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

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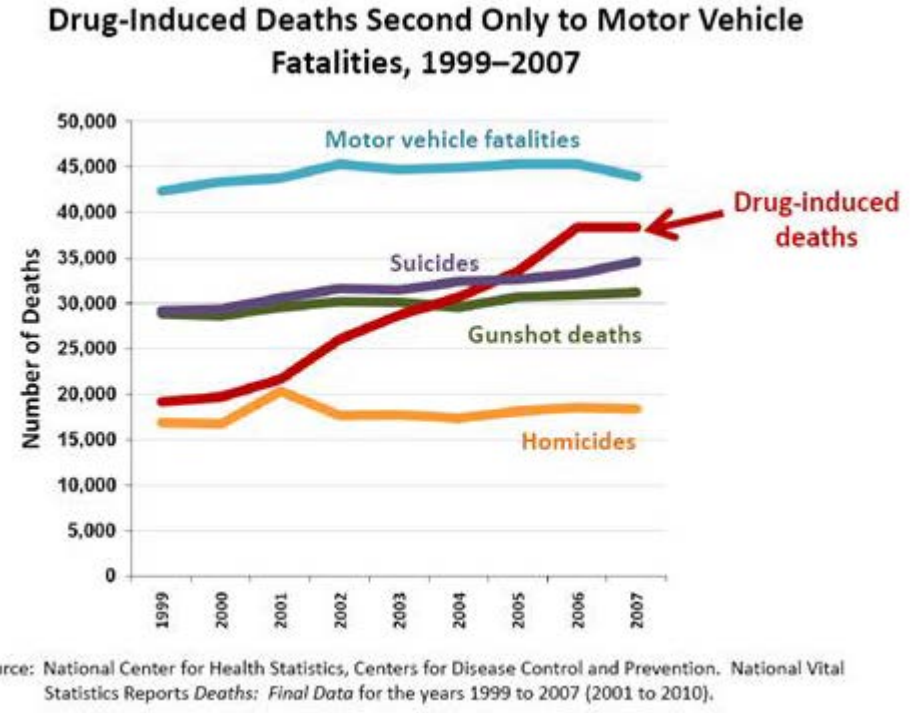
Increasing Abuse of Prescription Drugs

- 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



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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

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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

Guidance for Industry
Assessment of Abuse Potential of Drugs
DRAFT GUIDANCE

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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

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“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

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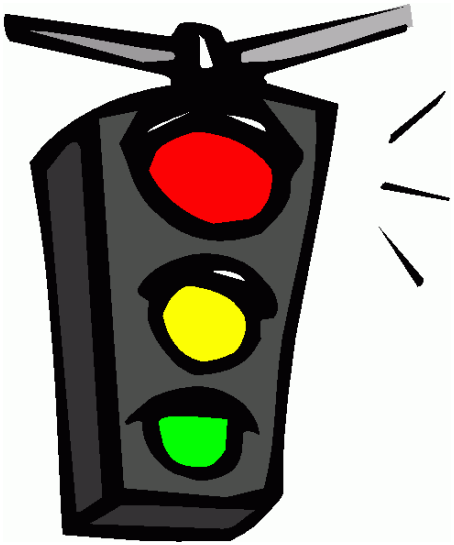
Decision Tree Purpose

- 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



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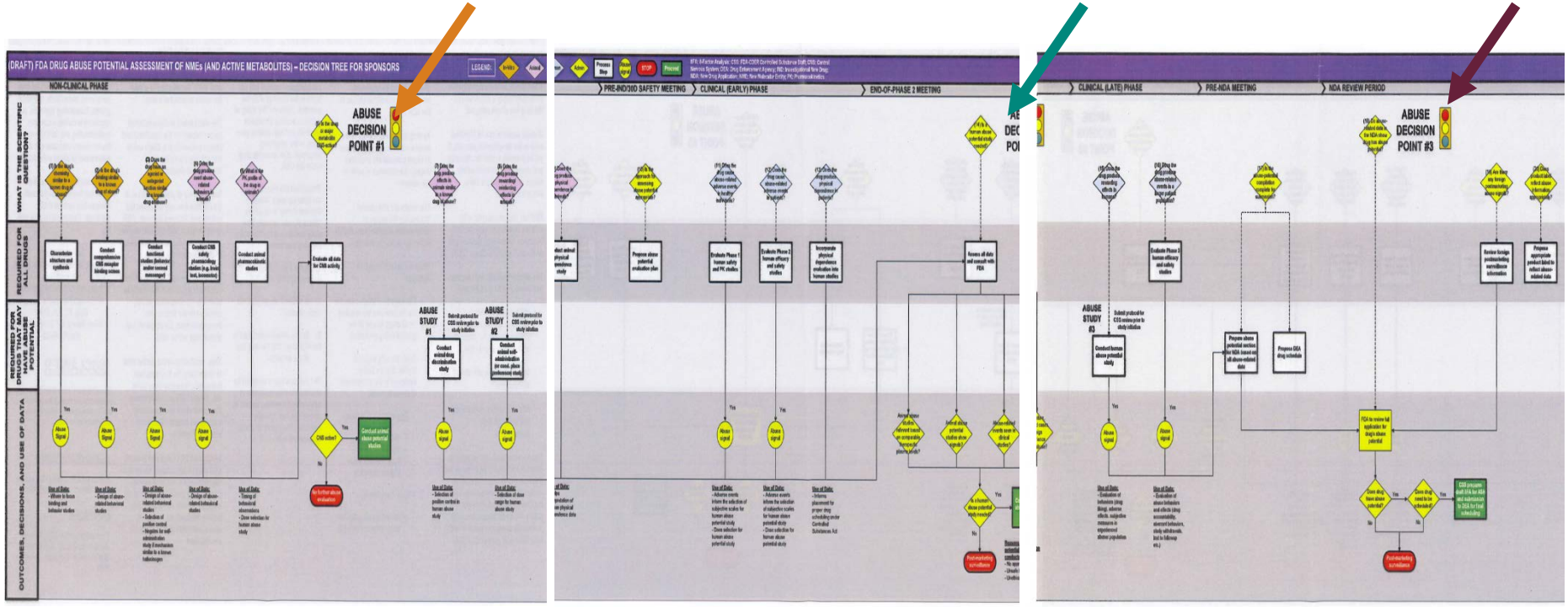
Flow Schema

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



Nonclinical phase

Early clinical – EOP2

Late clinical – NDA

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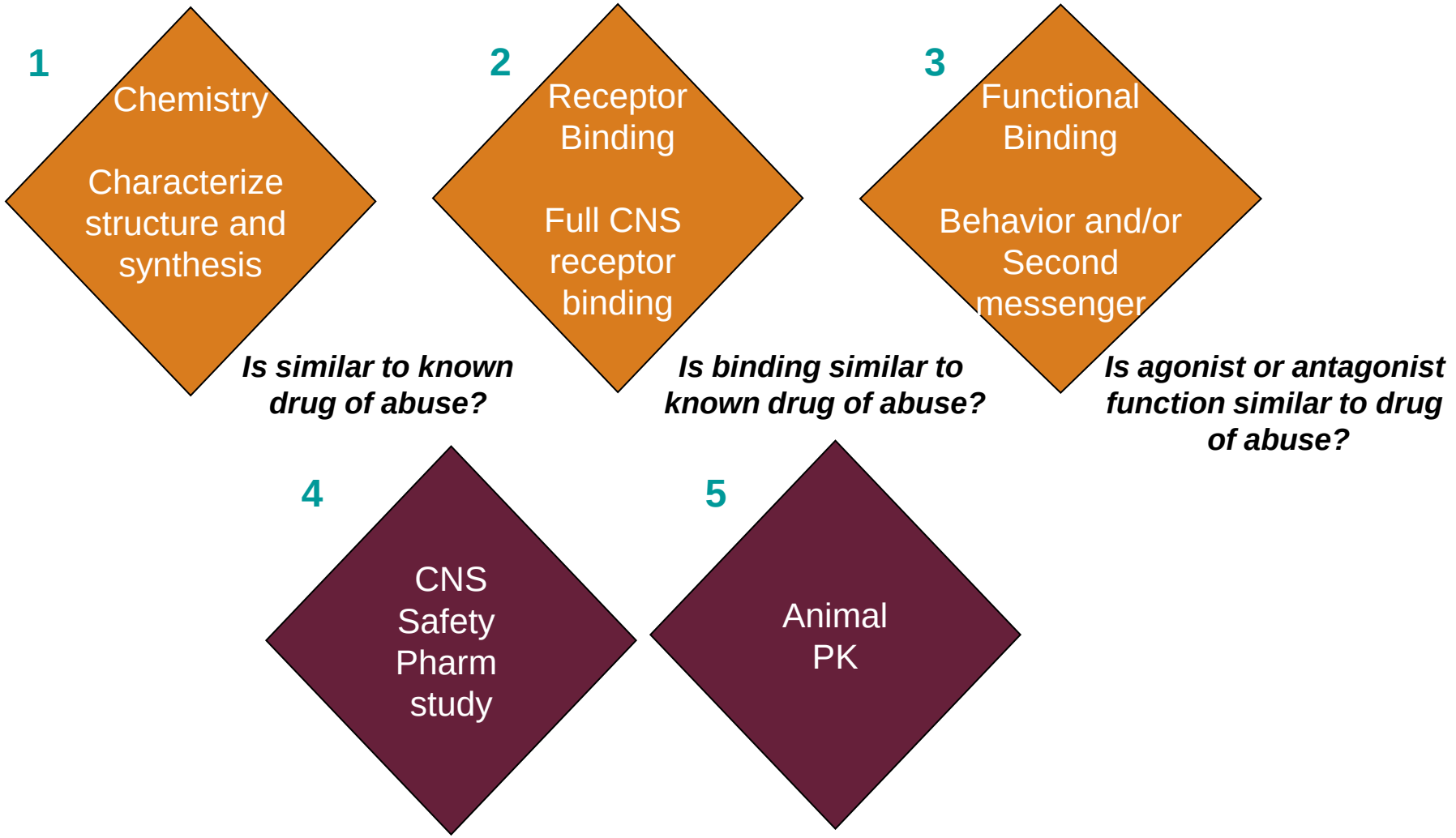
Path to Integrated Abuse Liability Package

- 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



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First Decision Point

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First Decision Point

Evaluate all CNS data

Is compound or major metabolite CNS-active?

YES → **Proceed to animal abuse liability studies**

NO

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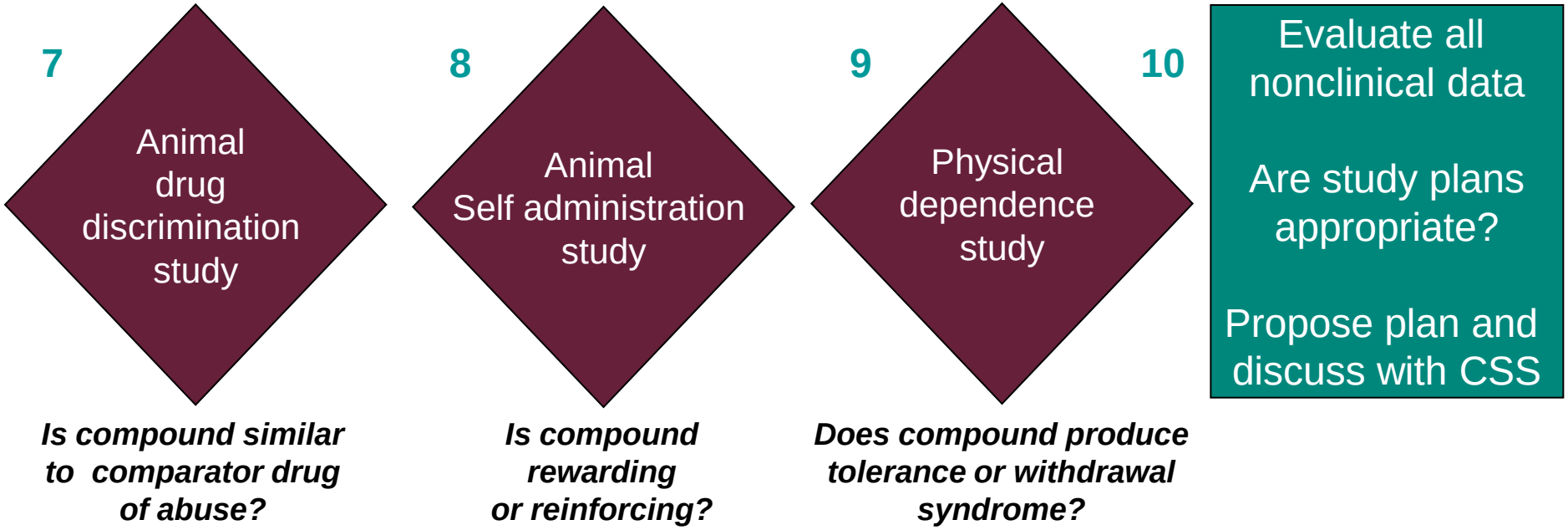
Animal Abuse Liability Studies

3 nonclinical studies typically associated with abuse liability assessment



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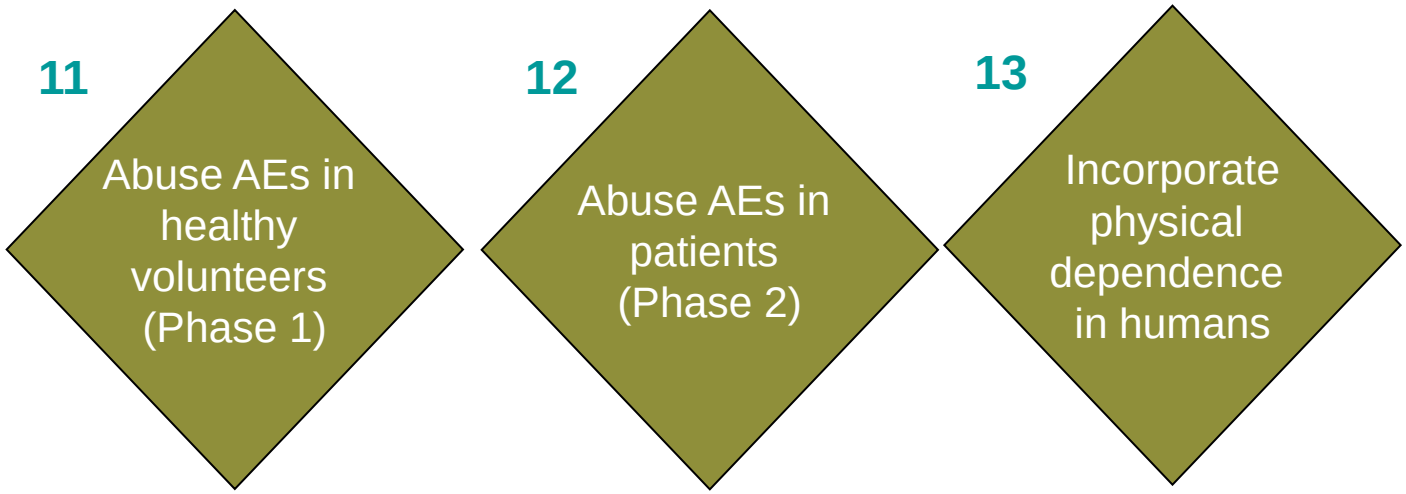
Early Clinical Phase



Does drug cause abuse-related AEs in healthy subjects?

Does drug cause abuse-related AEs in patients?

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

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Second Decision Point

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Second Decision Point

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

→ **YES** → **Consult with CSS and proceed to human abuse liability studies**

↓ **NO**

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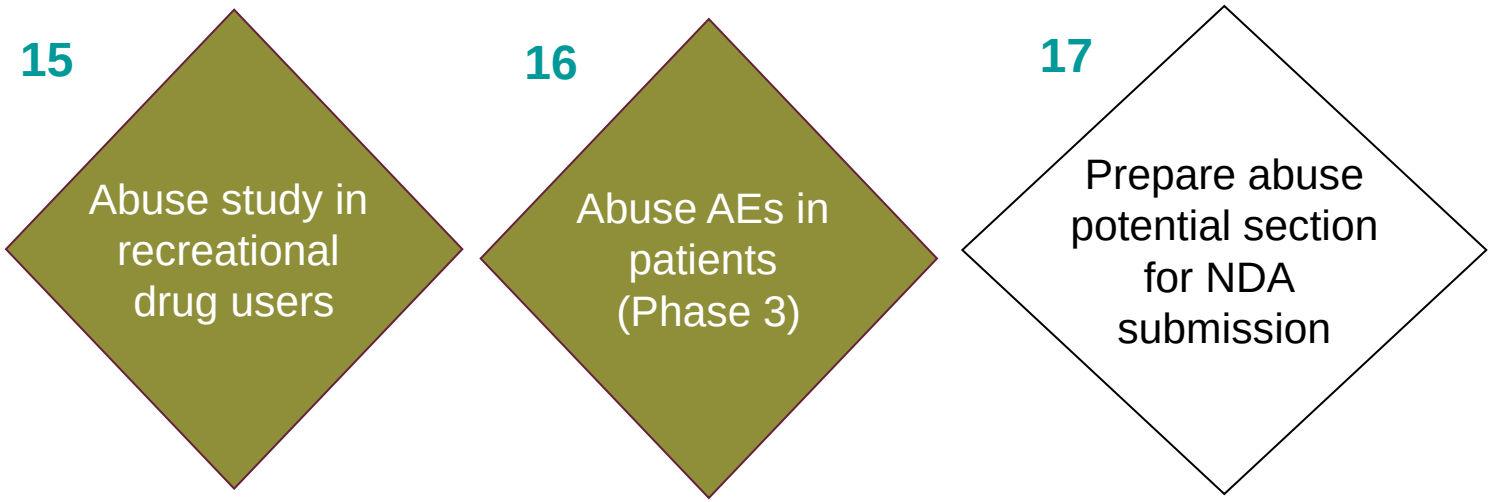
Late Clinical Stage



Does drug produce rewarding/reinforcing effects in humans?

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

Is section complete? Propose DEA drug schedule

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Third Decision Point

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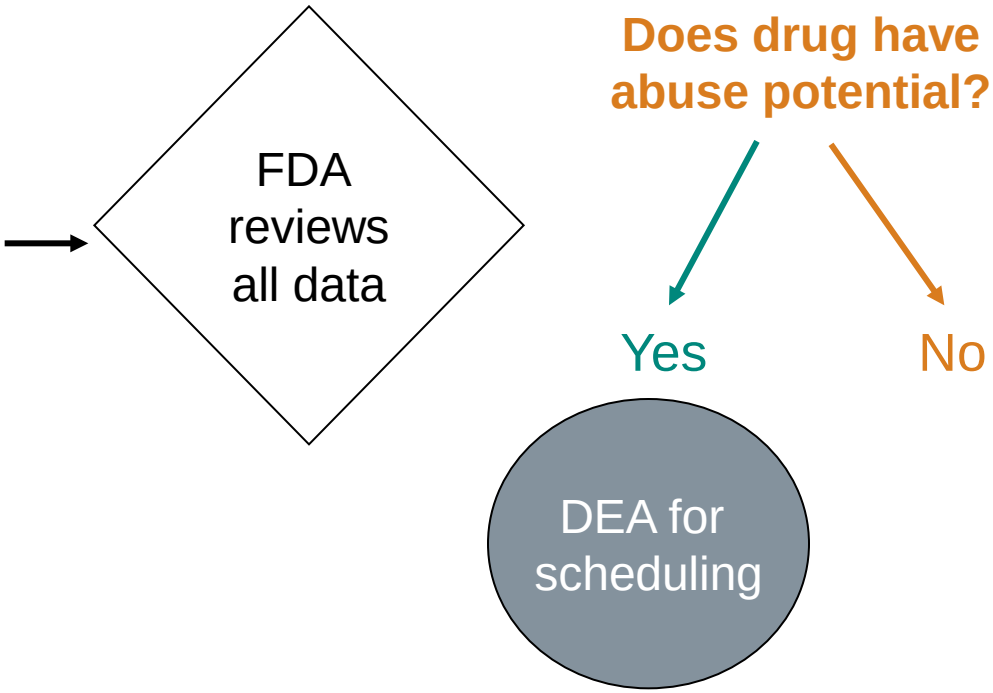
Third Decision Point

Do abuse data in NDA show abuse potential?



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Post-Marketing Surveillance

Are there foreign post-marketing abuse signals?

Does product label accurately reflect abuse potential information?

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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

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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

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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

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