PRA HEALTH SCIENCES

The Fundamentals of Human Abuse Potential (HAP) Studies: A 7-Point Checklist

Improving the science of abuse assessment before a drug is marketed is a unified goal for the FDA and pharmaceutical industry. It is the hope that public health will be protected through placing appropriate controls, such as accurate labeling information and marketing practices, to reduce the likelihood that a drug will be abused after FDA approval.

1. SHOULD A HUMAN ABUSE POTENTIAL (HAP) STUDY BE CONDUCTED? AND WHERE?

A HAP study assesses the likelihood that a drug with CNS activity may be abused. The study is conducted in individuals with a history of recreational drug use to measure drug liking. In determining whether a HAP study should be conducted, it is important to identify and assess abuse-related signals via evaluation of data from human and animal studies, including:

- General behavioral studies in animals looking for responses similar to known drugs of abuse
- Generalization (similar effects) to a known drug of abuse in animal drug discrimination studies
- Rewarding properties that support animal self-administration or conditioned place preference
- A profile of abuse-related Adverse Events (AEs), including those which are euphoria related in clinical studies in healthy individuals (phase 1) and in individuals with the disease of study (phase 2/3)

A HAP study would generally be conducted in an inpatient or outpatient human pharmacology setting.

2. SUBJECTS AND SAMPLE SIZE

HAP studies are conducted in participants with a history of recreational drug use, but are not physically dependent upon a given drug. Subjects generally have recent experiences of having taken sedatives, stimulants, opioids, or hallucinogens and are selected for study participation based upon the pharmacological category of the test drug. Subjects' recreational experience with the drug class enables them to report the most accurate information on the abuse potential of the test drug (e.g. good effects, bad effects, and the degree to which the participants would like to take the drug again either to relax or have fun).

3. STUDY DESIGN

A HAP study incorporates 4 phases: **screening, qualification, treatment, and follow-up.**

After screening potential subjects to find those as described in the previous section, the qualification is utilized to identify subjects who are capable of reporting drug liking in response to the positive control and demonstrate a meaningfully different response from that following placebo administration.

Subjects who qualify then move into participation in the treatment phase. This is usually a randomized, double-blind, double-dummy, placebo- and active-controlled, crossover study. Typically, HAP studies contain 6-arms, including 3 dose levels of the test compound, 2 dose levels of the positive control, and placebo. Importantly, an adequate washout period must be maintained between each treatment.

A follow-up generally constitutes a safety visit around 14 days after the last administration of the study drug depending on the pharmacologic and pharmacokinetic characteristics of the test drug and positive control.

4. OUTCOME MEASURES

2017 FDA guidelines state that outcome measures for a HAP study should include subjective measures, safety and physiological measures, pharmacokinetic data, and abuse-related AEs.

Subjects are given standard questionnaires to evaluate subjective effects such as ratings of at the moment drug liking as measured on a Visual Analog Scale (VAS), overall drug liking, the likelihood of taking the drug again and other measures. The VAS tests may be tailored to the pharmacologic class of study drug (eg: VAS for Agitation/Relaxation may be included for stimulant drugs). Additional tests may be included to measure relevant physical effects, including a behavioral and cognitive assessment and a mood profile as appropriate.

5. DATA ANALYSIS AND SUBMISSION

A HAP study is considered valid when a significant and meaningful difference in drug liking response between placebo and positive control is demonstrated in the treatment phase.

A New Drug Application (NDA) including HAP assessment submitted by the applicant should include all protocols and primary data along with statistical analysis.

The document should summarize all data suggesting the abuse potential of the drug, proposed labelling and a proposal for scheduling under the Controlled Substance Act (CSA), if appropriate.

Following Controlled Substance Staff (CSS) review of the NDA, a recommendation is made to the Drug Enforcement Agency (DEA) with regards to assignment of the drug to a drug schedule (eg: II-V or unscheduled). Appropriate labelling language is determined by the FDA review division in collaboration with the FDA Controlled Substance Staff (CSS).

6. POST MARKETING

Once a substance in a new drug product has been included in marketed medicines in the US and globally, post-marketing data can provide further detail on whether the drug substance produces abuse-related signals (e.g. potential rewarding effects or dependence) and help identify potential risks or safety issues.

Combined with data collected during drug development, real world data can contribute to a broader understanding of the abuse potential of a given medication.

7. PRA AND HUMAN ABUSE POTENTIAL.

PRA has more experience and has conducted more abuse potential assessments across multiple classes of compounds than any non-academic clinical research site in the US. Our expert clinical teams operate under the direction of Vice President of Scientific Affairs Lynn R Webster, MD, from our facilities in Salt Lake City, UT and Lenexa, KS. These teams consult with clients on HAP study design, manage all aspects of the study, and seamlessly execute the project within timelines. PRA's ongoing relationship with the FDA and the Controlled Substance Staff ensures that programs align with current regulatory guidelines. As a result, our facilities are recognized by global regulatory authorities.

NEXT STEPS
For additional information, please contact us at prahealthsciences@prahs.com.