Invited review

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

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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’.

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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...
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 is 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 opioids 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, phenycyclidine 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)
The abuse potential evaluation of stimulants is not different from that of other classes. Drugs with stimulant activity may be identified on the basis of its chemical similarity to other drugs with stimulant properties (such as, amphetamine, cocaine, and methylphenidate), pharmacological properties (monoamine reuptake inhibitors) or therapeutic indications (anorexiant, attention deficit disorder, narcolepsy, antidepressants).

In examining the chemistry of a novel stimulant drug, one of the first considerations is to determine if the drug is structurally similar to other known abused stimulants, such as phenylethylamines or cocaine. Observation of such structure activity similarities can be made as early as the time of drug discovery. Of note, although cocaine behaves pharmacologically as a potent stimulant, it is classified under the CSA as a narcotic drug [21 U.S.C. 802 (17) (D)]. The physicochemical properties of a substance, such as high water solubility or stability at vaporization temperatures, are taken under consideration in the entire abuse potential evaluation because they indicate that the drug may be suitable for abuse intravenously or by smoking, thus facilitating the rapid delivery of the drug into the brain. It is known that drugs that rapidly reach the brain produce a more rewarding experience, and are associated with high levels of abuse (McColl and Sellers, 2006; Hatsukami and Fischman, 1996; Henning and Griffin, 1995).

The high water solubility of salts of amphetamine and methylphenidate allow for abuse of these substances through the intravenous route. The stability of methamphetamine at high temperatures allows for smoking of the drug, whereas the low water solubility and instability of modafinil at high temperatures limit the abuse of modafinil through the oral route.

The effect of a novel drug on locomotor activity in animals constitutes a basic parameter indicative of stimulant (increase in locomotor activity) or sedative (decrease in locomotor activity) pharmacology. The evaluation of the effect of a drug on motor activity is one of the effects measured as part of the safety pharmacology core evaluation of drugs (FDA/CDER/CBER/ICH, 2001). In addition, the entire pharmacological profile of the drug and of its active metabolites, if it is the case, is fully evaluated. A full binding profile as well as data from in vitro and ex vivo studies is analyzed to understand the interaction of the stimulant at various receptor systems and at the three monoaminergic reuptake sites (norepinephrine, serotonin and dopamine). The affinity of the novel stimulant for the monoaminergic sites as well as the ability of the substance to stimulate the release of norepinephrine, serotonin and dopamine is evaluated and compared to that of other stimulants (Heal et al., 2013a, Heal et al., 1998).

Behavioral animal studies, such as drug discrimination and self-administration, are well established models for evaluation of the reinforcing and discriminative properties of the novel stimulant (Heal et al., 2013b). Animal self-administration studies have excellent predictive validity in assessing the abuse potential of a drug. Drugs that are self-administered by animals are typically self-administered by humans, and have a potential for abuse (Ator and Griffiths, 2003; Johanson and Balster, 1978; Schuster and Thompson, 1969). For example, stimulants such as cocaine and amphetamine, opioid analgesics such as morphine, and sedative drugs like zolpidem are all self-administered by laboratory animals and subject to abuse by humans.

Drug discrimination studies indicate whether a drug being studied is perceived by animals similarly to a known drug of abuse. A negative signal in drug discrimination or self administration studies is not conclusive of a lack of abuse potential. Drug discrimination is a sensitive and pharmacologically specific behavioral assay, in that general effects such as euphoria or somnolence do not appear to determine the outcome of the test (Ator and Griffiths, 2003).

Pharmacokinetic studies in animals and humans allow for an evaluation of the systemic exposure to the drug and metabolites. The abuse potential of human metabolites that are present at 10 percent or greater of parent drug systemic exposure at steady state, also need to be characterized (FDA/CDER, 2008). Pharmacokinetic studies provide data on the maximum concentration, time to onset, time to maximum concentration and total exposure. In addition, these studies, which are conducted in healthy volunteers, capture safety related pharmacodynamic outcomes of the drug.

Clinical abuse potential studies constitute one of the accepted methodologies to assess the relative abuse potential of a new drug in humans (Schoedel and Sellers, 2008; Griffiths et al., 2003). The objectives of these studies are to provide information on the relative abuse potential of a new drug in humans, and to contribute to predicting the likelihood of abuse when the drug becomes available for marketing. These studies are typically conducted in a population experienced in the recreational use of drugs of the same pharmacological class to that of the study drug. The selection of the appropriate positive comparators should be based on pharmacological similarity; for example the selection of phentermine as a positive control might not be adequate when trying to study the abuse potential of a novel stimulant drug that does not show the same activity at monoaminergic sites.

The evaluation of the adverse events profile of a drug from clinical trials is also taken under consideration when evaluating the abuse potential of drug. The systematic categorization, tabulation, and analysis of safety data related to mood elevation, as well as events that mirror those of typical stimulants such as amphetamine can provide relevant information on the whole abuse potential assessment. The adverse event profile of the drug may be different depending on the population being studied and the doses being tested. Phase 1, safety and pharmacokinetic studies, provide data on the adverse events profile of the drug in healthy volunteers and in addition data for higher doses than the identified therapeutic dose. Phase 2 and Phase 3 studies can provide data on the adverse event profile of the drug on the population to treat, and a different adverse event profile might be observed for the same drug in different populations. For example, a different adverse event profile may be observed for the same stimulant drug when being studied for different indications, such as an anorexiant vs. an antidepressant.

If the human abuse potential studies and the adverse events profile from clinical studies do not provide a signal, or indicate the presence of rewarding effects or other abuse-related behaviors, a recommendation for scheduling would be unlikely.

Physical dependence studies are also conducted as part of the overall safety and abuse potential assessment of drugs. These studies are conducted to inform one of the three required findings for a scheduling recommendation, and to assess the safety and health consequences associated with the withdrawal syndrome manifested upon discontinuation or significant dose reduction of the drug. Physical dependence per se is not considered a sign of abuse potential, because it constitutes a physiological state of adaptation in response to repeated drug abuse. Physical dependence can develop to any drug independent of the abuse potential of the drug. For example, physical dependence to propranolol, a beta-blocker agent used in the management of high blood pressure, is well recognized. Abrupt discontinuation of propranolol may be followed by a “propranolol withdrawal syndrome” resulting in increased blood pressure temporarily higher than that prior to beginning the medication, headache, chest pain, palpitations and sweating (O’Brien, 1996).

Information on physical dependence is incorporated in the drug product label to inform health care practitioners about the safety
risks associated with drug withdrawal, and it is also considered as one of the factors in scheduling determinations.

In general, physical dependence is assessed in animal models or in the clinical environment through the evaluation of signs or symptoms following discontinuation of the drug (Ator and Griffiths, 2003).

3. Drug scheduling

The USA Controlled Substances Act (CSA) establishes five schedules for control of drugs and categorizes drugs in one of the five schedules based on relative abuse potential, medical usefulness, and dependence liability of the drug. Table 1 describes the criteria for control associated with each of these five schedules. For example, a drug is placed in Schedule II of the CSA if a) the drug has a high potential for abuse, b) it has a currently accepted medical use in treatment in the United States or a currently accepted medical use with severe restrictions, and c) abuse of the drug may lead to severe psychological or physical dependence.

At the international level, the United Nations adopted two drug control conventions, the 1961 Single Convention on Narcotic Drug and the 1971 Convention on Psychotropic Substances (World Health Organization, 1961, 1971). These international Conventions establish regulatory schedules for narcotic and psychotropic substances based on the therapeutic value and risk of abuse and health dangers of these substances.

In developing drug scheduling recommendations other countries and international organizations, such as European Member States and the World Health Organization, rely on similar data and procedures to those described in this review. However there is some variation in how other countries classify drugs within their domestic legislations. For example the United Kingdom and Sweden list substances in five Schedules that are similar to those established under the CSA; whereas for example Germany lists substances under three schedules based primarily on the medical benefit of the substance, and exempts certain pharmaceutical preparations that contain the active substance at exclusively low concentrations, such as benzodiazepines (EMCDDA).

Each schedule under the CSA includes a set of regulations or measures required to protect the public health minimizing abuse and diversion while at the same time not interfering with therapeutic access to the drug for legitimate therapeutic purposes. The controls and regulations of the CSA are most restrictive for the Schedule I and II substances, and they are relatively less restrictive for the Schedule III to V drugs, respectively. Drugs in Schedule I have no accepted medical use in treatment in the United States. Depending on the Schedule (from II to V), controls may include manufacturing and production quotas, varying degrees of manufacturing and distribution site security requirements, dispensing and prescribing limitations, a range of record-keeping and reporting requirements, and import/export regulations. Prescribers, dispensers, drug manufacturers, and distributors are required to register with the USA Drug Enforcement Administration (DEA). In addition to the regulations, different penalties are also associated with the various Schedules.

A recommendation for scheduling, also known as an “Eight Factor analysis,” is a legal document based on scientifically sound and legally defensible data relevant to each substance considered for scheduling.

As briefly delineated in the Introduction, the DEA has final authority regarding scheduling decisions, and makes the ultimate decision on the schedule of a drug, after receiving input from FDA and NIDA, through the ASH/HHS. There has not been much written in the public domain about the specific role of the DEA in the scheduling process; one review (McClain and Sapienza, 1989) was found to address drug control procedures in the USA, and offered DEA’s view of the data needed to support a scheduling recommendation. A more recent article (Rocha, 2013) offers an overview of the legal framework of drug scheduling, describes the roles of FDA and DEA in the process, and touches upon the procedural complexity of drug scheduling.

Regarding the control of stimulant drugs, all stimulants currently controlled under the CSA have similar pharmacological activity as the prototypical stimulant d-amphetamine. Stimulant actions include CNS stimulation in humans and animals, as well as amphetamine-like effects in animals such as self-administration behavior, which is a major preclinical indicator of a drug’s abuse potential, and production of psychological and physical dependence. Often times, they are recognized as amphetamine-like by volunteers with a prior history of abuse, at therapeutic and supratherapeutic doses.

Analogues that have been illicitly manufactured and/or diverted and abused have been listed in Schedule I or II of the CSA. These include Schedule I substances such as aminorex, N-benzylpiperazine, cathinone, fenethylamine, methcathinone, N-ethylamphetamine and N,N-dimethylamphetamine. Three stimulants recently controlled in Schedule I, though listed under the CSA as hallucinogens, include: mephedrone, methylendioxypyrovalerone,

Table 1

<table>
<thead>
<tr>
<th>Schedule</th>
<th>Criteria for control under the U.S.A Controlled Substances Act (CSA) [21 U.S.C. 812 (b) (1), (2), (3), (4), (5)].</th>
</tr>
</thead>
<tbody>
<tr>
<td>I (CI)</td>
<td>A) The drug or other substance has a high potential for abuse.</td>
</tr>
<tr>
<td></td>
<td>B) The drug or other substance has not currently accepted medical use in the treatment in the United States.</td>
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<tr>
<td></td>
<td>C) There is a lack of accepted safety for the use of the drug or other substance under medical supervision.</td>
</tr>
<tr>
<td>II (CII)</td>
<td>A) The drug or other substance has a high potential for abuse.</td>
</tr>
<tr>
<td></td>
<td>B) The drug or other substances has a currently accepted medical use in treatment in the United States or a currently accepted medical use with severe restrictions.</td>
</tr>
<tr>
<td></td>
<td>C) Abuse of the drug or other substances may lead to severe psychological or physical dependence.</td>
</tr>
<tr>
<td>III (CIII)</td>
<td>A) The drug or other substance has a potential for abuse less than the drugs or other substances in Schedule I and II.</td>
</tr>
<tr>
<td></td>
<td>B) The drug or other substance has a currently accepted medical use in the treatment in the United States.</td>
</tr>
<tr>
<td></td>
<td>C) Abuse of the drug or other substance may lead to moderate or low physical dependence or high psychological dependence.</td>
</tr>
<tr>
<td>IV (CV)</td>
<td>A) The drug or other substance has low potential for abuse relative to the drugs or other substances in Schedule III.</td>
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<tr>
<td></td>
<td>B) The drug or other substance has a currently accepted medical use in the treatment in the United States.</td>
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<tr>
<td></td>
<td>C) Abuse of the drug or other substance may lead to limited physical dependence or psychological dependence relative to the drug or other substances in Schedule III.</td>
</tr>
<tr>
<td>V (CV)</td>
<td>A) The drug or other substance has low potential for abuse relative to the drugs or other substances in Schedule IV.</td>
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<tr>
<td></td>
<td>B) The drug or other substance has a currently accepted medical use in treatment in the United States.</td>
</tr>
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<td></td>
<td>C) Abuse of the drug or other substance may lead to limited physical or psychological dependence relative to the drugs or other substances in Schedule IV.</td>
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(MDVP), and methylone. These substances also belong to the phenethylamine class, and are found to be pharmacologically similar to amphetamine, methylenedioxyamphetamine (MDMA) and cathinone (DEA, 2013a,b). For a comprehensive assessment of the chemistry and pharmacology of these stimulants the reader is directed to the review in this Special Issue on designer stimulants (Iversen, 2014).

Stimulants listed in Schedule II include amphetamine, methamphetamine, phenmetrazine methylphenidate and lisdexamfetamine. Though not listed as stimulants, cocaine and ergonovine as well as their derivatives are legally Schedule II narcotic substances.

Other stimulants are controlled in Schedule III or Schedule IV of the CSA. Schedule III stimulants include benzphetamine, chlorphenetermine, clortermine, and phendimetrazine. Stimulants in Schedule IV include cathine, diethylpropion, fencamfamine, fenproporex, mazindol, mephedrone, modafinil, pemoline, phentermine, pipradrol, sibutramine, and lefetamine.

As a guidance for the scheduling recommendation the CSA establishes that eight factors be considered when determining the need for scheduling a drug [21 U.S.C. 811 (c)]. These factors are:

1. Its actual or relative potential for abuse.
2. Scientific evidence of the drug's pharmacological effects, if known.
3. The state of current scientific knowledge regarding the drug or other substance.
4. Its history and current patterns of abuse.
5. The scope, duration and significance of abuse.
6. What, if any, risk there is to the public health.
7. Its psychic or physiological dependence liability.
8. Whether the substance is an immediate precursor of a substance already controlled.

Guidance regarding the definition of abuse potential of a drug or substance with stimulant, depressant or hallucinogenic effect can be found in the legislative history of the CSA (House of Representatives, 1970). However, this criterion refers to the risk to the individual or the public health, diversion, and to the use of the drug or substance outside the medical advice. There is no mention in the CSA of the type of medical and scientific data required to assess abuse potential for scheduling purposes. Early eight factor documents or recommendations for scheduling may be the best source of information for better understanding how scheduling decisions are supported. Until recently, these eight factor analysis were not available to the public; however, currently these eight factors could be accessed electronically at the US Federal Government regulations website. This site allows access to proposed regulations, comments and related documents published by the U.S. Federal Government (Regulations.Gov site).

It is important to note that when a scheduling recommendation is initiated for a drug that is being evaluated for safety and efficacy under a NDA, FDA considers all scientific data that is related to abuse that has been submitted by the drug sponsor to the Agency for review. When the FDA prepares an eight factor analysis, all data related to the abuse potential of a drug is evaluated in relation to that of other controlled substances. As described above, abuse potential is a relative term. The abuse potential assessment of a novel substance is determined relative to that of one or more pharmacologically similar substances, which often are structurally similar and/or indicated for the same therapeutic indication, with recognized abuse potential and already scheduled under the CSA.

As guidance, the remainder of this section briefly describes the scientific and medical data generally described under each of the eight factors. The HHS Secretary needs to consider these data when making the findings to support a scheduling recommendation. As mentioned in the prior section, the methodological and scientific principles of the data required for a full abuse potential assessment can be found in the FDA/CDER draft Guidance for Industry on the Assessment of Abuse Potential of a Drug (January 27, 2010).

In general, Factor 1, “Its (The drug’s) actual or relative potential for abuse,” offers an overview of all the data related to abuse of the novel substance, in comparison to other similar scheduled drugs. Specifically, this Factor will include brief summaries of the in vitro and ex vivo data for the novel substance and compare that data to other scheduled substances. This Factor also will include a brief description of the findings from behavioral animal data, as well as data generated in human abuse potential studies, and any data indicative of abuse and diversion from clinical trials, from foreign reports if the substance is marketed abroad, or from both sources. For a novel stimulant, Factor 1 will include information about the abuse potential of the novel stimulant relative to that of amphetamine or to that of other stimulants used as positive controls in human abuse potential studies; a discussion of the pharmacokinetic profile of the substance and its active metabolites, if identified, with particular emphasis on the time of onset and duration of action; data indicating if the novel stimulant maintains self-administration in animals; data indicating if the drug produces tolerance and physical dependence, as well as discrimination studies; adverse event data from clinical trials indicative of a similar pharmacological effect to that of other controlled stimulants. These adverse events may include alterations in mood, perception, and thinking, as well as typical cardiovascular sympathetic effects, and any data available on physical dependence that may have been measured either in animals or in clinical trials.

Factor 2, “Scientific evidence of the drug’s pharmacological effects, if known,” will include all data related to the pharmacology of the novel stimulant in comparison to the pharmacological profile of other controlled stimulants. For example, data on the affinity of the novel stimulant and that of other stimulants (controlled and uncontrolled), and its active metabolites, if relevant, for monoaminergic sites and other receptors systems as determined by in vitro binding assays in various animal tissues. In addition, this factor may describe the ability of the stimulant to affect release of norepinephrine, serotonin, and dopamine in comparison to other controlled and non-controlled stimulants, as well as data from other animal models that will provide data on the interaction of the substance with the monoaminergic systems. This factor will also include a full description and interpretation of the data collected from behavioral studies, human abuse potential studies, and clinical trials.

Factor 3, “The state of current scientific knowledge regarding the drug or other substance,” will include all scientific data related to the substance, other than the pharmacology. This Factor will include data on the chemistry of the substance including a description of the physicochemical properties, which may impact the abuse potential by addressing the manner of abuse of the substance. Water solubility and vapor stability at high temperatures, ease of synthesis and synthetic pathways are significant issues. This Factor will fully describe the pharmacokinetics profile of the substance and will include data on absorption, distribution, metabolism and excretion and describe any type of drug–drug interaction, food and alcohol effects.

Factor 4, “Its history and current patterns of abuse,” will include data on abuse of the substance, foreign experience and marketing information, if the substance is available in other countries. If the substance is not available in other countries, this section will rely on other data from clinical trials and from human abuse potential studies. Specifically, this section will describe the adverse events profile of the substance, and the clinical responses observed in
clinical trials, including subjective data predictive of a similar pattern of abuse to that of a comparative stimulant that is already scheduled. The clinical data considered under this Factor will be collected from Phase 1 trials conducted in healthy volunteers, from Phase 2 and 3 trials conducted in the population to treat, and from human abuse potential studies conducted in healthy volunteers with a prior history of abuse of stimulants.

For a novel drug, Factor 5, “The scope, duration and significance of abuse,” would include foreign data, if the substance were available in other countries. In addition, this Factor will include an analysis of the data collected in human abuse potential studies, since the subjective and objective responses in drug experienced individuals to both the novel drug and a reference are accepted measures predictive of abuse potential of a new drug. This Factor will include an assessment of the potential routes of abuse of the new stimulant based on the physicochemical properties, as it is relevant to the predictive patterns and significance of abuse. For example, low water solubility and instability at high temperatures may decrease the likelihood of abuse of the substance through the intravenous route and smoking, decreasing in this way the abuse potential of the novel stimulant relative to that of other stimulants, such as amphetamine or methylphenidate.

Factor 6, “What is the risk there is to the public health,” may be viewed as a risk-benefit analysis, where the risks associated with the potential for abuse and the toxicity associated with the abuse of the drug are balanced against the medical benefits of the drug. Consequently, this Factor is weighed heavily in the overall assessment.

Individual adverse events reports indicative of toxicity generally associated with higher doses of the stimulant, from clinical trials or of foreign origin are of great importance in assessing the risk to the public health. Of particular interest are events that include, among others, psychosis, delirium, paranoid psychosis, hallucinations, depersonalization, aggression, marked excitation associated with destructive behaviors, mood changes, and of course any indication of abuse, misuse and addiction.

Considering that misuse, abuse and addiction constitute serious risks to the public health, this section may also include any evidence from clinical trials of these behaviors. It is also relevant to consider an epidemiological assessment of the current levels of abuse, misuse, and addiction associated with an abused stimulant, to which the novel stimulant was found to have a similar abuse potential in human abuse potential studies. For example, if the novel stimulant were found to be similar to modafinil in human abuse potential studies, this section would include an assessment of the current levels of abuse, misuse and addiction associated with modafinil as predictive of the levels that could be seen with the novel stimulant once marketed. Epidemiological data may include, among others, emergency department admissions, admissions to drug treatment centers, survey data representative of the number of individuals abusing or misusing the drug, and medical examiners data.

The DEA also considers diversion and trafficking data under this factor. However, FDA’s assessment is focused on the medical and toxicological risks associated with the drug at the individual level and its effect on society as a whole.

Factor 7, “Physical or psychological dependence liability,” is self-explanatory. Data on psychological dependence, also defined as addiction or drug dependence, can be inferred from animal self-administration studies or from actual reports of abuse and addiction. The self-administration paradigm is widely used to determine whether or not a drug can control behavior (that is, function as a positive reinforcer), as well as to evaluate the abuse potential of the substance. Self-administration studies using nonhuman primates and rats have been shown to be a valid and reliable predictor of the psychological dependence potential of a substance. There is a strong concordance between the types of drugs that serve as reinforcers in animals and drugs associated with problems of addiction, dependence or abuse by humans (Ator and Griffiths, 2003; Johanson and Balster, 1978; Schuster and Thompson, 1969).

Physical dependence as manifested by a withdrawal syndrome is analyzed under this Factor, and attention is given to the severity and health-related consequences of the withdrawal. Animal data and clinical data are analyzed, and the symptoms associated with the withdrawal of the novel drug are compared to those associated with other stimulants such as amphetamine.

Factor 8, “Whether the substance is an immediate precursor of a substance already controlled,” will assess if the novel substance meets the criteria to be considered as an “immediate precursor” as defined in the CSA [21 U.S.C. 802(2)]. An “immediate precursor” is a substance: (A) which the Attorney General has found to be and by regulation designated as being the principal compound used, or produced primarily for use, in the manufacture of a controlled substance; (B) which is an immediate chemical intermediary used or likely to be used in the manufacture of such controlled substance; and (C) the control of which is necessary to prevent, curtail, or limit the manufacture of such controlled substance.

In summary, under the Eight Factor analysis, all data related to abuse that has been generated throughout the entire development process of the drug, is taken under consideration to support the three findings or the criteria for scheduling under one of the five schedules of the CSA.

4. Conclusions

From the regulatory perspective, a systematic assessment of the potential for abuse of a novel drug should be considered when the drug affects the central nervous system, when the drug is chemically or pharmacologically similar to other drugs with known abuse potential, or when the drug has opioid, cannabinoid, nicotinic, hallucinogenic, stimulant, or depressant properties.

The characterization of the abuse potential of drugs is relevant because it constitutes one aspect of the safety evaluation of drugs under development, and it is a determinant for control of the drug under the legal framework provided by the CSA. Drugs are placed in one of the five schedules established under the CSA, based on their abuse potential, medical usefulness and the potential for producing physical dependence and psychological dependence (substance dependence, addiction), and each schedule imposes a varying degree of controls and penalties.

The assessment of the abuse potential of a drug requires a multidisciplinary approach, and consists of a comprehensive evaluation of the chemistry, pharmacology (preclinical and clinical), pharmacokinetics and pharmacodynamic profiles of the drug, adverse events observed in clinical trials, as well as anticipated public health risks that may follow introduction of the drug onto the U.S. marketplace.

Considerable research has been conducted on the various approaches for assessing abuse potential of various drug classes. Preclinical animal and human abuse potential studies have proved to be predictive of the abuse potential of drugs that fall within very well studied classes, such as the stimulants. However, the assessment of the abuse potential of novel substances with stimulant properties that may have a different mechanism of action from that of the well-characterized stimulants proves to be challenging.

In developing drug scheduling recommendations other nations and international organizations rely on similar data and procedures to those described in this review.
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