# Regulatory Requirements for Assessing Physical Dependence and Withdrawal in Human Subjects

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# Disclaimer

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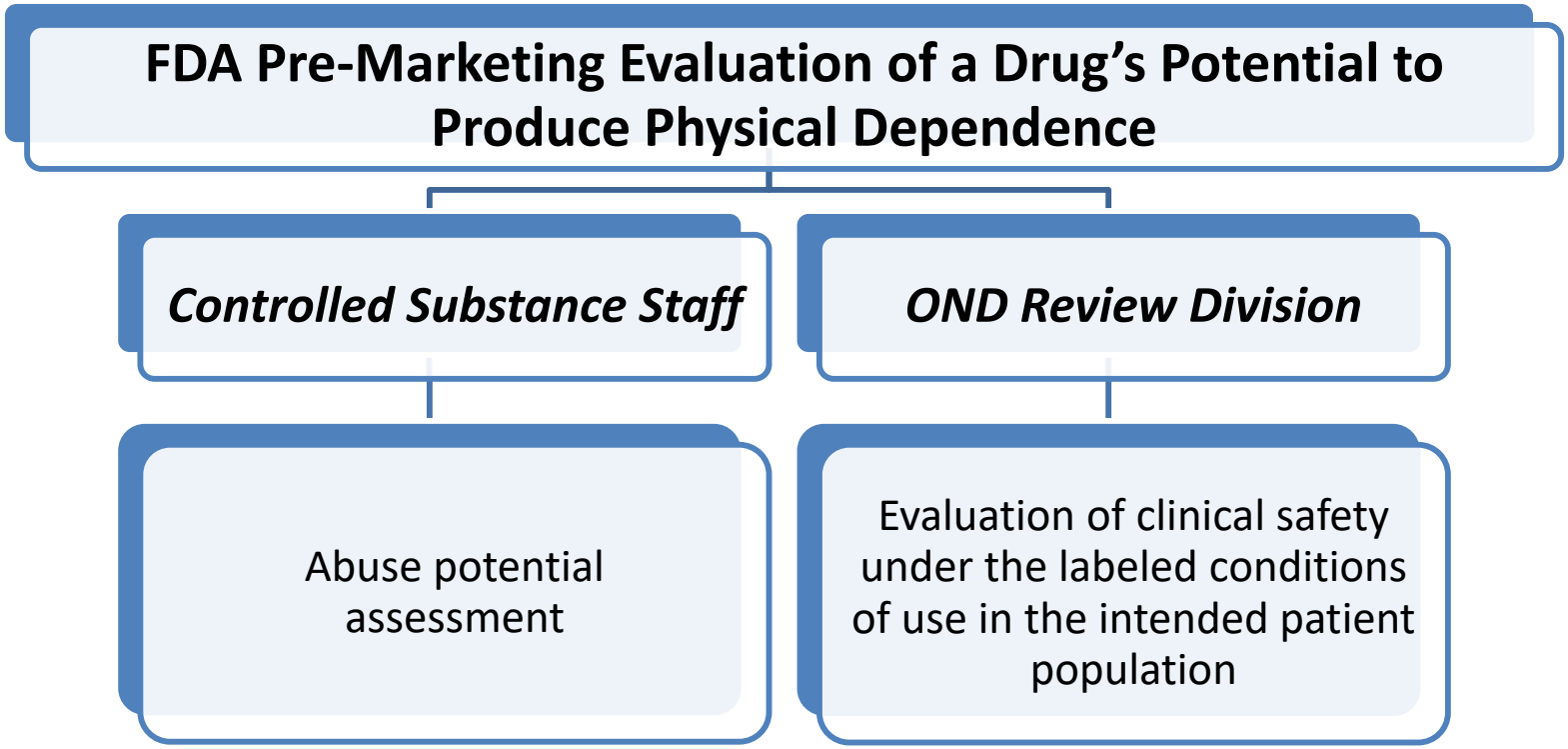
# Outline

- Approach to the clinical evaluation of physical dependence
- Methodological considerations for clinical evaluation of physical dependence
- Limitations in the clinical evaluation of physical dependence
- Conclusions

# Background

- ***Physical dependence*** is a state that develops as a result of physiological adaptation in response to repeated drug use, manifested by drug class-specific withdrawal symptoms after abrupt discontinuation or a significant dose reduction of a drug
- Certain drug classes are associated with a well-characterized withdrawal syndrome
  - ***Opioids*** – gastrointestinal symptoms (e.g., nausea, vomiting), flu-like symptoms (e.g., rhinorrhea, shivering, piloerection), cardiovascular and central nervous system effects (e.g., mydriasis, anxiety, irritability, insomnia, tremor)
  - ***Benzodiazepines*** – anxiety, blurred vision, gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea), headache, irritability, insomnia, tachycardia, tremor, as well as life-threatening reactions, including psychosis and seizures


FDA Pre-Marketing Evaluation of a Drug's Potential to Produce Physical Dependence
Controlled Substance Staff
OND Review Division
Abuse potential assessment
Evaluation of clinical safety under the labeled conditions of use in the intended patient population

# Approach to the Evaluation of Physical Dependence

- Abuse potential assessment
  - Provide information that FDA will use in determining whether a drug will be recommended for scheduling under the CSA, and if so, which schedule will be recommended (see 21 U.S.C. 811(c)(7))
  - Provide accurate information in labeling regarding the risks of physical dependence
    - Inform prescribers of the signs and symptoms of withdrawal
- Evaluation of physical dependence is an important component of the abuse potential assessment of new molecular entities with central nervous system (CNS) activity
  - However, may also be required for controlled substances with already approved medical indications (e.g., 505(b)(2) NDA)
    - New indication, higher therapeutic dose than previously approved, increase in dosing frequency, increase in treatment duration

# Approach to the Evaluation of Physical Dependence

- Evaluation of the clinical safety of the drug under the labeled conditions of use in the intended patient population
  - Relapse of symptoms of the underlying condition
  - Rebound of symptoms of the underlying condition
    - e.g., increased severity and/or frequency of anxiety, depression, suicidal ideation, seizures, psychosis
  - Need for tapering with discontinuation or dose reduction
    - For serious safety concerns associated with abrupt drug discontinuation such as seizures, cardiovascular effects, psychiatric effects, etc.
- Also, an important component of the safety evaluation of drugs that produce physical dependence but without abuse potential
  - e.g., beta-blockers, monoamine reuptake inhibitors (e.g., SSRIs)

# Objectives of Clinical Evaluation of Physical Dependence

- Characterize the signs and symptoms
  - Different pharmacological classes of drugs may produce unique withdrawal symptoms that are often opposite to the responses produced during drug administration
- Characterize the time course of acute withdrawal upon the drug discontinuation
  - Different drug class may have different time course of acute withdrawal upon drug discontinuation
  - Acute withdrawal may start at 24-96 hours after the last dose, peak within one week and last for a couple of weeks
- Characterize the severity of withdrawal
  - Severity of acute withdrawal generally is associated with higher doses, longer treatment duration, and increasing dosing frequency
  - Severity also depends on the drug class (e.g., potential for life-threatening withdrawal with benzodiazepines) and, potentially, the pharmacokinetic properties of the drug

# Study Design Considerations

- Clinical evaluation does not typically involve a dedicated study
- May be incorporated into an ongoing or planned Phase 2 or 3 clinical study in the intended patient population
  - Double-blind, placebo- or comparator treatment-controlled
  - Maximum therapeutic doses
  - Minimum 4-week treatment duration for evaluation of physical dependence (feasible for chronic indications)
    - For non-chronic indications, where less than a 4-week treatment duration is employed in clinical studies, the evaluation may occur after treatment at the intended therapeutic duration
  - Monitored discontinuation period
  - Use of abrupt drug discontinuation

# Study Design Considerations

- Other approaches may be considered for clinical study populations that would be at particular risk due to abrupt drug discontinuation (e.g., epilepsy, schizophrenia, etc.)
  - Dedicated dependence study in healthy volunteers – ethical considerations, adequate informed consent
  - Multiple dose PK study of sufficient duration
- Study design and risk of dependence may also be informed by available nonclinical data related to dependence

# Observation Period and Assessments

- Duration of observation after last dose of study drug should cover the anticipated time course of the acute withdrawal period
  - At least 3 weeks and to cover at least 5 half-lives of the test drug or major active metabolite(s)
    - e.g., drugs with a longer half-life may require a longer observation period (more than 3 weeks)
- Evaluation consists of an assessment of adverse events (AEs) and vital signs, as well as drug-class specific withdrawal scale(s) and other assessments if relevant
  - Timing – daily for the first week; at least every other day during the subsequent weeks
  - At-home evaluations may be acceptable with appropriate systematic methodology (e.g., daily diary)

# Drug Class Specific Withdrawal Scales

Examples of scales that have been used in regulatory applications for measuring drug class-based withdrawal syndromes:

- Clinical opiate withdrawal scale (COWS)
  - Subjective and Objective versions (SOWS, OOWS)
- Benzodiazepine withdrawal scale
  - Physician Withdrawal Checklist (PWC)
- Stimulant withdrawal scales
  - Amphetamine Withdrawal Questionnaire (AWQ)
  - Cocaine Selective Severity Assessment (CSSA)
- Cannabinoid withdrawal scales
  - Cannabis Withdrawal Scale (CWS) and Marijuana Withdrawal Checklist (MWC)

# Data Analysis Considerations

- Discontinuation emergent adverse events
  - Phase 2/3 clinical study where dependence was systematically evaluated
  - Additionally pooled analyses of other studies with a follow-up period after drug discontinuation (including early discontinuation) or inter-treatment period where AEs were assessed
    - Other Phase 2/3 clinical studies
    - Phase 1 multiple-dose, double-blind, pharmacokinetic and/or pharmacodynamic studies
  - Standardized MedDRA Queries(SMQ) for the specific preferred terms may be helpful for test drug with known drug class specific acute withdrawal syndromes
  - Active drug vs placebo; on-treatment vs off-treatment
- Vital signs
  - Maximum change of mean from baseline (last dose)
  - Active drug vs placebo
- Drug Class Specific Withdrawal Scales analysis
  - Plot of mean score over time
  - Maximum change of mean score from baseline (last dose)
  - Percentage of subjects with mild, moderate, or severe withdrawal as defined by drug class specific withdrawal scale
  - Active drug vs placebo

# Limitations of the Clinical Evaluation of Physical Dependence

- Therapeutic doses and treatment durations may not be sufficient to produce physical dependence for the test drug
  - Shorter intended treatment durations
  - Phase 1 studies typically involve supratherapeutic doses; however, they are of limited duration
- Effects of the underlying condition in Phase 2/3 studies
  - Symptoms may obscure signs and symptoms of acute withdrawal
  - Additionally, the test drug may differentially affect symptoms in the placebo group vs the treatment group at the end of treatment phase
- Effects of concomitant medications in Phase 2/3 studies
  - Need to switch to standard of care
- Points for further discussion to address some of these limitations
  - Add on double -blind, placebo-controlled, withdrawal period at the end of treatment phase in a planned long term, open label, safety study
  - Add on double blind, placebo-controlled withdrawal period at the end of treatment phase in planned Phase 1 double-blind, multiple-dose, PK and safety study

# Conclusions

- The clinical assessment of dependence is based on a systematic evaluation of signs and symptoms after abrupt drug discontinuation in at least one study, along with a review of data after drug discontinuation from other clinical studies

- Overall conclusions about whether a drug produces physical dependence and labeling describing those risks are based on data from
  - Animal studies (physical dependence and toxicology)
  - Human studies (physical dependence and other studies)
  - Published literature and epidemiological databases, if applicable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