

(ii) *Indications for use.* For reduction of the incidence of cervical abscesses; treatment of bacterial swine enteritis (salmonellosis or necrotic enteritis caused by *Salmonella choleraesuis* and vibronic dysentery); prevention of these diseases during times of stress; and maintenance of weight gains in the presence of atrophic rhinitis.

(iii) *Limitations.* Feed as the sole ration. Withdraw 15 days prior to slaughter.

§ 558.145 [Amended]

■ 3. In § 558.145, in paragraph (a)(2), remove “Nos. 048164 and 054771” and in its place add “No. 048164”.

Dated: June 25, 2014.

Bernadette Dunham,

Director, Center for Veterinary Medicine.

[FR Doc. 2014–15274 Filed 6–30–14; 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: Final rule.

SUMMARY: With the issuance of this final rule, the Deputy Administrator of the Drug Enforcement Administration places the substance 2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)cyclohexanol (tramadol), including its salts, isomers, and salts of isomers, into schedule IV of the Controlled Substances Act. This scheduling action is pursuant to the Controlled Substances Act which requires that such actions be made on the record after opportunity for a hearing through formal rulemaking. This action imposes 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 with, or possess) or propose to handle tramadol.

DATES: Effective August 18, 2014.

FOR FURTHER INFORMATION CONTACT: Erika Gehrman, Office of Diversion Control, Drug Enforcement Administration; Mailing Address: 8701 Morrisette Drive, Springfield, Virginia 22152; Telephone: (202) 598–6812.

SUPPLEMENTARY INFORMATION:

Legal Authority

The Drug Enforcement Administration (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, every controlled substance is classified in one of five schedules based upon its potential for abuse, currently accepted medical use, and the degree of dependence the drug or other substance may cause. 21 U.S.C. 812. The initial 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 [21 U.S.C. 812(b)] for the schedule in which such drug is to be placed * * *.” The Attorney General has delegated scheduling authority under 21 U.S.C. 811 to the Administrator of the DEA, 28 CFR 0.100, who in turn has redelegated that authority to the Deputy Administrator of the DEA, 28 CFR part 0, appendix to subpart R.

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 Department of Health and Human Services (HHS),¹ or (3) on

¹ As discussed in a memorandum of understanding entered into by the Food and Drug Administration (FDA) and the National Institute on Drug Abuse (NIDA), the FDA acts as the lead agency

the petition of any interested party. 21 U.S.C. 811(a). This action was initiated by four petitions to schedule tramadol under the CSA, and is supported by, *inter alia*, a recommendation from the Assistant Secretary of the HHS and an evaluation of all relevant data by the DEA. This action imposes the regulatory controls and administrative, civil, and criminal sanctions applicable to schedule IV controlled substances on persons who handle or propose to handle tramadol.²

Background

Tramadol is a centrally acting opioid analgesic that produces its primary opioid-like action through an active metabolite, referred to as the “M1” metabolite (O-desmethyiltramadol). It was first approved for use in the United States by the U.S. Food and Drug Administration (FDA) in 1995 under the trade name ULTRAM®. Subsequently, the FDA approved for marketing generic, combination, and extended release tramadol products.

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.³

HHS and DEA Eight-Factor Analyses

On September 16, 2010, the Assistant Secretary of the HHS provided to the DEA a scientific and medical evaluation and scheduling recommendation entitled “Basis for the Recommendation to Schedule Tramadol in Schedule IV of the Controlled Substances Act.” After considering the eight factors in 21

within the HHS in carrying out the Secretary’s scheduling responsibilities under the CSA, with the concurrence of NIDA. 50 FR 9518, Mar. 8, 1985. The Secretary of the HHS has delegated to the Assistant Secretary for Health of the HHS the authority to make domestic drug scheduling recommendations. 58 FR 35460, July 1, 1993.

² See *infra* note 3.

³ For simplicity, 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.

U.S.C. 811(c), as well as the substance's abuse potential, legitimate medical use, and dependence liability, the Assistant Secretary of the HHS recommended that tramadol be controlled in schedule IV of the CSA under 21 U.S.C. 812(b). The DEA conducted its own eight-factor analysis of tramadol pursuant to 21 U.S.C. 811(c). Both the DEA and HHS analyses are available in their entirety in the public docket for this rule (Docket No. DEA-351) at <http://www.regulations.gov> under "Supporting and Related Material."

Determination To Schedule Tramadol

After a review of the available data, including the scientific and medical evaluation and the scheduling recommendation from the HHS, the Deputy Administrator of the DEA published in the **Federal Register** a notice of proposed rulemaking (NPRM) entitled "Schedules of Controlled Substances: Placement of Tramadol Into Schedule IV" which proposed to place tramadol in schedule IV of the CSA. 78 FR 65923, Nov. 4, 2013. The proposed rule provided an opportunity for interested persons to file a request for hearing in accordance with DEA regulations by December 4, 2013. No requests for such a hearing were received by the DEA. The NPRM also provided an opportunity for interested persons to submit written comments on the proposed rule on or before January 3, 2014.

Comments Received

The DEA received 27 comments on the proposed rule to schedule tramadol. Sixteen commenters expressed support for controlling tramadol as a schedule IV controlled substance, nine commenters were opposed to tramadol being placed into schedule IV of the CSA, and two commenters did not take a position.

Support of the Proposed Rule

Sixteen commenters supported controlling tramadol as a schedule IV controlled substance. Among those 16 commenters expressing support were two State Boards of Pharmacy. One veterinary distributor's association stated that it supports the DEA designating tramadol as a schedule IV controlled substance because it will enable distributors to operate with efficiency and consistency across the United States along with requiring an increased level of due diligence and monitoring. A national veterinary medical association, a national healthcare association, and a national pharmacy association were also among

those who expressed support for the rule.

Several commenters supporting the rule expressed their concern regarding the abuse potential and resulting threat to public health posed by tramadol. Writing in support of scheduling tramadol, a local multi-agency prescription drug abuse task force described tramadol as a "'loop hole' drug which is addictive, abused, and diverted," but which is not yet realized as such by many patients and prescribers due to its current non-controlled status. One commenter stated that given the abuse potential of tramadol (which according to the commenter is often abused in combination with other controlled substances), scheduling this drug will ensure that it is subject to the same controls as other similarly addictive controlled substances. Yet another commenter noted that although analgesics are addictive to a very small percentage of people that use them, scheduling this drug would reduce the number of emergency room visits and number of overdose deaths.

A certified pharmacy technician described her experiences of witnessing the abuse of tramadol by patients on a daily basis. She stated the stricter controlled substance laws of the State of Mississippi have seemed to lessen the abuse. A group of pharmacy students noted that tramadol, marketed as ULTRAM®, is currently the only uncontrolled opioid on the market. Another commenter who supported the rule stated: "In the field of pharmacy, some patients have expressed concern about the reclassification of tramadol, believing that new regulations could complicate or impede new and chronic patients from receiving their prescriptions." This commenter noted that this is a common misconception since schedule IV controlled medications are in fact readily available for those with a valid prescription and the appropriate medical condition. In addition, the commenter noted that these types of prescriptions also have the added convenience of being easily transferrable between pharmacies, phoned-in by prescribers, and refilled five times over a six month period.

DEA Response: The DEA appreciates the support for the rule.

Opposition to the Proposed Rule

1. Access to Pain Medication by the Elderly

An association for consulting pharmacists stated that controlling tramadol would limit access to needed pain medications for elderly patients

and opposed the proposed scheduling until a workable solution to ensure timely access for patients in long-term care facilities (LTCFs) can be reached. Specifically, the commenter expressed concern that, should tramadol become a controlled substance, LTCF nurses would no longer be able to call-in or fax a chart order directly to the pharmacy. According to the commenter, in LTCFs, prescribers must call, hand deliver, or fax controlled substance prescriptions to pharmacies, and this in turn involves LTCF employees having to track down the (often non-employee) prescriber. This practice, according to the commenter, can severely impede delivery of prescription medications to LTCF patients.

DEA Response: The processes and procedures associated with dispensing a controlled substance are not relevant factors to the determination whether a substance should be controlled or under what schedule a substance should be placed if it is controlled. See 21 U.S.C. 811 and 812. Nonetheless, controlling tramadol as a schedule IV controlled substance should not hinder legitimate access to the medicine, whether within the LTCF setting or elsewhere. As summarized by a State Board of Pharmacy who wrote in support of controlling tramadol: "Scheduling a medication does not make it impossible to prescribe, dispense and administer the medication. However, it does alert practitioners, dispensers and perhaps even some patients that the medication has some potential dangers for addiction and misuse, and frequent monitoring and evaluation by practitioners and dispensers of such drugs is necessary for appropriate patient care."

Currently, tramadol is a non-controlled medication that the FDA has approved only for prescription use. Tramadol, as a schedule IV controlled substance, will continue to require a prescription, either orally or in writing. 21 U.S.C. 829(b). The CSA allows for the legitimate prescribing and use of controlled substances; therefore, the control of tramadol should not hinder patient access to the medication. The prescription for tramadol, as a controlled substance, may only be issued by an individual practitioner who is either registered with the DEA or exempt from registration. 21 CFR 1306.03. A prescription for a controlled substance must also be issued for a legitimate medical purpose by an individual practitioner acting in the course of his professional practice. 21 CFR 1306.04(a). Upon the effective date of this rule, tramadol prescriptions may be filled up to six months after the date prescribed, and may be refilled up to

five times within six months after the date on which such prescription was issued. 21 U.S.C. 829(b); 21 CFR 1306.22 (a) and (e); *see also* 21 CFR 1306.23 (b) and (c). In addition, there are no dosage unit limitations for prescriptions for schedule III, IV, or V controlled substances unless the controlled substance is prescribed for administration to an ultimate user who is institutionalized. 21 CFR 1306.24(c).

The substantive requirement that a practitioner acting in the usual course of professional practice determine that tramadol is medically necessary to treat the patient does not hinder legitimate access; the procedural requirements relating to transmission of a legitimate prescription do not hinder legitimate access either. Once an individual practitioner makes a medical determination to prescribe a schedule III through V controlled substance, a prescriber's agent may call-in or fax a prescription for it. *See* 21 CFR 1306.03(b), 1306.21(a). The DEA recognizes the unique challenges pertaining to handling and using controlled substances at LTCFs and has previously addressed related concerns.⁴ A DEA registered practitioner may not delegate to a nurse, a pharmacist, or anyone else his or her authority to make a medical determination whether to prescribe a particular controlled substance. However, oral prescriptions for controlled substances in schedules III–V may be communicated to a pharmacy by an employee or agent of the prescribing practitioner, 21 CFR 1306.03(b). Note that the prescribing practitioner remains responsible for ensuring that the prescription conforms “in all essential respects to the law and regulations,” 21 CFR 1306.05(f). 75 FR 61613, 61614, Oct. 6, 2010. This requires the practitioner alone to determine—on a prescription by prescription basis—whether the prescription is supported by a legitimate medical purpose and that all the essential elements of the prescription are met.

2. Fear of Criminal Action

Some commenters expressed concern that scheduling tramadol would deter prescribers from properly treating pain for fear of facing criminal action.

DEA Response: One of the most important principles underlying the CSA is that every prescription for a controlled substance must be issued for

a legitimate medical purpose by an individual practitioner acting in the usual course of his professional practice. 21 CFR 1306.04(a); *U.S. v. Moore*, 423 U.S. 122 (1975) (holding registered physicians may be prosecuted for violation of the CSA when their activities fall outside the usual course of professional practice). The DEA Policy Statement entitled “Dispensing Controlled Substances for the Treatment of Pain,” 71 FR 52715 (Sept. 6, 2006), makes clear that this longstanding requirement should in no way interfere with the legitimate practice of medicine or cause any practitioner to be reluctant to provide legitimate pain treatment. Providers (as well as ultimate users) become subject to administrative, civil, and/or criminal proceedings when their activity involving controlled substances is not authorized by, or in violation of, the CSA.

3. Shift to the Black-Market

Several commenters stated that scheduling tramadol would limit their access to tramadol, causing them to have to buy tramadol on the street.

DEA Response: As discussed above, schedule IV controlled medications are readily available for legitimate medical use.

4. Scientific Data Not Sufficient

One commenter reviewed selected published literature and submitted a short review document with a conclusion that “the current available scientific evidence supports the continuation of a non-controlled classification” of tramadol.

DEA Response: The CSA mandates that both the HHS and DEA conduct a review of the drug or other substance as related to the eight factors enumerated in 21 U.S.C. 811(c): (1) Its actual or relative potential for abuse; (2) scientific evidence of its pharmacological effect, if known; (3) the state of current scientific knowledge regarding the drug or other substance; (4) its history and current pattern of abuse; (5) the scope, duration, and significant of abuse; (6) what, if any, risk there is to the public health; (7) its psychic or physiological dependence liability; and (8) whether the substance is an immediate precursor of a substance already controlled. The Assistant Secretary of the HHS provided a scientific and medical evaluation and a scheduling recommendation to control tramadol as a schedule IV controlled substance. In accordance with 21 U.S.C. 811(c), the DEA conducted its own analysis of the eight factors determinative of control. Besides published literature, various other data as detailed in the supporting documents

were considered in making the scheduling determination for tramadol. Thus, the scheduling determination is based on a comprehensive evaluation of all available data as related to the above mentioned eight factors. The summary of each factor as analyzed by the HHS and the DEA, and as considered by the DEA in this scheduling action, was provided in the proposed rule. Both the DEA and the HHS analyses have been made available in their entirety under “Supporting and Related Material” of the public docket for this rule at <http://www.regulations.gov> under Docket No. DEA–351.

As discussed in detail in the DEA's eight-factor analysis, collectively, the available information regarding tramadol supports an abuse potential that is less than that of schedule III and similar to that for schedule IV. Preclinical self-administration studies show that tramadol produces limited reinforcing effects, consistent with schedule IV. At supra-therapeutic doses, tramadol can produce subjective reinforcing effects similar to that of morphine (C–II) and approaching that of oxycodone (C–II). At high doses (but not therapeutic doses), tramadol can produce subjective reinforcing effects similar to propoxyphene (C–IV). For both tramadol and propoxyphene, the doses required to produce significant subjective reinforcing effects are in a range causing sufficient adverse effects. These observations indicate that the subjective reinforcing effects, a reflection of abuse potential, of tramadol are less than that of morphine or oxycodone, but similar to that of propoxyphene.

Based on the review of the HHS evaluation and scheduling recommendation and all other relevant data, the DEA has found that tramadol has an abuse potential and meets the requirements for schedule IV controls under the CSA.

5. Disagreement With Tramadol Classification as an Opioid

One commenter who supported the rule stated that tramadol should not be compared to hydrocodone because hydrocodone is an opioid and tramadol is psychotropic in nature and very similar to, if not the same as, a serotonin-norepinephrine reuptake inhibitor (SNRI).

DEA Response: In the NPRM and supporting documents, the DEA compared tramadol mainly to propoxyphene (narcotic schedule IV). Based on both the HHS and the DEA analyses, there is strong scientific evidence that tramadol and propoxyphene are similar regarding

⁴ E.g., “Preventing the Accumulation of Surplus Controlled Substances at Long Term Care Facilities,” 66 FR 20833, Apr. 25, 2001; “Role of Authorized Agents in Communicating Controlled Substance Prescriptions to Pharmacies,” 75 FR 61613, Oct. 6, 2010.

their behavioral pharmacology and abuse potential pattern, thus suggesting that it is appropriate to control tramadol as a schedule IV controlled substance.

In addition, as stated in the supporting scientific documents, both the HHS and the DEA deem tramadol to be an opioid because tramadol shares similar pharmacological activities with opioids that are controlled under the CSA (schedules II–IV). (The labeling for FDA approved tramadol products states that tramadol is a centrally acting opioid analgesic.) An examination of the general pharmacology (including behavioral pharmacology) of tramadol reveals that tramadol produces many pharmacological effects similar to those of other opioids. These pharmacological effects include, but are not limited to, analgesia, respiratory depression, miosis, cough suppression, and inhibition of bowel mobility, and as such, tramadol is considered an opioid. The opioid pharmacology of tramadol primarily resides with its metabolite, O-desmethyiltramadol, designated “M1,” and to a much lesser extent with tramadol, the parent drug. In addition, tramadol resembles some opioids insofar as it has the additional pharmacological effects of blocking the reuptake of norepinephrine and serotonin.

The CSA defines an “opiate” as “any drug or other substance having an addiction-forming or addiction-sustaining liability similar to morphine or being capable of conversion into a drug having such addiction-forming or addiction-sustaining liability.” 21 U.S.C. 802(18). Opium, opiates, derivatives of opium and opiates, including their isomers, whether produced directly or indirectly by extraction from substances of vegetable origin, or independently by means of chemical synthesis, are “narcotic drugs” as defined by the CSA, 21 U.S.C. 802(17).⁵ As discussed in the supporting eight-factor documentation, preclinical studies demonstrate that tramadol, as 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 (narcotic schedule IV).

Although, generally, the controls imposed by the CSA on drugs and other

substances depend on the schedule into which they are placed, there are certain additional requirements and restrictions for narcotic drugs. For example, narcotic drugs in schedule III, IV, or V may not be imported into the United States unless it is found that such importation is needed to provide for the legitimate medical, scientific, or other legitimate purposes under the specified, limited circumstances described in 21 U.S.C. 952(a). Narcotic controlled substances may not be exported unless the conditions imposed by 21 U.S.C. 953(a) are satisfied.

6. Never-Ending Practice of Drug Scheduling

Two commenters raised concerns that, despite the scheduling of drugs such as tramadol, individuals will always find substances to abuse, thus creating “a never ending story of scheduling drugs.”

DEA Response: Pursuant to 21 U.S.C. 811(a), the CSA authorizes the DEA, under authority delegated by the Attorney General, to add to such a schedule any drug or other substance if it is found that the 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). As such, the scheduling authority established by Congress specifically allows new substances to be added to the list of controlled substances without regard to the number of substances already controlled. *See also* 21 U.S.C. 812(a) (“Such schedules shall *initially* consist of * * *” (*emphasis added*)).

Requests for Staggered Implementation of Various Portions of the Rule

A national association that represents primary healthcare distributors commented that although they recognized the underlying reasons for scheduling tramadol and agreed with the reasoning and basis for controlling tramadol, the DEA should provide an extended time period before implementation to allow registrants to become compliant with portions of the rule regarding security, labeling and packaging, and reporting.⁶ The association requested that the requirement for conducting inventory of tramadol products within wholesale distribution centers take place as of the effective date of the final scheduling

decision. The association’s concerns (as well as the DEA’s responses) are outlined and discussed below.

1. Request for Staggered Effective Dates, Generally

The association requested that the DEA implement handling requirements for tramadol in stages. For example, they requested that the requirement for conducting inventory of tramadol products within wholesale distribution centers take place as of the effective date of the final scheduling decision but delaying the requirements for compliance with the security provisions of 21 CFR 1301.71–1301.93.

DEA Response: Generally, scheduling actions for drugs and other substances currently marketed in the United States are effective 30 days from the date of publication of the final rule in the **Federal Register**. In order to ensure the continued availability of tramadol for legitimate medical use, while also ensuring it is not subject to misuse, abuse, and diversion, the DEA is establishing an effective date of this final rule for all handling requirements 45 days from the date of publication. This 45-day period will provide a reasonable time for registrants to comply with the handling requirements for a schedule IV controlled substance and was established upon a full consideration of the totality of circumstances specific to tramadol.

Although the DEA has in the past, for some scheduling actions, allowed for additional time for compliance with certain handling requirements beyond the general effective date, the DEA has specifically chosen to forgo staggered implementation dates of handling requirements as different implementation dates leads to confusion and inconsistent application of the law.

2. Security

The association recommended a minimum of 120 days from the date of the final rule to allow for compliance in order to provide storage, revise operating procedures, train staff, and amend monitoring systems.

DEA Response: In order to ensure the continued availability of tramadol for legitimate medical use, while also ensuring it is not subject to misuse, abuse, and diversion, the DEA is establishing an effective date of this final rule, including security requirements, 45 days from the date of publication. Upon promulgation, registrants must comply with the applicable security provisions of 21 CFR 1301.71–1301.93. This 45-day period will provide a reasonable time for registrants to comply with the security

⁵ Including their isomers, esters, ethers, salts, and salts of isomers, whenever the existence of such isomers, esters, ethers, and salts is possible within the specific chemical designation; however, does not include the isoquinoline alkaloids of opium.

⁶ Pursuant to 5 U.S.C. 553(d) and in accordance with 21 CFR 1308.45, a final rule scheduling a substance shall not be effective less than 30 days from the date of its publication in the **Federal Register** unless the Administrator finds that conditions of public health or safety necessitate an earlier effective date.

requirements for a schedule IV controlled substance. As noted by the association, it is believed that distributors of tramadol already have adequate space within their warehouse cages to store the anticipated volume of tramadol and “thus construction or expansion of cage space is unlikely to result * * *.” Accordingly, it is reasonably likely that handlers and proposed handlers of tramadol have already instituted or made plans to institute the necessary modifications regarding security, including amendments to their suspicious orders monitoring systems to include tramadol orders. In order to provide handlers of tramadol a reasonable time period to comply with schedule IV handling requirements, including those for security, the DEA is allowing an additional 15 days, as compared to the generally allotted 30 days, from publication in the **Federal Register** before this rule becomes effective. After 45 days from the date of the final rule, tramadol will be subject to schedule III-V security requirements.

The DEA has carefully considered the security requirements for compliance with this rule. As confirmed by the association, current distributors of tramadol are DEA registrants with existing controlled substance storage that complies with DEA regulations. The DEA understands that handlers of tramadol may need to make modifications to their current security procedures for compliance. These modifications necessary for security compliance will be a one-time modification to provide for the appropriate storage, revision of operating procedures, training of staff, and amendments to suspicious order monitoring systems to include customer verifications. The DEA believes that a 45-day period will provide handlers of tramadol adequate time to implement these one-time modifications in compliance with the DEA security regulations. Registrants are familiar with the applicable security regulations, and already have systems in place with respect to other controlled substances. Accordingly, revising operating procedures, amending monitoring systems, and training staff with respect to tramadol should be easily accomplished within the 45-day compliance timeframe. The DEA strongly advises current registrants (and those entities that may seek registration as a result of this action) to work closely with their local DEA office regarding the applicable security requirements and any necessary modifications due to

compliance with this rule. 21 CFR 1301.71(d).

3. Distribution of Products With the Pre-Control Label

The association stated that in accordance with 21 CFR 1302.05, the DEA has the authority to set a date on which labeling and packaging requirements will become effective, and requested clarification of when the distribution of products with the pre-scheduling label should cease. The association also requested clarification as to whether the cessation of the manufacture of products for commercial containers with the pre-scheduling labeling will also mean that manufacturers would be required to cease distribution to wholesale distributors of products they might have in stock bearing the pre-scheduling label. The association stated that the ambiguity of the compliance period poses a dilemma for those in the tramadol supply chain, and requested the DEA to act to meet healthcare needs and avoid waste by allowing products bearing the pre-scheduling label to move through the supply chain until the inventory is depleted. Alternatively, the association suggested that the DEA allow distributors to continue to sell pre-scheduling labeled product for at least 180 days after the effective date of the final rule.

DEA Response: As of the effective date of the final rule, pursuant to 21 U.S.C. 821, 825, and 958(e) and in accordance with 21 CFR 1302.03, manufacturers are required to print upon the labeling of each commercial container of tramadol they distribute the designation of tramadol as “C-IV.” It shall be unlawful for commercial containers of tramadol to be distributed without bearing the label properly identifying it as a schedule IV controlled substance in accordance with 21 CFR part 1302. As clearly stated in 21 CFR 1302.05, “[a]ll labels on commercial containers of, and all labeling of, a controlled substance which either is transferred to another schedule or is added to any schedule shall comply with the requirements of § 1302.03, on or before the effective date established in the final order for the transfer or addition.” Accordingly, the DEA is requiring that commercial containers of tramadol distributed on or after 45 days from the date of publication of the final rule be labeled as “C-IV” and be packaged in accordance with 21 CFR part 1302.

From the 2007 Economic Census, the DEA estimates that the inventory

turnover ratio for the industry⁷ is approximately 11.3.⁸ The inventory turnover ratio represents the number of times the inventory sells (turns) in a year. The 11.3 inventory turnover ratio equates to an average of 32 days to sell inventory. The 11.3 turnover ratio is consistent with that of large distributors where financial information was publicly available and reviewed. Publicly reviewed data reports that about 85% of all revenues (an indirect indicator of dosage units moved) from drug distribution in the United States come from three public wholesalers, each with annual revenue in the billions. The DEA additionally notes that many regional and specialist pharmaceutical wholesalers have been acquired by the largest three distribution companies. The inventory turnover ratio is a reasonable estimate for the entire industry and all products under the circumstances. Because the 32 days to sell inventory is an average based on industry-wide census data, it is possible for an individual company and/or product line to have shorter or longer time to sell.

Since tramadol is a widely prescribed drug, with nearly 40 million prescriptions written in 2012,⁹ the DEA expects distributors to receive and distribute tramadol at high volume and with regularity; thus, anticipating shorter than average days to sell tramadol than overall industry average inventory. However, to accommodate those distributors that have lower than average industry turnover ratio, the DEA is establishing an effective date of this final rule, including labeling and packaging requirements, 45 days from the date of publication. The DEA believes this will provide a reasonable time for distributors to sell existing stock with pre-control labeling and packaging and to stock inventory with post-control labeling and packaging.

Additionally, the DEA believes that any distributor that requires more than 45 days to sell tramadol inventory under normal circumstances can make minor modifications to ordering and stocking procedure for a transitional period to meet the established effective date at minimal cost. Distributors also have the option of returning excess stock of tramadol product without the “C-IV”

⁷ NAICS 424210—Drugs and druggists’ sundries merchant wholesalers; Merchant wholesalers, except manufacturers’ sales branches and offices.

⁸ The inventory turnover ratio of 11.3 was calculated by dividing the 2007 “cost of goods sold” for the industry of \$280,481,051,000 by the average end-of-year 2006 total inventories of \$24,782,835,000.

⁹ IMS Health, National Sales Perspective™ (NSP).

label to the manufacturer, as authorized by 21 CFR 1307.12.

The DEA takes this opportunity to clarify that the regulation pertaining to labeling of commercial containers applies only to distributions by manufacturers and distributors. The DEA does not regulate the labeling and packing of commercial containers of controlled substances downstream of distributors.

As summarized in the NPRM, and discussed in detail in the supporting eight factor analyses, tramadol meets the statutory requirements for control and for placement in schedule IV. Based upon the reasons discussed above, the DEA believes that 45 days is a reasonable amount of time for registrants to modify their operations so that the necessary safeguards are in place to prevent the abuse and diversion of tramadol.

4. Automation of Reports and Consolidated Orders System ("ARCOS") Reporting

The association stated that only schedule I and II (and some schedule III) products are subject to reporting under the DEA's Automation of Reports and Consolidated Orders System ("ARCOS"), so it would be an error to require distributors to report tramadol (a schedule IV narcotic) to ARCOS.

DEA Response: DEA regulations do not require distributors to file ARCOS reports for schedule IV narcotics.

Scheduling Conclusion

Based on consideration of all comments, 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 other relevant data constitute substantial evidence of potential for abuse of tramadol. As such, the DEA is scheduling tramadol as a controlled substance under the CSA.

Determination of Appropriate Schedule

The CSA establishes five schedules of controlled substances known as schedules I, II, III, IV, and V. The CSA outlines the findings required for placing a drug or other substance in any particular schedule. 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 relevant and 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 controlled substance propoxyphene;

2. Tramadol has a currently accepted medical use in treatment in the United States. Tramadol and other tramadol-containing products are 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, including its salts, isomers, and salts of isomers, warrants control in schedule IV of the CSA. 21 U.S.C. 812(b)(4).

Requirements for Handling Tramadol

Upon the effective date of this final rule, any person who handles tramadol is subject to the CSA's schedule IV regulatory controls and administrative, civil, and criminal sanctions applicable to the manufacture, distribution, dispensing, importing, exporting, engagement in research, and conduct of instructional activities, of schedule IV controlled substances including the following:

Registration. Any person who handles (manufactures, distributes, dispenses, imports, exports, engages in research, or conducts instructional activities with) tramadol, or who desires to handle tramadol, must 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 as of August 18, 2014. Any person who currently handles tramadol and is not registered with the DEA must submit an application for registration and may not continue to handle tramadol as of August 18, 2014 unless the DEA has approved that application, pursuant to 21 U.S.C. 822, 823, 957, and 958, and in accordance with 21 CFR parts 1301 and 1312.

Disposal of stocks. Any person who does not desire or is not able to obtain a schedule IV registration must surrender all quantities of currently held tramadol in accordance with the procedures outlined in 21 CFR 1307.21 on or before August 18, 2014, or may transfer all quantities of currently held tramadol to a person registered with the DEA on or before August 18, 2014.

Security. Tramadol is subject to schedule III–V security requirements and must be handled and stored pursuant to 21 U.S.C. 821 and 823, and in accordance with 21 CFR 1301.71–1301.93 as of August 18, 2014.

Labeling and Packaging. All labels and labeling for commercial containers of tramadol must comply with 21 U.S.C. 825 and 958(e), and be in accordance with 21 CFR part 1302 as of August 18, 2014.

Inventory. Every DEA registrant who possesses any quantity of tramadol on the effective date of this final rule must take an inventory of all stocks of tramadol on hand as of August 18, 2014, pursuant to 21 U.S.C. 827 and 958, 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 August 18, 2014 must take an initial inventory of all stocks of controlled substances (including tramadol) 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 (a) and (b).

After the initial inventory, every DEA registrant must take a new inventory of all stocks of controlled substances (including tramadol) on hand every two years, pursuant to 21 U.S.C. 827 and 958, and in accordance with 21 CFR 1304.03, 1304.04, and 1304.11.

Records and Reports. All DEA registrants must maintain records with respect to tramadol pursuant to 21 U.S.C. 827 and 958 and in accordance with 21 CFR parts 1304 and 1312 as of August 18, 2014.

Prescriptions. All prescriptions for tramadol or products containing tramadol must comply with 21 U.S.C. 829, and be issued in accordance with 21 CFR part 1306 and subpart C of 21 CFR part 1311 as of August 18, 2014.

Importation and Exportation. All importation and exportation of tramadol must be in compliance with 21 U.S.C. 952, 953, 957, and 958, and be in accordance with 21 CFR part 1312 as of August 18, 2014.

Liability. Any activity involving tramadol not authorized by, or in violation of, the CSA, occurring as of August 18, 2014 is unlawful, and may subject the person to administrative, civil, and/or criminal action.

Regulatory Analyses

Executive Orders 12866 and 13563

In accordance with 21 U.S.C. 811(a), this 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 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 rulemaking does not have federalism implications warranting the application of Executive Order 13132. The rule does 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 rule does not have tribal implications warranting the application of Executive Order 13175. This rule 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.

Regulatory Flexibility Act

The Deputy Administrator, in accordance with the Regulatory Flexibility Act (RFA) (5 U.S.C. 601–612), has reviewed this final 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 final rule is to place tramadol, including its salts, isomers, and salts of isomers, into schedule IV of the CSA. By this final rule, tramadol will remain in schedule IV unless and until additional scheduling action is taken to either transfer it between the schedules or to remove it from the list of schedules. See 21 U.S.C. 811 and 812. No less restrictive measures (i.e., non-control or control in schedule V) enable the DEA to meet its statutory obligations under the CSA.

This rule affects approximately 1.5 million DEA registrations, representing approximately 376,904 entities. The DEA estimates that 367,046 (97%) of these entities are “small entities” in accordance with the RFA and SBA size standards. 5 U.S.C. 601(6) and 15 U.S.C. 632.

In accordance with the RFA, the DEA evaluated the impact of this rule on small entities. Specifically, the DEA examined the registration, storage, inventory and recordkeeping, and disposal requirements for the 367,046 small entities estimated to be affected by the rule: 55 manufacturers; 1,418 distributors/importers/exporters; 50,032 pharmacies; and 315,541 entities employing or holding registrations as individual practitioners/mid-level practitioners/hospitals/clinics. Ten States 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 discussed in the NPRM. Entities in these States are not economically impacted by this rule.

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 cost of \$245.01 for all entities and an additional \$10,000 for secure storage for 50% of distributors, importers, and exporters. As discussed in the EIA prepared in association with the development of this final rule, manufacturers, pharmacies, physician offices/hospitals/clinics/other health care facilities, and 50% of distributors, importers, and exporters are assumed to meet the requirement of the rule without the need to expand secure storage area. The DEA estimates these costs, on an annualized basis, will have significant economic impact (cost greater than 1% of annual revenue) on 0 of 55 (0%) of small manufacturers; 50 of 1,418 (3.5%) of small distributors; 107 of 50,032 (0.2%) small business pharmacies; and 661 of 315,541 (0.2%) of individual practitioners/mid-level practitioners/hospitals/clinics, totaling 818 of 367,046 (0.2%) of all small entities. The percentage of small entities with significant economic impact is not substantial, and therefore, this rule will not result in 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. 1501 *et seq.*), the DEA has determined and certifies pursuant to UMRA 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 million 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 requirement 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.

Congressional Review Act

This rule is not a major rule as defined by section 804 of the Small Business Regulatory Enforcement Fairness Act of 1996 (Congressional Review Act (CRA)). This rule will not result in: an annual effect on the economy of \$100 million or more; a major increase in costs or prices for consumers, individual industries, Federal, State, or local government agencies, or geographic regions; or significant adverse effects on competition, employment, investment, productivity, innovation, or on the ability of United States-based companies to compete with foreign-based companies in domestic and export markets. However, pursuant to the CRA, the DEA has submitted a copy of this final rule to both Houses of Congress and to the Comptroller General.

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 amended as follows:

PART 1308—SCHEDULES OF CONTROLLED SUBSTANCES

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

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

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

§ 1308.14 Schedule IV.

* * * * *

(b) * * *

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

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Dated: June 27, 2014.

Thomas M. Harrigan,
Deputy Administrator.

[FR Doc. 2014-15548 Filed 7-1-14; 8:45 am]

BILLING CODE 4410-09-P

DEPARTMENT OF THE TREASURY

Internal Revenue Service

26 CFR Part 1

[TD 9674]

RIN 1545-BM07

Guidelines for the Streamlined Process of Applying for Recognition of Section 501(c)(3) Status

AGENCY: Internal Revenue Service (IRS), Treasury.

ACTION: Final and temporary regulations.

SUMMARY: This document contains final and temporary regulations that provide guidance to eligible organizations seeking recognition of tax-exempt status under section 501(c)(3) of the Internal Revenue Code (Code). The final and temporary regulations amend current regulations to allow the Commissioner of Internal Revenue to adopt a streamlined application process that eligible organizations may use to apply for recognition of tax-exempt status under section 501(c)(3). The text of the temporary regulations also serves as the text of the proposed regulations (REG-110948-14) set forth in the notice of proposed rulemaking on this subject in the Proposed Rules section in this issue of the **Federal Register**.

DATES: *Effective date:* These regulations are effective on July 1, 2014.

Applicability date: For dates of applicability, see §§ 1.501(a)-1T(f)(1), 1.501(c)(3)-1T(h)(1), 1.508-1T(c)(1).

FOR FURTHER INFORMATION CONTACT: James R. Martin or Robin Ehrenberg at (202) 317-5800 (not a toll-free number).

SUPPLEMENTARY INFORMATION:

Background

Section 508 requires an organization seeking tax-exempt status under section 501(c)(3), as a condition of its exemption, to notify the Secretary of the Treasury (or his delegate) that it is applying for recognition of exempt status in the manner prescribed in the Treasury Regulations, unless it is specifically excepted from the requirement. Section 1.508-1(a) describes the process for giving notice, and requires that an organization “submit[] a properly completed and

executed Form 1023, exemption application.” Section 1.501(c)(3)-1(b)(1)(v) states that an organization must, to establish its exemption, submit a detailed statement of its proposed activities with and as a part of its application for exemption. Similarly, § 1.501(a)-1(b)(1)(iii) provides that an organization described in section 501(c)(3) shall submit with, and as part of, an application, a detailed statement of its proposed activities. Section 1.501(a)-1(b)(2) states that the Commissioner may require any additional information deemed necessary for a proper determination of whether a particular organization is exempt, and when deemed advisable in the interest of an efficient administration of the internal revenue laws, the Commissioner may, in the cases of particular types of organizations, prescribe the form in which the proof of exemption shall be furnished.

Detailed procedures for applying for recognition of exemption are set out in Rev. Proc. 2014-9, 2014-2 IRB 281, and in the instructions to Form 1023, “Application for Recognition of Exemption Under Section 501(c)(3) of the Internal Revenue Code.” See § 601.601(d)(2)(ii)(b) of this chapter.

Explanation of Provisions

The Treasury Department and the IRS have considered how the process of meeting the notice requirement of section 508 can be made more efficient for certain smaller organizations. The IRS is developing a streamlined form and process for these organizations. Accordingly, this Treasury decision amends §§ 1.501(a)-1, 1.501(c)(3)-1, and 1.508-1 to permit eligible organizations to use a streamlined process, described in guidance published in the Internal Revenue Bulletin, to meet the notice requirements of section 508.

Specifically, this Treasury decision amends §§ 1.501(a)-1 and 1.501(c)(3)-1 to authorize the Treasury Department and the IRS to prescribe, in applicable regulations or other guidance published in the Internal Revenue Bulletin, an exception to the requirement that an organization applying for tax-exempt status provide a detailed statement of its proposed activities. This document also amends the § 1.501(a)-1 provisions relating to the Commissioner’s ability to revoke a determination because of a change in the law or regulations, or for other good cause, to reference the Commissioner’s authority to retroactively revoke a determination under section 7805(b). No substantive change is intended by this amendment.

This Treasury decision also amends the requirement in § 1.501(a)-1(b)(3) that an organization claiming to be exempted from filing annual returns file a statement supporting its claim with and as a part of its application. This amendment would provide flexibility for the Treasury Department and the IRS to prescribe in published guidance other methods of notifying the IRS that the organization is claiming an annual filing exemption.

In addition, this document amends § 1.508-1 to provide that eligible organizations may use Form 1023-EZ, “Streamlined Application for Recognition of Exemption Under Section 501(c)(3) of the Internal Revenue Code,” to notify the Commissioner of their applications for tax-exempt status under section 501(c)(3). This Treasury decision also amends §§ 1.501(a)-1 and 1.508-1 to state that the office to which applications should be submitted will be published in the Internal Revenue Bulletin or instructions to the Form 1023 or Form 1023-EZ.

Finally, this Treasury decision makes certain technical revisions to the regulations. In § 1.501(a)-1, the reference to “internal revenue district” is removed because such reference has been made obsolete by the enactment of the Internal Revenue Service Restructuring and Reform Act of 1998, Public Law 105-206, 112 Stat. 685. References to a district director in §§ 1.501(a)-1, 1.501(c)(3)-1, and 1.508-1 are also modified, as those positions no longer exist within the IRS. Proposed regulations in the Rules and Regulations section of this issue of the **Federal Register** use the text of these temporary regulations as the text of the proposed regulations. Treasury and the IRS seek comments on all aspects of the proposed rules, including whether additional technical revisions are necessary. Simultaneously with the publication of this Treasury decision, the Treasury Department and the IRS will release for publication a Revenue Procedure that provides procedures for applying for recognition of exemption using Form 1023-EZ.

Special Analyses

It has been determined that this Treasury decision is not a significant regulatory action as defined in Executive Order 12866, as supplemented by Executive Order 13563. Therefore, a regulatory assessment is not required. It also has been determined that section 553(b) of the Administrative Procedure Act (5 U.S.C. chapter 5) does not apply to these regulations. For the applicability of the