Regulatory and Methodological Considerations in the Assessment of Physical Dependence

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FDA Definition of Physical Dependence

- ***Physical dependence*** is a state that develops as a result of physiological adaptation in response to repeated drug use.
- Physical dependence manifests by drug class-specific withdrawal symptoms after abrupt discontinuation or a significant dose reduction of a drug.
- The appearance of a withdrawal syndrome when administration of the drug is terminated is the only actual evidence of physical dependence.
- Physical dependence is associated not only with the repeated use of known drugs of abuse, but with drugs with no abuse potential as well.

Regulatory Evaluation of Physical Dependence

- Physical dependence is evaluated as a safety issue at FDA.
- The primary regulatory question is:

  Can the drug be discontinued abruptly without risk of adverse events (e.g., a withdrawal syndrome), or should the drug be tapered during discontinuation?

- The determination of whether a drug produces physical dependence is primarily the responsibility of the review Divisions.
- However, Divisions rely on the expertise of CSS regarding the study design and data evaluation of physical dependence studies in animals and humans.

Why Does FDA Evaluate Physical Dependence?

If a drug produces physical dependence, this had implications for:

- Drug labeling
- Scheduling placement under the Controlled Substances Act (CSA)

Why Does FDA Evaluate Physical Dependence?

Drug Labeling:

- **Section 9 *Drug Abuse and Dependence* includes**:
  - **9.1 Scheduling**

    Drug placement under the CSA, if applicable
  - **9.2 Abuse**

    Detailing of human and animal abuse-related data
  - **9.3 Dependence**

    Detailing available data on physical dependence, as shown by the ability of a drug to produce withdrawal symptoms upon drug discontinuation

Why Does FDA Evaluate Physical Dependence?

Drug Labeling:

Section 9.3 *Dependence*

- Conveys information to health care providers (HCPs) and patients regarding the likelihood that withdrawal symptoms will emerge upon abrupt drug discontinuation
- This will inform HCPs whether tapered drug discontinuation is advisable, which may be described in Section 2 *Dosage and Administration*, or Section 5 *Warnings and Precautions*.

Why Does FDA Evaluate Physical Dependence?

Scheduling under the CSA (21 UCS 812(b)):

- The ability of a drug with currently accepted medical use in the U.S. to produce physical or psychological dependence influences the scheduling placement of drugs under the CSA (e.g., drugs in Schedules II, III, IV, or V).
- Criteria for each placement includes consideration of "Abuse of the drug may lead to [*severe/moderate/low/limited*] physical dependence and/or [*severe/high/limited*] psychological dependence."
- For Schedules IV and V, the dependence is "relative to drugs" in Schedules III and IV, respectively.
- Illicit drugs in Schedule I are not placed based on dependence.

Confusion with the Term “Dependence”

- The neurological state of physical dependence has often been confused with “drug dependence”, which is a psychiatric term.
- Previously, DSM-IV-R described diagnostic criteria for both “substance abuse” and “substance dependence”, with the latter involving criteria for physical dependence and tolerance.

Confusion with the Term "Dependence"

- The revised DSM-5 combines those two diagnostic categories into a single disorder measured on a continuum of 10 or 11 criteria, ranging from mild (2-3 criteria) to moderate (4-5 criteria) to severe (>6 criteria).
- "Withdrawal" is one of these criteria, but is not required. It is manifested by either: "The characteristic withdrawal syndrome for that substance (as specified in the DSM-5)" or "The use of a substance (or a closely related substance) to relieve or avoid withdrawal symptoms."

“Addiction” vs. “Physical Dependence”

- However, FDA does not engage in the diagnosis of addiction in evaluating whether a drug can produce physical dependence (or drug abuse).
- Instead, we rely on changes in behavior, physiological symptoms, and adverse events that are observed or reported during drug discontinuation following prolonged drug administration.
- Although we recognize that a withdrawal syndrome can persist for many weeks or months after drug discontinuation, for regulatory purposes, we limit the required assessment period to 2-4 weeks after the subject has stopped taking the drug.

Guidance: Assessment of Abuse Potential of Drugs

This presentation will focus on the assessment of physical dependence for drugs that act on the CNS, based on our 2017 guidance for industry: *Assessment of the Abuse Potential of Drugs*:

- Any drug with CNS activity will need to be assessed for abuse potential, so the assessment of physical dependence falls under that evaluation.
- However, even if a drug does not have abuse potential, it may still produce physical dependence.
- Although physical dependence is assessed during the safety evaluation of a drug, it is also considered to be part of the abuse potential assessment because of the role aversive withdrawal can play in maintaining abuse of certain classes of drugs.

Assessment of Physical Dependence in Animals

- An animal physical dependence study evaluates whether chronic administration of a test drug at therapeutic plasma levels produces a withdrawal syndrome upon drug discontinuation.
- This assessment may be conducted in animals at the conclusion of a toxicology study or in a dedicated study.

Design of Animal Physical Dependence Study

- Drug administration should typically occur for at least four weeks at stable doses that produce plasma levels similar to those produced by therapeutic (and possibly supratherapeutic) doses.
- In order to validate the study, a positive control (a scheduled drug with known abuse potential, preferably in the same pharmacological class as the test drug) should produce withdrawal behaviors that are greater than those produced by vehicle.
- Withdrawal is preferentially initiated in animals through abrupt drug discontinuation, although tapered drug discontinuation and antagonist precipitation may provide additional safety information.

Behavioral Observations to Detect Withdrawal

- Behavioral observations of animals should begin several days before drug discontinuation to establish a how the drug affects behavior.
- Observations should then continue 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.
- Generally this includes evaluations of changes in food intake, body weight, temperature, and behavioral observations (activity level, appearance, overt behaviors, handling responses, etc.).

Behavioral Responses During Withdrawal

- Different pharmacological classes of drugs tend to produce different withdrawal syndromes (although there can be overlapping responses).
- These withdrawal signs often are opposite to the signs observed during drug administration:
  - benzodiazepine withdrawal may produce hyperactivity and seizures
  - stimulant withdrawal may produce hypoactivity and sleep

Usefulness of Animal Physical Dependence Studies

- If the abrupt withdrawal of the drug is likely to cause serious adverse events in humans, then an animal physical dependence study may be sufficient. This is especially true if the animal study showed severe distress in animals following drug discontinuation.

- For a drug with a novel mechanism of action, an animal physical dependence study should be conducted prior to a human assessment, to obtain information about which signs and symptoms should be monitored during drug discontinuation in humans.

Limits on the Need for a Human Assessment

After an assessment of physical dependence in animals, a human evaluation of physical dependence may not be required if:

- There are no signals of withdrawal in animals
- There are no signals of withdrawal in individual humans who discontinue the drug abruptly due to dropping out of the clinical study
- It is known the drug produces a withdrawal syndrome upon drug discontinuation that includes serious adverse events
- The clinical study population would be put at risk because abrupt drug discontinuation would cause a return of disease symptoms (e.g., epilepsy, schizophrenia, etc.) or because withdrawal symptoms would be too risky.

Manifestation of Physical Dependence in Humans

- In humans, discontinuation of many CNS-active drugs produce drug withdrawal symptoms indicative of physical dependence.
- Classic withdrawal signs that are common to many drug classes include: headache, anxiety, nausea/vomiting, tremor, chills, decreased concentration, agitation/irritability, sleep disturbances, and mood changes.

Physical Dependence ≠ Abuse Potential

- FDA recognizes that physical dependence does not inherently indicate that a drug has abuse potential.
- Indeed, some drug classes that are known to produce physical dependence are not abused and are not scheduled under the CSA, such as:
  - Beta-blockers
  - Monoamine reuptake inhibitors (e.g., SSRIs)
- However, all drugs with CNS activity are assessed for whether they have abuse potential or produce physical dependence, so there is no exclusion of these evaluations based on drug class.

Unique Withdrawal Syndromes Based on Drug Class

- Different pharmacological classes of drugs may produce unique withdrawal symptoms that are often opposite to the responses produced during drug administration.
- For example:
  - opioids may produce constipation during drug administration but diarrhea during drug discontinuation
  - amphetamines may produce mental acuity during administration but cognitive impairment during drug discontinuation.

Assessment of Physical Dependence in Humans

- The assessment of physical dependence in humans does not typically involve a dedicated study.
- Instead, physical dependence is usually assessed at the conclusion of a Phase 2/3 clinical efficacy study at therapeutic doses through a monitored discontinuation period.
- Use of abrupt drug discontinuation -- rather than tapered discontinuation or precipitated withdrawal through antagonist administration -- is necessary in order to produce naturalistic conditions under which patients stop taking medication.

Duration of Withdrawal Observation Period

- The duration of observation during drug discontinuation should persist for a period equivalent to at least 5 half-lives of the test drug or major active metabolite(s), when the drug has been fully eliminated.
- Typically, though, withdrawal evaluations last for 2-4 weeks, even if the duration of 5 half-lives is shorter than that period.
- Evaluations should occur daily for the first week, and at least every other day during the subsequent weeks.
- It is preferable that evaluations occur under controlled conditions, but at-home evaluations may be acceptable with appropriate systematic methodology.

Methods to Evaluate Human Physical Dependence

- Use of drug class-specific withdrawal scales
- Use of disease-specific scales for evaluation of potential symptom rebound
- Assessment of AEs before and after drug discontinuation
- Use of VAS assessing withdrawal symptoms and mood states
- Use of daily diary by study subject
- Collection of physiological measures and vital signs
- Blood sampling for association of pharmacokinetics and withdrawal signs and symptoms

Drug Class Specific Withdrawal Scales

Scales used for regulatory assessments should be validated for measuring drug class-based withdrawal syndromes, such as:

- Clinical opioid withdrawal scale (COWS)
  - also 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)

Need For a Dedicated Physical Dependence Study

- There are some cases in which a clinical patient population cannot be used to assess physical dependence.
- Our 2017 *Guidance* discussed the possibility of conducting a dedicated physical dependence study conducted in healthy controls when:
  - Clinical efficacy studies with the test drug are conducted in a vulnerable population
  - Abrupt discontinuation of a test drug may pose a safety concern due to return of disease symptoms (e.g., seizures in study subjects with epilepsy or psychotic responses in subjects with schizophrenia)

Need For a Dedicated Physical Dependence Study

- However, it may not be ethical to expose healthy individuals to drugs with abuse potential for 2-4 weeks and then abruptly discontinue the drug.
- Instead, it may be possible to use healthy individuals who have received the drug in repeat-dose Phase 1 pharmacokinetic and safety studies and make systematic observations for changes in behavior, physiological symptoms, and adverse events upon drug discontinuation as an indication of whether the drug may produce physical dependence.
- For regulatory purposes, though, an appropriately designed animal study often provides sufficient information regarding the ability of a drug to produce physical dependence.

Final Determination of Physical Dependence

FDA makes a conclusion about whether a drug produces physical dependence on the basis of the appearance of a withdrawal syndrome upon discontinuation of the drug during:

- Animal physical dependence studies
- Human physical dependence studies
  - Phase 2/3 clinical efficacy study with discontinuation phase
  - Phase 1 pharmacokinetic study with discontinuation phase
  - Data from individuals exposed to the drug who left the study

Additionally, FDA considers physical dependence information from:

- The medical and scientific literature
- Epidemiological databases

Final Determination of Physical Dependence

- Physical dependence is a neuroadaptational state that can produce behavioral and physiological changes in drugs with and without abuse potential.
- FDA assesses physical dependence in order to inform:
  - Section 9.3 *Dependence* of the drug label
  - Sections 2 *Dosage and Administration* 5 *Warnings and Precautions* of the drug label regarding need for tapered discontinuation
  - Scheduling placements under the Controlled Substances Act (CSA), if the drug has also been assessed to have abuse potential.


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