

DEPARTMENT OF JUSTICE**Drug Enforcement Administration****21 CFR Part 1308**

[Docket No. DEA-338]

**Schedules of Controlled Substances:
Placement of Propofol Into Schedule IV****AGENCY:** Drug Enforcement Administration, Department of Justice.**ACTION:** Notice of proposed rulemaking.

SUMMARY: This proposed rule is issued by the Deputy Administrator of the Drug Enforcement Administration (DEA) to place the substance propofol, including its salts, isomers, and salts of isomers whenever the existence of such salts, isomers, and salts of isomers is possible, into schedule IV of the Controlled Substances Act (CSA). This proposed action is based on a recommendation from the Assistant Secretary for Health of the Department of Health and Human Services (DHHS) and on an evaluation of the relevant data by DEA. If finalized, this action would impose the regulatory controls and criminal sanctions of schedule IV on those who handle propofol and products containing propofol.

DATES: Written comments must be postmarked on or before December 27, 2010, and electronic comments must be sent on or before midnight Eastern time December 27, 2010.

ADDRESSES: To ensure proper handling of comments, please reference "Docket No. DEA-327" on all written and electronic correspondence. Written comments sent via regular or express mail should be sent to the Drug Enforcement Administration, Attention: DEA Federal Register Representative/ODL, 8701 Morrisette Drive, Springfield, Virginia 22152. Comments may be sent to DEA by sending an electronic message to dea.diversion.policy@usdoj.gov. Comments may also be sent electronically through <http://www.regulations.gov> using the electronic comment form provided on that site. An electronic copy of this document is also available at the <http://www.regulations.gov> Web site. DEA will accept electronic comments containing Microsoft Word, WordPerfect, Adobe PDF, or Excel file formats only. DEA will not accept any file format other than those specifically listed here.

Please note that DEA is requesting that electronic comments be submitted before midnight Eastern Time on the day the comment period closes because <http://www.regulations.gov> terminates

the public's ability to submit comments at midnight Eastern Time on the day the comment period closes. Commenters in time zones other than Eastern Time may want to consider this so that their electronic comments are received. All comments sent via regular or express mail will be considered timely if postmarked on the day the comment period closes.

FOR FURTHER INFORMATION CONTACT: Christine A. Sannerud, PhD, Chief, Drug and Chemical Evaluation Section, Office of Diversion Control, Drug Enforcement Administration, 8701 Morrisette Drive, Springfield, Virginia 22152, Telephone: (202) 307-7183.

SUPPLEMENTARY INFORMATION:

Posting of Public Comments: Please note that all comments received are considered part of the public record and made available for public inspection online at <http://www.regulations.gov> and in the Drug Enforcement Administration's public docket. Such information includes personal identifying information (such as your name, address, etc.) voluntarily submitted by the commenter.

If you want to submit personal identifying information (such as your name, address, etc.) as part of your comment, but do not want it to be posted online or made available in the public docket, you must include the phrase "PERSONAL IDENTIFYING INFORMATION" in the first paragraph of your comment. You must also place all the personal identifying information you do not want posted online or made available in the public docket in the first paragraph of your comment and identify what information you want redacted.

If you want to submit confidential business information as part of your comment, but do not want it to be posted online or made available in the public docket, you must include the phrase "CONFIDENTIAL BUSINESS INFORMATION" in the first paragraph of your comment. You must also prominently identify confidential business information to be redacted within the comment. If a comment has so much confidential business information that it cannot be effectively redacted, all or part of that comment may not be posted online or made available in the public docket.

Personal identifying information and confidential business information identified and located as set forth above will be redacted and the comment, in redacted form, will be posted online and placed in the Drug Enforcement Administration's public docket file. Please note that the Freedom of Information Act applies to all comments

received. If you wish to inspect the agency's public docket file in person by appointment, please see the **FOR FURTHER INFORMATION CONTACT** paragraph.

Background

On March 18, 2008, the Drug Enforcement Administration (DEA) received a petition requesting that 21 CFR 1308.13 be amended so that propofol be controlled as a schedule III substance under the CSA. The basis of the petition was the reports of increased incidences of propofol abuse during the past decade. The petitioner stated as the main argument in support of the request that:

*"Propofol is the most common intravenous anesthetic in the United States today but over the course of the decade, documented cases of abuse have been steadily increasing over the past 10 years * * * Unfortunately, there is also a very high mortality rate (greater than 33%) associated with this abuse."*

The petitioner stated that controlling propofol as a scheduled drug would require all practitioners to strictly monitor the access and use of propofol and possibly save lives.

Propofol was approved in 1989 and is an ultra-short acting intravenous (i.v.) anesthetic under the commercial name, Diprivan[®]. Propofol is also marketed as a generic drug under three trade names. Two veterinary versions, Rapinovet and PropoFlo/PropoVet were approved for marketing in 1999 and 2000, respectively. Propofol is indicated in adults for the initiation and maintenance of Monitored Anesthesia Care (MAC) sedation, combined sedation, and regional anesthesia. It is also indicated for Intensive Care Unit (ICU) sedation of intubated and mechanically ventilated patients. For children, propofol is indicated for induction and maintenance of general anesthesia. Diprivan[®] is an injectable emulsion (10 mg/mL).

Propofol, or 2,6-diisopropylphenol, is slightly soluble in water and is formulated in an oil-in-water emulsion that is milky-white in appearance. Fospropofol, the water-soluble O-methyl-phosphate disodium salt prodrug of propofol, has been recently controlled as a schedule IV substance under the CSA.

Propofol binds to the gamma-aminobutyric acid (GABA_A) receptors and acts as a modulator by potentiating the activity of GABA at these receptors. Other psychoactive drugs that are controlled under the CSA, e.g., barbiturates (schedule II and III) and benzodiazepines (schedule IV), potentiate the activity of GABA at the GABA_A receptors.

Animal self-administration studies demonstrate the reinforcing effects of propofol in rat, mouse, and primate models. It has been demonstrated that drugs that are self-administered by animals also have drug abuse potential in humans. Propofol has been demonstrated to have reinforcing effects comparable to methohexital, a schedule IV sedative-hypnotic. A study found that both drug-naïve and methohexital-trained (a schedule IV barbiturate) rats self-administer propofol under a fixed ratio schedule. In baboons, low-to-high levels of self-administration were maintained by subanesthetic doses of propofol after substituting for cocaine. There have been published abuse liability studies of propofol in humans in which the reinforcement and reward effects have been demonstrated. These studies showed that propofol produces subjective effects most comparable to schedule IV sedatives. Generally, the studies demonstrated that propofol dose-dependently increased the reporting by the subject feeling “high,” relative to the placebo.

The motivation for abuse of propofol is generally for its sedative and relaxing properties and induction of euphoric effects. There have also been reports that propofol’s ability to induce sexual illusions and disinhibition contributes to its appeal as a drug of abuse. Anecdotal reports of propofol abusers described their experiences as “pleasant,” “euphoric,” and “relaxing”.

The current abuse profiles of propofol indicate that it is abused by medical professionals since they have access to the drug in medical facilities which perform anesthesia (Adverse Event Reporting System (AERS) DataMart database). In the AERS database, there are reports of propofol diversion and abuse, some of which resulted in death. In 96 percent of these cases, the abusers were health care providers or were in training programs to become health care professionals. Propofol is not currently controlled by either the Federal Government or State governments, and may not be a target or priority of law enforcement; therefore, information on reported seizures and cases from Federal, State and local law enforcement agencies is very limited.

Schedule IV sedative-hypnotics, such as methohexital and midazolam, are known to produce euphoric moods and have histories of abuse in the United States and other countries. There have been published case reports of individuals who became dependent on propofol. These reports indicated that the individuals expressed a “craving” for propofol, causing them to compulsively self-inject daily. They were abusing

propofol for its relaxing and euphoric effects. In a survey of academic anesthesiology programs, 18 percent reported diversion or abuse of propofol. Twenty-eight percent of the reported abusers of propofol had died due to propofol overdose. The individuals who died were affiliated with health care facilities in which there were no pharmacy or security mechanisms to control access to propofol. In a published survey of certified registered nurse anesthetists, propofol was reported to be the fourth most preferred drug to misuse among this population. Propofol abuse is associated with significant adverse health effects, including death. The known major side effects include pancreatitis, pulmonary edema, cardiovascular depression, and respiratory depression. The cause of death with propofol toxicity is due to severe respiratory depression.

Withdrawal symptoms observed upon ceasing long-term administration of a substance are indicative of a substance’s ability to produce physical dependence. There have been published reports of withdrawal symptoms upon an abrupt cessation of administration of propofol after a prolonged treatment. The symptoms include agitation, tremors, tachycardia, tachypnea, hyperpyrexia, confusion, and hallucinations. These symptoms are similar to the symptoms observed upon withdrawal from benzodiazepines. Withdrawal symptoms improve once administration of propofol is reinitiated. A delusional state lasting up to seven days may occur before full mental functioning returns. It should be noted that after a prolonged administration of propofol, the cessation of administration should be done cautiously and the patient should be monitored for any signs of a withdrawal syndrome.

Propofol has been on the market since 1989, but, due to propofol being unavailable to the general public, the seizures of propofol on the Federal, State and local levels are very low. Medical professionals are the predominant population who are abusers of propofol. Subsequent to DEA gathering and evaluating the available data on propofol, on July 2, 2009, DEA requested that DHHS provide a scientific and medical evaluation of the available information and a scheduling recommendation for propofol, in accordance with 21 U.S.C. 811(b). On May 14, 2010, the Assistant Secretary for Health, DHHS, sent the Deputy Administrator of DEA a scientific and medical evaluation and a letter recommending that propofol be placed into schedule IV of the CSA. Enclosed with the April 30, 2010, letter was a

document prepared by the Food and Drug Administration (FDA) entitled, “Basis for the Recommendation for Control of Propofol and Its Salts in Schedule IV of the Controlled Substances Act (CSA).” The document contained a review of the factors which the CSA requires the Secretary to consider (21 U.S.C. 811(b)).

The references to the studies used in the evaluations for DHHS’ scheduling recommendation and DEA’s independent analysis can be found in both documents. These documents are available on the electronic docket associated with this rule making.

The factors considered by the Assistant Secretary of Health and DEA with respect to propofol were:

- (1) Its actual or relative potential for abuse;
- (2) Scientific evidence of its pharmacological effects;
- (3) The state of current scientific knowledge regarding the drug;
- (4) Its history and current pattern 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; and
- (8) Whether the substance is an immediate precursor of a substance already controlled under this subchapter. (21 U.S.C. 811(c))

Based on the recommendation of the Assistant Secretary for Health, received in accordance with section 201(b) of the Act (21 U.S.C. 811(b)), and the independent review of the available data by DEA, the Deputy Administrator of DEA, pursuant to sections 201(a) and 201(b) of the Act (21 U.S.C. 811(a) and 811(b)), finds that:

- (1) Propofol has a low potential for abuse relative to the drugs or substances in schedule III. The abuse potential of propofol is comparable to the schedule IV substances, methohexital and midazolam;
- (2) Propofol has a currently accepted medical use in treatment in the United States; propofol under the trade name Diprivan® was approved for marketing as a product indicated for monitored anesthesia care by FDA in 1989; and
- (3) Abuse of propofol may lead to limited psychological dependence or physical dependence relative to the drugs or other substances in schedule III.

Based on these findings, the Deputy Administrator of DEA concludes that propofol, including its salts, isomers, and salts of isomers, whenever the existence of such salts, isomers, and salts of isomers is possible, warrants

control in schedule IV of the CSA (21 U.S.C. 812(b)(4)).

Comments and Requests for Hearing

In accordance with the provisions of the CSA (21 U.S.C. 811(a)), this action is a formal rulemaking “on the record after opportunity for a hearing.” Such proceedings are conducted pursuant to the provisions of the Administrative Procedure Act (5 U.S.C. 556 and 557). All persons are invited to submit their comments or objections with regard to this proposal. Requests for a hearing may be submitted by interested persons and must conform to the requirements of 21 CFR 1308.44 and 1316.47. The request should state, with particularity, the issues concerning which the person desires to be heard and the requestor’s interest in the proceeding. Only interested persons, defined in the regulations as those “adversely affected or aggrieved by any rule or proposed rule issuable pursuant to section 201 of the Act (21 U.S.C. 811),” may request a hearing (21 CFR 1308.42). Please note that DEA may grant a hearing only “for the purpose of receiving factual evidence and expert opinion regarding the issues involved in the issuance, amendment, or repeal of a rule issuable” pursuant to 21 U.S.C. 811(a). All correspondence regarding this matter including comments, objections, and requests for hearing should be submitted to DEA using the address information provided above.

Requirements for Handling Propofol

If this rule is finalized as proposed, propofol would be subject to CSA regulatory controls and administrative, civil, and criminal sanctions applicable to the manufacture, distribution, dispensing, importing, and exporting of a schedule IV controlled substance, including the following:

Registration. Any person who manufactures, distributes, dispenses, imports, exports, engages in research, or conducts instructional activities with propofol, or who desires to manufacture, distribute, dispense, import, export, engage in instructional activities, or conduct research with propofol, would need to be registered to conduct such activities in accordance with 21 CFR part 1301.

Security. Propofol would be subject to schedules III–V security requirements and would need to be manufactured, distributed, and stored in accordance with 21 CFR 1301.71, 1301.72(b), (c), and (d), 1301.73, 1301.74, 1301.75(b) and (c), 1301.76, and 1301.77.

Labeling and Packaging. All labels and labeling for commercial containers of propofol which are distributed on or

after finalization of this rule would need to comply with requirements of 21 CFR 1302.03–1302.07.

Inventory. Every registrant required to keep records and who possesses any quantity of propofol would be required to keep an inventory of all stocks of propofol on hand pursuant to 21 CFR 1304.03, 1304.04 and 1304.11. Every registrant who desires registration in schedule IV for propofol would be required to conduct an inventory of all stocks of the substance on hand at the time of registration.

Records. All registrants would be required to keep records pursuant to 21 CFR 1304.03, 1304.04, 1304.21, 1304.22, and 1304.23.

Prescriptions. All prescriptions for propofol or prescriptions for products containing propofol would be required to be issued pursuant to 21 CFR 1306.03–1306.06 and 1306.21, 1306.22–1306.27.

Importation and Exportation. All importation and exportation of propofol would need to be in compliance with 21 CFR part 1312.

Criminal Liability. Any activity with propofol not authorized by, or in violation of, the CSA or the Controlled Substances Import and Export Act occurring on or after finalization of this proposed rule would be unlawful.

Regulatory Certifications

Executive Order 12866

In accordance with the provisions of the CSA (21 U.S.C. 811(a)), this action is a formal rulemaking “on the record after opportunity for a hearing.” Such proceedings are conducted pursuant to the provisions of 5 U.S.C. 556 and 557 and, as such, are exempt from review by the Office of Management and Budget pursuant to Executive Order 12866, section 3(d)(1).

Regulatory Flexibility Act

The Deputy Administrator, in accordance with the Regulatory Flexibility Act (5 U.S.C. 601–612), has reviewed this proposed rule and by approving it certifies that it will not have a significant economic impact on a substantial number of small entities. Propofol products are used for the initiation and maintenance of MAC sedation, combined sedation, and regional anesthesia for adult and pediatric patients undergoing diagnostic or therapeutic procedures. Handlers of propofol will also handle other controlled substances used for sedation which are already subject to the regulatory requirements of the CSA.

Executive Order 12988

This regulation meets the applicable standards set forth in Sections 3(a) and 3(b)(2) of Executive Order 12988 Civil Justice Reform.

Executive Order 13132

This rulemaking does not preempt or modify any provision of State law; nor does it impose enforcement responsibilities on any State; nor does it diminish the power of any State to enforce its own laws. Accordingly, this rulemaking does not have federalism implications warranting the application of Executive Order 13132.

Unfunded Mandates Reform Act of 1995

This rule will not result in the expenditure by State, local and Tribal governments, in the aggregate, or by the private sector, of \$120,000,000 or more (adjusted for inflation) in any one year, and will not significantly or uniquely affect small governments. Therefore, no actions were deemed necessary under provisions of the Unfunded Mandates Reform Act of 1995.

Congressional Review Act

This rule is not a major rule as defined by section 804 of the Small Business Regulatory Enforcement Fairness Act of 1996 (Congressional Review Act). This rule will not result in an annual effect on the economy of \$100,000,000 or more; a major increase in costs or prices; Or significant adverse effects on competition, employment, investment, productivity, innovation, or on the ability of United States-based companies to compete with foreign based companies in domestic and export markets.

List of Subjects in 21 CFR Part 1308

Administrative practice and procedure, Drug traffic control, Narcotics, Prescription drugs.

Under the authority vested in the Attorney General by section 201(a) of the CSA (21 U.S.C. 811(a)), and delegated to the Administrator of DEA by Department of Justice regulations (28 CFR 0.100), and redelegated to the Deputy Administrator pursuant to 28 CFR 0.104, the Deputy Administrator hereby proposes that 21 CFR part 1308 be amended as follows:

PART 1308—SCHEDULES OF CONTROLLED SUBSTANCES

1. The authority citation for 21 CFR part 1308 continues to read as follows:

Authority: 21 U.S.C. 811, 812, 871(b) unless otherwise noted.

2. Section 1308.14 is amended by redesignating paragraphs (c)(46) through

(c)(52) as paragraphs (c)(47) through
(c)(53) and adding a new paragraph
(c)(46) as follows:

§ 1308.14 Schedule IV.

* * * * *
(c) * * *
(46) Propofol
* * * * *

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Dated: October 19, 2010.

Michele M. Leonhart,
Deputy Administrator.

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