Abuse Potential Assessment Considerations of Discordant Findings from Nonclinical, Clinical and Epidemiological data

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Opinions expressed in this presentation are my own and do not necessarily reflect the views and policies of the FDA

Objectives

- To hear from the community and stimulate discussion among panel participants about approaches that may help to identify measures or methodologies to predict drug preferences among drugs with similar pharmacological effects (e.g., depressants, stimulants) at the premarket stage.
  - Focusing on examples in which the nonclinical assessment of a drug with a novel mechanism of action is not predictive of the abuse potential of the drug, while clinical data (i.e., reports of euphoria in clinical trials, and subjective measures predictive of abuse collected in human abuse potential studies) indicate the contrary.

Background

- The abuse potential assessment of a drug includes a comprehensive evaluation of the nonclinical and clinical effects of the drug.
  - The abuse potential of a drug is always measured in relation to that of a known drug of abuse, chemically related or with similar pharmacology. Thus, the assessment is challenging when evaluating a drug with a novel mechanism of action and not chemically related to a drug of abuse.
- The nonclinical data that contributes to the assessment include chemistry, receptor binding and functional assays, observational behavioral studies, and abuse-related behavioral studies such as drug discrimination (DD), self-administration (SA) and condition place preference (CPP) studies.
- The clinical component of the analysis includes evaluation of abuse-related adverse events (AEs) reported in clinical trials, and findings from human abuse potential (HAP) studies.
- The need for a HAP evaluation is based on the identification of a positive signal in DD and SA, *or* the occurrence of abuse-related adverse events (AEs) in clinical trials, *or* both.

Abuse Potential Assessment of Selected Anticonvulsants and of Dual Orexin Receptor Antagonists (DORAs)- Premarket

- Nonclinical studies conducted with selected anticonvulsants (lacosamide, ezogabine and brivaracetam) and DORAs (suvorexant, lemborexant and daridorexant) show that these drugs:
  - Have depressant effects,
  - Did not generalize or partially generalized to the selected training drugs in DD studies. The outcome of these studies point out the challenge of selecting a training drug when characterizing the discriminative properties of a drug with a novel mechanism of action,
  - Did not maintain self-administration in SA models. The outcome of these studies point out at the unknown predictive validity of the SA model for drugs that do not belong to classes typically known to be self-administered.
- AEs indicative of potential for abuse including euphoria were reported in clinical trials.
- HAP studies conducted in subjects with history of recreational use of sedatives or polysubstance use indicate that the selected drugs have abuse potential.
  - Emax scores for Drug Liking, Take Drug Again and Overall Drug Liking were greater than placebo and similar to those produced by the positive controls selected (alprazolam when evaluating anticonvulsants; zolpidem and suvorexant when evaluating DORAs).
  - Levetiracetam ("negative control") data was suggestive of abuse potential.

Approval and Controlled Status of Selected Anticonvulsants and DORAs

- The selected drugs were recommended for scheduling at the time of approval, based on the totality of the data collected, and primarily on data from HAP studies and clinical data.
  - Anticonvulsants were placed by DEA in Schedule V of the Controlled Substances Act (CSA), whereas DORAs were placed in Schedule IV of the CSA.
  - Lacosamide was approved in 2009; ezogabine in 2011 (discontinued in 2017) and brivaracetam in 2016.
  - Suvorexant was approved in 2014, lemborexant in 2019 and daridorexant in 2022.
  - Levetiracetam ("negative control") is not scheduled under the CSA. However, its abuse potential was not assessed at the time of approval of the drug in 1999.

Post-marketing Data on Abuse Need to be Evaluated in Context of Drug Utilization Levels

- Minimal or no cases involving a drug in a large safety database may reflect limited utilization of that drug.

Estimated Oral Solid Dosage Units Dispensed, U.S. Poison Center Abuse Case Numbers, and Utilization-Adjusted Rates, 2019

Active Pharmaceutical Ingredient	Estimated Oral Solid Dosage Units Dispensed, N	Poison Center Abuse Cases, N	Abuse Cases per 10M Oral Solid Dosage Units Dispensed
Brivaracetam	8,976,753	0	[cases too scarce]
Suvorexant	15,577,851	2	[cases too scarce]
Lacosamide	76,028,042	2	[cases too scarce]
Levetiracetam (negative control in HAP studies)	797,350,307	24	0.3
Zolpidem (positive control in HAP studies)	858,060,798	270	3.1
Alprazolam (positive control in HAP studies)	2,108,152,107	2,304	10.9

Source: Analyses of America's Poison Centers National Poison Data System and Symphony Health Metys™ conducted by the Office of Surveillance and Epidemiology, CDER

Conclusions

- Preclinical and HAP studies are considered to have a good predictive value of the abuse potential of a drug at the premarket stage.
- Preliminary postmarketing evaluation may not be consistent with a positive signal in HAP studies and the abuse-related AEs reported in clinical trials. However, postmarketing abuse patterns may be influenced by many factors, such as:
  - Low drug utilization,
  - Controlled status, which minimize diversion and abuse,
  - Indication, cost, and community knowledge, among other human and external factors.
- Low levels of abuse of levetiracetam cannot be explained by low drug utilization or by the controlled status of the drug. Thus, for the anticonvulsant selected drugs there may other effects that are not captured in HAP studies that may influence levels of abuse postmarketing (e.g., occurrence of adverse events associated with repeated exposure).

Questions

- For drugs with novel mechanism of action and for which nonclinical studies may be suggestive of no abuse potential,
  - Are there any approaches that could help us to identify and measure subjects' drug seeking preferences among drugs producing similar overall pharmacological effects?
- HAP studies are generally conducted in a healthy population with a prior history of recreational use of drugs with similar overall pharmacological effects to the drug being studied, and who are not physical dependent.
  - Could these studies be used as a framework for drug preference questionnaires or other approaches? (e.g., money vs drug choice analysis or other parameters from a behavioral economics assessment)