Tufts Health Care Institute Program on Opioid Risk Management

Guidelines for the Development of Abuse-Deterrent Opioid Formulations

November 9 – 10, 2006: Preclinical

Tufts Health Care Institute

Tufts University School of Medicine

Studies required of all “abuse-deterrent” opioid formulations (A)

- Current Studies (NCE compounds): i.v. or s.c. dosing in rats, monkeys

1. Primary physical dependence
2. Single dose substitution
3. Reinforcing effects: self administration, ICSS, place preference
4. Drug discrimination

- **No reference oral data!**

Preclinical basic science needed! $$$ to develop techniques

- **Oral** PK- analgesic PD and abuse liability studies
- (Other non-iv routes: dermal, buccal, nasal, inhalation)

Oxycodone	Hydromorphone
Hydrocodone	Oxymorphone
Morphine	Buprenorphine
Fentanyl	Methadone

Studies required of all “abuse-deterrent” opioid formulations (B)

- Comparative abuse liability by oral route w/ reference non-ADF compound

1. Primary physical dependence
2. Single dose substitution
3. Reinforcing effects: self administration
4. Drug discrimination

- Studies by intended commercial route (e.g. oral) and by i.v. (may simulate PK profiles)

Potential label claims related to preclinical breakout group

- Claim A: Product “X” produces less therapy-independent reinforcement (euphoria, reward) than Reference “Y”
- Claim B: Product “X” produces less physical dependence than Reference “Y”
- Claim C: Product “X” does not substitute for morphine in physical dependence

Scientific studies needed to support each claim

- Claim A: Product “X” produces less therapy-independent reinforcement (euphoria, reward) than Reference “Y”

1. Self-administration (rats, monkeys per ADME profile): oral and i.v.
    - Drug discrimination (functional equivalence to standard opioid)

Scientific studies required to support specific claims

- Claim B: Product “X” produces less physical dependence than Reference “Y”

1. Primary physical dependence test: oral, i.v.
    - Determine maximum physiologically-tolerated chronic dose; use for primary dependence

Scientific studies needed to support specific claims

- Claim C: Product “X” does not substitute for morphine in physical dependence

1. Single dose substitution: oral, i.v.
   - May precipitate massive withdrawal
   - May substitute for morphine
   - Other aversive properties
   - Differential effects per route used

Run-through of examples (½ hr)

- "Tamper-resistant" ADF
  - Resistant to physical manipulation
  - Resistant to chemical manipulation
  - Resistant to extraction with alcohol
- Opioid with sequestered antagonist
- "Prodrugs"
- Opioids with aversive ingredients

Miscellaneous issues (½ hr)

- Addressing potential safety issues
- Addressing potential issues with drug interactions
- Addressing potential issues with combination products
- Considerations for labeling and promotion
- What data would be required to reconsider product schedule?