



Microgram

Bulletin

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- DECEMBER 2010 -

- PROPOSED RULE -

[Editor's Preface: The following notice has been edited for *Microgram Bulletin*. See the Federal Register: October 27, 2011, (Volume 75, Number 207) (Rules and Regulations) (Pages 66195-66199) for the complete text of the proposed rule.]

DEPARTMENT OF JUSTICE

Drug Enforcement Administration

21 CFR Part 1308

[Docket No. DEA-338]

Schedules of Controlled Substances: Placement of Propofol Into Schedule IV; Proposed Rule

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.

[Editor's Note: See the Federal Register for further information on the posting comments and requests not to post personal identifying information.]

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[supreg]. 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[supreg] 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 (GABAA) 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 GABAA receptors.

[Editor's Note: See the Federal Register for information on Animal self-administration studies.]

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;

SELECTED REFERENCES

[The Selected References section is a compilation of recent publications of presumed interest to forensic chemists. Unless otherwise stated, all listed citations are published in English. Abbreviated mailing address information duplicates that which is provided by the abstracting service. Patents and Proceedings are reported only by their *Chemical Abstracts* citation number.]

1. Zhang X, Jia B, Huang K, Hu B, Chen R, Chen H. **Tracing origins of complex pharmaceutical preparations using surface desorption atmospheric pressure chemical ionization mass spectrometry.** *Analytical Chemistry* 2010;82(19):8060-8070. [Editor's Notes: A novel strategy to trace the origins of commercial pharmaceutical products has been developed based on the direct chemical profiling of the pharmaceutical products by surface desorption atmospheric pressure chemical ionization mass spectrometry (DAPCI-MS). Besides the unambiguous identification of active drug components, various compounds present in the matrixes are simultaneously detected without sample pretreatment, providing valuable information for drug quality control and origin differentiation. Four sources of commercial amoxicillin products made by different manufacturers have been successfully differentiated. This strategy has been extended to screening six sources of Liuwei Dihuang Teapills, which are herbal medicine preparations with extremely complex matrixes. The photolysis status of chemical drug products and the inferior natural herd medicine products prepared with different processes (e.g., extra heating) were also screened using the method reported here. The limit of detection achieved in the MS/MS experiments was estimated to be 1 ng/g for amoxicillin inside the capsule product. The experimental data demonstrate that DAPCI-MS is a useful tool for rapid pharmaceutical analysis, showing promising perspectives for tracking the entire pharmaceutical supply chain to prevent counterfeit intrusions. Contact: Department of Applied Chemistry, East China Institute of Technology, Fuzhou, Jiangxi 344000, Peoples Republic of China.]

Additional References of Possible Interest:

1. Marini RD, Rozet E, Montes MLA, Rohrbasser C, Roht S, Rheme D, Bonnabry P, Schappler J, Veuthey JL, Hubert Ph, Rudaz S. **Reliable low-cost capillary electrophoresis device for drug quality control and counterfeit medicines.** *Journal of Pharmaceutical and Biomedical Analysis* 2010;53(5):1278-1287. [Editor's Notes: Presents title study. Contact: Laboratory of Analytical Chemistry, Centre Interfacultaire de Recherche du Medicament, Institute of Pharmacy, CHU, University of Liege, B36, Liege B-4000, Belgium.]
2. Rodionova OYe, Pomerantsev AL. **NIR-based approach to counterfeit-drug detection.** *Trends in Analytical Chemistry* 2010;29(8):795-803. [Editor's Notes: Presents title study. Contacts: Semenov Institute of Chemical Physics RAS, Moscow 119991, Russia.]

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The Journal/Textbook Collection Exchange is a service intended to facilitate the transfer of unwanted journals and textbooks to forensic libraries or other *Microgram* subscribers. The current donations are listed below. The offers are First Come/First Serve (except **libraries have preference**). There are no charges to the requestor. Please provide a full mailing address in the request. **Important!:** Do not provide an address that irradiates mail!

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1998: September (#5)
2000: January (#1), March (#2), May (#3), July (#4), September (#5)
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2004: Complete set
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2006: Complete set
2007: January (#1), March (#2), November (#6)

Forensic Science Review:

1999: December (#2)
2000: January (#1-2)

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THE DEA FY 2011 STATE AND LOCAL FORENSIC CHEMISTS SEMINAR SCHEDULE

The FY 2011 schedule for the State and Local Forensic Chemists Seminar is as follows:

March 7-11, 2011
June 6-10, 2011
September 12-16, 2011

The school is open only to forensic chemists working for law enforcement agencies. It is intended for chemists who have completed their agency's internal training program and have also been working on the bench for at least one year. There is no tuition charge. The course is held at the Hyatt Place Dulles North Hotel in Sterling, Virginia (near the Washington/Dulles International Airport). A copy of the application form is reproduced on the last page of this issue of *Microgram Bulletin*. Completed applications should be mailed to the Special Testing and Research Laboratory (Attention: J. Head) at 22624 Dulles Summit Court, Dulles, VA 20166. For additional information, call (703) 668-3349.

SCIENTIFIC MEETINGS

Title: American Academy of Forensic Sciences 2011 Annual Meeting
Sponsoring Organization: American Academy of Forensic Sciences
Inclusive Dates: February 21-26, 2011
Location: Hyatt Regency (Chicago, IL)
Contact Information: See website
Website: www.aafs.org

MICROGRAM EMAIL ADDRESS CHANGE

Effective January 1, 2011, the email address for the Microgram Editor will be:

DEA-Microgram -at- usdoj.gov (Replace "-at-" with "@")

The current email address (dea-microgram-2010 -at- mailsnare.net) will be monitored until January 31, 2011. An automated response will direct senders to the new address until April 1, 2011, at which point the account will lapse.

Important Notes to All Subscribers: All subscribers with filters on their accounts should immediately "whitelist" the DEA-Microgram -at- usdoj.gov email address. In addition, it is recommended that the current and previous email addresses used for Microgram (dea-microgram-2010 -at- mailsnare.net) be automatically filtered (blocked) after January 1, 2011. This address will no longer be used by Microgram after this date; therefore, any subsequent emails from any previous Microgram email address will be spam.

All subscribers should notify their IT security personnel of all the above changes.

DEA State and Local Forensic Chemist Seminar Application

Name: (PRINT NAME EXACTLY AS IT IS TO APPEAR ON CERTIFICATE)	Title:
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Employer:

Your Office Mailing Address (include city, state, and zip code):	Length of Service:
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Business Telephone: () -	Business Fax: () -	Date of Application:
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Email Address:

Education

College or University	Degree	Major

Please Check Which Techniques or Equipment Are Used in Your Laboratory

Color Tests	UV
Column Chromatography	IR
Microcrystal Tests	CE
Thin Layer Chromatography	GC/MS
GC	Other (please specify)
HPLC	Other (please specify)

Indicate Analytical Problem(s) Nominee Would Like to Have Covered:

Choice of Seminar Dates:

1st Choice: _____ 2nd Choice: _____

Laboratory Chief/Director:

Printed Name: _____ Signature: _____

Title: _____ Date: _____

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