

comments not submitted electronically or by hand.

FOR FURTHER INFORMATION CONTACT: Gordon Bingham, Foreign Air Carrier Licensing Division, U.S. Department of Transportation, Room 6412, 400 Seventh Street, SW., Washington, DC 20590. Telephone (202) 366-2404.

Issued in Washington, DC on March 15, 2002.

Read C. Van De Water,

Assistant Secretary for Aviation and International Affairs.

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DEPARTMENT OF JUSTICE

Drug Enforcement Administration

21 CFR PART 1308

[DEA-225P]

Schedule of Controlled Substances: Proposed Rule: Rescheduling of Buprenorphine From Schedule V to Schedule III

AGENCY: Drug Enforcement Administration (DEA), Department of Justice.

ACTION: Notice of proposed rulemaking.

SUMMARY: This proposed rule is issued by the Administrator of the Drug Enforcement Administration (DEA) to increase the regulatory controls placed on buprenorphine by rescheduling buprenorphine from a Schedule V narcotic to a Schedule III narcotic. This proposed action is based on a formal rescheduling recommendation by the Department of Health and Human Services (DHHS) and a DEA review indicating that buprenorphine meets the definition of a Schedule III narcotic. If finalized, this action will impose the regulatory controls and criminal sanctions of a Schedule III narcotic on those person who handle buprenorphine or products containing buprenorphine.

DATES: Comments must be received by April 22, 2002.

ADDRESSES: Comments should be submitted to the Administrator, Drug Enforcement Administration, Washington, DC 20537; Attention: DEA Federal Register Representative/CCR.

FOR FURTHER INFORMATION CONTACT: Frank Sapienza, Chief, Drug and Chemical Evaluation Section, Drug Enforcement Administration, Washington, DC 20537, (202) 307-7183.

SUPPLEMENTARY INFORMATION:

What Is Buprenorphine?

Buprenorphine is a derivative of thebaine, a major constituent of opium, presently marketed in the United States as an injectable formulation under the brand name of Buprenex® for the treatment of pain. It is classified as a narcotic agonist-antagonist, or partial agonist, with an analgesic potency far greater than morphine (generally reported to be about 20 to 30 times that of morphine sulfate in humans). DEA placed buprenorphine in Schedule V of the Controlled substances Act (CSA) in 1985 (50 FR 8104).

Buprenorphine has also been investigated for the treatment of narcotic addiction. Two New Drug Applications (NDA) have been submitted to the Food and Drug Administration (FDA) for this indication. Applications for marketing approval for these high-dose sublingual tablet products remain pending at FDA. However, approvable letters have been issued for both products and they are likely to receive final marketing approval in 2002.

Why Is DEA Issuing This Notice?

As part of the NDA review process for the high-dose sublingual tablet formulations for buprenorphine, the FDA reviewed and evaluated the scientific and medical data relating to scheduling under the CSA pursuant to 21 U.S.C. 811(b), (c), and (f). Since the original review conducted by the FDA in the early 1980s (prior to the marketing of Buprenex®), a substantial amount of human experience with buprenorphine products as well as a number of scientific studies have provided new information. These data have prompted a reevaluation of buprenorphine's status under the CSA. The eight factors used to determine the appropriate placement of buprenorphine under the CSA include:

- (1) Its actual or relative potential for abuse;
- (2) Scientific evidence of its pharmacological effects;
- (3) The state of current scientific knowledge regarding the drug;
- (4) Its history and current pattern of abuse;
- (5) The scope, duration, and significance of abuse;
- (6) What, if any, risk there is to the public health;
- (7) Its physic or physiological dependence liability; and
- (8) Whether the substance is an immediate precursor of a substance already controlled under this subchapter.

On December 4, 2001, the Assistant Surgeon General and Acting Principal

Deputy Assistant Secretary for Health, Department of Health and Human Services (DHHS), Arthur J. Lawrence, signed and forwarded a letter to the DEA recommending that buprenorphine be rescheduled as a Schedule III substance. This recommendation was based on FDA's scientific and medical evaluation. After considering the FDA's evaluation and the DHHS scheduling recommendation and reviewing all the available relevant data regarding the eight factors determinative of control (21 U.S.C. 811(b)(c)), the DEA concludes that buprenorphine should be placed in Schedule III of the CSA.

Why Did DEA Conclude That Buprenorphine Should Be Placed in Schedule III of the Controlled Substances Act?

The DEA found that buprenorphine met the definition of a Schedule III substance. In accordance with 21 U.S.C. 812(b):

1. Buprenorphine has a potential for abuse less than the drugs or other substances in Schedule I or II.

Buprenorphine is a long-acting partial agonist with a high affinity for and slow dissociation from opioid receptors.

Buprenorphine produces effects similar to other pure mu agonists (like morphine or hydromorphone) including euphoria, drug liking, respiratory depression, pupillary constriction and sedation. It is recognized as morphine or heroin-like by experienced narcotic abusers.

Little abuse or diversion of buprenorphine has been noted in the U.S. (reflecting very limited prescription, distribution and product formulation: only low-dose injectable buprenorphine has been marketed). However, significant abuse of buprenorphine has been reported in many countries where it has been more available and other formulations have been marketed. In those countries, buprenorphine has been abused via the intravenous, sublingual, intranasal and inhalation routes by many abuser populations. Buprenorphine products have been diverted from legitimate channels through theft, doctor shopping and fraudulent prescriptions. Significant amounts of buprenorphine have been trafficked across international borders and law enforcement authorities have seized large amounts of buprenorphine involved in these activities.

The above data suggest that the abuse potential of buprenorphine is high and closely resembles other narcotics in Schedule II. However, buprenorphine effects are less dose-dependent than pure mu agonists and a "ceiling effect"

has been demonstrated for many of the actions of buprenorphine. This attenuation in effects at high doses may have a blunting effect on the continued escalation in dose to obtain greater reinforcing effects. Although buprenorphine is capable of producing significant respiratory depression and numerous deaths have been associated with injection and abuse of high-dose sublingual tablets in combination with other psychoactive drugs in France, buprenorphine is a safer drug in overdose than other schedule II narcotics. Therefore, buprenorphine appears to have somewhat less abuse potential than Schedule I or II narcotic substances but more abuse potential than partial agonists in Schedule IV. Schedule IV partial agonists are less potent, less likely to produce pure mu agonists effects over a wide range of doses and are generally not recognized as heroin-like by experienced opioid abusers.

2. Buprenorphine has a currently accepted medical use in treatment in the United States.

Buprenex[®], a low-dose (0.3 mg/ml) buprenorphine product, is approved for use as a parenteral narcotic analgesic for pain management. Subutex[®] and Subozone[®], high-dose (2 and 8 mg) sublingual tablets for the treatment of narcotic addiction, have not, as yet, received final marketing approval in the U.S. If/When final approval is granted, they will have current accepted medical use in the United States.

3. Abuse of buprenorphine may lead to moderate or low physical dependence or high psychological dependence.

Data from a number of studies indicate that chronic use of buprenorphine is associated with a withdrawal syndrome that is of less intensity and, often, of longer duration than other opioids in Schedule I or II. The withdrawal effects have been characterized as mild to moderate. In addition, about 20 percent of babies born to mothers in treatment with buprenorphine substitution for opioid dependence have exhibited an abstinence syndrome severe enough to require treatment. Drug craving after discontinuation of buprenorphine use has been reported. Buprenorphine-dependent patients can easily return to heroin use and vice versa. These data suggest that buprenorphine produces low to moderate physical dependence and high psychological dependence.

It is likely that the approval and marketing of high-dose buprenorphine sublingual tablets (and any other buprenorphine products that may be marketed in the future) will increase the availability of buprenorphine in the

United States. The Schedule V controls presently in effect for buprenorphine are insufficient to prevent the diversion and abuse of buprenorphine that is likely to occur with its increased availability. Both foreign data on buprenorphine and the U.S. experience with other drugs like buprenorphine have been viewed by both the DHHS and the DEA as significant and relevant to the control of buprenorphine under the CSA.

According to the United Nations International Narcotics Control Board (UN/INCB), worldwide usage and availability of buprenorphine has increased substantially in recent years. Buprenorphine production has grown from 35 kg in 1980 to 460 kg in 1998. In France, imports increased from 5 kg in 1994 to 159 kg in 1998. The increased availability of buprenorphine in France coincides with the marketing of high-dose sublingual tablets and has been accompanied by increased diversion and abuse and over 100 buprenorphine-related deaths.

In the United States, expansion in the use of mixed agonists-antagonists or partial agonists has been accompanied by significant increases in their diversion, abuse and public health risks. For example, both pentazocine (Talwin[®]) and butorphanol (Stadol[®]) were initially marketed as injectable solutions for analgesia. The use of these products were limited and very few abuse-related problems were identified. However, when pentazocine became available in a table formulation and a butorphanol nasal spray was introduced, these fewer formulations greatly increased the availability of these substances. Significant abuse and diversion of these products resulted in their control under the CSA.

What Is the Effect of This Notice?

This proposed rule, if finalized, would specifically list buprenorphine as a Schedule III narcotic. All products containing buprenorphine or salts or buprenorphine would be subject to Schedule III narcotic regulatory requirements. The Schedule III placement will not prevent any future buprenorphine products approved by the FDA for the treatment of narcotic addiction from being used in office based treatment of narcotic addiction in accordance with the Drug Addiction Treatment Act of 2000 (Pub. L. 106-310). This Act amended the CSA to allow qualified physicians, under certification by the DHHS, to prescribe Schedule III-V narcotic drugs (FDA-approved for the indication of narcotic addiction treatment) to narcotic addicts outside the context of clinic-based narcotic treatment programs. The DEA

recognizes the need to expand narcotic treatment and this factor was a consideration in proposing Schedule III placement for buprenorphine. However, buprenorphine's abuse potential and psychological dependence profile may result in significant abuse and diversion of the sublingual tablets once they are available for use in the U.S. Should this occur, the DEA will initiate action to further increase the regulatory controls on buprenorphine.

This notice also provides an opportunity for interested persons to comment, in writing, with regard to any information they feel may have a bearing on this matter. Requests for a hearing should state, with particularity, the issues concerning which the person desires to be heard. All correspondence regarding this matter should be submitted to the Administrator, Drug Enforcement Administration, Washington, DC 20537. In the event that comments, objections, or requests for a hearing raise one or more questions that the Administrator finds warrants a hearing, the Administrator shall publish a hearing notice in the **Federal Register** summarizing the issues to be heard and setting the time for the hearing.

What Regulatory Requirements Will Be Applied to Handlers of Buprenorphine?

Persons currently involved with the manufacture or handling of this substance are not expected to comply with DEA regulations applicable to a schedule III narcotic substance until such time as a final rule is published in the **Federal Register**. If/When a final rule is published in the **Federal Register**, persons who are currently engaged in manufacturing, distributing, dispensing, importing, exporting, storing or conducting research with buprenorphine will be provided with delayed dates for compliance with Federal regulation in order to avoid imposing any special hardship.

Regulatory Certifications

Regulatory Flexibility Act

The Administrator hereby certifies that this rulemaking has been drafted in a manner consistent with the principles of the Regulatory Flexibility Act (5 U.S.C. 605(b)). It will not have a significant economic impact on a substantial number of small business entities. Buprenorphine is already controlled under the CSA. Individuals who are currently engaged in activities with buprenorphine are already registered to handle controlled substances and are subject to the regulatory requirements of the CSA.

Executive Order 12866

In accordance with the provisions of the CSA (21 U.S.C. 811(a)), this action is a formal rulemaking "on the record after opportunity for a hearing." Such proceedings are conducted pursuant to the provisions of 5 U.S.C. 556 and 557. The Administrator certifies that this proposed rulemaking has been drafted in accordance with the principles in Executive Order 12866, Section 1(b). DEA has determined that this is not a significant rulemaking action. Therefore, this action has not been reviewed by the Office of Management and Budget. Buprenorphine is already controlled under the CSA. Individuals who are currently engaged in activities with buprenorphine are already registered to handle controlled substances and are subject to the regulatory requirements of the CSA.

Executive Order 12988

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

Executive Order 13132

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

Unfunded Mandates Reform Act of 1995

This proposed rule will not result in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of \$100,000,000 or more in any one year, and will not significantly or uniquely affect small governments. Therefore, no actions were deemed necessary under the provisions of the Unfunded Mandates Reform Act of 1995.

Small Business Regulatory Enforcement Fairness Act of 1996

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

based companies in domestic and export markets.

List of Subjects in 21 CFR Part 1308

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

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

PART 1308—[AMENDED]

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

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

2. Section 1308.13 is proposed to be amended by revising paragraph (e) to read as follows:

§ 1308.13 Schedule III.

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(e) Narcotic drugs. Unless specifically excepted or unless listed in another schedule:

(1) Any material, compound, mixture, or preparation containing any of the following narcotic drugs, or their salts calculated as the free anhydrous base or alkaloid, in limited quantities as set forth below:

(i) Not more than 1.8 grams of codeine per 100 milliliters or not more than 90 milligrams per dosage unit, with an equal or greater quantity of an isoquinoline alkaloid of opium 9803

(ii) Not more than 1.8 grams of codeine per 100 milliliters or not more than 90 milligrams per dosage unit, with one or more active, nonnarcotic ingredients in recognized therapeutic amounts 9804

(iii) Not more than 300 milligrams of dihydrocodeinone (hydrocodone) per 100 milliliters or not more than 15 milligrams per dosage unit, with a fourfold or greater quantity of an isoquinoline alkaloid of opium 9805

(iv) Not more than 300 milligrams of dihydrocodeinone (hydrocodone) per 100 milliliters or not more than 15 milligrams per dosage unit, with one or more active nonnarcotic ingredients in recognized therapeutic amounts 9806

(v) Not more than 1.8 grams of dihydrocodeine per 100 milliliters or not more than 90 milligrams per dosage unit, with one or more active nonnarcotic ingredients in recognized therapeutic amounts 9807

(vi) Not more than 300 milligrams of ethylmorphine per 100 milliliters or not more than 15 milligrams per dosage unit, with one or more active, nonnarcotic ingredients in recognized therapeutic amounts 9808

(vii) Not more than 500 milligrams of opium per 100 milliliters or per 100 grams or not more than 25 milligrams per dosage unit, with one or more active, nonnarcotic ingredients in recognized therapeutic amounts 9809

(viii) Not more than 50 milligrams of morphine per 100 milliliters or per 100 grams, with one or more active, nonnarcotic ingredients in recognized therapeutic amounts 9810

(2) Any material, compound, mixture, or preparation containing any of the following narcotic drugs or their salts, as set forth below:

(i) Buprenorphine 9064
(ii) [Reserved.]

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3. Section 1308.15 (b) introductory text is proposed to be revised and paragraph (b) (1) is proposed to be removed and reserved to read as follows:

§ 1308.15 Schedule V.

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(b) Narcotic drugs. Unless specifically excepted or unless listed in another schedule, any material, compound, mixture, or preparation containing any of the following narcotic drugs and their salts, as set forth below:

(1) [Reserved]

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Dated: March 11, 2002.

Asa Hutchinson,
Administrator.

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