interpretation criteria for:
   - in vitro dissolution studies
   - extractability studies
2. Specification of when in vivo human studies are needed
3. Specification of primary and secondary dependent variables and critical differences for human in vivo studies e.g. Cmax, AUC, selected PD measures
4. By what criteria would an alcohol effect be deemed to alter the abuse deterrent properties of the ADF?

Key elements that need to be included in the FDA guidance

6. Specification of preferred designs for human studies:
   - fasting feeding, timing drug/ethanol, sex, age, concomitant meds, menstrual cycle, opiate naïve/users, acute chronic dosing, subject selection, preferred PK and PD measures, timing of measures, type of ethanol etc.
   - Any requirements that may relate to impact on efficacy
   - Preferred guidance would be that studies should try to simulate situations of risk and conditions of use of the ADF
7. Specify relationship of in vivo and in vitro studies in anticipation of labeling.
8. For pharmacodynamic studies specify the preferred endpoints e.g sedation, motor coordination, vigilance, respiratory depression

Key elements that need to be included in the FDA guidance

9. Clarification of the situations under which naltrexone block is preferred or required.
10. Identify the risk populations of concern e.g. alcoholics, pain patients, drug abusers, elderly, college students.
11. Specify product characteristics that would make it clear under what circumstances generic ADF products would require same studies.

Scientific Literature and Data

1. A lot about ethanol interactions in vitro and in vivo
   - Doses, timing and design of ethanol interaction studies
2. High variability in opiate and ethanol PK in vivo
3. Relation of opiate PK and PD highly variable among and within humans under conditions of acute and chronic use
4. Epidemiology of ethanol use and opiate use
5. In vitro drug concentrations do not have (much/any) utility in predicting clinical efficacy, safety or public health risk

Scientific Literature and Data

1. Some evidence naltrexone may affect the biotransformation of opiates
2. How to select of appropriate and sensitive pharmacodynamic endpoints and how to collect high quality data is known
3. Some what sparse literature suggests pharmacodynamic interaction between ethanol and opiates (ADF or IR) probably not very large – not supra-additive
4. Recent unpublished clinical data with ADF confirm this
5. Efficient designs to answer public health and labeling requirements are known and straight forward

Studies: Framework Labeling not Claims

1. No warning label
2. Possible to include results of study
3. Label A: Existing class label for alcohol interaction with opiate e.g., IR Morphine or MS Contin
   - *Warning: ..should be used with great caution and in reduced dosage in patients ....receiving CNS depressants including.....alcohol*
4. Label B: Enhanced risk label e.g., Opana
   - *Boxed Warning: Patients must not consume alcoholic beverages or prescription or non-prescription medications containing alcohol while on Opana ER. The co-ingestion of alcohol with Opana ER may result in increased plasma levels and a potentially fatal overdose of oxymorphone.*
5. Not approved or withdrawn

Scientific studies needed to support each labeling

- In vitro
  - Dissolution – f(t), composition etc
  - Extraction
- At present no evidence in vitro leads to “trip wire” yes or no on issue of importance
- Note – Ex vivo or pre-systemic effects on formulation dissolution is only one way in which ethanol can (importantly?) alter the PK of a drug)
- The in vitro effects are getting dissociated from the bigger issue of when and how are alcohol PK or PD interactions important

Scientific studies needed to support each claim

- Avoid Label B:
  - Demonstrate bioequivalence (80%-125% 90% confidence limit) of ADF product with and without ethanol – minimal study would be with 240ml 40% ethanol 15min ingestion
  - Fasted Ss
  - No need for naltrexone
  - Include BE for each active constituent in ADF

Scientific studies required to support specific claims

- <u>If not bioequivalent: choices</u>

1. Accept Label B and possible inclusion of data
2. Demonstrate that do not warrant label B
   - Pharmacodynamic – pharmacokinetic
   - Fed
   - Chronic use in pain patients
   - Clinical trial data
   - Different doses and times of ethanol administration

- These data may have value in competitive marketplace or help characterize the pharmacology and circumstance of risk; relative position in marketplace
- No drug left behind!