essential to, or that yields information that is essential to, the restoration or continuation of a bodily function important to the continuation of human life.

Meaningful disruption means a change in production that is reasonably likely to lead to a reduction in the supply of a biological product by a manufacturer that is more than negligible and affects the ability of the manufacturer to fill orders or meet expected demand for its product, and does not include interruptions in manufacturing due to matters such as routine maintenance or insignificant changes in manufacturing so long as the manufacturer expects to resume operations in a short period of time.

Significant disruption means a change in production that is reasonably likely to lead to a reduction in the supply of blood or blood components by a manufacturer that substantially affects the ability of the manufacturer to fill orders or meet expected demand for its product, and does not include interruptions in manufacturing due to matters such as routine maintenance or insignificant changes in manufacturing so long as the manufacturer expects to resume operations in a short period of time.

Dated: October 28, 2013.

Leslie Kux,

Assistant Commissioner for Policy.

[FR Doc. 2013–25956 Filed 10–31–13; 11:15 am]

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DEPARTMENT OF JUSTICE

Drug Enforcement Administration

21 CFR Part 1308

[Docket No. DEA–351]

Schedules of Controlled Substances: Placement of Tramadol Into Schedule IV

AGENCY: Drug Enforcement Administration, Department of Justice.

ACTION: Notice of proposed rulemaking.

SUMMARY: The Drug Enforcement Administration (DEA) proposes to place the substance 2-((dimethylamino)methyl)-1-(3-methoxyphenyl)cyclohexanol, its salts, isomers, salts of isomers, and all isomeric configurations of possible forms including tramadol (the term ''isomers'' includes the optical and geometric isomers) 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 (HHS) and an evaluation of all other relevant data by the DEA. If finalized, this action would impose the regulatory controls and administrative, civil, and criminal sanctions applicable to Schedule IV controlled substances on persons who handle (manufacture, distribute, dispense, import, export, engage in research, conduct instructional activities, or possess) or propose to handle tramadol.

DATES: Interested persons may file written comments on this proposal pursuant to 21 CFR 1308.43(g). Electronic comments must be submitted, and written comments must be postmarked, on or before January 3, 2014. Commenters should be aware that the electronic Federal Docket Management System will not accept comments after midnight Eastern Time on the last day of the comment period.

Interested persons, defined 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),'' 21 CFR 1300.01, may file a request for hearing pursuant to 21 CFR 1308.44 and in accordance with 21 CFR 1316.45 and 1316.47. Requests for hearing, notices of appearance, and waivers of an opportunity for a hearing or to participate in a hearing must be received on or before December 4, 2013.

ADDRESSES: To ensure proper handling of comments, please reference ''Docket No. DEA–351'' on all electronic and written correspondence. The DEA encourages that all comments be submitted electronically through the Federal eRulemaking Portal, which provides the ability to type short comments directly into the comment field on the Web page or attach a file for lengthier comments. Go to *http://www.regulations.gov* and follow the on-line instructions at that site for submitting comments. An electronic copy of this document and supplemental information to this proposed rule are also available at the *http://www.regulations.gov* Web site for easy reference. Paper comments that duplicate electronic submissions are not necessary. All comments submitted to *http://www.regulations.gov* will be posted for public review and are part of the official docket record. Should you, however, wish to submit written comments in lieu of electronic comments, they should be sent via regular or express mail to: Drug Enforcement Administration, Attention: DEA Federal Register Representative/ODW, 8701 Morrissette Drive, Springfield, Virginia 22152. All requests for hearing must be sent to Drug Enforcement Administration, Attention: Hearing Clerk/LJ, 8701 Morrissette Drive, Springfield, Virginia 22152.

FOR FURTHER INFORMATION CONTACT: Ruth A. Carter, Chief, Policy Evaluation and Analysis Section, Office of Diversion Control, Drug Enforcement Administration, 8701 Morrissette Drive, Springfield, Virginia 22152; Telephone (202) 598–6812.

SUPPLEMENTARY INFORMATION: *Posting of Public Comments:* Please note that comments received in response to this NPRM are considered part of the public record and will be made available for public inspection and posted at *http://www.regulations.gov* and in the DEA'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 made public, you must include the phrase ''PERSONAL IDENTIFYING INFORMATION'' in the first paragraph of your comment. You must also place all of the personal identifying information you do not want to be made publicly available 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 made publicly available, 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 made publicly available.

Comments containing personal identifying information and confidential business information identified and located as set forth above will be made available in redacted form. The Freedom of Information Act (FOIA) applies to all comments received. If you wish to personally inspect the comments and materials received or the supporting documentation the DEA used in preparing the proposed action, these materials will be available for public inspection by appointment. To arrange a viewing, please see the **FOR FURTHER INFORMATION CONTACT** paragraph, above.

Request for Hearing, Notice of Appearance at or Waiver of Participation in Hearing

Pursuant to 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 (APA) (5 U.S.C. 551–559). 21 CFR 1308.41–1308.45, and 21 CFR part 1316 subpart D. In accordance with 21 CFR 1308.44(a)–(c), requests for hearing, notices of appearance, and waivers of an opportunity for a hearing or to participate in a hearing may be submitted only by interested persons, defined 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).'' 21 CFR 1300.01. Such requests or notices must conform to the requirements of 21 CFR 1308.44(a) or (b), and 1316.47 or 1316.48, as applicable, and include a statement of the interest of the person in the proceeding and the objections or issues, if any, concerning which the person desires to be heard. Any waiver must conform to the requirements of 21 CFR 1308.44(c) and 1316.49, including a written statement regarding the interested person's position on the matters of fact and law involved in any hearing.

Please note that pursuant to 21 U.S.C. 811(a), the purpose and subject matter of a hearing is restricted to ''(A) find[ing] that such drug or other substance has a potential for abuse, and (B) mak[ing] with respect to such drug or other substance the findings prescribed by subsection (b) of section 812 of this title for the schedule in which such drug is to be placed. * * *'' Requests for hearing, notices of appearance at the hearing, and waivers of an opportunity for the hearing or to participate in the hearing should be submitted to the DEA using the address information provided above.

Legal Authority

The DEA implements and enforces titles II and III of the Comprehensive Drug Abuse Prevention and Control Act of 1970, as amended. Titles II and III are referred to as the ''Controlled Substances Act'' and the ''Controlled Substances Import and Export Act,'' respectively, but they are collectively referred to as the ''Controlled Substances Act'' or the ''CSA'' for the purposes of this action. 21 U.S.C. 801–971. The DEA publishes the implementing regulations for these statutes in title 21 of the Code of Federal Regulations (CFR), parts 1300 to 1321. The CSA and its implementing regulations are designed to prevent, detect, and eliminate the diversion of controlled substances and listed chemicals into the illicit market while providing for the legitimate medical, scientific, research, and industrial needs of the United States. Controlled substances have the potential for abuse and dependence and are controlled to protect the public health and safety.

Under the CSA, controlled substances are classified in one of five schedules based upon their potential for abuse, their currently accepted medical use, and the degree of dependence the substance may cause. 21 U.S.C. 812. The schedules of controlled substances established by Congress are found at 21 U.S.C. 812(c), and the current list of scheduled substances is published at 21 CFR part 1308. Pursuant to 21 U.S.C. 811(a)(1), the Attorney General may, by rule, ''add to such a schedule or transfer between such schedules any drug or other substance if he (A) finds that such drug or other substance has a potential for abuse, and (B) makes with respect to such drug or other substance the findings prescribed by subsection (b) of section 812 of this title for the schedule in which such drug is to be placed * * *.'' Pursuant to 28 CFR 0.100(b), the Attorney General has delegated this scheduling authority to the Administrator of the DEA, who has further delegated this authority to the Deputy Administrator of the DEA. 28 CFR 0.104.

The CSA provides that scheduling of any drug or other substance may be initiated by the Attorney General (1) on his own motion; (2) at the request of the Secretary of the HHS; or (3) on the petition of any interested party. 21 U.S.C. 811(a). This proposed action is based on a recommendation from the Assistant Secretary for Health of the HHS and on an evaluation of all other relevant data by the DEA. If finalized, this action would impose the regulatory controls and administrative, civil, and criminal sanctions of Schedule IV controlled substances on persons who handle (manufacture, distribute, dispense, import, export, engage in research, conduct instructional activities, or possess) or propose to handle tramadol.[1]

Background

Tramadol is an opioid analgesic that produces its primary opioid-like action through an active metabolite, referred to as the ''M1'' metabolite (O-desmethyltramadol). Since March 1995, tramadol has been available as a non-controlled and centrally acting opioid analgesic under the trade name ULTRAM® approved by the Food and Drug Administration (FDA) in the United States. Subsequently, the FDA approved generic, combination, and extended release products of tramadol.

Because of its chemical structure, 2-((dimethylamino)methyl)-1-(3-methoxyphenyl)cyclohexanol can exist as different isomeric forms. Thus, various prefixes can be associated with the name. Some examples of these prefixes include dextro, levo, d, l, R, S, cis, trans, erythro, threo, (+), (−), racemic, and may include combinations of these prefixes sometimes with numerical designations. Any such isomer is, in fact, 2-((dimethylamino)methyl)-1-(3-methoxyphenyl)cyclohexanol. Tramadol is typically formulated as a racemic mixture identified as (±)-*cis*-2-((dimethylamino)methyl)-1-(3-methoxyphenyl)cyclohexanol hydrochloride.[2]

Proposed Determination To Schedule Tramadol

The DEA received four petitions between October and November 2005 requesting that tramadol be controlled as a scheduled substance under the CSA. Three of these petitions specifically requested the placement of tramadol into Schedule III; the remaining petition did not specify a schedule for control. One of the petitioners stated that ''tramadol has significant abuse potential, consistent with its pharmacology. This abuse has significant public health policy implications.''

Pursuant to 21 U.S.C. 811(b) of the CSA, the DEA gathered the necessary data on tramadol and, on April 25, 2007 submitted it to the Assistant Secretary of the HHS with a request for a scientific and medical evaluation and the Secretary's recommendation as to whether or not tramadol should be added as a controlled substance, and, if so, in which schedule. On September 16, 2010, the HHS provided to the DEA a written scientific and medical evaluation and scheduling recommendation entitled ''Basis for the Recommendation to Schedule Tramadol in Schedule IV of the Controlled Substances Act.'' In this recommendation, the HHS presented its eight-factor analysis as required under 21 U.S.C. 811(b), and recommended that

[1] See *infra* footnote 2.

[2] For simplicity's sake, from this point forward in the document, ''tramadol'' is used to refer to 2-((dimethylamino)methyl)-1-(3-methoxyphenyl)cyclohexanol, its salts, isomers, salts of isomers, and all isomeric configurations of possible forms.

tramadol be added to Schedule IV of the CSA. In response, the DEA reviewed the scientific and medical evaluation and scheduling recommendation provided by the HHS and all other relevant data, and completed an eight-factor review document pursuant to 21 U.S.C. 811(c) in February 2011. Included below is a brief summary of each factor as analyzed by the HHS in its 2010 transmittal and the DEA in its 2011 analysis, and as considered by the DEA in its proposed scheduling decision. Please note that both the DEA and HHS analyses are available in their entirety under ''Supporting and Related Material'' of the public docket for this rule at *http://www.regulations.gov* under docket number ''DEA–351.'' Full analysis of, and citations to, information referenced in the summary may also be found in the supporting material.

1. *The Drug's Actual or Relative Potential for Abuse:* Data gathered by the DEA and HHS indicate that since the initial marketing of tramadol in 1995, tramadol has been, and currently is, abused for its opioid effects. The DEA has considered all relevant data and found that:

a. Individuals Are Taking Tramadol in Amounts Sufficient To Create a Hazard to Their Health or to the Safety of Other Individuals or to the Community

Published case reports, case series, and data from databases such as the Drug Abuse Warning Network (DAWN) suggest that individuals are taking tramadol in amounts sufficient to create a hazard to their health, to the safety of other individuals, and to the community. Tramadol abuse is associated with serious adverse events including death, drug dependence, drug withdrawal symptoms, seizures, serotonin syndrome, and other serious medical problems.

DAWN is a database, managed by the Substance Abuse and Mental Health Services Administration (SAMHSA), which collects data on drug-related emergency department (ED) visits from a nationally representative sample of hospitals in the United States and a selection of metropolitan areas. The HHS reviewed and analyzed DAWN data from 2004 through 2008 and found that the estimated annual non-medical [3] Emergency Department (ED) visits from non-medical use of tramadol and its combinations (hereinafter ''tramadol/combinations'') continually increased from 4,849 ED visits to 11,850 ED visits. The DEA also evaluated more recent DAWN data and found that this increasing trend for tramadol continued in 2009 and 2010 (15,349 and 16,251 ED visits, respectively).

The American Association of Poison Control Centers (AAPCC) manages the National Poison Data System (NPDS), which is the only near real-time comprehensive poisoning surveillance database in the United States. The NPDS collects information from the poison centers across the United States. The HHS reviewed the NPDS data and found that the number of case mentions of human toxic exposures to tramadol during 2004 through 2008 increased annually from 3,769 to 9,623. The DEA reviewed the more recent NPDS data and found that in 2009, 2010, and 2011, the number of reported tramadol poison exposures, alone and in combination with other drugs, totaled 10,255; 11,225; and 12,424, respectively. Of these totals, intentional exposures to tramadol alone (i.e., exposures not including tramadol/combinations or tramadol in combination with any other substances) were 2,677; 2,867; and 3,170, resulting in four deaths in 2009, three deaths in 2010, and six deaths in 2011.

b. There Is a Significant Diversion of Tramadol From Legitimate Drug Channels

The National Forensic Laboratory Information System (NFLIS) is a DEA database that collects scientifically verified data on analyzed samples in state and local forensic laboratories. It also includes data from the System to Retrieve Information from Drug Evidence (STRIDE), which includes data on analyzed samples from DEA laboratories. The data show that for each of the years from 2000 through 2012, tramadol was present in drug exhibits seized in the course of law enforcement activity.[4] The tramadol exhibits seized by law enforcement involving drug abuse indicate the diversion of tramadol in the United States [5] Tramadol exhibits increased from a total of 82 in 2000 to 1,806 in 2012 (NFLIS data). In 2010, this number was greater than the number of exhibits shown to contain pentazocine (96, Schedule IV), but less than the number of hydrocodone (45,627, Schedule III), codeine (3,679, Schedules II, III, V), and buprenorphine (10,167, Schedule III) exhibits (NFLIS data). The number of tramadol exhibits is similar to that of propoxyphene (1,320, Schedule IV) (2010 NFLIS data). However, the reduced number of propoxyphene exhibits (561) in 2011 is significantly less than that of tramadol (1,704) due to the FDA's recommendation to withdraw propoxyphene from the United States market.

A post-marketing study published in 2002 and cited by the HHS's review document reported that among 140 health care professionals who had at least one positive tramadol urine specimen, 87 cases were associated with illegal prescriptions for obtaining tramadol. Another study referred to in the HHS review noted that from January 2002 through March 2004 there were 72 cases involving the diversion of tramadol from all 50 state law enforcement agencies. However, the number of tramadol diversion cases was less than the number of diversion cases associated with hydrocodone and oxycodone.

c. Individuals Are Taking Tramadol on Their Own Initiative Rather Than on the Basis of Medical Advice From a Practitioner Licensed by Law to Administer Such Drugs

The DEA's evaluation found that current evidence indicates that individuals take tramadol on their own initiative without medical consultation. This evidence includes case reports of abuse and dependence on tramadol in the medical literature, national drug abuse monitoring systems, and epidemiological data (DAWN, NFLIS, STRIDE, AAPCC, and the National Survey on Drug Use and Health (NSDUH)).

DAWN data show that from 2004 to 2010, the national annual estimates of ED visits related to non-medical use or

[3] As defined by the DAWN glossary, non-medical use of pharmaceuticals includes prescription and over-the-counter pharmaceuticals in ED visits that are of the following types of cases:

Overmedication—Patient took too much of his/her prescription medication.

Malicious poisoning—Drug use in which the patient was administered a drug by another person for a malicious purpose.

Other—This category includes all drug-related ED visits that could not be assigned into any of the other classifications used by DAWN (suicide, attempt, seeking detox, alcohol only (under 21), adverse reaction, overmedication, malicious poisoning, and accidental ingestion).

Non-medical use may involve pharmaceuticals alone or pharmaceuticals in combination with illicit drugs or alcohol.

[4] Because the primary focus of law enforcement agencies (with respect to drugs) is on investigating the *unlawful* distribution of drugs, the incidents in which tramadol has been seized in the course of law enforcement investigations supports a finding that the drug is being abused and/or diverted from legitimate channels. Moreover, because tramadol is not controlled in most states there is reason to believe that many laboratories may not report those incidents in which they have identified a substance as tramadol. This suggests that tramadol would likely rank substantially higher in NFLIS data were it controlled nationally.

[5] While NFLIS data is not direct evidence of abuse, it can lead to an inference that a drug has been diverted or abused. 76 FR 77330, 77332, Dec. 12, 2011.

abuse [6] of tramadol/combinations increased from 4,849 to 16,251. Upon normalization of the number of non-medical ED visits relative to 100,000 prescriptions dispensed, the rate of ED visits for tramadol/combinations was found similar to the rates for propoxyphene.

The NSDUH, operated by SAMHSA, provides information on the non-medical use of drugs in the United States population age 12 and older and its database provides annual estimates on the lifetime non-medical use of opioids and pain relievers. The estimated number of individuals who have used tramadol products non-medically at least once in their lifetime increased from 994,000 in 2002 to 2,614,000 in 2011.

The NPDS from AAPCC reported that the number of tramadol exposures increased each year between 2004 (3,769 cases) and 2011. In 2011, the number of reported tramadol poison exposures totaled 12,424. Of these total poison exposures in 2011, the intentional exposures to tramadol alone (i.e., not tramadol/combinations or in combination with other substances) were 3,170—six of which resulted in death. These findings indicate that tramadol poses a significant threat to the public health.

d. Tramadol 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 It Will Have the Same Potential for Abuse as Such Substance, 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

According to the HHS review, tramadol shares many similar pharmacological activities with some opioids scheduled under the CSA. As such, the abuse potential of tramadol would be expected to be related to its opioid properties. As a result, tramadol would be expected to be diverted from legitimate sources, be used without medical supervision, and consequently be a safety concern to individuals and the community.

The opioid activity of tramadol is primarily due to the ''M1'' metabolite. Compared to other opioids, tramadol showed a longer onset of action due to accumulation of the active metabolite and its effects include analgesia, respiratory depression, miosis, cough suppression, and inhibition of bowel motility. Preclinical studies demonstrate that tramadol, like other opioids in Schedules I through IV, exhibits complete generalization to morphine and is able to produce some reinforcing effects. Repeated administration of tramadol in animals caused dependence development, evidenced by a withdrawal syndrome similar in intensity to pentazocine (Schedule IV) or propoxyphene (Schedule IV). Human studies reveal that tramadol produces some reinforcing subjective effects at high doses. A similar dose response pattern at high doses with propoxyphene to produce reinforcing subjective effects was also observed. Thereby, propoxyphene may serve as an appropriate comparator drug for tramadol with respect to generating reinforcing effects. According to the HHS review, several studies examining chemical abuse potential suggest that the subjective reinforcing effect of tramadol is less than that of Schedule II opioids and more comparable to that of propoxyphene.

In summary, the abuse potential of tramadol is similar to that of substances in Schedule IV (such as propoxyphene) of the CSA. The accumulated information demonstrates that individuals take tramadol non-medically and in amounts sufficient to create a hazard to their health. Tramadol is diverted from legitimate sources and produces effects similar to other CSA-controlled opioids known to have an abuse potential. Furthermore, the available information regarding reinforcing effects and drug dependence shows that the abuse potential of tramadol is less than that of morphine (Schedule II), oxycodone (Schedule II), or buprenorphine (Schedule III), but similar to that of propoxyphene (Schedule IV). Additionally, epidemiological data also support an abuse potential for tramadol that is similar to substances in Schedule IV of the CSA. These data suggest that tramadol has an abuse potential warranting control under the CSA.

The DEA and HHS believe that an evaluation of the accumulated information demonstrates that the indicators of a drug's potential for abuse, as described in the legislative history of the CSA, are present for tramadol. Obtained or diverted from legitimate sources, individuals take tramadol in the absence of medical supervision and in amounts sufficient to create a hazard to their health. Tramadol produces effects similar to opioids known to have an abuse potential and that are controlled under the CSA.

2. *Scientific Evidence of the Drug's Pharmacological Effects, if Known:* The DEA and HHS recognize tramadol as an opioid analgesic with monoaminergic activity that contributes to its analgesic effects. The M1 metabolite of tramadol contributes to its opioid effects and may be the cause of the delayed and prolonged activity associated with tramadol administration. Tramadol can block the reuptake of norepinephrine and serotonin, effects also produced by such opioids as meperidine (Schedule II), methadone (Schedule II), and levorphanol (Schedule II).

Preclinical animal studies found that tramadol demonstrated a dose-related anti-nociceptive effect. Its analgesic effects were compared to other Schedule III and IV opioid analgesics. In clinical trials for treatment in human subjects, tramadol was less effective than hydrocodone/acetaminophen (Schedule III), but displayed an analgesic effect similar to that of pentazocine (Schedule IV), and superior or similar to the propoxyphene/acetaminophen combination (Schedule IV) in relieving postoperative pain.

Tramadol produces abuse liability-related effects in various animal models and humans. It has been self-administered by monkeys, producing reinforcing effects which qualitatively show a similarity to opioids. In a drug discrimination study using rats, tramadol was shown to produce systematic generalization to morphine. Similar to other opioids in Schedules II through IV, tramadol fully substituted for discriminative effects of morphine and morphine fully substituted for tramadol. Drug discriminative studies showed that tramadol is comparable to other Schedule III and IV opioids. Physical dependence of tramadol has been demonstrated in studies on animals and humans.

Most adverse effects are related to tramadol's opioid activity including sedation, nausea, vomiting, constipation, and respiratory depression. However, a small but significant portion of individuals who use tramadol will experience seizures. The risk of seizures increases with dose and is relatively common among tramadol abusers. Further, clinical studies show that tramadol, at a single dose greater than the therapeutically prescribed-dose, produces subjective reinforcing effects that are significantly greater than those of placebos, and are similar to or approach those produced by morphine and oxycodone. A similar dose dependency in producing subjective reinforcing effects was also

[6] Since 2004, DAWN has defined ''drug misuse or abuse'' as a group of ED visits including all visits associated with the non-medical use of pharmaceuticals.

observed with propoxyphene at doses greater than the therapeutically prescribed dose. This similarity between tramadol and propoxyphene provides support for a similar abuse potential and placement of tramadol into Schedule IV.

3. *The State of Current Scientific Knowledge Regarding the Drug or Other Substance:* The chemical name of tramadol hydrochloride is (±)-*cis*-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl) cyclohexanol hydrochloride. Tramadol hydrochloride has a molecular formula of $C_{16}H_{25}NO_2$ HCl with a molecular weight of 299.84. Because of tramadol's chemical structure, it can exist as different isomeric forms. Thus, various prefixes can be associated with the name. Some examples of these prefixes include dextro, levo, d, l, R, S, cis, trans, erythro, threo, (+), (-), racemic, and may include combinations of these prefixes sometimes with numerical designations. Any such isomer is, in fact, 2-[(dimethylamino) methyl]-1-(3-methoxyphenyl)cyclohexanol. It is typically formulated as a racemic mixture identified as (±)-*cis*-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl) cyclohexanol hydrochloride. Tramadol hydrochloride is a white, crystalline, and odorless powder soluble in water and ethanol.

Tramadol is readily absorbed from the gastrointestinal tract, with both enantiomers as well as the M1 metabolite found in the blood following administration. Tramadol undergoes extensive metabolism in the liver, while 90 percent of tramadol and its metabolites are excreted via the kidneys. Approximately 10 to 30 percent of the parent drug is excreted un-metabolized with an elimination half-life of about 5.5 hours. This extensive metabolism, in part, provides for possible interactions between tramadol and a variety of other drugs that undergo metabolism by the CPY2D6 enzyme.

4. *Its History and Current Pattern of Abuse:* Tramadol has been abused since its marketing approval in 1995 by a wide spectrum of individuals of different ages, alone and in combination with other psychoactive substances. Data from Surveillance Data, Inc. (SDI)'s prescription database comparing tramadol and other analgesics in terms of annual prescriptions dispensed show that in 2007 and 2008, more prescriptions were written for tramadol than for any other opioid other than hydrocodone combination products [7] (Schedule III) and oxycodone (Schedule II). The annual number of prescriptions for tramadol surpassed the annual number of prescriptions for propoxyphene (Schedule IV) and codeine (Schedules II, III, V) in 2007 and 2008. Over each of the five years from 2003 to 2007, there was a consistent multi-fold greater number of prescriptions written for tramadol compared to such analgesics as morphine (Schedule II), fentanyl (Schedule II), methadone (Schedule II), hydromorphone (Schedule II), buprenorphine (Schedule III), meperidine (Schedule II), butorphanol (Schedule IV), pentazocine (Schedule IV), and oxymorphone (Schedule II). Updated information from another major national prescription database, IMS Health's National Prescription Audit Plus™, demonstrated a similar trend from 2009 to 2011: more prescriptions were written for tramadol than for any other opioid other than hydrocodone and oxycodone.

According to the HHS, abuse-related ED visits involving tramadol as reported in DAWN increased from 1995 (645 cases) to 2002 (1,714 cases), peaking in 2001 (2,329 cases).[8] Tramadol abuse-related deaths increased from 45 cases in 1997 to 88 cases in 2002. Over the period of 2004 through 2008, the number of estimated ED visits from non-medical use of tramadol/combinations showed a continuous increase from 4,849 ED visits to 11,850 ED visits. The DEA further reviewed the DAWN data for 2009 and 2010 and found that the national annual ED visits involving tramadol increased to 15,349 in 2009 and 16,251 in 2010.

The HHS reviewed DAWN data and calculated the rates of estimated non-medical ED visits per 100,000 prescriptions dispensed for tramadol/combinations as well as other selected opioids. The HHS found that from 2004 to 2007, the annual rates of non-medical tramadol/combination ED visits ranged between 28.4 and 33.9. In 2008, there was a substantial increase in the rate of ED visits of tramadol/combinations to 45.8 ED visits per 100,000 prescriptions. Over the five year period (2004 to 2008), annual rates of tramadol ED visits were substantially below that of rates for oxycodone/combinations (Schedule II), methadone (Schedule II), hydromorphone (Schedule II), morphine (Schedule II), fentanyl/combinations (Schedule II), meperidine/combinations (Schedule II), hydrocodone/combinations (Schedule III), and buprenorphine/combinations (Schedule III).[9] Over the period of 2004 through 2008, the rates of estimated non-medical ED visits for tramadol/combinations were more closely in the range for the rates of codeine/combinations (Schedules II, III, V) and proproxyphene/combinations (Schedule IV). For example, in 2008, the rate of non-medical ED visits per 100,000 prescriptions of tramadol/combinations was 45.8 which was between that for proproxyphene/combinations (62.7 ED visits per 100,000 prescriptions) and that for codeine/combinations (40.2 ED visits per 100,000 prescriptions). Overall, these data suggest that the abuse potential of tramadol is less than that of Schedule II and III substances and most similar to that of propoxyphene (Schedule IV).

According to the annual NSDUH report, the number of individuals who used tramadol non-medically at least once in their lifetime increased from approximately 994,000 in 2002 to 2,614,000 in 2011. For each year surveyed, the absolute number regarding tramadol was lower than that of hydrocodone combination products or oxycodone products. Additionally, for each of the years from 2002 to 2007, the estimated number of individuals who initiated use and reported non-medical use of tramadol was less than 100,000 (with the highest at 95,000 in 2003 and the lowest at 22,000 in 2006). By contrast, for each of the years from 2002 to 2007, the number of past year initiates for use of any pain reliever who also used hydrocodone (>1,200,000) and oxycodone (>450,000) non-medically was greater than that of tramadol. The DEA further analyzed the updated NSDUH data and found that the estimated number of individuals who have used tramadol products non-medically at least once in their lifetime are 1,990,000; 2,181,000; 2,282,000; and 2,614,000 in 2008, 2009, 2010, and 2011, respectively. Furthermore, these numbers are lower than that of oxycodone (Schedule II) and hydrocodone combination products (Schedule III). Collectively, the information from NSDUH shows that tramadol is used non-medically and supports placement of tramadol in a

[7] The various studies cited throughout this rule interchangeably use the terms ''hydrocodone products,'' ''hydrocodone combinations,'' and ''hydrocodone combination products'' to refer to the controlled substance hydrocodone combined with one or more active ingredients (Schedule III). The DEA uses the term ''hydrocodone combination products'' to refer to these controlled substances.

[8] DAWN was redesigned in early 2003, which resulted in a permanent disruption in trends for the years prior to 2003. Therefore, comparisons cannot be made between the previous DAWN system (before 2002) and the current DAWN system. Additionally, before 2002, DAWN collected data on ''drug abuse cases'' whereas now it collects data on all types of ''drug-related'' ED visits'' (i.e., ''non-medical visits'').

[9] Only data from 2006 to 2008 was available for buprenophrine/combinations.

schedule less restrictive than Schedule III.

NFLIS and STRIDE databases provide evidence that tramadol has been diverted from legitimate use and encountered by law enforcement personnel. Furthermore in 2010, forensic laboratories analyzed 1,485 such exhibits and the tramadol-containing exhibits were close in number to that of exhibits for propoxyphene (Schedule IV) (1,320). The relative lower number of propoxyphene exhibits in 2011 and 2012 is because in November 2010, the FDA recommended that propoxyphene be withdrawn from the United States market due to the risk of cardiac toxicity. These exhibits from criminal investigations involving tramadol provide evidence of the significant diversion and non-medical use of tramadol in the United States.

The NPDS demonstrates that from 2004 to 2011, the number of human poison exposures to tramadol increased annually from 3,769 to 12,424. However, the number of exposures for tramadol is also less than the number of exposures for hydrocodone combination products (Schedule III) or oxycodone (Schedule II). The HHS calculated the number of case mentions per 100,000 prescriptions for tramadol and several other opioids and found that the tramadol case mentions per 100,000 prescriptions increased from 22 in 2004 to 37 in 2008. The HHS also found that from 2004 to 2007, the NPDS rates of tramadol case mentions per 100,000 prescriptions were lower than for oxycodone (Schedule II), morphine (Schedule II), and methadone (Schedule II). For the years 2004, 2005, and 2006, the rates of tramadol cases were similar to that of propoxyphene (Schedule IV). In 2007 and 2008, tramadol surpassed codeine (Schedules II, III, V) and propoxyphene (Schedule IV) in the number and rate of case mentions. These data indicate that tramadol represents a significantly growing risk to the public.

Collectively, data from DAWN, NSDUH, NFLIS, STRIDE, and AAPCC–NPDS databases demonstrate the misuse, abuse, and diversion of tramadol in the United States. With respect to the rates of non-medical ED visits found in DAWN, the number of NFLIS exhibits, and the increasing rates of AAPCC's NPDS reporting, tramadol data most closely resembles that of propoxyphene (Schedule IV).

5. *The Scope, Duration, and Significance of Abuse:* The scope, duration, and significance of tramadol abuse is evidenced by findings of national monitoring databases for drug abuse, review of studies of abuse potential, and clinical case reports. The HHS concluded its 15 years of post-marketing epidemiologic abuse-related data in the scientific literature and from the adverse events reporting system (AERS) since tramadol's commercial availability in the United States. The case reports describe abnormal behavior that demonstrates an addiction liability of tramadol: drug craving, increasing the tramadol dose, performing self-injury in order to be prescribed more tramadol, taking high doses despite adverse effects that result, and visiting multiple physicians in order to obtain more prescriptions for tramadol. Approximately 15 years of post-marketing history now show that tramadol can be, and is being, abused both in the United States and other countries.

Clinical case reports in the medical literature provide information on patterns of tramadol abuse when prescribed for clinical pain management. The case reports listed by the HHS review describe abuse of tramadol for its euphorigenic and sedating effects. The depicted behavior illustrates an addiction to tramadol: Drug craving, increasing the tramadol dose, inflicting self-injury in order to be prescribed more tramadol, taking high doses despite adverse effects that result, and visiting multiple doctors in order to obtain more prescriptions for tramadol. These reports provide information on characteristics and patterns of actual tramadol abuse with the development of dependence. Development of iatrogenic addiction to tramadol due to medical treatments is also reported.

The NSDUH data, discussed in detail in Factor 4, also provides evidence of the non-medical use of tramadol. According to the NSDUH data, the estimated number of individuals who have used tramadol products non-medically at least once in their lifetime increased from 994,000 in 2002 to 2,614,000 in 2011. For each year from 2002 to 2007, the number of individuals reporting either lifetime non-medical use or past-year non-medical use of tramadol was lower than the number of that of hydrocodone or oxycodone. The estimated number of individuals who have used tramadol products non-medically at least once in their lifetime increased from 2008 to 2011, but these numbers for tramadol are still lower than that of oxycodone (Schedule II) and hydrocodone combination products (Schedule III).

According to DAWN data, in 2010, an estimated 16,251 ED visits nationally were for non-medical use of tramadol. There is an increasing annual trend of non-medical ED visits from 2004 through 2010. Furthermore, the HHS reviewed the national estimates of ED visits related to non-medical use and to rates of these visits per 100,000 prescriptions from 2004 to 2008, and found tramadol most closely compares to propoxyphene (Schedule IV) and to codeine (Schedules II, III, V).

Collectively, the data shows that tramadol has less abuse potential than other pure mu-receptor agonists currently controlled in Schedule II. As evaluated by the HHS and the DEA, the DAWN data indicates tramadol most closely compares to propoxyphene (Schedule IV) and codeine (Schedules II, III, V). The NSDUH data from 2002 to 2007, cited by the HHS, also indicates the number of individuals reporting non-medical use of tramadol was lower than that of individuals using hydrocodone combination products (Schedule III) and oxycodone (Schedule II) products, suggesting an abuse potential less than that of Schedule III.

Tramadol's similarity to other controlled opioids and clear evidence of significant non-medical use and abuse, accompanied by serious adverse events, indicate that tramadol has sufficient abuse potential and incidence of drug dependence and addiction to warrant control as a Schedule IV controlled substance under the CSA.

6. *What, if any, Risk There is to the Public Health:* The DEA analysis indicates that there are numerous risks to the public health that may result from tramadol abuse. Tramadol and its M1 metabolite are opiate agonists devoid of opioid antagonist activity. Adverse effects occurring with tramadol are consistent with adverse effects associated with other opioids. The incidence of reported adverse effects increased as the time of tramadol therapy increased. The overall incidence rates of adverse effects of tramadol were similar to that of codeine containing drugs. Other adverse effects associated with tramadol included seizures, serotonin syndrome, and respiratory depression. Case studies of tramadol overdoses from United States poison centers reported that tramadol overdoses presented multiple systematic symptoms ranging from cardiovascular toxicity to significant neurologic toxicity including lethargy, nausea, tachycardia, agitation, seizures, coma, hypertension, and respiratory depression. The toxic mechanism of tramadol overdose is closely related to its μ-opioid receptor activity and its monoamine oxidase inhibition activity.

Information from the DAWN database shows that the rates of ED visits due to non-medical use of tramadol have been

similar to that of propoxyphene (Schedule IV) but lower than that of Schedule II and III opioids from 2004 to 2008. The HHS reviewed DAWN data and found that a total of 395 tramadol abuse-related deaths were reported to DAWN from 1997 to 2002 in selected areas. The result demonstrates a risk to the public health associated with the non-medical use of tramadol that is similar to that of propoxyphene (Schedule IV).

An increased number of exposure and death cases were reported by the AAPCC's NPDS database. It showed that from 2004 to 2011, annual tramadol exposures increased from 3,769 to 12,424. The HHS found that tramadol ranked third behind hydrocodone combination products (Schedule III) and oxycodone (Schedule II) in terms of the number of poison case mentions of opioids in 2007 and 2008. Over this period, the rates of case mentions per 100,000 prescriptions for tramadol increased from 22 to 37. In addition, the rate of tramadol case mentions was lower than for oxycodone (Schedule II), morphine (Schedule II), and methadone (Schedule II). For the years 2004, 2005, and 2006, the rates of tramadol case mentions were similar to that of propoxyphene (Schedule IV).

The labeling information approved by the FDA states that tramadol in excessive doses, alone or in combination with other central nervous system depressants, including alcohol, is a cause of drug-related deaths. Deaths associated with tramadol were also documented in the medical literature. Other reports document tramadol as a contributing factor to deaths in combination with other drugs such as, but not limited to, benzodiazepines, serotonergic drugs, and other antidepressants. The annual number of tramadol-related deaths reported by medical examiners in the DAWN database gradually increased from 1997 to 2004.

Reports of tramadol associated deaths from the Florida Department of Law Enforcement (FDLE) were also reviewed by the HHS and it was found the number of deaths involving tramadol increased from 106 in 2003 to 235 in 2008. According to FDLE's data, tramadol-related deaths were higher than heroin-related deaths between 2005 and 2008. For each of those years, the number of deaths involving tramadol was less than the number of deaths involving hydrocodone combination products (Schedule III), fentanyl (Schedule II), morphine (Schedule II), oxycodone (Schedule II), methadone (Schedule II), and propoxyphene (Schedule IV). The DEA reviewed the data for the years 2009 to 2011, and found that tramadol-related deaths continued to increase. There were 268 tramadol-related deaths in 2009, 275 tramadol-related deaths in 2010, and 379 tramadol-related deaths in 2011.

In summary, the collected data from a number of sources indicate that tramadol presents risks to the public health and, as such, supports the scheduling of tramadol. The DAWN, AAPCC, and FDLE data suggest a lower schedule for tramadol than Schedule III.

7. *Its Psychic or Physiological Dependence Liability:* The HHS reviewed available information from pre-clinical and clinical studies and found that repeated dosing with tramadol resulted in dependence development, and withdrawal syndromes resulted from termination of tramadol treatment. Additionally, medical literature also documents numerous case reports of physiological and physical dependence to tramadol.

Preclinical studies using monkeys and rats found that the tested animals displayed withdrawal signs after the termination of tramadol. Tramadol's potential to produce physical dependence was evidenced by naloxone precipitated withdrawal in observed animals. The results also supported that tramadol produced a degree of physical dependence similar to that of propoxyphene (Schedule IV). Infusion of tramadol in rats found that the total withdrawal scores of tramadol were lower than that of morphine (Schedule II) following naloxone administration. By comparing physical dependence development resulting from repeated subcutaneous administration of either morphine or tramadol to mice, another study concluded that tramadol produced a lesser degree of physical dependence than morphine. These findings suggest that tramadol can produce mild to moderate levels of physical dependence and the degree of dependence of tramadol is less than that of Schedule II, but similar to that of Schedule IV drugs such as pentazocine and propoxyphene.

A number of clinical studies examined the ability of tramadol to substitute for other opioids in individuals who are opioid dependent. A study compared the effectiveness of tramadol versus buprenorphine (Schedule III) in the treatment of opiate withdrawal and found that tramadol and buprenorphine effectively managed acute opioid withdrawal syndrome displayed by patients with mild to moderate addiction to heroin. Another study compared the use of tramadol to that of clonidine (not controlled under the CSA) for management of acute heroin (Schedule I) withdrawal and found that tramadol was more effective in managing withdrawal than clonidine. One study revealed a cross dependence development between tramadol and morphine (Schedule II) in opioid-dependent adults. A modest suppression of opioid withdrawal produced by tramadol was also reported in subjects with a mild to moderate degree of opioid physical dependence and this finding was also supported by several published case reports.

According to the HHS review, as of September 9, 2009, ''Withdrawal symptoms may occur'' was documented in the ''Warning'' section of the label for a tramadol containing product. Combining studies of cross dependence, tramadol produces a modest suppression of withdrawal in subjects dependent on other opioids and this suppression appears less than that produced by morphine (Schedule II) or buprenorphine (Schedule III).

In conclusion, the HHS states that collectively the data shows tramadol can produce a modest level of physical dependence, with the studies suggesting a degree of physical dependence development less than that of Schedule II and III opioids but similar to opioids in Schedule IV.

8. *Whether the Substance is an Immediate Precursor of a Substance Already Controlled Under the CSA:* Both the HHS and DEA state that tramadol is not an immediate precursor of any substance already controlled under the CSA.

Conclusion: Based on consideration of the scientific and medical evaluation and accompanying recommendation of the HHS, and based on the DEA's consideration of its own eight-factor analysis, the DEA finds that these facts and all relevant data constitute substantial evidence of potential for abuse of tramadol. As such, the DEA hereby proposes to schedule tramadol as a controlled substance under the CSA.

Proposed Determination of Appropriate Schedule

The CSA outlines the findings required to place a drug or other substance in any particular schedule (I, II, III, IV, or V). 21 U.S.C. 812(b). After consideration of the analysis and recommendation of the Assistant Secretary for Health of the HHS and review of all available data, the Deputy Administrator of the DEA, pursuant to 21 U.S.C. 812(b)(4), finds that:

1. Tramadol has a low potential for abuse relative to the drugs or substances in Schedule III. The abuse potential of

tramadol is comparable to the Schedule IV substance propoxyphene;

2. Tramadol has a currently accepted medical use in treatment in the United States. Tramadol and other tramadol-containing products were approved for marketing by the FDA to manage moderate to moderately severe pain; and

3. Abuse of tramadol may lead to limited physical dependence or psychological dependence relative to the drugs or other substances in Schedule III.

Based on these findings, the Deputy Administrator of the DEA concludes that tramadol [2-((dimethylamino)methyl)-1-(3-methoxyphenyl)cyclohexanol, its salts, isomers, salts of isomers, and all isomeric configurations of possible forms including tramadol, warrant control in Schedule IV of the CSA (21 U.S.C. 812(b)(4)).

Requirements for Handling Tramadol

If this rule is finalized as proposed, persons who handle tramadol would be subject to the CSA's Schedule IV regulatory controls and administrative, civil, and criminal sanctions applicable to the manufacture, distribution, dispensing, import, export, research, and conduct of instructional activities, including the following:

Registration. Any person who handles (manufactures, distributes, dispenses, imports, exports, engages in research with, or conducts instructional activities with) tramadol, or who desires to handle tramadol would need to be registered with the 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 handles tramadol, and is not registered with the DEA, would need to be registered with the DEA to conduct such activities by the effective date of the final rule.

Security. Tramadol would be subject to Schedules III–V security requirements and would need to be handled and stored in accordance with 21 CFR 1301.71–1301.93 pursuant to 21 U.S.C. 821, 823, and 871(b).

Labeling and Packaging. All labels and labeling for commercial containers of tramadol distributed on or after finalization of this rule would need to be in accordance with 21 CFR 1302.03–1302.07, pursuant to 21 U.S.C. 825, and 958(e).

Inventory. Every DEA registrant who possesses any quantity of tramadol on the effective date of the final rule would be required to take an inventory of all stocks of tramadol on hand as of the effective date of the rule, pursuant to 21 U.S.C. 827, 958(e), and in accordance with 21 CFR 1304.03, 1304.04, and 1304.11(a) and (d). Any person who becomes registered with the DEA after the effective date of the final rule would be required to take an initial inventory of all stocks of controlled substances (including tramadol) on hand at the time of registration, pursuant to 21 U.S.C. 827, 958(e), and in accordance with 21 CFR 1304.03, 1304.04, and 1304.11(a) and (b). After the initial inventory, every DEA registrant would be required to take a biennial inventory of all controlled substances (including tramadol) on hand, pursuant to 21 U.S.C. 827, 958(e), and in accordance with 21 CFR 1304.03, 1304.04, and 1304.11.

Records. All registrants would be required to maintain records for tramadol or products containing tramadol pursuant to 21 U.S.C. 827, 958(e), and in accordance with 21 CFR parts 1304 and 1312, including reports to Automation of Reports and Consolidated Orders System (ARCOS).

Prescriptions. All prescriptions for tramadol or prescriptions for products containing tramadol would be required to be issued pursuant to 21 U.S.C. 829 and in accordance with 21 CFR part 1306.

Importation and Exportation. All importation and exportation of tramadol would need to be done in accordance with 21 CFR part 1312, pursuant to 21 U.S.C. 952, 953, 957, and 958.

Liability. Any activity with tramadol not authorized by, or in violation of, the CSA, occurring on or after finalization of this proposed rule would be unlawful, and may subject the person to administrative, civil, and/or criminal sanctions.

Regulatory Analyses

Executive Orders 12866 and 13563

In accordance with 21 U.S.C. 811(a), this proposed scheduling action is subject to formal rulemaking procedures done ''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 criteria for scheduling a drug or other substance. Such actions are exempt from review by the Office of Management and Budget (OMB) pursuant to Section 3(d)(1) of Executive Order 12866 and the principles reaffirmed in Executive Order 13563.

Executive Order 12988

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

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

Executive Order 13175

This proposed rule will not have tribal implications warranting the application of Executive Order 13175. The proposed rule will 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.

Regulatory Flexibility Act

The Deputy Administrator, in accordance with the Regulatory Flexibility Act (5 U.S.C. 601–612) (RFA), 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. The purpose of this proposed rule is to place tramadol, including its salts, isomers, salts of isomers, and all isomeric configurations of possible forms, into Schedule IV of the CSA. No less restrictive measures (i.e., non-control or control in Schedule V) would enable the DEA to meet its statutory obligations under the CSA.

This proposed rule affects approximately 1.5 million DEA registrants. If finalized, the proposed rule on the placement of tramadol into Schedule IV of the CSA will affect all persons who handle, or propose to handle, tramadol. Tramadol handlers primarily include: manufacturers, distributors, pharmacies, individual practitioners, mid-level practitioners, and hospital/clinics. For the purpose of this analysis, the DEA assumes all legally operating manufacturers, distributors, importers/exports, pharmacies, individual practitioners, mid-level practitioners, and hospitals/clinics that handle tramadol are registered with the DEA and all distributors, importers/exporters, pharmacies, individual practitioners, mid-level practitioners, and hospital/clinics registered with the DEA are tramadol handlers. While the number of

DEA registrations forms the basis of the number of businesses affected by this rule, the number of manufacturers affected by this rule is based on industry data. Other than manufacturers, the DEA-estimated ''Business-to-Registrant Ratio'' is used to estimate the number of businesses represented by DEA registrants, and the ''Percent of Business Below SBA Size Standard'' is used to determine the number of businesses that are below the Small Business Administration (SBA) size standard (or number of businesses represented by DEA registrants that are small business.'' The DEA estimates that approximately 367,046 of these to be small entities. When there are no special considerations for ''substantial number'' or criteria prescribed by external sources, the DEA uses a general criteria based on percentage. For the purposes of this analysis, a ''substantial number'' is defined as greater than 30 percent. Therefore, the DEA has determined that this proposed rule will not have an impact on a substantial number of small entities.

In accordance with the RFA, the DEA evaluated the impact of this proposed rule on small entities. Specifically, the DEA examined the registration, storage, inventory and recordkeeping, and disposal requirements for the 367,046 small businesses estimated to be affected by the proposed rule. (While approximately 1.5 million DEA registrations are estimated to be affected by this rule, 273,485 registrations are in the 10 states that currently control tramadol as a Schedule IV controlled substance under state law, with requirements that meet or exceed the DEA's requirements for Schedule IV controlled substances. These states include Arkansas, Illinois, Kentucky, Mississippi, New Mexico, New York, North Dakota, Oklahoma, Tennessee, and Wyoming. Therefore, only approximately 1.2 million registrations are estimated to be *economically impacted* by this rule.) The DEA estimates that 298,354 small businesses total (across all States) would be *economically impacted* by this rule.

When there are no special considerations for ''significant economic impact'' or criteria prescribed by external sources, the DEA uses one of two general criteria, revenue-based or profit based. The revenue-based criteria are widely used, while the profit-based criteria can be used for some high-profit industries. For the purposes of this analysis the revenue-based general criteria is used, where if the cost of the rule is greater than one percent of annual revenue, the rule has a ''significant'' economic impact of the business. To estimate the number of businesses ''significantly'' impacted by the proposed rule, the DEA first estimated the revenue level associated with the 1 percent criteria for each North American Industry Classification System (NAICS) code associated with the affected entities. Then, using the revenue profile from the 2007 Economic Census, estimated the number of businesses where the cost of the rule is one percent or more than the revenue. This methodology was applied to all NAICS codes, except manufacturers. The estimate of small business manufacturers with significant economic impact is based on publically available data for annual sales data. The DEA estimates that the proposed rule would have a significant economic impact on 573 small businesses (0 manufacturers, 47 distributors/importers/exporters, 74 pharmacies, and 452 practitioners). Based on the DEA's estimate of 376,904 businesses to be affected by the proposed rule, and 367,046 of these estimated to be small businesses, including businesses located in states where tramadol is controlled as Schedule IV under state law, 573 (0.2 percent) of the 367,046 small businesses affected by the proposed rule are estimated to be significantly impacted economically.

The DEA examined the disproportionality of the economic impact. The DEA did not have a basis for differentiating costs for different business sizes, thus one cost estimate was made for each of the registrant business activities. The estimate suggests disproportionality, where smaller (of the small) businesses will bear a larger economic impact as a percentage of revenue. However, the DEA believes that the disproportionality will be mitigated by business volume. A smaller business will handle a lower volume of tramadol, thus requiring less secure storage.

Based on the DEA's understanding of its registrants' operations and facilities, the DEA estimates a non-recurring expense for system modification and initial inventory of $172.24 for all businesses and an additional $10,000 for secure storage for 50 percent of distributors, importers, and exporters. (Fifty percent of distributors, importers, and exporters are estimated to meet the requirements of the proposed rule without the need to expand secure storage area.) The DEA estimates these costs will have significant economic impact on 0 percent of small business manufacturers, 3.3 percent of small business distributors, 0.1 percent of small business pharmacies, and 0.1 percent of practitioners (other than pharmacies), totaling 0.2 percent of all businesses if the proposed rule were finalized. The percentage of small businesses with significant economic impact is below the 30 percent threshold for all registrant categories.

The annual economic effect on the economy is the annual cost per business times the number of affected businesses. The DEA estimated that 306,375 businesses, in States where tramadol is not controlled, were economically affected by the proposed rule. The annual cost of $974.39 is applied to the assumed 50 percent (588) of 1,175 Distributor/Importer/Exporters affected by the proposed rule. Annual cost of $30.46 is applied to remaining businesses affected by the proposed rule: 51 Manufacturer, 587 Distributor/Importer/Exporter, 40,797 Pharmacy, and 264,352 businesses that employ or hold Individual Practitioner, Mid-level Practitioner, and/or Hospital/Clinic registrations. To be conservative in analysis, the higher values for annual costs of $974.39 and $30.46 at 7 percent discount and interest rates is used rather than the annual costs of $698.22 and $26.06 at 3 percent discount and interest rates. The total annual cost is estimated to be $9,887,561.

The DEA's assessment of economic impact by size category indicates that the proposed rule will not have a significant economic impact on a substantial number of small entities.

Unfunded Mandates Reform Act of 1995

On the basis of information contained in the ''Regulatory Flexibility Act'' section above, the DEA has determined and certifies pursuant to the Unfunded Mandates Reform Act (UMRA) of 1995 (2 U.S.C. 1501 *et seq.*), that this 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 for inflation) in any one year[. . . .]'' Therefore, neither a Small Government Agency Plan nor any other action is required under provisions of UMRA of 1995.

Paperwork Reduction Act of 1995

This action does not impose a new collection of information under the Paperwork Reduction Act of 1995, 44 U.S.C. 3501–3521. This action would not impose recordkeeping or reporting requirements on State or local governments, individuals, businesses, or organizations. 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.

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) unless otherwise noted.

■ 2. Amend § 1308.14 by adding a new paragraph (b)(3) to read as follows:

§ 1308.14 Schedule IV.

* * * * *

(b) * * *

(3) Tramadol [2-((dimethylamino)methyl)-1-(3-methoxyphenyl)cyclohexanol, its salts, optical and geometric isomers and salts of these isomers]—9752

* * * * *

Dated: October 25, 2013.

Thomas M. Harrigan,

Deputy Administrator.

[FR Doc. 2013–25933 Filed 11–1–13; 8:45 am]

BILLING CODE 4410–09–P

DEPARTMENT OF THE TREASURY

Internal Revenue Service

26 CFR Part 300

[REG–144990–12]

RIN 1545–BL37

User Fees for Processing Installment Agreements and Offers in Compromise; Hearing Cancellation

AGENCY: Internal Revenue Service (IRS), Treasury.

ACTION: Cancellation of a notice of public hearing on proposed rulemaking.

SUMMARY: This document cancels a public hearing on proposed regulations that amend the provider user fees for installment agreements and offers in compromise.

DATES: The public hearing originally scheduled for October 1, 2013 at 10 a.m. is cancelled.

FOR FURTHER INFORMATION CONTACT: Oluwafunmilayo Taylor of the Publications and Regulations Branch, Legal Processing Division, Associate Chief Counsel (Procedure and Administration) at (202) 622–7180 (not a toll-free number).

SUPPLEMENTARY INFORMATION: A notice of proposed rulemaking and a notice of public hearing that appeared in the **Federal Register** on Friday August 30, 2013 (78 FR 53702) announced that a public hearing was scheduled for October 1, 2013, at 10 a.m. in the IRS Auditorium, Internal Revenue Building, 1111 Constitution Avenue NW., Washington, DC. The subject of the public hearing is under sections 6159 and 7122 of the Internal Revenue Code.

The public comment period for these regulations expired on September 30, 2013. The notice of proposed rulemaking and notice of public hearing instructed those interested in testifying at the public hearing to submit a request to speak and an outline of the topics to be addressed. The hearing was not held on October 1, 2013, due to the closure of the Federal Government. As of October 17, 2013, the date of the reopening of the Federal Government, there were no requests to speak. Therefore, the public hearing scheduled for October 1, 2013, is cancelled and will not be rescheduled.

Martin V. Franks,

Chief, Publications and Regulations Branch, Legal Processing Division, Associate Chief Counsel, (Procedure and Administration).

[FR Doc. 2013–26280 Filed 11–1–13; 8:45 am]

BILLING CODE 4830–01–P

DEPARTMENT OF LABOR

Occupational Safety and Health Administration

29 CFR Parts 1910 and 1926

[Docket No. OSH–2013–0005]

RIN No. 1218–AC77

Updating OSHA Standards Based on National Consensus Standards; Signage

AGENCY: Occupational Safety and Health Administration (OSHA), Department of Labor.

ACTION: Proposed rule; withdrawal.

SUMMARY: With this notice, OSHA is withdrawing the proposed rule that accompanied its direct final rule revising its signage standards for general industry and construction.

DATES: Effective November 4, 2013, OSHA is withdrawing the proposed rule published June 13, 2013 (78 FR 35585).

FOR FURTHER INFORMATION CONTACT:

General information and press inquiries: Contact Frank Meilinger, Director, OSHA Office of Communications, Room N–3647, U.S. Department of Labor, 200 Constitution Avenue NW., Washington, DC 20210; telephone: (202) 693–1999; email: *meilinger.francis2@dol.gov.*

Technical information: Contact Ken Stevanus, Directorate of Standards and Guidance, Room N–3609, OSHA, U.S. Department of Labor, 200 Constitution Avenue NW., Washington, DC 20210; telephone: (202) 693–2260; fax: (202) 693–1663; email: *stevanus.ken@dol.gov.*

SUPPLEMENTARY INFORMATION:

Copies of this Federal Register notice: Electronic copies of this **Federal Register** notice are available at *http://www.regulations.gov.* This **Federal Register** notice, as well as news releases and other relevant information, also is available at OSHA's Web page at *http://www.osha.gov.*

Withdrawal of the proposal: On June 13, 2013, OSHA published a companion proposed rule (NPRM) along with the direct final rule (DFR) (*see* 78 FR 35585) updating its signage standards for general industry and construction. In the DFR, OSHA stated that it would withdraw the companion NPRM and confirm the effective date of the DFR if it received no significant adverse comments to the DFR by the close of the comment period, July 15, 2013. OSHA received eight favorable and no adverse comments on the DFR by that date (*see* ID: OSHA–2013–0005–0008 thru –0015 in the docket for this rulemaking). Accordingly, OSHA is withdrawing the proposed rule. In addition, OSHA is publishing two separate **Federal Register** notices, one confirming the effective date of the DFR, and the other making minor, nonsubstantive additions and corrections to 29 CFR 1910.6, 1926.6, and 1926.200(b) and (c).

List of Subjects in 29 CFR Parts 1910 and 1926

Signage, Occupational safety and health, Safety.

Authority and Signature

David Michaels, Ph.D., MPH, Assistant Secretary of Labor for Occupational Safety and Health, U.S. Department of Labor, 200 Constitution Avenue NW., Washington, DC 20210, authorized the preparation of this document. OSHA is issuing this document pursuant to 29 U.S.C. 653, 655, and 657, 5 U.S.C. 553, Secretary of Labor's Order 1–2012 (77 FR 3912), and 29 CFR part 1911.