Neuropharmacology xxx (2014) 1–7

Contents lists available at ScienceDirect

Neuropharmacology

journal homepage: www.elsevier.com/locate/neuropharm

Invited review

A regulatory perspective on the abuse potential evaluation of novel stimulant drugs in the United States

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Keywords:
Abuse potential stimulants
Drug scheduling
Eight factor analysis

A B S T R A C T

In the United States of America (USA), the abuse potential assessment of a drug is performed as part of the safety evaluation of a drug under development, and to evaluate if the drug needs to be subject to controls that would minimize the abuse of the drug once on the market. The assessment of the abuse potential of new drugs consists of a scientific and medical evaluation of all data related to abuse of the drug. This paper describes the regulatory framework for evaluating the abuse potential of new drugs, in general, including novel stimulants. The role of the United States Food and Drug Administration (FDA) in the evaluation of the abuse potential of drugs, and its role in drug control are also discussed. A definition of abuse potential, an overview of the currently accepted approaches to evaluating the abuse potential of a drug, as well as a description of the criteria that applies when recommending a specific level of control (i.e., a Schedule) for a drug under the Controlled Substances Act (CSA).

This article is part of a special issue 'CNS Stimulants'.

1. Introduction

In the USA, two distinct laws provide the regulatory framework for the assessment of the abuse potential of new drugs. These laws are the Federal Food, Drug, and Cosmetic Act (FFD&CA), and the Controlled Substances Act (CSA). Within this framework, the FDA is the organization tasked with assessing the scientific and medical evaluation of all data related to abuse of a new drug and evaluation of its abuse potential. In the context of this manuscript, the term "drug" refers to pharmaceuticals. Characterization of the abuse potential of a drug provides important safety information and ensures that the drug is appropriately labeled, and, if needed, scheduled under the CSA. Labeling, not only describes the appropriate use of the drug and offers an overview of the safety and efficacy of the drug, but determines how the new drug product is advertised, promoted and marketed. Scheduling under the CSA imposes controls intended to reduce the abuse and diversion of drugs with abuse potential, while ensuring that these drugs remain available for medical, scientific and industrial purposes.

Under the regulations of the FFD&CA, sponsors developing a drug with potential for abuse must submit as part of the new drug application (NDA) "a description and analysis of studies or information related to abuse of the drug, including a proposal for scheduling under the Controlled Substances Act." In addition, the NDA must include a description "of any studies related to overdose, including information on dialysis, antidotes, or other treatments, if known" [21 CFR 314.50(d)(5)(vii)].

An abuse potential assessment is carried out as part of the general safety and efficacy studies performed for all new drugs with central nervous system (CNS) activity. For some classes of medications, for example, analgesics or weight control medications, abuse potential may be considered a major side effect that has to be evaluated early in development.

According to the CSA [21 U.S.C. 811 (f)], the Secretary of the Department of Health and Human Services (HHS) is required to submit information to the Drug Enforcement Administration (DEA), relevant to the scheduling of a substance, if at the time an NDA is submitted for a drug having a stimulant, depressant or hallucinogenic effect on the CNS, it appears that the substance has an abuse potential. The CSA establishes five schedules for control (Schedule I–Schedule V), and a recommendation for scheduling a drug in one of the five Schedules is based upon the relative abuse potential, accepted medical use for treatment in the USA and dependence liability of the drug. The DEA has final authority in scheduling actions. The regulatory responsibilities for scheduling are described

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[1] Opinions and assertions contained herein are those of the authors, and are not to be construed as representing those of the Food and Drug Administration.

http://dx.doi.org/10.1016/j.neuropharm.2014.04.001
0028-3908/

in 21 U.S.C. 811 and 812, as well as in 21 CFR Part 1300, with delegation of authority from HHS to the FDA. Within FDA, this authority was delegated to the Center for Drug Evaluation and Research (CDER), and within CDER to the Controlled Substance Staff (CSS). CSS performs the scientific evaluation of the abuse potential of a drug for HHS; the National Institute on Drug Abuse (NIDA) provides advice on the recommendation. In this process FDA will determine if additional controls regarding the manufacturing, distribution and prescribing of the drug are needed to reduce its abuse, while ensuring its availability for appropriate medical use, and consequently will recommend to the Assistant Secretary for Health, the designee of the Secretary of HHS, to submit a scheduling recommendation to the DEA (FDA/CDER, 2010).

The next sections provide an overview of the scientific aspects of the evaluation of the abuse potential of new drugs, as well as the regulatory framework and criteria applied in making recommendations for scheduling with particular emphasis on the evaluation of stimulant drugs.

2. Abuse potential assessment

The term *abuse potential* of a drug, or substance, refers to the likelihood that a drug with effects in the central nervous system will be used in nonmedical situations, repeatedly or sporadically, for the positive psychoactive effects it produces. Examples of the psychoactive effects that drugs may produce include sedation, euphoria, perceptual and other cognitive distortions, hallucinations, and mood changes (FDA/CDER, 2010). Comparable definitions in the CSA refer to "habit forming" or "addiction-sustaining liability" for opiates and for other CNS active agents, and a "potential for abuse" because of a drug's stimulant, depressant or hallucinogenic effects [21 U.S.C. 802 (1), (9), (18), (29)].

In the USA, the assessment of the abuse potential of a drug is based upon the comprehensive evaluation of the chemical, pharmacological, and pharmacokinetic characteristics of the drug, clinical data (human abuse studies, clinical trial data relative to abuse), and epidemiological data, if available. There is not a single study that in isolation will address the abuse potential of a drug.

Abuse potential is a relative term. In performing these assessments, the abuse potential of the new drug is compared to that of a known drug of abuse. The terms abuse potential and abuse liability have often been used interchangeably because they represent similar concepts. However, the term abuse liability more frequently captures human social and environmental factors that can affect the consequences of abuse or liability of abuse and which can be very difficult to predict prior to marketing of the drug.

A systematic assessment of the potential for abuse of a drug should be considered when the drug has effects in the central nervous system, when the drug is chemically or pharmacologically similar to other drugs with known abuse potential, or when the drug produces psychoactive effects such as sedation, euphoria and mood changes, which are considered predictive of the likelihood of abuse of the drug. Drugs with known abuse potential fall within any of the following drug classes: opioids (analgesics and anesthetics), depressants (sedative-hypnotics, benzodiazepines and others), stimulants (cocaine, amphetamines and others), hallucinogens, phencyclidine and similar drugs active at the NMDA receptor, cannabinoids (marijuana and related compounds), and nicotine-like drugs. Abuse potential assessments are not limited to the study of new molecular entities or new drug products, as these assessments may also be performed as part of the characterization of new dosage forms of drug substances already controlled under the CSA. For example, an abuse potential assessment might be necessary for a marketed drug product that presents an unexpected adverse event profile, or that is being re-evaluated for new indications or to be used through a new route of administration. The assessment of the abuse potential of a substance should not be confused with the assessment of the abuse deterrent properties of a formulation. FDA has recently issued guidance in this area, focusing specifically on the characterization of the abuse deterrent properties of opioid formulations developed to deter abuse (FDA/CDER, 2013).

The abuse potential assessment is submitted as a section of the original NDA. The data that comprises the assessment may be collected throughout all phases of development and at the research and development stage. This assessment does not only serve as a basis for describing the drug's abuse potential and dependence liability in the drug labeling, but also serves in determining the appropriate scheduling of the drug, if deemed necessary. Consequently, the selection of the positive controls, to be used in the various models designed to assess the abuse potential of the drug, needs to consider not only the pharmacological properties of the positive control but the scheduling status as well.

FDA's current understanding of the preclinical and clinical studies that are considered to provide the data on the abuse potential of a new drug, for which there is no marketing history, is outlined and described in the draft FDA Guidance for Industry on the Assessment of Abuse Potential of Drugs (FDA/CDER, 2010). We direct the reader to this draft Guidance for the detailed methodological information on the current approaches to evaluate the abuse potential of drugs. The approaches for assessing abuse potential described in this guidance have been developed, applied and tested for their reliability by the scientific community through the years (Balster and Bigelow, 2003). However, the FDA/CDER guidance provides a considerable degree of scientific flexibility regarding models and methodology, because the assessment of abuse potential of a drug is an evolving area of research.

The 2010 FDA/CDER guidance, similarly to the Canadian guidance (Health Canada, 2007), emphasizes that the abuse potential assessment of a drug relies not only on preclinical studies but on the assessment of abuse potential in humans as well. In general, it is accepted that human data will be given a greater weight than non-human data in the assessment. For example, a positive signal in human abuse potential studies will be given greater weight than a negative signal in preclinical animal behavioral studies, such as self-administration and drug discrimination. Preclinical animal and human models have proved to be predictive of the abuse potential of drugs that fall within very well studied classes, such as stimulants, opioids and depressants. However, the assessment of the abuse potential of novel substances that do not fit within these well characterized classes is still challenging. The European Medicine Agency also issued guidance on the assessment of the dependence potential (abuse potential and physical dependence) of medicinal products, but recommends conducting general pharmacology and specific behavioral studies (EMEA/CHMP, 2006).

In reviewing the abuse potential of a drug, the focus is on all data related to the following properties of the drug:

a. Chemistry
b. Preclinical pharmacology (animal and in vitro receptor binding studies)
c. Animal behavioral and dependence pharmacology
d. Pharmacokinetics and pharmacodynamics
e. Human abuse potential laboratory studies
f. Clinical trial data relative to abuse and dependence potentials
g. Integrated summaries of safety and efficacy
h. Foreign experience with the drug if the drug is marketed in other countries. (Adverse events, abuse potential, marketing and labeling)

Please cite this article in press as: Calderon, S.N., Klein, M., A regulatory perspective on the abuse potential evaluation of novel stimulant drugs in the United States, Neuropharmacology (2014), http://dx.doi.org/10.1016/j.neuropharm.2014.04.001