FDA Flow Schema for Abuse Liability Assessment of New Pharmaceuticals

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Overview

• **Background**
  – Comments on draft FDA guidance
  – Ongoing dialogue between CSS and industry

• **Importance of flow schema**
  – EMA flow diagram
  – Complexity of abuse liability assessments

• **20-step walk-through**
  – Emphasis on key decision points
  – Necessary data
  – Comments and suggestions
Background

- Assessment of the potential for abuse for a new pharmaceutical is complex.
- Since the Controlled Substances Act (1970), drugs in classes known to be commonly abused have been evaluated and subject to scheduling:
  - Opioids
  - CNS depressants
  - CNS stimulants
  - Hallucinogens
  - Cannabinoids
  - Anabolic steroids
Increasing Abuse of Prescription Drugs

- **NIDA**
  - 7 million people use psychotherapeutics non-medically

- **Office of National Drug Control Policy**
  - While cocaine use ↓, in active military, prescription drug abuse ↑ 5%-12% (2005-2008)

- **CDC**
  - “Prescription drug abuse is the fastest growing drug problem in the United States”
    
    CDC Grand Rounds, 13 January 2012
Expanded Evaluation

- Recent guidances indicate the need to evaluate all CNS-active pharmaceuticals for abuse potential, not just those in identified abuse categories
  - 2006 EMA
  - 2009 M3(R2)
  - 2010 FDA draft + decision tree

- Evaluation encompasses various aspects of abuse potential
  - Reinforcing/rewarding properties
  - Physical dependence properties
  - Similarity to known drugs of abuse

- Includes preclinical and clinical studies
  - Supporting data to determine if studies are warranted
  - Preclinical studies in rats or monkeys
  - Clinical studies in recreational drug users
Guidances on Abuse Potential

• EMA guidance 2006

GUIDELINE ON THE NON-CLINICAL INVESTIGATION OF THE DEPENDENCE POTENTIAL OF MEDICINAL PRODUCTS

– Covers nonclinical strategy and studies

• ICH M3(R2) guidance 2009

• M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals

– Section 15 NONCLINICAL ABUSE LIABILITY
FDA Draft Guidance

- Before and after draft guidance released, Industry and CSS/FDA engaged in series of dialogue sessions
  - Unique ongoing series of interactions
  - Topic is science of abuse liability assessment, not process

- Interaction ongoing since 2008
  - Focused dialogue sessions with industry and CSS participants
  - Recently held dialogue session to discuss decision tree
  - Also symposia and workshops at national meetings
    - 2-4 each year
    - SOT, CPDD, SPS, ACT, NESOT, ISCCTM
Scope of Draft Guidance

• **2010 draft guidance – comprehensive**
  
  – Preclinical studies
    • Self-administration, drug discrimination, physical dependence
    • Supporting data
      – Chemical, pharmacology, PK
  
  – Clinical studies
    • Lab studies, recreational drug users
  
  – Chemistry and Manufacturing
  
  – Post-marketing experience
  
  – References labeling and scheduling

• **Extensive comments returned on draft guidance from many sources**
“Decision Tree” Request

• Among comments, request from various sources for a decision tree to help navigate complexities of abuse liability assessment
  – Individual companies, PhRMA, CCALC

• 2011 CSS revealed a draft decision tree
  – Poster presentation: Bonson & Sun, Science of Abuse Liability Assessment, Rockville MD November 2011

• Comments on decision tree are invited; discussion continues
Decision Tree Purpose

- The decision tree is designed to complement the guidance
  - Improve efficiency, transparency and consistency in abuse liability assessment

- Aligns preclinical and clinical data into comprehensive package

- Provides further guidance
  - Key questions to ask at each step
  - Identifies Go/No Go points
Flow Schema

- **Draft Decision Tree for abuse liability assessment**
  - 3 key decision points identified
  - detailed

Nonclinical phase

Early clinical – EOP2

Late clinical – NDA
Path to Integrated Abuse Liability Package

- **20 steps to integrated data set**
  - Grouped into 3 sections that lead to a key decision point based on data generated
    1. Is the drug or metabolite CNS-active?
    2. Is a human abuse potential study needed?
    3. Do the abuse-related data in the NDA show that the drug has abuse potential?

- **Timing for each decision point**
  1. Pre-IND
  2. End of phase 2 meeting
  3. NDA submission
Nonclinical Phase

1. Chemistry
   Characterize structure and synthesis

   *Is similar to known drug of abuse?*

2. Receptor Binding
   Full CNS receptor binding

   *Is binding similar to known drug of abuse?*

3. Functional Binding
   Behavior and/or Second messenger

   *Is agonist or antagonist function similar to drug of abuse?*

4. CNS Safety Pharm study

   *Does produce overt drug of abuse-related behaviors?*

5. Animal PK

   *What is PK profile in animals?*
First Decision Point

Evaluate all CNS data

Is compound or major metabolite CNS-active?

6

NO

STOP

YES

Proceed to animal abuse liability studies
Animal Abuse Liability Studies

3 nonclinical studies typically associated with abuse liability assessment

1. **Animal drug discrimination study**
   - Is compound similar to comparator drug of abuse?

2. **Animal Self administration study**
   - Is compound rewarding or reinforcing?

3. **Physical dependence study**
   - Does compound produce tolerance or withdrawal syndrome?

4. **Evaluate all nonclinical data**
   - Are study plans appropriate?

5. **Propose plan and discuss with CSS**
Early Clinical Phase

11
Abuse AEs in healthy volunteers (Phase 1)

*Does drug cause abuse-related AEs in healthy subjects?*

12
Abuse AEs in patients (Phase 2)

*Does drug cause abuse-related AEs in patients?*

13
Incorporate physical dependence in humans

*Does drug cause physical dependence in humans?*

Some AE-related terms

- Euphoria-related
- Dissociative/psychotic
- Impaired mood, cognition, attention or psychomotor events
- Inappropriate affect
- Medication tampering
Second Decision Point

- Evaluate early clinical AEs and animal abuse liability data
- Is human abuse potential study needed?
- Consult with CSS

Consult with CSS and proceed to human abuse liability studies

YES

NO

STOP
Late Clinical Stage

15
Abuse study in recreational drug users

Does drug produce rewarding/reinforcing effects in humans?

16
Abuse AEs in patients (Phase 3)

Does drug cause abuse-related AEs in larger number of patients?

17
Prepare abuse potential section for NDA submission

Is section complete?
Propose DEA drug schedule
Third Decision Point

Do abuse data in NDA show abuse potential?

FDA reviews all data

Does drug have abuse potential?

Yes → DEA for scheduling

No
Post-Marketing Surveillance

19

Review ex-US reports for signs of abuse potential

Are there foreign post-marketing abuse signals?

20

Propose appropriate product label for abuse liability

Does product label accurately reflect abuse potential information?
Comments on Decision Path

• Draft decision tree is the result of ongoing communication between industry representatives and CSS staff

• Comments are still welcome on the decision tree
  – PhRMA is not sending comments
    • Did comment on draft guidance
  – CCALC offers comments from the working groups to any participating company

• Comments can be sent to
  – Corinne P Moody
    CDER, FDA
    10903 New Hampshire Ave, Bldg 51, Room 5144
    Silver Spring, MD 20933-0002
    301-796-5402
Areas of Ongoing Discussion

• Areas for continued discussion, points for further resolution still exist
  – Nonclinical
  • Timing of data – pre-IND may mean studies will need to be re-done when clinical efficacious concentrations are known
  • How to handle compounds that don’t cross the BBB and/or are PGP substrates
  • Comparator drugs for novel mechanism compounds in drug discrimination study and training drug for self administration study continues to be a difficult area to address
  • Scope of physical dependence evaluation; some suggestion that it might apply to all compounds
Ongoing Discussion Points

• Early clinical/late clinical
  – Discussion of acceptable terms and hallmark AEs suggestive of abuse potential is ongoing
  – Role of human physical dependence study and how the data could impact scheduling
  – If no human abuse study is needed, according to the decision tree, no further work is needed until post-marketing surveillance; does this mean looking for abuse related AEs in Phase 3 is not necessary?
Advantages of Decision Tree

• Creation of the decision tree by CSS staff is acknowledged to be a huge undertaking, and is appreciated

• It provides an invaluable guide through complex territory

• Aligns preclinical and clinical data for the creation of an integrated abuse potential assessment

• Should help make easier navigation through abuse liability assessment
Ongoing Dialogue

• Decision Tree is, in part, the product of an ongoing dialogue between industry experts and CSS staff on the science of abuse liability assessment

• Unique and productive collaboration that is enhancing assessment of abuse liability for new pharmaceuticals

• There are still areas for discussion and resolution, but the foundation for an open relationship has been laid by the past Dialogue Sessions and ongoing symposia at national scientific meetings