Draft Decision Tree for Assessment of Abuse Potential

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INTRODUCTION

For central nervous system (CNS)-active drugs, an important aspect of evaluating safety is determining if the drug has abuse potential.

If abuse potential can be identified early in the development process, it will be possible to plan for, describe and manage the inherent safety issues while the drug is being brought to market.

FDA has drafted a step-by-step decision tree based upon the draft *Guidance for Industry: Assessment of Abuse Potential of Drugs* (2010).

The objectives of this draft decision tree are to provide a model that:

- Will improve regulatory efficiency, consistency, and transparency in the assessment of drug's abuse potential
- Aligns with real-world clinical development
- Allows for active dialogue with and feedback from stakeholders

The decision tree is not intended to determine whether a drug has abuse potential and whether it should be recommended for scheduling under the Controlled Substances Act (CSA). These decisions cannot be made until data submitted in an NDA have been fully reviewed by FDA.

METHODS

The decision tree is aligned to the phases of drug development, ranging from nonclinical studies to the NDA review.

As drug development progresses, various scientific questions related to abuse potential are answered through the outcomes of each of the studies.

The results are also used in determining the design or interpretation of subsequent studies further down the decision tree.

There are several important highlights:

- The majority of studies listed in the decision tree are required for all drugs as part of the general safety evaluation.
- There are only three (3) studies that are solely dedicated to the assessment of abuse potential:
  - Two nonclinical studies:
    - Self-administration (Abuse Study #1)
    - Drug discrimination (Abuse Study #2)
  - One clinical study:
    - Human abuse potential study (Abuse Study #3)

Physical dependence is a neuroadaptive process that can occur in the absence of abuse potential. However, the ability of a drug to produce physical or psychological dependence plays a role in the scheduling placement of an abusable drug under the CSA.

Throughout this process, there are three (3) major "Abuse Decision Points" in which the "abuse signals" resulting from study outcomes help answer the following questions:

1) Is the drug (or major 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?

This decision tree is designed for and limited to the evaluation of new molecular entities, as well as other drugs that have not previously undergone an abuse assessment in the U.S.

DISCUSSION

This presentation is the initial FDA draft of the decision tree to assess the abuse potential of a drug.

The assessment of abuse potential occurs throughout the nonclinical and clinical evaluation of a drug's safety and efficacy during the drug development process.

The sequence of studies depicted in the decision tree may not reflect the optimal plan for every Sponsor. FDA recognizes that abuse-related studies are conducted throughout all phases of drug development.

However, if the drug exposure in the nonclinical and clinical abuse-related studies is not comparable to that produced by the final human therapeutic dose, the abuse-related studies may not be valid.

Thus, conducting abuse studies prior to determining the final proposed therapeutic dose may carry some risk, if the initially proposed human therapeutic dose changes during subsequent clinical efficacy and safety evaluations.

Throughout the FDA review process, CSS may be consulted to review and comment on the design of abuse-related study protocols prior to study initiation. CSS is also available to provide feedback on the overall abuse evaluation plan throughout development.

The expectation is that a simplified and transparent process such as a stepwise decision tree will aid drug companies, consultants, advocacy groups, federal drug agencies, and regulators in having a common understanding and consistency of the necessary evaluations in the assessment of abuse potential.

The Controlled Substance Staff welcomes feedback on this draft decision tree and the draft guidance. Comments may be sent to:

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DISCLAIMER

The opinions and information in this presentation are those of the authors and do not necessarily reflect the views and policies of the FDA.

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REFERENCE

Food and Drug Administration. *Draft Guidance for Industry: Assessment of Abuse Potential of Drugs.* January 2010.