CONTROLLED SUBSTANCE ANALOGUES

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Introduction

During the 1980s the United States experienced a proliferation of the trafficking and abuse of illicitly produced substances, known as "designer drugs" or controlled substance analogues. Controlled substance analogues refer to substances of abuse that produce the "high" or euphoria of controlled substances (narcotics, stimulants, depressants and hallucinogens) but which have chemical structures slightly different from those of controlled substances. Because each individual substance was not specifically listed under the United States Controlled Substances Act (CSA), they were not subject to the provisions of this law at that time. Similarly, these types of substances were not controlled under international treaties unless specifically listed. Many of these substances were phenethylamine stimulants or ring-substituted amphetamine derivatives.

Controlled substance analogues are generally produced in clandestine laboratories by altering the synthesis of controlled substances. Either the immediate precursor or a reagent is altered to obtain the desired end-product. For example, the reaction of ephedrine with hydriodic acid and red phosphorus yields methamphetamine, while the reaction of phenylpropanolamine (PPA) with these same reagents yields amphetamine. Thus, the production of these analogues also may have an impact on chemical control programs since it is impossible to specifically list all precursors or reactants. By selling these analogues, traffickers avoided the penalties that would have been levied against those involved in the manufacture and distribution of controlled substances. This phenomenon seems to have diminished in the United States in recent years, in part, due to the enactment of legislation specifically targeting this activity. Available information indicates that Europe and other areas are currently experiencing a proliferation of analogues produced in illicit laboratories. Following is a description of the analogue phenomenon, as it occurred in the United States, and the initiatives taken to counteract it.

The Controlled Substance Analogue Phenomenon

The concept of designing pharmacologically active, chemically related substances is neither new nor restricted to illicit laboratories. In fact, most controlled substance analogues were not designed by clandestine chemists, but are substances that were developed by legitimate pharmaceutical chemists. Information about these substances was generally published in the scientific literature. In the quest for better medicinal agents, pharmaceutical companies synthesize and test numerous analogues of a parent compound to find the one with the most and best desirable effects and the least side-effects. Many of these analogues mimic the qualitative actions of the original compound, but may vary in potency, onset or duration of action. For example, consider the large number of variations within the benzodiazepine family of drugs, in which the parent drug is chlordiazepoxide (Librium). Many analogues of chlordiazepoxide (e.g., diazepam,

alprazolam, flunitrazepam, etc.) are now legitimately marketed and have similar therapeutic and psychoactive properties. There are an equally large number of phenethylamine analogues used therapeutically as well as for abuse purposes.

The illicit synthesis of analogues for the purpose of avoiding controlled substance laws also is not new. This phenomenon surfaced in the 1960s with the synthesis and distribution of ring-substituted amphetamine analogues such as 3,4-methylenedioxyamphetamine (MDA), 4-methyl-2,5-dimethoxyamphetamine (DOM/STP), 3,4,5-trimethoxyamphetamine (TMA), para-methoxyamphetamine (PMA), 4-bromo-2,5-dimethoxyamphetamine (DOB), and 2,5-dimethoxyamphetamine (DMA). Each of these hallucinogenic amphetamines was subsequently controlled individually under the CSA and the Convention on Psychotropic Substances, 1971. This clandestine laboratory activity in the United States was pivotal in the establishment of an administrative scheduling provision in the U.S. CSA. In the 1970's, analogues of phencyclidine (PCP) and methaqualone were controlled under the CSA after substantial quantities were illicitly produced, distributed and abused.

The more recent problem with controlled substance analogues in the United States occurred in the 1980s and centered around narcotic, stimulant and hallucinogenic analogues. Analogues of narcotics included variations on fentanyl and pethidine (meperidine). Fentanyl is a short-acting, highly potent substance used as an analgesic and anesthetic. Over ten fentanyl analogues, known as China White and synthetic heroin, with potencies of up to several thousand times that of fentanyl, were synthesized in illicit laboratories, distributed and responsible for scores of overdose deaths in the United States. Meperidine analogues included MPPP (1-methyl-4-phenyl-4-propionoxypiperidine) and PEPAP [1-(2-phenethyl)-4-phenyl-4-acetoxypiperidine]. Samples of MPPP also contained a neurotoxic by-product, MPTP (1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine) which is formed during the synthesis of MPPP. A number of individuals who used the MPPP/MPTP mixture developed a severe Parkinson's disease-like state as a consequence. Neurological damage produced by MPTP is irreversible and worsens with time.

Modification of the phenethylamine and amphetamine molecule has produced the most analogues identified in the illicit traffic. These modifications can lead to substances with pure central nervous system stimulant activity (e.g., methcathinone), hallucinogenic activity (e.g., 4-bromo-2,5-dimethoxyphenethylamine (2C-B)) or a combination of both depending upon the dose (e.g., 3,4-methylenedioxyamphetamine (MDA)). Changes to the phenyl ring may lead to substances with hallucinogenic activity while changes to the ethylamine chain usually result in varying levels of stimulant activity. The synthesis and activity of many of these analogues have been reviewed by Glennon (See "Synthesis and Evaluation of Amphetamine Analogues", in Clandestinely Produced Drugs, Analogues and Precursors, M. Klein, F. Sapienza, H. McClain, Jr. and I. Khan, Editors, 1989). Additional data on many of these substances can be found in a World Health Organization publication entitled Information Manual on Designer Drugs, Programme on Substance Abuse.

Several analogues of the hallucinogenic amphetamine, 3,4-methylenedioxyamphetamine (MDA) have been clandestinely manufactured and abused in the United States and around the world. These include 3,4-methylenedioxymethamphetamine (MDMA), 3,4-methylenedioxy-N-

ethylamphetamine (MDE), 3,4-methylenedioxy-N-hydroxyamphetamine, N-methyl-1-(3,4-methylenedioxyphenyl)-2-butanamine (MBDB). Each produces effects similar, at least, in part, to MDA. Under the U.S. CSA, MBDB is controlled in Schedule I as a positional isomer of MDE. Other ring-substituted amphetamines or phenethylamines, such as 2C-B (4-bromo-2,5-dimethoxyphenethylamine) and PMMA (para-methoxymethamphetamine) have also been identified in the illicit traffic. Scores of similar substances are described by Shulgin (See Shulgin and Shulgin, in PIHKAL, A chemical Love Story, 1995)

Analogues of amphetamine and other central nervous system stimulants include N,N-dimethylamphetamine, methcathinone (Ephedrone), aminorex and 4-methylaminorex. Each has been produced in clandestine laboratories and identified in the illicit traffic in the United States and elsewhere.

U.S. Government Response

Until 1984, the United States had to rely on traditional administrative scheduling or legislative control to add a substance to the list of controlled substances. Traditional administrative scheduling under the U.S. CSA provides a role for both the law enforcement (DEA) and health (Department of Health and Human Services; DHHS) authorities. It involves the collection of all types of data by DEA, a scientific and medical evaluation of that data by DHHS and an independent evaluation by DEA. DEA must then make specific findings regarding the abuse potential, accepted medical use and safety and physical and psychological dependence potentials of the substance under review before determining its appropriate control status. The process allows for comments from interested parties and the opportunity for a hearing, if requested. Under the best of circumstances, this process takes six months to one year. If a hearing is requested it may take several years. The scheduling of MDMA, for example was initiated in 1984 and finalized in 1988. This was not an effective response against the analogue phenomenon.

In 1984, the U.S. Congress amended the CSA to include a provision for DEA to temporarily place a substance into Schedule I for a period of one year if it was found necessary to do so to avoid an imminent hazard to the public safety. This control could be extended one time for six months as long as procedures to permanently control the substance had been initiated. This procedure can not be applied to substances already controlled in another schedule and to marketed or investigational substances. DEA is not required to solicit or receive a scientific and medical evaluation from the health authorities, only to provide a notification of its intent to temporarily control the substance. DEA is required to consider the substance's history and current pattern of abuse, its scope, duration and significance of abuse, and its risk to the public health, in making a determination of whether the substance should be subject to emergency controls. Emergency scheduling imposes the full range of regulatory controls and criminal sanctions on the substance and those who handle it. DEA first used its emergency scheduling authority in April 1986 and has placed 21 substances under emergency control since then. These have included fentanyl and meperidine analogues, stimulant amphetamine analogues, hallucinogenic amphetamine analogues and a tryptamine analogue. These substances were placed into Schedule I on an emergency basis because of their appearance in the illicit drug traffic,

chemical similarity to known controlled substances, and known or predicted pharmacological similarity to controlled substances. When specific pharmacological data was not available, structure activity relationships formed an important basis for initial control. Once sufficient scientific data was obtained, permanent scheduling followed each of these emergency actions.

Although this emergency scheduling process greatly reduced the amount of time required to place a "new" substance under the CSA, clandestine laboratory operators continued to synthesize new analogues before the DEA could control them, even on an emergency basis. The emergency controls continued to be reactive and took a few months to complete. The U.S. government looked for a way to become proactive. Two basic alternatives were considered. The first was class scheduling. This would list chemical structural parameters for different classes of substances subject to abuse and control. All substances which fell within these parameters would be considered controlled. Defining these parameters was rather difficult for the many classes of controlled substances. Additionally, this method would impose regulatory controls on thousands of substances and could negatively impact legitimate drug development.

The second alternative was to impose only criminal sanctions on the activity of manufacturing and distributing an analogue intended for human consumption. This was the approach taken and in 1986, the CSA was again amended. The Controlled Substance Analogue Enforcement Act of 1986 (See attached) provided that a controlled substance analogue, to the extent intended for human consumption, could be treated as a Schedule I substance. It defined a controlled substance analogue as a substance which (1) has a chemical structure substantially similar to that of a controlled substance in Schedule I or II; (2) produces a stimulant, depressant or hallucinogenic effect substantially similar to or greater than that produced by a Schedule I or II controlled substance; or (3) is represented by an individual to produce such an effect. Again, marketed substances, or those under active investigation, are exempt from this provision. With this provision, analogues of controlled substances are covered under the criminal, but not the regulatory, provisions of the CSA. The requirement that analogues be intended for human consumption and the exemptions for marketed and investigational substances ensure that legitimate research and development are not hindered.

It is important to note that there is no list of controlled substance analogues. Whether a substance is a controlled substance analogue is determined at each criminal proceeding. Once a substance is permanently controlled under the CSA, there is little debate as to whether that substance is classified as a controlled substance and subject to the criminal provisions of the CSA. Individuals who are prosecuted for manufacture or distribution of a controlled substance analogue can force the prosecution to prove on each occasion to a judge and/or a jury that a substance meets the definition of a controlled substance analogue. Expert testimony may be heard in each criminal proceeding to determine if a substance meets the definition of a controlled substance analogue. Forensic chemists are used to describe the points of similarity between the structure of the analogue compared to that of a controlled substance. Biological data, if available, or structure activity relationships, are used to determine the pharmacological similarity between the controlled substance and the analogue. If an analogue is identified in the illicit traffic on several occasions, emergency controls are usually imposed and ultimately, the substance is permanently scheduled under the CSA.

The U.S. government has successfully prosecuted a substantial number of individuals under this provision for the manufacture and distribution of various analogues. These have included analogues of MDA, amphetamine, methamphetamine, meperidine, fentanyl and others. It appears that most, if not all, of the substances described in "PIHKAL" could meet the definition of controlled substance analogue, and if intended for human consumption, would fall under the analogue provision of the CSA. Individuals manufacturing and distributing these substances can and have been successfully prosecuted. Both the emergency scheduling and the analogue provisions of the CSA have withstood challenges in the courts.

Conclusion

An examination of the scheduling actions under the CSA since 1980 show that there were a large number of illicit substances (each could be considered an analogue) controlled and emergency scheduled in the 1980s (See attached). This activity has dramatically decreased since 1990 with only four substances placed under emergency control. Additionally there are currently no controlled substance analogues under review in the United States for emergency or permanent control. This decrease in the production and distribution of analogues can be attributed, at least in part, to the passage of the emergency and analogue provisions of the CSA, successful prosecutions under these provisions, and unsuccessful challenges to these statutes in the courts. Both of these statutes, but particularly the analogue statute, have proven to be successful and effective tools in attacking the problem of controlled substance analogues. Similar legislation, consistent with individual legal systems, should be considered by other countries.

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