le 4410-09-P

DEPARTMENT OF JUSTICE

Drug Enforcement Administration

21 CFR Part 1308

[Docket No. DEA1155]

Schedules of Controlled Substances: Placement of Diphenidine in Schedule I

AGENCY: Drug Enforcement Administration, Department of Justice.

ACTION: Notice of proposed rulemaking.

SUMMARY: The Drug Enforcement Administration proposes placing diphenidine (1-(1,2-diphenylethyl)piperidine),including its salts, isomers, and salts of isomers whenever the existence of such salts, isomers, and salts of isomers is possible, in schedule I of the Controlled Substances Act. This action is being taken, in part, to enable the United States to meet its obligations under the 1971 Convention on Psychotropic Substances. If finalized, this action would impose the regulatory controls and administrative, civil, and criminal sanctions applicable to schedule I controlled substances on persons who handle (manufacture, distribute, reverse distribute, import, export, engage in research, conduct instructional activities or chemical analysis with, or possess) or propose to handle diphenidine.

DATES: Comments must be submitted electronically or postmarked on or before [INSERT DATE 30 DAYS AFTER PUBLICATION IN THE FEDERAL REGISTER]. The electronic Federal Docket Management System will not accept comments after 11:59 p.m. Eastern Time on the last day of the comment period.

Interested persons may file a request for a hearing or waiver of hearing pursuant to 21 CFR 1308.44 and in accordance with 21 CFR 1316.47 and/or 1316.49, as applicable. Requests for a hearing and waivers of an opportunity for a hearing or to participate in a hearing, together with a written statement of position on the matters of fact and law

involved in the hearing, must be received on or before [INSERT DATE 30 DAYS AFTER PUBLICATION IN THE FEDERAL REGISTER].

ADDRESSES: Interested persons may file written comments on this rulemaking in accordance with 21 CFR 1308.43(g). To ensure proper handling of comments, please reference "Docket No. DEA1155" on all correspondence, including any attachments.

- *Electronic comments:* The Drug Enforcement Administration (DEA) encourages commenters to submit all comments electronically through the Federal eRulemaking Portal, which provides the ability to type short comments directly into the comment field on the webpage or attach a file for lengthier comments. Please go to *https://www.regulations.gov* and follow the online instructions at that site for submitting comments. Upon completion of your submission, you will receive a Comment Tracking Number for your comment. Submitted comments are not instantaneously available for public view on Regulations.gov. If you have received a Comment Tracking Number, your comment has been successfully submitted and there is no need to resubmit the same comment. Commenters should be aware that the electronic Federal Docket Management System will not accept comments after 11:59 p.m. Eastern Time on the last day of the comment period.

- *Paper comments:* Paper comments that duplicate electronic submissions are not necessary and are discouraged. Should you wish to mail a paper comment *in lieu* of an electronic comment, it should be sent via regular or express mail to: Drug Enforcement Administration, Attn: DEA Federal Register Representative/DPW, 8701 Morrissette Drive, Springfield, Virginia 22152.

- *Hearing requests:* All requests for a hearing and waivers of participation, together with a written statement of position on the matters of fact and law asserted in the hearing, must be filed with the DEA Administrator, who will make the determination of whether a hearing will be needed to address such matters of fact and law in the

rulemaking. Such requests must be sent to: Drug Enforcement Administration, Attn: Administrator, 8701 Morrissette Drive, Springfield, Virginia 22152. For informational purposes, a courtesy copy of requests for hearing and waivers of participation should also be sent to: (1) Drug Enforcement Administration, Attn: Hearing Clerk/OALJ, 8701 Morrissette Drive, Springfield, Virginia 22152; and (2) Drug Enforcement Administration, Attn: DEA Federal Register Representative/DPW, 8701 Morrissette Drive, Springfield, Virginia 22152.

FOR FURTHER INFORMATION CONTACT: Terrence L. Boos, Drug and Chemical Evaluation Section, Diversion Control Division, Drug Enforcement Administration; Telephone: (571) 362-3249.

As required by 5 U.S.C. 553(b)(4), a summary of this rule may be found in the docket for this rulemaking at www.regulations.gov.

SUPPLEMENTARY INFORMATION:

The Drug Enforcement Administration (DEA) proposes to schedule diphenidine (1-(1,2-diphenylethyl)piperidine) in schedule I of the Controlled Substances Act (CSA), including its salts, isomers, and salts of isomers whenever the existence of such salts, isomers, and salts of isomers is possible within the specific chemical designation.

Posting of Public Comments

All comments received in response to this docket are considered part of the public record. DEA will make comments available for public inspection online at *https://www.regulations.gov*, unless reasonable cause is given. Such information includes personal or business identifiers (such as name, address, state or federal identifiers, etc.) voluntarily submitted by the commenter.

Commenters submitting comments which include personal identifying information (PII), confidential, or proprietary business information that the commenter does not want to be made publicly available should submit two copies of the comment. One copy must

be marked "CONTAINS CONFIDENTIAL INFORMATION" and should clearly identify all PII or business information the commenter does not want to be made publicly available, including any supplemental materials. DEA will review this copy, including the claimed PII and confidential business information, in its consideration of comments. The second copy should be marked "TO BE PUBLICLY POSTED" and must have all claimed confidential PII and business information already redacted. DEA will post only the redacted comment on https://www.regulations.gov for public inspection. DEA generally will not redact additional information contained in the comment marked "TO BE PUBLICLY POSTED." The Freedom of Information Act applies to all comments received.

For easy reference, an electronic copy of this document and supplemental information to this proposed rule are available at *https://www.regulations.gov*.

Request for Hearing or Appearance; Waiver

Pursuant to 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 (APA).[1] Interested persons, as defined in 21 CFR 1300.01(b), may file requests for a hearing in conformity with the requirements of 21 CFR 1308.44(a) and 1316.47(a), and such requests must:

(1) state with particularity the interest of the person in the proceeding;

(2) state with particularity the objections or issues concerning which the person desires to be heard; and

(3) state briefly the position of the person regarding the objections or issues.

Any interested person may file a waiver of an opportunity for a hearing or to participate in a hearing in conformity with the requirements of 21 CFR 1308.44(c),

[1] 5 U.S.C. 551–559. 21 CFR 1308.41–1308.45; 21 CFR part 1316, subpart D.

together with a written statement of position on the matters of fact and law involved in any hearing.[2]

All requests for a hearing and waivers of participation, together with a written statement of position on the matters of fact and law involved in such hearing, must be sent to DEA using the address information provided above. The decision whether a hearing will be needed to address such matters of fact and law in the rulemaking will be made by the Administrator. If a hearing is needed, DEA will publish a notice of hearing on the proposed rulemaking in the *Federal Register*.[3] Further, once the Administrator determines a hearing is needed to address such matters of fact and law in rulemaking, he will then designate an Administrative Law Judge (ALJ) to preside over the hearing. The ALJ's functions shall commence upon designation, as provided in 21 CFR 1316.52.

In accordance with 21 U.S.C. 811 and 812, the purpose of a hearing would be to determine whether diphenidine meets the statutory criteria for placement in schedule I, as proposed in this rulemaking.

Legal Authority

The CSA provides that proceedings for the issuance, amendment, or repeal of the scheduling of any drug or other substance may be initiated by the Attorney General (delegated to the Administrator of DEA pursuant to 28 CFR 0.100) on her own motion, at the request of the Secretary of Health and Human Services (HHS), or on the petition of an interested party.[4] This proposed action is initiated on the Administrator's own motion and supported by, *inter alia*, a recommendation from the then-Assistant Secretary for Health of the Department of HHS (Assistant Secretary) and an evaluation of all other relevant data by DEA. If finalized, this action would impose the regulatory controls and

[2] 21 CFR 1316.49.
[3] 21 CFR 1308.44(b), 1316.53.
[4] 21 U.S.C. 811(a).

administrative, civil, and criminal sanctions applicable to schedule I controlled substances on persons who handle or propose to handle diphenidine.

In addition, the United States is a party to the 1971 United Nations Convention on Psychotropic Substances (1971 Convention), February 21, 1971, 32 U.S.T. 543, 1019 U.N.T.S. 175, as amended. Procedures respecting changes in drug schedules under the 1971 Convention are set forth in 21 U.S.C. 811(d)(2)-(4). When the United States receives notification of a scheduling decision pursuant to Article 2 of the 1971 Convention indicating that a drug or other substance has been added to a schedule specified in the notification, the Secretary of HHS (Secretary),[5] after consultation with the Attorney General, shall first determine whether existing legal controls under subchapter I of the CSA and the Federal Food, Drug, and Cosmetic Act meet the requirements of the schedule specified in the notification with respect to the specific drug or substance.[6] In the event that the Secretary did not consult with the Attorney General, and the Attorney General did not issue a temporary order, as provided under 21 U.S.C. 811(d)(4), the procedures for permanent scheduling set forth in 21 U.S.C. 811(a) and (b) control.

Pursuant to 21 U.S.C. 811(a)(1), the Attorney General (as delegated to the Administrator of DEA) may, by rule, add to such a schedule or transfer between such schedules any drug or other substance, if he finds that such drug or other substance has a potential for abuse, and makes with respect to such drug or other substance the findings prescribed by 21 U.S.C. 812(b) for the schedule in which such drug or other substance is to be placed.

---

[5] As discussed in a memorandum of understanding entered into by the Food and Drug Administration (FDA) and the National Institute on Drug Abuse (NIDA), FDA acts as the lead agency within HHS in carrying out the Secretary's scheduling responsibilities under the CSA, with the concurrence of NIDA. *Memorandum of Understanding with the National Institute on Drug Abuse*, 50 FR 9518 (Mar. 8, 1985). The Secretary has delegated to the Assistant Secretary for Health of HHS the authority to make domestic drug scheduling recommendations. *Comprehensive Drug Abuse Prevention and Control Act of 1970, Public Law 91-513, As Amended; Delegation of Authority*, 58 FR 35460 (July 1, 1993).

[6] 21 U.S.C. 811(d)(3).

Background

Diphenidine (1-(1,2-diphenylethyl)piperidine) is a dissociative hallucinogen of the 1,2-diarylethylamine class that has been identified in the United States' illicit drug market. It was first synthesized in 1924 but not encountered for recreational use until 2014. Diphenidine has no approved medical use in the United States.

On June 10, 2021, the Secretary-General of the United Nations advised the Secretary of State of the United States that the Commission on Narcotic Drugs (CND), during its 64th Session in April 2021, voted to place diphenidine in Schedule II of the 1971 Convention (CND Decision 64/5). As a signatory to the 1971 Convention, the United States is required, by scheduling under the CSA, to place appropriate controls on diphenidine to meet the minimum requirements of the treaty. The relevant treaty provisions and domestic statutes executing those provisions are below.

To begin, Article 2, paragraph 7(b), of the 1971 Convention sets forth the minimum requirements that the United States must meet when a substance has been added to Schedule II of the 1971 Convention. Pursuant to the 1971 Convention, the United States must require licenses for the manufacture, export and import, and distribution of diphenidine. The CSA's registration requirement as set forth in 21 U.S.C. 822, 823, 957, and 958, as well as implementing regulations in 21 CFR parts 1301 and 1312, set forth this licensing requirement.

In addition, the United States must adhere to specific export and import provisions that are provided in the 1971 Convention. The CSA's export and import provisions established in 21 U.S.C. 952, 953, 957, and 958, and implemented in 21 CFR part 1312, execute these requirements.

Likewise, under Article 13, paragraphs 1 and 2, of the 1971 Convention, a party to the 1971 Convention may notify through the U.N. Secretary-General that it prohibits the importation of a substance in Schedule II, III, or IV of the 1971 Convention. If such

notice is presented to the United States, the United States shall take measures to ensure that the named substance is not exported to the country of the notifying party. The CSA's above-mentioned export provisions set forth these procedures.

Further, under Article 16, paragraph 4, of the 1971 Convention, the United States is required to provide annual statistical reports to the International Narcotics Control Board (INCB). Using INCB Form P, the United States shall provide the following information: (1) In regard to each substance in Schedule I and II of the 1971 Convention, quantities manufactured, exported to and imported from each country or region as well as stocks held by manufacturers; (2) in regard to each substance in Schedule III and IV of the 1971 Convention, quantities manufactured, as well as quantities exported and imported; (3) in regard to each substance in Schedule II and III of the 1971 Convention, quantities used in the manufacture of exempt preparations; and (4) in regard to each substance in Schedule II-IV of the 1971 Convention, quantities used for the manufacture of non-psychotropic substances or products.

Lastly, under Article 2, paragraph 7(b)(vi) of the 1971 Convention, the United States must adopt measures in accordance with Article 22 to address violations of any statutes or regulations that are adopted pursuant to its obligations under the 1971 Convention. The United States complies with this provision, as persons acting outside the legal framework established by the CSA are subject to administrative, civil, and/or criminal action.

DEA notes that there are differences between the schedules of substances in the 1971 Convention and the CSA. The CSA has five schedules (schedules I-V) with specific criteria set forth for each schedule. Schedule I is the only possible schedule in which a drug or other substance may be placed if it has high potential for abuse and no currently accepted medical use in treatment in the United States.[7] In contrast, the 1971 Convention

[7] *See* 21 U.S.C. 812(b).

has four schedules (Schedules I-IV) but does not have specific criteria for each schedule. The 1971 Convention simply defines its four schedules, in Article 1, to mean the correspondingly numbered lists of psychotropic substances annexed to the Convention and altered in accordance with Article 2.

Proposed Determination to Schedule Diphenidine

Pursuant to 21 U.S.C. 811(b), DEA gathered the necessary data on diphenidine and, on January 24, 2022, submitted it to the then-Assistant Secretary for Health of HHS with a request for a scientific and medical evaluation of available information and a scheduling recommendation for diphenidine.

On November 26, 2022, HHS provided DEA a scientific and medical evaluation entitled, "Basis for the Recommendation to Control 1-(1,2-Diphenylethyl)piperidine (Diphenidine) and its Salts in Schedule I of the Controlled Substances Act," and a scheduling recommendation. Pursuant to 21 U.S.C. 811(b), following consideration of the eight factors and findings related to this substance's abuse potential, legitimate medical use, and safety or dependence liability, HHS recommended that diphenidine and its salts be controlled in schedule I of the CSA under 21 U.S.C. 812(b).

In response, DEA reviewed the scientific and medical evaluation and scheduling recommendation provided by HHS, and all other relevant data, and completed its own eight-factor analysis in accordance with 21 U.S.C. 811(c). Included below is a brief summary of each factor as analyzed by HHS and DEA in their respective eight-factor analyses, and as considered by DEA in this proposed scheduling determination. Please note that both the DEA and HHS analyses, including the evaluation of the eight factors determinative of control along with their supporting data and citations, are available in their entirety under the tab "Supporting Documents" of the public docket for this proposed rule at *https://www.regulations.gov* under docket number "DEA1155."

1. *Its Actual or Relative Potential for Abuse*

In addition to considering the information HHS provided in its scientific and medical evaluation document for diphenidine, DEA also considered all other relevant data regarding actual or relative potential for abuse of diphenidine. The term "abuse" is not defined in the CSA; however, the legislative history of the CSA suggests the consideration of the following four criteria in determining whether a particular drug or substance has a potential for abuse:[8]

a. There is evidence that individuals are taking the drug or drugs containing such a substance in amounts sufficient to create a hazard to their health or to the safety of other individuals or of the community; or

b. There is significant diversion of the drug or other substance from legitimate drug channels; or

c. Individuals are taking the drug or drugs containing such a substance on their own initiative rather than on the basis of medical advice from a practitioner licensed by law to administer such drugs in the course of his professional practice; or

d. The drug or drugs containing such a substance are new drugs so related in their action to a drug or drugs already listed as having a potential for abuse to make it likely that the drug will have the same potentiality for abuse as such drugs, thus making it reasonable to assume that there may be significant diversions from legitimate channels, significant use contrary to or without medical advice, or that it has a substantial capability of creating hazards to the health of the user or to the safety of the community.

DEA reviewed the scientific and medical evaluation provided by HHS and all other data relevant to the abuse potential of diphenidine. These data as presented below demonstrate that diphenidine has a high potential for abuse.

a. There is evidence that individuals are taking the drug or other substance in amounts sufficient to create a hazard to their health or to the safety of other individuals or to the community.

[8] Comprehensive Drug Abuse Prevention and Control Act of 1970, H.R. Rep. No. 91-1444, 91st Cong., 2nd Sess. (1970) reprinted in 1970 U.S.C.C.A.N. 4566, 4603.

Data show that diphenidine has been encountered by law enforcement in the United States (see Factor 5 below, discussing evidence of abuse in the United States), indicating diphenidine is available for abuse. Case reports of overdoses and fatalities where diphenidine had been positively confirmed in biological fluids have been published. Adverse effects appear similar to those induced by dissociative drugs such as methoxetamine (MXE, schedule I controlled substance), phencyclidine (PCP) (schedule II controlled substance), and ketamine (schedule III controlled substance) and include agitation, disorientation, altered conscious state, tachycardia, an increased respiratory rate, miotic pupils, muscular rigidity, metabolic acidosis, and rhabdomyolysis. Additionally, reports of driving under the influence with diphenidine have been reported in the United States, Japan, Belgium, Italy, Sweden, France, and the United Kingdom. According to HHS, individuals are using diphenidine and taking amounts sufficient to create a hazard to the individual or to the safety of other individuals or to the community.

b. There is significant diversion of the drug or substance from legitimate drug channels.

Diphenidine is not a Food and Drug Administration (FDA)-approved drug for treatment or legally marketed as a drug in the United States, nor marketed in any country in which its use is legal. Legitimate drug channels are limited to research conducted with the drug and manufacturing facilities and to the supply chain that produces the drug for legitimate research. However, HHS noted that FDA is not aware of any diversion from research or legitimate manufacturing activities for diphenidine. Therefore, HHS concluded this characteristic of abuse is not applicable.

c. Individuals are taking the substance on their own initiative rather than on the basis of medical advice from a practitioner licensed by law to administer such substance.

Diphenidine is not approved for medical use and is not formulated or available for clinical use. Diphenidine has been sold on the internet. Case reports of overdoses and

fatalities with biological confirmation of diphenidine with toxicological analysis have been reported. Therefore, it is assumed that individuals are taking diphenidine on their own initiative, rather than based on medical advice from a practitioner licensed by law to administer drugs.

d. The drug or substance is so related in its action to a drug or other substance already listed as having a potential for abuse to make it likely that the drug or substance will have the same potential for abuse as such drugs, thus making it reasonable to assume that there may be significant diversion from legitimate channels, significant use contrary to or without medical advice, or that it has a substantial capability of creating hazards to the health of the user or to the safety of the community.

Diphenidine has high-binding affinity and functions as an antagonist at the *N*-methyl-D-aspartate (NMDA) receptor similar to known drugs of abuse MXE, PCP, and ketamine. HHS notes that in rats, diphenidine disrupts pre-pulse inhibition (PPI) of acoustic startle, an effect indicative of NMDA receptor antagonism. Since diphenidine shares the same NMDA receptor binding and antagonism effects with already listed substances known to have potential for abuse, HHS stated it's reasonable to assume that diphenidine will be subject to significant use contrary to or without medical advice. Based on this assessment DEA expects diphenidine to have a high abuse potential and pose a high risk to public health.

2. *Scientific Evidence of Its Pharmacological Effects, If Known*

Diphenidine is structurally related to and shares pharmacological properties with PCP and ketamine. Based on non-clinical *in vitro* studies, diphenidine binds to the glutamatergic NMDA receptor and acts as an antagonist at this receptor with high affinity. Diphenidine also interacts with monoamine transmission through binding at the norepinephrine and dopamine transporters and increasing neurotransmitter transmission. Non-clinical *in vivo* studies indicate diphenidine produces a similar pharmacological

profile to that of other NMDA receptor antagonists assessed via pre-pulse inhibition, locomotor activity, and conditioned place preference assays. Although no clinical studies have been performed for diphenidine, case reports of human exposure show that the effects of diphenidine are similar to abuse of, or intoxication with, ketamine or MXE.

3. *The State of Current Scientific Knowledge Regarding the Drug or Other Substance*

Diphenidine is a substance belonging to the 1,2-diarylethylamine class and shares structural similarities with schedule II and III dissociative hallucinogens, such as PCP and ketamine. Diphenidine (Chemical Abstracts Service Registry Number 36794-52-2) has a molecular formula of $C_{19}H_{23}N$ and a molecular weight of 265.4 g/mol. Diphenidine is highly lipophilic and high concentrations of diphenidine have been detected in fat tissue in postmortem samples. Diphenidine is metabolized by at least two distinct pathways, glucuronidation and a multi-step process starting with hydroxylation (mono- and bis-hydroxylation), which is followed by methylation of one of the hydroxy groups (*N*,*N*-bis-dealkylation). Cytochrome (CYP) enzymes such as CYP1A2, CYP2B6, CYP2C9, and CYP3A4 are thought to play a role in the metabolism of diphenidine.

As HHS states in its review, there is no currently accepted medical use for diphenidine in treatment in the United States, and a World Health Organization (WHO) critical review states there are no known therapeutic applications. A PubMed search conducted by HHS and DEA did not identify any established therapeutic uses. Thus, DEA concludes that diphenidine has no currently accepted medical use according to established DEA procedures and case law.

4. *Its History and Current Pattern of Abuse*

Diphenidine was first encountered in the United States by law enforcement in 2014. A limited number of encounters of diphenidine have been reported in the years since (see Factor 5). The WHO reports that diphenidine was first observed in the illicit drug market

in 2013. Based on the WHO Critical Review and available scientific and medical literature, HHS noted that diphenidine has been sold on the internet as "herbal blends" and "research chemicals," and at times promoted as producing a "legal high." Diphenidine is generally sold in powder form. Anecdotal reports suggest that diphenidine may induce dissociative effects with various routes of administration (e.g., oral, sublingual, insufflation [snorting], smoking, and intravenous injection). HHS noted that online user reports suggest the onset of action is 10-30 minutes and the duration of action is generally between 2.5 to 6 hours.

5. *The Scope, Duration, and Significance of Abuse*

Internationally, evidence of abuse of diphenidine initially appeared in 2013, one year earlier than was reported in the United States. Based on the WHO 2020 review of diphenidine, there were 61 total international reports of drug seizures between 2018 to 2020. Additionally, eight countries (including six from the European region, one from the Americas, and one from the Western pacific region) reported that diphenidine was being used by individuals for its psychoactive properties. Data from DEA's National Forensic Laboratory Information System (NFLIS-Drug)[9] indicate that, starting in 2014, diphenidine was found in 22 samples in Indiana and Alabama. Diphenidine has been encountered in 11 states (Alabama, California, Colorado, Florida, Illinois, Indiana, Iowa, Louisiana, New Hampshire, South Dakota, and Texas). These reports show evidence of trafficking, distribution, and abuse of diphenidine in the United States.

Diphenidine was reported in several published toxicology-related cases in several countries outside of the United States, including Japan, Belgium, Italy, Sweden, France,

[9]NFLIS-Drug represents an important resource in monitoring illicit drug trafficking, including the diversion of legally manufactured pharmaceuticals into illegal markets. NFLIS-Drug is a comprehensive information system that includes data from forensic laboratories that handle more than 96 percent of an estimated 1 million distinct annual federal, state, and local drug analysis cases. NFLIS-Drug includes drug chemistry results from completed analyses only. While NFLIS-Drug data are not direct evidence of abuse, these can lead to an inference that a drug has been diverted and abused. *See Schedules of Controlled Substances: Placement of Carisoprodol Into Schedule IV,*76 FR 77330, 77332 (Dec. 12, 2011). NFLIS-Drug data were queried on May 7, 2026.

and the United Kingdom. Based on available abuse data, public health risk, and drug trafficking data, the WHO recommended to the United Nations that diphenidine be controlled internationally. In April 2021, the CND voted to place diphenidine into Schedule II of the 1971 Convention.

6. *What, if Any, Risk There is to the Public Health*

Diphenidine shares similar mechanisms of action with and produces similar physiological and subjective effects (see Factor 2 for more information) as other schedule II and III hallucinogens, such as PCP and ketamine. Thus, diphenidine poses the same risks to public health as similar hallucinogens. Predominantly, the risks to public health are borne by users (i.e., hallucinogenic effects, sensory distortion, impaired judgement, strange or dangerous behaviors), but they can affect the general public, as with driving under the influence. There have been reports of distressing responses and death associated with diphenidine in medical literature; however, all have been reported as poly-substance use. Adverse events associated with diphenidine included agitation or agitated delirium, anxiety, dilated pupils, disorientation, dissociation, frothing from the mouth, hypertension, tachycardia, and urinary retention. At least five fatalities have been associated with diphenidine use. Thus, based on the review of both HHS and DEA, serious adverse events that may include death represent a risk to the individual drug users and to public health.

7. *Its Psychic or Physiological Dependence Liability*

HHS noted that there are no clinical studies evaluating the dependence potential of diphenidine. However, diphenidine has similar pharmacological properties of MXE, PCP, and ketamine, which do have well-demonstrated dependence potential. Thus, the HHS and DEA reviews both concluded that it is probable that diphenidine has a dependence profile similar to these known substances.

8. *Whether the Substance is an Immediate Precursor of a Substance Already Controlled under the CSA*

Diphenidine is not an immediate precursor of any controlled substance of the CSA, as defined by 21 U.S.C. 802(23).

Conclusion:

Based on consideration of the scientific and medical evaluation and accompanying recommendation of HHS, and on DEA's own eight-factor analysis, DEA finds that the facts and all relevant data constitute substantial evidence of potential for abuse of diphenidine. As such, DEA proposes to schedule diphenidine as a schedule I controlled substance under the CSA. This proposed action would also enable the United States to meet its obligations under the 1971 Convention.

Proposed Determination of Appropriate Schedule

The CSA establishes five schedules of controlled substances known as schedules I, II, III, IV, and V. The CSA also outlines the findings required to place a drug or other substance in any particular schedule.[10] After consideration of the analysis and recommendation of the Assistant Secretary for Health of HHS and review of all other available data, the Administrator of DEA, pursuant to 21 U.S.C. 811(a) and 21 U.S.C. 812(b)(1), finds that:

1. Diphenidine has a High Potential for Abuse

Diphenidine's pharmacological profile, including its high binding affinity and function as an antagonist at the NMDA receptor, is indicative that it has a high potential for abuse. Binding and antagonism to the NMDA receptor are also characteristic of and believed to be important in the subjective and mind-altering effects of other dissociative drugs, such as MXE, PCP, and ketamine, all known drugs that are abused. Published

[10] 21 U.S.C. 812(b).

case reports support that the subjective effects and use patterns are similar to other NMDA receptor antagonists that have known high abuse.

2. Diphenidine has No Currently Accepted Medical Use in Treatment in the United States

Diphenidine is not legally marketed in the United States. As noted in the HHS's review, diphenidine lacks current marketing approval under a new drug application or an abbreviated new drug application and is not subject to an investigational new drug application. There are no known medically approved uses worldwide at this time. There is no evidence that diphenidine has a currently accepted medical use in treatment in the United States.[11]

3. There is a Lack of Accepted Safety for Use of Diphenidine Under Medical Supervision

Because diphenidine has no approved medical use and has not been thoroughly investigated as a new drug, its safety for use under medical supervision is not determined.

---

[11] Pursuant to 21 U.S.C. 812(b)(1)(B), when placing a drug or other substance in schedule I, DEA must consider whether the substance has a currently accepted medical use in treatment in the United States. First, DEA looks to whether the drug or substance has FDA approval. When no FDA approval exists, DEA has traditionally applied a five-part test to determine whether a drug or substance has a currently accepted medical use: (1) the drug's chemistry must be known and reproducible; (2) there must be adequate safety studies; (3) there must be adequate and well-controlled studies proving efficacy; (4) the drug must be accepted by qualified experts; and (5) the scientific evidence must be widely available. *See Marijuana Scheduling Petition; Denial of Petition; Remand*, 57 FR 10499 (Mar. 26, 1992), pet. for rev. denied, *Alliance for Cannabis Therapeutics v. Drug Enforcement Admin*., 15 F.3d 1131, 1135 (D.C. Cir. 1994). DEA and HHS applied the traditional five-part test for currently accepted medical use in this matter and concluded the test was not satisfied. In a recent published letter in a different context, HHS applied an additional two-part test to determine currently accepted medical use for substances that do not satisfy the five-part test: (1) whether there exists widespread, current experience with medical use of the substance by licensed health care practitioners operating in accordance with implemented jurisdiction-authorized programs, where medical use is recognized by entities that regulate the practice of medicine, and, if so, (2) whether there exists some credible scientific support for at least one of the medical conditions for which part (1) is satisfied. On April 11, 2024, the Department of Justice's Office of Legal Counsel (OLC) issued an opinion, which, among other things, concluded that HHS' two-part test would be sufficient to establish that a drug has a currently accepted medical use. Office of Legal Counsel, Memorandum for Merrick B. Garland, Attorney General, Re: Questions Related to the Potential Rescheduling of Marijuana at 3 (April 11, 2024). For purposes of this proposed rule, there is no evidence that health care providers have widespread experience with medical use of diphenidine or that the use of diphenidine is recognized by entities that regulate the practice of medicine, so the two-part test also is not satisfied.

Thus, there is a lack of accepted safety for use of this substance under medical supervision.

Based on these findings, the Administrator concludes that diphenidine (1-(1,2-diphenylethyl)piperidine) warrants control in schedule I of the CSA. More precisely, because of its dissociative hallucinogenic effects, and because it may produce hallucinogenic-like dependence in humans, DEA proposes to place diphenidine, including its salts, isomers, and salts of isomers whenever the existence of such salts, isomers, and salts of isomers is possible within the specific chemical description, in 21 CFR 1308.11(d) (the hallucinogens category of schedule I).

Requirements for Handling Diphenidine

If this rule is finalized as proposed, diphenidine would be subject to the CSA's schedule I regulatory controls and administrative, civil, and criminal sanctions applicable to the manufacture, distribution, reverse distribution, dispensing, import, export, engagement in research, conduct of instructional activities or chemical analysis with, and possession of schedule I controlled substances, including the following:

1. Registration. Any person who handles (manufactures, distributes, reverse distributes, dispenses, imports, exports, engages in research, or conducts instructional activities or chemical analysis with, or possesses), or who desires to handle diphenidine would need to be registered with DEA to conduct such activities pursuant to 21 U.S.C. 822, 823, 957, and 958, and in accordance with 21 CFR parts 1301 and 1312.

Any person who currently handles diphenidine and is not registered with DEA to conduct research with a schedule I controlled substance must submit an application for registration and may not continue to handle diphenidine, unless DEA has approved that application for registration pursuant to 21 U.S.C. 822, 823, 957, 958, and in accordance with 21 CFR parts 1301 and 1312.

Notwithstanding the foregoing, pursuant to 21 U.S.C. 822(h), if, on the date the final rule is effectuated, a person is conducting research on diphenidine and is already registered to conduct research with another controlled substance in schedule I, the person may continue to conduct research on diphenidine if they submit a completed application for registration or modification of existing registration, as applicable, to conduct research with diphenidine not later than 90 calendar days after the date of effectuation of the final rule. The person may continue to conduct such research until the person withdraws the application or the Administrator serves on the person an order to show cause proposing denial of the application pursuant to 21 U.S.C. 824(c) and in accordance with 21 CFR 1301.37. If the Administrator serves an order to show cause proposing denial of the application or modification, the person may not continue to conduct research with diphenidine and may not receive or otherwise obtain additional diphenidine. If an order to show cause is served and the person requests a hearing in accordance with 21 CFR 1301.37(d), the hearing shall be held in accordance with 21 CFR 1301.41-1301.46 on an expedited basis and not later than 45 calendar days after the request is made, except that the hearing may be held at a later time if so requested by the person. If the person sends a copy of the application to a manufacturer or distributor of diphenidine, receipt of the copy by the manufacturer or distributor constitutes sufficient evidence that the person is authorized to receive diphenidine pursuant to 21 U.S.C. 822(h)(4). Continuation of research under 21 U.S.C. 822(h) does not authorize any other handling (e.g., distribution) of diphenidine.

Retail sales of schedule I controlled substances to the general public are not allowed under the CSA. Possession of any quantity of a schedule I controlled substance in a manner not authorized by the CSA is unlawful and those in possession of any quantity may be subject to prosecution pursuant to the CSA.

2. *Disposal of Stocks.* Any person unwilling or unable to obtain a schedule I registration must surrender or transfer all quantities of currently held diphenidine to a person registered with DEA before the effective date of the final scheduling action in accordance with all applicable Federal, State, local, and Tribal laws. Diphenidine must be disposed of in accordance with 21 CFR part 1317, in addition to all other applicable Federal, State, local, and Tribal laws.

3. *Security.* Diphenidine would be subject to schedule I security requirements and must be handled and stored pursuant to 21 U.S.C. 821 and 823, and in accordance with 21 CFR 1301.71–1301.76. Non-practitioners handling this substance also would need to comply with the screening requirements of 21 CFR 1301.90-1301.93.

4. Labeling and Packaging. All labels, labeling, and packaging for commercial containers of diphenidine would need to comply with 21 U.S.C. 825 and 958(e) and be in accordance with 21 CFR part 1302.

5. Quota. Generally, only registered manufacturers would be permitted to manufacture diphenidine in accordance with a quota assigned pursuant to 21 U.S.C. 826, and in accordance with 21 CFR part 1303.

6. Inventory. Every DEA registrant who would handle diphenidine must have an initial inventory of all stocks of controlled substances including diphenidine on hand on the date the registrant first engages in the handling of controlled substances pursuant to 21 U.S.C. 827 and 958, and in accordance with 21 CFR 1304.03, 1304.04, and 1304.11.

After the initial inventory, every DEA registrant would need to take an inventory of all controlled substances (including diphenidine) on hand every two years, pursuant to 21 U.S.C. 827 and 958(e), and in accordance with 21 CFR 1304.03, 1304.04, and 1304.11.

7. Records and Reports. Every DEA registrant would need to maintain records and submit reports with respect to diphenidine, pursuant to 21 U.S.C. 827, 832(a), and 958(e), and in accordance with 21 CFR 1301.74 and 1301.76, and parts 1304, 1312, and 1317.

Manufacturers and distributors would need to submit reports regarding diphenidine to the Automated Reports and Consolidated Ordering System pursuant to 21 U.S.C. 827, and in accordance with 21 CFR parts 1304 and 1312.

8. Order Forms. Every DEA registrant who distributes diphenidine would need to comply with the order form requirements, pursuant to 21 U.S.C. 828 and 21 CFR part 1305.

9. Importation and Exportation. All importation and exportation of diphenidine would need to comply with 21 U.S.C. 952, 953, 957, and 958, and in accordance with 21 CFR part 1312.

10. Liability. Any activity involving diphenidine not authorized by, or in violation of, the CSA or its implementing regulations would be unlawful, and may subject the person to administrative, civil, and/or criminal sanctions.

Regulatory Analyses

Executive Orders 12866, 13563, 14192, and 14294

In accordance with 21 U.S.C. 811(a), this proposed scheduling action is subject to formal rulemaking procedures performed "on the record after opportunity for a hearing," which are conducted pursuant to the provisions of 5 U.S.C. 556 and 557. The CSA sets forth the procedures and criteria for scheduling a drug or other substance. Such actions are exempt from review by the Office of Management and Budget pursuant to section 3(d)(1) of Executive Order (E.O.) 12866 and the principles reaffirmed in E.O. 13563. DEA scheduling actions are not subject to either E.O. 14192, Unleashing Prosperity Through Deregulation, or E.O. 14294, Fighting Overcriminalization in Federal Regulations.

Executive Order 12988, Civil Justice Reform

This proposed regulation meets the applicable standards set forth in sections 3(a) and 3(b)(2) of E.O. 12988 to eliminate drafting errors and ambiguity, minimize litigation,

provide a clear legal standard for affected conduct, and promote simplification and burden reduction.

Executive Order 13132, Federalism

This proposed rulemaking does not have federalism implications warranting the application of E.O. 13132. The proposed rule does not have substantial direct effects on the States, on the relationship between the National Government and the States, or on the distribution of power and responsibilities among the various levels of government.

Executive Order 13175, Consultation and Coordination with Indian Tribal Governments

This proposed rule does not have Tribal implications warranting the application of E.O. 13175. It does not have substantial direct effects on one or more Indian tribes, on the relationship between the Federal government and Indian tribes, or on the distribution of power and responsibilities between the Federal government and Indian tribes.

Paperwork Reduction Act

This proposed rule would require compliance with the following existing OMB collections: 1117-0003, 1117-0004, 1117-0006, 1117-0008, 1117-0009, 1117-0010, 1117-0012, 1117-0014, 1117-0021, and 1117-0056. An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Regulatory Flexibility Act

The 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.

DEA proposes placing the substance diphenidine (chemical name: 1-(1,2-diphenylethyl)piperidine), including its salts, isomers, and salts of isomers whenever the existence of such salts, isomers, and salts of isomers is possible within the specific chemical designation, in schedule I of the CSA. This action is being taken, in part, to

enable the United States to meet its obligations under the 1971 Convention. If finalized, this action would impose the regulatory controls and administrative, civil, and criminal sanctions applicable to schedule I controlled substances on persons who handle or propose to handle diphenidine.

The entities affected by this rule include the manufacturers, distributors, importers, exporters, and researchers of diphenidine. DEA determined the North American Industry Classification System (NAICS) industries that best represent these business activities. Table 1 lists the business activities and corresponding NAICS industries.[12]

Table 1: Business Activity and Corresponding NAICS Industries.

Business Activity	NAICS Code	NAICS Industry Description
Manufacturer	325412	Pharmaceutical Preparation Manufacturing
Distributor, Importer, Exporter	424210 424690	Drugs and Druggists' Sundries Merchant Wholesalers Other Chemical and Allied Products Merchant Wholesalers
Researcher	541715 611310	Research and Development in the Physical, Engineering, and Life Sciences (except Nanotechnology and Biotechnology) Colleges, Universities and Professional Schools

From Statistics of U.S. Businesses (SUSB) data, DEA determined the number of firms and small firms for each of the affected industries, and by comparing the number of affected small entities to the number of small entities for each industry, DEA determined whether a substantial number of small entities are affected in any of the industries. Table 2 lists the number of firms, small firms, and percent small firms in each affected industry.

Table 2: Percent Small Entities by Industry.

[12] Executive Office of the President Office of Management and Budget, North American Industry Classification System, United States, 2022, https://www.census.gov/naics/reference_files_tools/2022_NAICS_Manual.pdf. (Accessed 2/5/2026)

NAICS Industry	Firms[13]	SBA Size Standard[14]	Small Firms[15]	Percent Small Entities (%)
325412-Pharmaceutical Preparation Manufacturing	1,179	1,300 employees	1,099	93.2
424210-Drugs and Druggists' Sundries Merchant Wholesalers	7,012	250 employees	6,703	95.6
424690-Other Chemical and Allied Products Merchant Wholesalers	5,487	175 employees	5,197	94.7
541715-Research and Development in the Physical, Engineering, and Life Sciences (except Nanotechnology and Biotechnology)	10,042	1,000 employees	9,599	95.6
611310-Colleges, Universities and Professional Schools	2,494	$34.5 million	1,515	60.8

Based on the American Chemical Society's SciFinder database,[16] DEA identified three domestic entities supplying diphenidine across these industries. Suppliers include 325412, 424210, and 424690 industries. Even if all affected suppliers were small entities, they would account for only 0.02 percent of the small entities in those industries, not a substantial number.[17] Additionally, DEA expects the number of researchers working with diphenidine is small because diphenidine lacks current marketing approval under a new drug application or an abbreviated new drug application, and is not subject to an investigational new drug application as noted in the HHS review. Also, DEA believes the researchers working with diphenidine may also work with other controlled substances; hence, they have probably already registered with DEA and are qualified to handle controlled substances. For these reasons DEA believes the number of affected researchers that are small entities is not a substantial number of small entities in 541715 and 611310 industries.

[13] Statistics of U.S. Businesses, 2022 SUSB Annual Data Tables by Establishment Industry, https://www.census.gov/data/tables/2022/econ/susb/2022-susb-annual.html (Accessed 2/5/2026)
[14] U.S. Small Business Administration, Table of size standards, Version March 2023, Effective: March 17, 2023, https://www.sba.gov/document/support-table-size-standards. (Accessed 2/5/2026) Size standards are based on the number of employees or annual receipts depending on industry.
[15] Based on the estimated number of firms below the SBA size standard for each industry.
[16] SciFinder; Chemical Abstracts Service: Columbus, OH; https://scifinder.cas.org (accessed 2/6/2026).
[17] 3 / (1,179 + 7,012 + 5,487) = 0.02%

In summary, an insubstantial number of small entities will be affected by this proposed rule. As such, the proposed rule, if finalized, is not expected to result in a significant economic impact on a substantial number of small entities.

Unfunded Mandates Reform Act of 1995

In accordance with the Unfunded Mandates Reform Act (UMRA) of 1995, 2 U.S.C. 1532, DEA has determined and certifies that this proposed action would not result in any Federal mandate that may result "in the expenditure by State, local, and Tribal governments, in the aggregate, or by the private sector, of $100,000,000 or more (adjusted annually for inflation) in any 1 year . . . ." Therefore, neither a Small Government Agency Plan nor any other action is required under UMRA of 1995.

List of Subjects in 21 CFR Part 1308

Administrative practice and procedure, Drug traffic control, Reporting and recordkeeping requirements.

For the reasons set out above, 21 CFR part 1308 is proposed to be amended to read 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), 956(b), unless otherwise noted.

2. In § 1308.11:

a. Add paragraph (d)(117) to read as follows:

§ 1308.11 Schedule I.

* * * * *

(d) * * *

* * * * * * *	
(117) Diphenidine (Other names: 1-(1,2-diphenylethyl)piperidine)	7292
* * * * * * *	

* * * * *

SIGNING AUTHORITY

This document of the Drug Enforcement Administration was signed on May 14, 2026, by DEA Administrator Terrance C. Cole. That document with the original signature and date is maintained by DEA. For administrative purposes only, and in compliance with requirements of the Office of the Federal Register, the undersigned DEA Federal Register Liaison Officer has been authorized to sign and submit the document in electronic format for publication, as an official document of DEA. This administrative process in no way alters the legal effect of this document upon publication in the Federal Register.

Heather Achbach,
Federal Register Liaison Officer,
Drug Enforcement Administration.

.

[FR Doc. 2026-10380 Filed: 5/22/2026 8:45 am; Publication Date: 5/26/2026]