FDA Perspective on Best Practices for the Preclinical Evaluation of Physical Dependence and Withdrawal (PDW)

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I do not have any disclosures.

Topics to Highlight Today

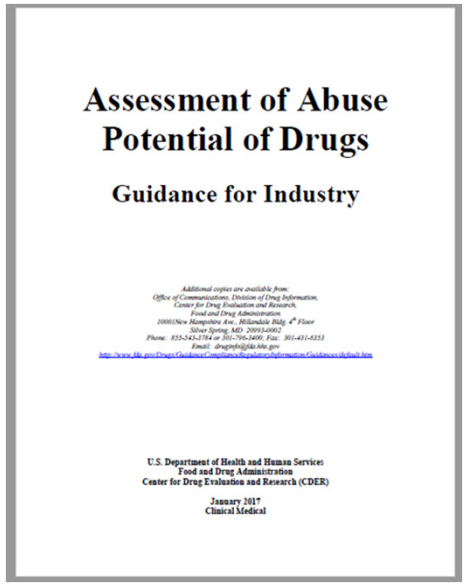
- What is the current FDA guidance for evaluating physical dependence and withdrawal from a nonclinical perspective?

- What are some common nonclinical dependence and withdrawal questions addressed by CSS?

Controlled Substance Staff (CSS)

CSS functions as a consulting group within and across CDER, as well as the FDA

- CSS evaluates drug products for drug abuse potential, as well as for dependence and withdrawal
- Guidance on the assessment of abuse potential of drugs is available; published in January 2017
  - for nonclinical drug abuse studies: see Section IV. "Abuse-related data from chemistry and nonclinical studies," including dependence and withdrawal in Subsection D.5. "Evaluation of physical dependence and withdrawal behaviors"
    - » We evaluate physical dependence as part of the NDA review to inform the product label and drug scheduling



Nonclinical Physical Dependence Study

The nonclinical physical dependence and withdrawal study evaluates whether chronic administration of a drug at therapeutic plasma levels produces a withdrawal syndrome upon drug discontinuation.

Methodological recommendations:

- Assessment may be conducted in animals at the conclusion of a toxicology study or in a dedicated study
- Administer the drug for 4 weeks at stable doses that produce drug plasma levels equivalent to those produced by clinical therapeutic (and possibly supratherapeutic) doses
- Use scheduled drugs as positive controls
- Use abrupt drug discontinuation

Nonclinical Physical Dependence Study (Continued)

- Behavioral observations of animals should begin several days before drug discontinuation to establish how the drug affects behavior
- Observations should be assessed daily for at least 7 days after drug discontinuation, or for a duration equivalent to the time when the test drug is eliminated (whichever is longer)
- A standardized checklist of expected withdrawal behaviors for pharmacological drug classes should be used
- Study should be conducted in accordance with the United States Department of Health and Human Services, Food and Drug Administration, United States Code of Federal Regulations, Title 21, Part 58: Good Laboratory Practice for Nonclinical Laboratory Studies

Examples of Recommendations

Nonclinical physical dependence and withdrawal advice/guidance and determinations conveyed to an applicant based on submitted drug abuse and dependence information (protocols, study reports, data) have included:

- Need for additional information (e.g., receptor binding, or adverse event assessment)
- Propose phase 2 or 3 clinical dependence and withdrawal assessments
- Advice on study design/methods, positive controls, or other comparator drugs
- Provide advice on, or propose drug dependence-related language for the product label (Section 9)
- Respond to dependence and withdrawal-related clarifying questions

COMMON QUESTIONS INVOLVING NONCLINICAL PDW

Question 1

When should a nonclinical study of physical dependence and withdrawal be conducted?

Depending on study information and data submitted to the Agency at the time of the IND/NDA submission (or information request),

- If nonclinical drug abuse-related studies were recommended a nonclinical physical dependence and withdrawal study should be conducted at EOP2 when human therapeutic doses (and possibly final-to-be-marketed dosage form) have been determined.
- -If nonclinical drug abuse-related studies were not recommended, a nonclinical physical dependence and withdrawal study may not be needed unless there is still the potential for withdrawal symptoms when the drug is discontinued in patients, as determined by the applicant or the OND review division.

Question 2

What are the appropriate doses? Should we consider going higher than 2-3X therapeutic to look for a signal of physical dependence and withdrawal?

When testing in animals, use doses that will product plasma levels that are equivalent to, and possibly 2-3 times greater than the human plasma levels produced by the highest therapeutic dose. Thus, supratherapeutic doses also should be evaluated when conducting nonclinical physical dependence and withdrawal assessments.

- Conducting nonclinical studies allow investigators/applicants to evaluate supratherapeutic doses for extended time periods.
- Study results captured with supratherapeutic doses can help inform applicants on the experimental methods and drug doses to be used in clinical dependence assessments.

Drug dose recommendations will also depend on the study information and data submitted to the Agency at the time of the IND/NDA submission (or information request).

Question 3

Are there specific behaviors or outcome measures to look for when conducting a nonclinical physical dependence and withdrawal study? Are these class or indication specific?

Yes, “a standardized checklist of expected withdrawal behaviors" (e.g., vocalization, chewing, posturing, grooming, locomotor horizontal, vertical, and stereotypy activity, seizures, and hypoactivity) "for pharmacological drug classes should be used. Different pharmacological classes of drugs tend to produce different withdrawal syndromes (although there can be overlapping responses) (source: *the guidance, Assessment of Abuse Potential of Drugs, page 20*).”

With that said, “the drug selected as the positive control should be in the same pharmacological class as the test drug, whenever possible, and should be scheduled under the CSA…For a test drug with a mechanism of action that is novel or does not correspond to a drug currently controlled under the CSA, the Agency will consider sponsor proposals for an alternative positive control. This may be a drug that has a therapeutic indication or behavioral profile that is similar to the test drug, even if the mechanism of action is different *(*source: *the guidance, Assessment of Abuse Potential of Drugs, page 16*)."

Question 4

What are the next step(s) if a nonclinical dependence study was shown to be negative? Do we still need a human assessment of physical dependence and withdrawal? If so, what is the primary purpose of the animal study?

Depending on submitted information, a clinical physical dependence study may still be needed, even if a nonclinical dependence study was shown to be negative.

- The applicant or the OND review division may determine that the discontinuation of the drug potentially will lead to withdrawal symptoms in patients (See also Slide 1).
- There is the potential for drug-related metabolic, PK or PD differences between animals and humans that may influence results
- There is the potential for drug discontinuation-related responses and symptoms that can only be captured (with a subject scale) by conducting a clinical dependence assessment

Question 4 (Continued)

What are the next step(s) if a nonclinical dependence study was shown to be negative? Do we still need a human assessment of physical dependence and withdrawal? If so, what is the primary purpose of the animal study?

- An "assessment of human physical dependence should not commence until information is available regarding the ability to safely discontinue the test drug in study subjects (as discussed in the guidance, Assessment of Abuse Potential of Drugs, Section V.E. Refer to Sections IV and V for typical study design elements, page 7)." Thus, conducting a nonclinical physical dependence study helps to establish support that it will be safe to use drug discontinuation methods with the drug in humans.
- Even if the nonclinical physical dependence study was negative, conducting the study allowed for testing supratherapeutic doses, and collecting study results, which would help inform applicants on protocol design and drug doses to be used in a clinical assessment of dependence.

Summary

The nonclinical assessment of physical dependence and withdrawal is:

- Used to identify physical dependence and withdrawal signals early during drug development
- Used to provide direction and inform design of human studies
- Useful when evaluating NMEs with novel mechanism of action
- Critical in the overall safety assessment, as well as providing necessary data for an Eight-Factor Analysis, if one will be conducted


Thank You!

Back-up Slides

Nonclinical Physical Dependence Studies

Strengths

- Strong correlation between animal withdrawal effects and drugs being abused by humans
- Well established models for several drug classes

Limitations

- Scarce data for novel drug classes
- False negatives