Exhibit 1

Assessment of Abuse Potential of Drugs

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

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Clinical Medical

B. Definitions

The CSA refers to the assessment of "potential for abuse," "addiction-forming or addiction-sustaining liability," and "dependence" in 21 U.S.C. 802, but does not define these terms. In this guidance, the following definitions are applicable:

Drug abuse is defined as the intentional, non-therapeutic use of a drug product or substance, even once, to achieve a desired psychological or physiological effect. Therefore, *abuse potential* refers to the likelihood that abuse will occur with a particular drug product or substance with CNS activity. Desired psychological effects can include euphoria, hallucinations and other perceptual distortions, alterations in cognition, and changes in mood. Throughout this guidance, the term *abuse potential* will be used, although *abuse liability* represents a similar concept.[7,8]

Dependence refers to *physical or psychological dependence*. *Physical dependence* is a state that develops as a result of physiological adaptation in response to repeated drug use, manifested by withdrawal signs and symptoms after abrupt discontinuation or a significant dose reduction of a drug. *Psychological (or psychic) dependence* refers to a state in which individuals have impaired control over drug use based on the rewarding properties of the drug (ability to produce positive sensations that increase the likelihood of drug use) or the psychological distress produced in the absence of the drug.[9]

Tolerance is a state that develops as a result of physiological adaptation characterized by a reduced response to a specific dose of drug after repeated administration of the drug (i.e., a higher dose of a drug is required to produce the same effect that was once obtained at a lower dose).

The presence of physical dependence or tolerance does not determine whether a drug has abuse potential. Many medications that are not associated with abuse, such as antidepressants, beta-blockers, and centrally acting antihypertensive drugs, can produce physical dependence and/or tolerance after chronic use. However, if a drug has rewarding properties, the ability of that drug to induce physical dependence or tolerance may influence its overall abuse potential.

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[7] See the DEA Web site for the schedules of drugs, contact information, pertinent information regarding the Controlled Substances Act, and related topics (http://www.deadiversion.usdoj.gov).

[8] "Conference on Abuse Liability Assessment of CNS Drugs," *Drug Alcohol and Dependence*, 70:3 Suppl. 2003.

[9] The term "psychological dependence" conveys a similar state to that of "addiction" (American Society for Addiction Medicine (ASAM), 2011) and "substance dependence" (American Society for Addiction Medicine (DSM)-IV-TR, 2000).

The recommended use of the clinical PK data in designing human abuse-related studies is described in detail below. The protocols for human abuse-related studies should include a justification of design elements based on phase 1 and 2 clinical PK data. All PK parameters utilized should be based on actual measurements, not estimations. When the NDA is submitted, all clinical PK studies and resultant data that informed the design and interpretation of human abuse-related studies should be cross-linked.

B. Abuse-Related Adverse Events in Clinical Safety and Efficacy Studies

All clinical safety and efficacy studies should be evaluated for CNS-related AEs that may suggest the test drug produces effects that will be sought out for abuse purposes. A positive signal from abuse-related AEs does not inherently mean that a test drug has abuse potential. However, evaluation of clinical AE data, in conjunction with nonclinical abuse-related data (chemistry, receptor binding, animal studies), will determine whether a human abuse potential study should be conducted.

The presence of a euphoria-like response is a key observation in the clinical assessment of whether a test drug has abuse potential. If euphoria-related AE(s) are reported, it will be important to further characterize the profile of the abuse-related signals to determine if the drug is similar to other known drugs of abuse (a stimulant, sedative, hallucinogen, etc.). In the absence of euphoria-related signals, AEs such as hallucination and dissociative state may also be indicative of abuse potential. If any of these abuse-related AEs are present, the test drug will likely need to be evaluated in a human abuse potential study before the FDA can approve it.

Abuse-related AEs should be interpreted in the context of the proposed therapeutic indication of a drug. Thus, not all CNS-related AEs are equally relevant for purposes of abuse assessment. For example, an antidepressant that produces "elevated mood" or a sleep aid that produces "somnolence" in the absence of a clear euphoric signal is not likely to be interpreted from these AE data alone as having abuse potential. Additionally, even though "dizziness" is listed under euphoria-related terms, this AE is not by itself indicative of abuse potential. At the time of publication of this guidance document, a ranking of relevant AEs as signals of abuse risk is not available, and all AEs are of interest for the Agency to consider in the overall assessment of risk to the public health. The Agency's interest extends to information about the timing of the AEs and the narratives from case report forms (CRFs), which are important in interpretation of the drug effects.

The list below is a compilation of abuse-related AE terms, related to the drug's pharmacology, as provided in the MedDRA (Medical Dictionary for Regulatory Activities) System Organ Classifications (SOC). We recommend sponsors and applicants use these terms when describing abuse-related AEs. Each of the lower level terms that are shown are coded on the basis of a longer list of verbatim terms, words or phrases from a patient or observer. Most preferred abuse-related terms relate to the drug's pharmacology and fall under SOC General disorders and administration site conditions, SOC Nervous system disorders, and SOC Psychiatric disorders.

Below are examples of MedDRA Preferred Terms (PTs), which may provide abuse-related information about a drug. This list is not exhaustive, however. A MedDRA search should

include additional PT terms that reflect any specific effect of a drug being abused and events that could be observed during drug abuse (for example, overdose, seizure), etc., coded in current MedDRA PTs.

Euphoria-related terms

Euphoric mood; Elevated mood; Feeling abnormal; Feeling drunk; Feeling of relaxation; Dizziness; Thinking abnormal; Hallucination; Inappropriate affect

Terms indicative of impaired attention, cognition, and mood

Somnolence; Mood disorders and disturbances

Dissociative/psychotic terms

Psychosis; Aggression; Confusion and disorientation

Related terms not captured elsewhere

Drug tolerance; Habituation; Drug withdrawal syndrome; Substance-related disorders

Abuse-related AE data from clinical safety and efficacy studies should be systematically categorized, tabulated, and analyzed to determine if AE patterns exist within different human populations following administration of the test drug. These AEs should be presented as both pooled studies and individual studies, separated by dose. When appropriate, full CRFs should be evaluated in order to understand the incident that led to the AEs, establish the time at which AEs appear following drug administration, the duration of the AEs, and which AEs overlap temporally. CRFs are also important to determine if other drugs were present at the time of the incident or whether the individual had other extenuating circumstances during the incident. All incidents that lead to hospitalization for serious neurological or psychiatric abuse-related AEs may provide relevant information about abuse potential. The history of a subject may be important in interpreting any abuse-related event. Clinical studies can also provide information about the incidence of signals suggestive of abuse, such as substance use disorders, overdose, drug diversion or drug loss.

Differences in AE profiles can occur between different phases of clinical drug development. For example, it is not unusual for there to be a greater incidence of abuse-related AEs from a test drug in healthy volunteers who participate in phase 1 studies, compared to the subject populations who participate in phase 2 and 3 studies. Several possibilities may account for this. One possibility is that phase 1 studies test a much broader range of doses than those tested in phase 2 and 3, including the larger doses that tend to produce a greater degree of abuse-related AEs. Another possibility is that phase 2 and 3 studies test individuals who may have an altered responsivity to a test drug because of their underlying disease state. For this reason, the tabulation of abuse-related AEs should occur not only by dose, but also by population tested. If a human abuse potential study is conducted later, the resultant data should be tabulated with other phase 1 data in the NDA.