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2003 HOUSE JUDICIARY

HB 1146

2003 HOUSE STANDING COMMITTEE MINUTES

BILL/RESOLUTION NO. HB 1146

House Judiciary Committee

☐ Conference Committee

Hearing Date 1-21-03

Tape Number	Side A	Side B	Meter #
1		xx	10-18

Committee Clerk Signature D Penrose

Minutes: 12 members present, 1 members absent (Rep. Bernstein)

Chairman DeKrey: We will open the hearing on HB 1146.

Howard Anderson, Jr., Exec. Dir. of ND State Board of Pharmacy: (see attached testimony)

Support.

Chairman DeKrey: How many drugs did we do last session.

Mr. Anderson: We had three or four last time.

Rep. Grande: The purpose of the second drug, what does it do?

Mr. Anderson: It is usually used for migraine headaches. The products that are marketed, are most often used for migraines.

Chairman DeKrey: Thank you, any further testimony in support? Any testimony in opposition? We will close the hearing. What are the committee's wishes.

Rep. Maragos: I recommend a Do Pass on HB 1146.

Rep. Wrangham: Seconded.

Chairman DeKrey: Any discussion.

12 YES 0 NO 1 ABSENT DO PASS CARRIER: Rep. Wrangham

Date: 1/21/03
Roll Call Vote #: 1

2003 HOUSE STANDING COMMITTEE ROLL CALL VOTES
BILL/RESOLUTION NO. 1146

House Judiciary Committee

☐ Check here for Conference Committee

Legislative Council Amendment Number _____

Action Taken Do Pass

Motion Made By Rep. Maragos Seconded By Rep. Wrangham

Representatives	Yes	No	Representatives	Yes	No
Chairman DeKrey	✓		Rep. Delmore	✓	
Vice Chairman Maragos	✓		Rep. Eckre	✓	
Rep. Bernstein	AB		Rep. Onstad	✓	
Rep. Boehning	✓				
Rep. Galvin	✓				
Rep. Grande	✓				
Rep. Kingsbury	✓				
Rep. Klemin	✓				
Rep. Kretschmar	✓				
Rep. Wrangham	✓				

Total (Yes) 12 No 0

Absent 1

Floor Assignment Rep. Wrangham

If the vote is on an amendment, briefly indicate intent:

REPORT OF STANDING COMMITTEE (410)
January 22, 2003 7:31 a.m.

Module No: HR-12-0879
Carrier: Wrangham
Insert LC: . Title: .

REPORT OF STANDING COMMITTEE

HB 1146: Judiciary Committee (Rep. DeKrey, Chairman) recommends **DO PASS** (12 YEAS, 0 NAYS, 1 ABSENT AND NOT VOTING). HB 1146 was placed on the Eleventh order on the calendar.

(2) DESK, (3) COMM

HR-12-0879

2003 SENATE JUDICIARY

HB 1146

2003 SENATE STANDING COMMITTEE MINUTES

BILL/RESOLUTION NO. HB 1146

Senate Judiciary Committee

☐ Conference Committee

Hearing Date 03/12/03

Tape Number	Side A	Side B	Meter #
2	X		0.0 - 10.1

Committee Clerk Signature Maria L. Solberg

Minutes: **Senator John T. Traynor, Chairman**, called the meeting to order. Roll call was taken and all committee members present. Sen. Traynor requested meeting starts with testimony on the bill:

Testimony in Support of HB 1146

Howard C. Anderson - Executive Director, Board of Pharmacy State of ND (meter .02) Read Testimony - Attachment #1. Pharmacists treat all or our drugs the same due to compliance with the Federal Law. When law enforcement look at a particular drug and tries to site someone then it needs to be listed under ND's controlled substance act.

Buphrenorphine - This drug has been scheduled before but now has gotten an increases usage of office treatment of narcotic addiction. Physicians in there office practice can use drug to detoxify patients that are addicted to narcotics. We have not previously had this ability. We used to only have Methadone Clinics (Mpls.)

Dichloralphenazone - Placed in schedule four. This drug has been available for a long time but increasing problems with abuse. Chlorohydrate, when the ol' cowboys used to slip the other guy the "Mickey Fin", this is what they used to put in there drink. Dichlorolphenazone has 2 molecules of chlorohydrate in it. Some companies marketed it as a controlled substance and some did not. The Federal government decided to clear any issues with this and place it in schedule four. Included is the Federal Register-Attachment #2

Sen. Traynor asked what the definition of the **Schedule** was. Schedule is 1-5 Five most Addictive:

1. No Approval Medical use in U.S. - Research Only
2. For Approved Drugs Highest Potential for Abuse/Addictive Quality i.e. Oxycoton, Hydramorophone, Ritalyn
3. Less Potential for Abuse-Usually in Combination with Over the Counter Combined with i.e., Tylenol III with codeine, Codeine alone Schedule 2
4. Tranquilizers, Velum, Have potential for abuse, some serious side effects, but not as likely to cause addition as in the higher schedules.
5. Less then 1/8 gram - Codeine Cough Syrup - Low potential for abuse.

Sen. Nelson discussed *buprenorphine* purpose (meter 5.0) For detoxification to Heron.

Dicloralphenazone is used in some Migraine headache medicines and combination headache medicines.

Testimony in Opposition of HB 1146

None

Testimony Neutral to HB 1146

None

Motion Made to DO PASS HB 1146 Sen. Trenbeath and seconded by Senator Dennis Bercier

Roll Call Vote: 6 Yes. 0 No. 0 Absent

Motion Passed

Floor Assignment: Senator Carolyn Nelson

Senator John T. Traynor, Chairman closed the hearing

Date: March 12, 2003
Roll Call Vote #: 1

2003 SENATE STANDING COMMITTEE ROLL CALL VOTES
BILL/RESOLUTION NO. HB 1146

Senate **JUDICIARY** Committee

☐ Check here for Conference Committee

Legislative Council Amendment Number

Action Taken DO PASS

Motion Made By Sen. Trenbeath Seconded By Sen. Bercier

Senators	Yes	No	Senators	Yes	No
Sen. John T. Traynor - Chairman	X		Sen. Dennis Bercier	X	
Sen. Stanley. Lyson - Vice Chair	X		Sen. Carolyn Nelson	X	
Sen. Dick Dever	X				
Sen. Thomas L. Trenbeath	X				

Total (Yes) SIX (6) No ZERO (0)

Absent ZERO (0)

Floor Assignment Sen. Nelson

If the vote is on an amendment, briefly indicate intent:

REPORT OF STANDING COMMITTEE (410)
March 12, 2003 1:11 p.m.

Module No: SR-44-4558
Carrier: Nelson
Insert LC: . Title: .

REPORT OF STANDING COMMITTEE

HB 1146: Judiciary Committee (Sen. Traynor, Chairman) recommends DO PASS (6 YEAS, 0 NAYS, 0 ABSENT AND NOT VOTING). HB 1146 was placed on the Fourteenth order on the calendar.

(2) DESK, (3) COMM

SR-44-4558

2003 TESTIMONY

HB 1146

BOARD OF PHARMACY
State of North Dakota

John Hoeven, Governor

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Fargo, Senior Member
Gary W. Dewhirst, R.Ph.
Hettinger
Dewey Schlittenhard, MBA, R.Ph.
Bismarck
Rick L. Detwiler, R.Ph.
Bismarck
William J. Grosz, Sc.D., R.Ph.
Wahpeton, Treasurer

House Bill 1146
Judiciary Committee
Tuesday January 21, 2003 – 2:00 PM – Prairie Room

Chairman Dekrey, members of the Judiciary Committee, for the record I am Howard C. Anderson Jr. R.Ph., Executive Director of the North Dakota State Board of Pharmacy

Thank you for the opportunity to appear before you today. This bill was introduced at the request of the State Board of Pharmacy and contains two drugs which have been rescheduled by the FDA and the DEA. We are now including these in the North Dakota statute to place them in the same schedule in which they have been placed federally.

Page 1 Line 24 places buprenorphine in schedule III of the Controlled Substances Act. I have attached the Federal Register which explains the federal scheduling.

Page 3 Line 12 Places dichloralphenazone in schedule IV of the Controlled Substances Act. I have again attached the Federal Register indicating the federal scheduling.

Thank you,

Howard C. Anderson, Jr, R.Ph.
Executive Director

transactions and whether they are exempt or excluded from being required be traded on one of the foregoing entities, foreign trading terminals, hedging exemptions, and the reporting of market positions shall be filed with the Director, Division of Market Oversight, Commodity Futures Trading Commission, Three Lafayette Centre, 1155 21st Street, NW., Washington, DC 20581. A request for a Letter relating to all other provisions of the Act or Commission rules shall be filed with the Director, Division of Clearing and Intermediary Oversight Commodity Futures Trading Commission, Three Lafayette Centre, 1155 21st Street, NW., Washington, DC 20581. A request for a Letter relating to all other provisions of the Act or Commission rules shall be filed with the Director, Division of Clearing and Intermediary Oversight, Commodity Futures Trading Commission, Three Lafayette Centre, 1155 21st Street, NW., Washington, DC 20581. The request must be submitted electronically using the e-mail address *dmoletters@cftc.gov* (for request filed with the Division of Market Oversight), or *dcioletters@cftc.gov* (for requests filed with the Division of Clearing and Intermediary Oversight), as appropriate, and a properly signed paper copy of the request must be provided to the Division of Market Oversight or the Division of Clearing and Intermediary Oversight, as appropriate, within ten days for purposes of verification of the electronic submission.

* * * * *

§ 140.100 [Removed]

6. Section 140.100 is removed.

Issued in Washington, DC, this 26th day of September, 2002, by the Commission.

Jean A. Webb,

Secretary of the Commission.

[FR Doc. 02–25049 Filed 10–4–02; 8:45 am]

BILLING CODE 6351–01–M

DEPARTMENT OF JUSTICE

Drug Enforcement Administration

21 CFR part 1308

[DEA–225F]

Schedules of Controlled Substances: Rescheduling of Buprenorphine From Schedule V to Schedule III

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

ACTION: Final rule.

SUMMARY: This final rule is issued by the Deputy Administrator of the Drug Enforcement Administration (DEA) to reschedule buprenorphine from a Schedule V narcotic to a Schedule III narcotic under the Controlled Substances Act (CSA). This action is based on a rescheduling recommendation by the Department of Health and Human Services (DHHS) and a DEA review indicating that buprenorphine meets the criteria of a Schedule III narcotic. The DEA published a proposed rule to reschedule buprenorphine on March 21, 2002 (67 FR 13114). The comment period was extended for an additional 30 days until May 22, 2002 (67 FR 20072). The DEA received ten comments but no requests for hearings.

This final action will impose the regulatory controls and criminal sanctions of a Schedule III narcotic on those persons who handle buprenorphine or products containing buprenorphine.

DATES: Effective Date: October 7, 2002. Compliance to some regulatory requirements may be delayed as noted in the Regulatory Requirements section of this document.

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

SUPPLEMENTARY INFORMATION:

Background

Buprenorphine is a semisynthetic opioid. As a derivative of thebaine, buprenorphine was controlled in Schedule II of the CSA in 1970 and remained in Schedule II during its research and development for marketing. In 1981, buprenorphine hydrochloride (Buprenex®) was approved for marketing in the United States as an injectable formulation (0.3 mg/ml) for the treatment of moderate to severe pain. The DEA proposed placement of buprenorphine in Schedule V of the CSA after receiving a medical and scientific evaluation and a Schedule V recommendation from the DHHS. However, buprenorphine was not placed in Schedule V of the CSA until April 1, 1985 (50 FR 8104, February 26, 1985) due to a hearing requested by the manufacturer of buprenorphine, Reckitt & Coleman (now Reckitt Benckiser). Since 1985, Buprenex® has remained in Schedule V. As an injectable analgesic, this product has had limited use outside hospital and clinic settings and is the only buprenorphine product presently marketed in the United States.

In December 2001, the DHHS forwarded a recommendation to reschedule buprenorphine to Schedule III of the CSA. This recommendation was based on a reevaluation of buprenorphine's abuse potential and dependence profile in light of numerous scientific studies and years of human experience with this drug. The DHHS compared buprenorphine with other drugs that share similar pharmacological properties and/or medical utility and considered both foreign and domestic data especially in regard to formulations of buprenorphine that are likely to become available for use in the United States. Two New Drug Applications (NDA) have been submitted to the Food and Drug Administration (FDA) for high dose sublingual (under the tongue) tablets. These potential addiction treatment products include: (1) Subutex®, a mono or single entity buprenorphine product (2 and 8 mg tablets), and (2) Suboxone®, a combination product in a 4:1 ratio of buprenorphine to naloxone (2: 0.5 and 8: 2 mg tablets). The Subutex® and Suboxone® NDAs remain pending at the FDA but approvable letters have been issued for both products and they are likely to receive final marketing approval in 2002. Low dose sublingual tablets (0.1 , 0.2 and 0.4 mg) have been available in numerous countries throughout the world and, in recent years, high dose sublingual tablets (2 and 8 mg) have been introduced in many countries for the treatment of opioid dependence.

After consideration of the DHHS scientific and medical evaluation and Schedule III recommendation, the DEA completed an independent eight factor analysis that included the following factors in accordance with 21 U.S.C. 811(c):

(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 psychic or physiological dependence liability; and

(8) Whether the substance is an immediate precursor of a substance already controlled under this subchapter.

On March 21, 2002, the DEA published a proposed rule to place buprenorphine in Schedule III of the CSA (67 FR 13114). This notice will

finalize that proposed rule. Schedule III control requires the DEA to make the following findings in accordance with 21 U.S.C. 812 (b):

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

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

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

Comments to the Proposed Rule

The DEA received comments from ten interested parties. Two commenters were in support of the proposed rule, seven commenters were in opposition to the proposed rule and one individual requested that the DEA be mindful of possible conflicts of interest by individuals/organizations responding to this proposed rule. One commenter felt that Schedule II more accurately reflected the abuse potential and dependence profile of buprenorphine while another commenter felt that the evidence suggests that buprenorphine should remain in Schedule V. Five commenters support differential scheduling of buprenorphine products and contend that the buprenorphine/naloxone product under development has less abuse potential. The following is a listing of all commenters and a brief summary of their comments:

1. The Medical Director of the American Psychiatric Association (APA) commented on behalf of this organization. He stated that the APA supports the proposed rule to reschedule this drug. However, once buprenorphine has been approved for use in opioid substitution treatment, the APA recommends that the DEA study and evaluate the actual abuse over a three-year period to more accurately determine whether placement in Schedule III is appropriate.

2. The President of the American Association for the Treatment of Opioid Dependence (AATOD) submitted comments on behalf of the Board of Directors of AATOD in support of a Schedule III narcotic classification for buprenorphine and its products.

3. The Chair Committee for the Treatment of Opioid Dependence of the California Society of Addiction Medicine (CSAM) and the President of CSAM recommended less restrictive scheduling of the buprenorphine/naloxone combination product (Suboxone®) compared to the mono buprenorphine product (Subutex®) should they be approved for marketing. They believe it is important to convey the message to physicians about the lower risk of abuse and diversion of the combined formulation. They believe that differential scheduling would encourage physicians to appropriately choose the combination product for treatment of addicted patients. No data was provided in support of their contentions.

4. A member of the Board of Directors of the American Academy of Addiction Psychiatry (AAAP) commented on behalf of this organization. The AAAP contends that the available literature and research on buprenorphine do not support the DEA recommendation and recommends differential scheduling of buprenorphine products. Because Buprenex® has been in Schedule V and has not been associated with widespread diversion and abuse, they believe there is no compelling reason to reschedule this medication. Further, they believe there are substantial differences between the two sublingual products intended for addiction treatment. They contend that the buprenorphine/naloxone product is being developed specifically to prevent diversion and illicit injection use. They believe that buprenorphine diversion in other countries has been limited to use by out-of-treatment, opioid dependent, injection drug users. Should both products be placed in Schedule III, they believe that there will be no incentive for physicians to differentially make use of one product. They recommend Schedule V for Buprenex® and Suboxone® and Schedule III for Subutex®. No data was submitted to the DEA in support of these comments.

5. The President of the American Society of Addiction Medicine (ASAM) commented on behalf of this organization. His views also represent those of the Chairmen of ASAM's Medication Development Committee and the Opioid Agonist Treatment Committee. They contend that placing all buprenorphine-containing products into the same schedule is not consistent with the pharmacology and the intended clinical use of the buprenorphine/naloxone sublingual tablets. They believe that sufficient evidence currently exists to support a lower parenteral abuse potential of the combination product as compared to the mono product. They feel that differentially scheduling these addiction medications would encourage physicians to prescribe the naloxone combination product in preference to the mono-product. No data was submitted to the DEA in support of these comments.

6. The President of the College on Problems of Drug Dependence (CPDD) commented on behalf of this organization. This commenter requests that the DEA consider differential scheduling for the potential addiction treatment medications, Suboxone® and Subutex®. She believes there is strong evidence to support differential scheduling: the combination product will lead to lower abuse liability and less parenteral abuse by individuals who are currently dependent on opioids because the naloxone will precipitate withdrawal. The mono-product will not precipitate withdrawal. No data was submitted to the DEA in support of these comments.

7. The President of Reckitt Benckiser Pharmaceuticals, the manufacturer of Buprenex® and the sponsor of the two NDAs for buprenorphine products in the treatment of opioid dependence, does not support the proposed rule for the following reasons:

(a) Little diversion or abuse of buprenorphine has been noted in the United States in the 15 years the product has been marketed.

(b) The DEA has disregarded data on the development of the naloxone combination product that shows significantly less potential for diversion and abuse.

(c) The DEA disregards the additional controls imposed on these newer products by the Drug Addiction Treatment Act of 2000 (DATA).

(d) The Schedule III control for all formulations of buprenorphine would thwart company efforts to ensure that the combination product, if approved, is the primary medication that should be utilized for addiction treatment. By not differentially scheduling these products, the DEA is removing the incentive for physicians to prescribe the combination product rather than the single entity product.

The company feels that Buprenex® should be left in Schedule V, and the addiction medications, if approved, should be placed in Schedule IV. Or, as an alternative, the substance, buprenorphine, should be placed in Schedule III (which would include Subutex®), Suboxone® should be placed in Schedule IV and buprenorphine products with less than 1 mg/ml should be placed in Schedule V. No data was provided to the DEA in support of these comments.

8. The law offices of Hogan & Hartson submitted comments on behalf of a client. Hogan & Hartson requests that DEA enter an order immediately placing buprenorphine and all products containing buprenorphine under Schedule II based on their contention that:

(a) Buprenorphine has a high potential for abuse consistent with the

abuse potential of Schedule II drugs. The partial agonist activity, including safety in overdose, is not supported and, even if true, does not warrant a change from the conclusion that buprenorphine has a high potential for abuse.

(b) Safety in overdose is not a relevant factor in deciding if a drug has less abuse potential than other similar drugs.

(c) The DEA failed to consider that the illusion of safety may result in greater potential for abuse.

(d) Scheduling under the CSA is a relative analysis and depends on aligning a drug with the closest set of comparators. Hogan and Hartson believe that the closest set of comparators are Schedule II.

(e) Buprenorphine is a gateway drug which compounds public health risks.

(f) The DEA failed to give adequate weight to the fact that buprenorphine is administered by many routes of administration and in combination with other drugs.

(g) The DEA has not been consistent in its decision making process and has failed to meet the non-arbitrary agency action requirements. The finding that buprenorphine has a potential for abuse less than Schedule I or II substances is arbitrary and capricious and not supported by the underlying administrative record.

(h) The DEA position that buprenorphine most closely resembles Schedule III substances with respect to physical and psychological dependence is contrary to the evidence (even if true, DEA must give greater weight to the abuse potential).

(i) The DEA erred in considering that buprenorphine be available for office-based use as it is not a relevant factor in the scheduling analysis.

(j) Placement of buprenorphine in Schedule III to make it available for office based care will have a significant impact on opioid treatment programs. The DEA is required to analyze this issue and follow the mandate of the Regulatory Flexibility Act.

(k) The CSA requires DEA to make a reasonable predictive judgment about a drug and should not take a reactive posture by stating "should significant abuse or diversion of buprenorphine occur, DEA will initiate actions to increase its regulatory control."

In support of these comments, Hogan & Hartson referred to various legal citations and statements made by DEA and FDA in the scheduling review documents on buprenorphine. No new scientific data was submitted.

9. The law offices of Hyman, Phelps & McNamara, P.C. commented on behalf of Purdue Pharma. After reviewing the information that the FDA and the DEA relied upon in order to reach a decision to propose Schedule III placement for buprenorphine, they contend that:

(a) The DEA has not presented an adequate basis for the proposed rulemaking.

(b) The proposed rule has not adequately described the pharmacology of the drug substance buprenorphine or the drug products that would be affected by this rule.

(c) Many facts cited by the DEA and FDA in their conclusions have been removed from their proper scientific context. This is particularly evident in the description of buprenorphine and in the basis for the DEA conclusion that buprenorphine may cause high psychological dependence.

(d) The DEA and FDA have not explained why data generated since the original scheduling action for buprenorphine in 1985 would alter the original conclusions that buprenorphine has a low potential for abuse and low potential for physical and psychological dependence.

(e) The DEA and FDA have inadequately described the conditions of use of Subutex® in France and the impact of such use on either the mortality associated with heroin addiction or the frequency of abuse of buprenorphine. It is asserted without supporting data that the conditions of use that will apply to Suboxone® and Subutex®, should they be approved for use in the United States, will inevitably lead to significant abuse of buprenorphine. There is no discussion of how the proposed use of Subutex® in the United States may differ from the use of this product in France. There is not an acknowledgment in the proposed rule that one of the products under development, which is not available in France, contains naloxone which is expected to deter intravenous abuse.

(f) The additional controls that would be provided by moving buprenorphine to Schedule III are not described and no rationale is provided for the assertion that the Drug Addiction Treatment Act will not provide adequate safeguards for the public health.

(g) The overwhelming scientific and medical evidence demonstrates that buprenorphine should not be rescheduled. If buprenorphine is rescheduled it should not be placed any higher than Schedule IV.

Hyman, Phelps & McNamara relied on data from the World Health Organization (WHO), United Nations (UN), International Narcotics Control Board (INCB) statistics, emergency department mentions in the Drug Abuse Warning Network (DAWN), DEA forensic laboratory data, literature cited in FDA and DEA review documents on buprenorphine and case law.

1. The Director of the Edmond de Rothschild Foundation, Chemical Dependency Institute of Beth Israel Medical Center in New York City, urged the DEA to assess possible conflict of interest of individuals/organizations submitting comments on the proposed rule to place buprenorphine in Schedule III of the CSA.

DEA Response to Comments

The DEA has thoroughly reviewed, analyzed and considered all the comments submitted in response to the proposed rule to place buprenorphine into Schedule III of the CSA. Most commenters averred that the DEA failed to consider data that demonstrates that buprenorphine has a lower (or higher) abuse potential/dependence profile than Schedule III substances. In most instances, no data was provided to support these contentions. Two commenters, however, provided data that they relied upon in opposing the proposed rule. The relevant data cited by these commenters were available to and considered by DHHS and DEA in deliberations regarding the proposal to reschedule buprenorphine. In several cases, the same medical, scientific and other data cited by FDA and/or DEA in scheduling review documents are interpreted differently by the commenters.

Fundamental to all of the comments in opposition to the proposed rule is the belief that buprenorphine and/or products containing buprenorphine have an abuse potential and dependence profile other than Schedule III. The following is a brief summary of the data used by the DEA to conclude that the most appropriate placement for buprenorphine and products containing buprenorphine is in Schedule III of the CSA classified as a narcotic. Following this summary (under the headings of Abuse Potential of Buprenorphine and Dependence Profile of Buprenorphine), specific questions or comments raised by the commenters are addressed.

Abuse Potential of Buprenorphine

The evaluation of the abuse potential of any substance considers a number of factors including (but not limited to) its chemistry (including ease of synthesis and evidence of clandestine production), pharmacology (including routes of administration, profile of effects under various conditions and populations, duration of action, drug interactions), intended use, populations at-risk of abuse and actual abuse data.

The subjective effects (alterations in mood, feeling and thinking) produced by a drug may lead to reinforcement of drug-taking behavior and abuse (Jasinski, 1991). The abuse potential criteria under the CSA is a relative one with Schedule I and II requiring substances to have a high abuse potential and Schedule III, IV and V substances having progressively lower abuse potentials. This necessitates the comparison of the abuse potential of the substance under review with other substances. Morphine, a Schedule II substance with high abuse potential, is often used as a standard for comparing the effects produced by other opiates; the more an opiate/opioid is morphine-like as perceived by the user, the more likely the substance, if available, will be abused.

Buprenorphine is a semi-synthetic opioid derived from thebaine. It has high affinity for, low intrinsic activity at, and slow dissociation from opioid receptors (for review see Johnson & McCagh, 2000). These properties contribute to its protracted occupancy at opioid receptors.

Buprenorphine is a partial agonist (activator) at the mu-opioid receptor and an antagonist (blocker) at the kappa-opioid receptor (Richards and Sadee, 1985; Sadee *et al.*, 1982). Mu receptor activation is associated with analgesia, miosis (pupillary constriction), respiratory depression, euphoria, reduced gastrointestinal motility and dependence. Kappa receptor activation produces analgesia, miosis, sedation, dysphoria and psychotomimetic effects including disorientation and/or depersonalization. As a partial agonist at the mu receptor, buprenorphine produces effects similar to pure mu agonists (like morphine) but effects are less dose-dependent producing a "ceiling effect" on both physiological and psychological properties: dose increases above the "ceiling dose" do not produce greater effects (Pickworth *et al.*, 1993; Walsh *et al.*, 1994, 1995). Various effects produced by buprenorphine have different ceiling doses. At clinically relevant doses, the "ceiling" for some effects produced by buprenorphine administration may not be reached. As a consequence, buprenorphine may act more like a pure mu agonist (depending on dose, effect being measured and individual variability) and may produce significant dose-related euphoria, drug liking, respiratory depression and sedation over a wide range of doses (*see* citations below). However, buprenorphine's unique pharmacology results in greater safety (less respiratory depression at very high doses), less physical dependence and greater flexibility in dose scheduling than pure mu agonists such as morphine (Johnson & McCagh, 2000).

Although poorly available by the oral route due to poor absorption and extensive metabolism in the small intestine and liver, buprenorphine can be taken sublingually (Walter *et al.*, 1996). As a drug of abuse, tablets have been crushed and snorted, smoked and placed in aqueous solutions and injected (for example: Strang, 1985, 1991; Gruer *et al.*, 1993; Kintz, 2001). The absolute bioavailability of sublingual tablets is approximately 30 percent when the extent of absorption of a sublingual solution is compared to an intravenous dose (Mendelson *et al.*, 1997a). Dissolving buprenorphine in aqueous alcohol enhances sublingual absorption: the bioavailability of the tablet is about 50 percent that of a sublingual aqueous alcohol solution containing equivalent amounts of buprenorphine (Nath *et al.*, 1999; Schuh *et al.*, 1999a). This difference in the bioavailability of sublingual aqueous alcohol solutions and sublingual tablets of buprenorphine may account for some of the variability in data involving dose effects. Data generated using animal models suggest that buprenorphine may have relatively high bioavailability in humans by the intranasal route (Brewster *et al.*, 1981; Lindhardt *et al.*, 2000).

The more ways a drug can be administered by various populations of abusers increases its likelihood to be abused. Individuals that only abuse pharmaceuticals by swallowing tablets or liquids (like most abusers of hydrocodone products) would be less likely to abuse buprenorphine. At the same time, the lack of oral bioavailability increases the likelihood that buprenorphine will be abused in a manner that enhances its reinforcing effects. Abuse data indicates that buprenorphine is often injected. While heroin addicts and experienced narcotic abusers have been the primary abusers of buprenorphine, data from England, France, Scotland, and Ireland demonstrate that, if available, buprenorphine is abused by young, non-dependent drug abusers (Coggans *et al.*, 1991; Forsyth *et al.*, 1993; Frischer, 1992; Hammersley *et al.*, 1990; O'Connor *et al.*, 1988).

The DEA has no evidence that buprenorphine is clandestinely produced; diverted pharmaceutical products are the only source of this drug for those who would choose to abuse it. Like all substances with abuse potential, the greater the availability of buprenorphine (greater use due to new dosage forms and new indications) the more likely it will be abused. High-dose, sublingual tablets intended for narcotic treatment and utilized outside the constraints of traditional narcotic treatment programs increases the risk that these products will be diverted, trafficked and abused. Simply stated, providing an abusable substance to known drug abusers imparts enhanced risks. While little diversion and abuse of the injectable formulation, Buprenex®, has occurred in the United States, the circumscribed use (few prescriptions and primary use in hospital settings) has limited the availability of this substance for abuse purposes. Recent increases in the use of Buprenex® may be related to the use of this product for narcotic treatment and detoxification: IMS National Disease and Therapeutic Index data and DEA field office reports indicate that many doctors are illegally using Buprenex® for narcotic treatment and detoxification. The Drug Addiction Treatment Act of 2000 (DATA) does not apply to Buprenex® as it has not been approved by the FDA for use in narcotic treatment.

Drug discrimination studies are among the most rigorous laboratory procedures for assessing the substitutability of psychoactive drugs and provide valuable information about the subjective effects produced by a drug (Schuster & Johanson, 1988). In drug discrimination studies, buprenorphine generally substitutes for mu agonists across several animal species including humans (for example: Leander, 1983; France *et al.*, 1984; Young *et al*, 1984; France & Woods, 1985; Hoffmeister, 1988; Picker & Dykstra, 1989; Negus *et al.*, 1990; Preston *et al.*, 1989, 1992; Bigelow and Preston, 1992; Paronis & Holtzman, 1994; Walker *et al.*, 1994). These studies suggest that buprenorphine shares more similar effects with pure mu agonists than with prototypic partial agonists (like butorphanol and pentazocine that are in Schedule IV of the CSA). For example, Preston & Bigelow (2000) conducted a drug discrimination study in adult males with histories of opioid abuse (but not physically dependent at time of study) trained to discriminate hydromorphone (a Schedule II pure mu agonist) from placebo (saline). Of the partial agonists tested (buprenorphine, butorphanol, pentazocine and nalbuphine) only buprenorphine fully substituted for hydromorphone and produced dose-related increases in hydromorphone-appropriate responses. Pentazocine showed an inverted U-shaped dose-response curve while butorphanol and nalbuhine did not

substitute for hydromorphone at any dose tested.

The subjective effects of buprenorphine, with or without naloxone, have been studied under a wide range of conditions including study subjects, dose ranges, routes of administration and timing intervals. In addition, opiate or naloxone challenge in buprenorphine maintained clients vary significantly with study conditions. Despite the methodological differences in these studies, certain conclusions can be made regarding the abuse potential of buprenorphine (with or without naloxone) in different populations of users. The following represents a sampling of those studies.

Studies conducted in non-drug abusers (for example: Manner *et al.*, 1987; Saarialho-Kere *et al.*, 1987; MacDonald *et al.*, 1989; Fullerton *et al.*, 1991; Zacny *et al.*, 1997) indicate that buprenorphine, like morphine, produces dose related impairment of psychomotor performance, euphoria, miosis, respiratory depression, somnolence and nausea. In studies with non-dependent, opioid-experienced subjects, the most consistent finding with buprenorphine administration (sublingual, intravenous, intramuscular, subcutaneous) is a dose-related increase in "drug liking" and "good drug effects" over a wide range of doses (for example: Jasinski *et al.*, 1978; Preston *et al.*, 1992; Weinhold *et al.*, 1992; Pickworth *et al.*, 1993; Preston and Bigelow, 1994; Foltin and Fischman, 1996; Greenwald *et al.*, 1999; Strain *et al.*, 2000; Comer *et al.*, 2002). In opioid dependent subjects, buprenorphine can substitute for heroin. Clinical data indicate that when equipotent doses of buprenorphine and methadone are used, buprenorphine is as effective as methadone in suppressing opioid withdrawal (Bickel *et al.*, 1988; Johnson *et al.*, 1992). Jasinski *et al.* (1978) reported that chronic subcutaneous administration of a daily dose of 8 mg of buprenorphine produced morphine-like subjective effects and euphoria equivalent to 30 mg of morphine sulfate administered four times daily. In a sample of experienced detoxified opiate abusers, Bedi *et al* (1998) examined the abuse liability of 0.5 mg of buprenorphine, 16 mg morphine and 30 mg pentazocine. Buprenorphine produced significant euphoria and was identified as heroin rather than pentazocine. In a study with opiate-dependent heroin abusers, intravenous administration of 2 mg of buprenorphine produced potent opiate agonist effects (Mendelson *et al.*, 1996). Seven of eight subjects estimated that this dose of buprenorphine had a street value between $5 and $20 but of lesser value than heroin. In subjects maintained on daily sublingual buprenorphine (8 mg), intramuscular injections of buprenorphine (4, 8, 16 mg) produced opioid agonist-like effects (Strain *et al.*, 1997). Collectively, these data suggest that buprenorphine has abuse potential in a wide spectrum of individuals. Vulnerable populations include drug naive individuals (new drug abusers), opiate experienced individuals and opiate dependent individuals.

Many of the comments to the proposed rule for buprenorphine rescheduling expressed concern about placing the buprenorphine/naloxone combination product in the same schedule as single entity products. They contend that the combination product has significantly less abuse potential warranting lesser control. However, the data regarding naloxone and buprenorphine/naloxone administration in various populations of users does not support a lower schedule.

Naloxone is an opioid antagonist that acts competitively at opioid receptors. It is used to reverse opioid central depression, including respiratory depression (the leading cause of death in narcotic overdoses), and has been given intravenously to precipitate withdrawal symptoms in the diagnosis of opioid dependence. It is generally injected and has a short duration of action. Taken sublingually, naloxone has little bioavailability.

The buprenorphine/naloxone combination product was specifically developed to inhibit intravenous abuse by heroin addicts. In theory, the injection of buprenorphine/naloxone combination in opioid-dependent subjects should precipitate a moderate to severe withdrawal syndrome similar to abrupt withdrawal from opioids. This withdrawal syndrome develops within minutes of injection and subsides in one to two hours. However, a substantial percentage of individuals currently abusing heroin or other opiates do not show any evidence of withdrawal when challenged with naloxone. Between 34 and 61 percent of patients applying for methadone maintenance may have minimal or no response to intravenous or intramuscular naloxone in doses ranging from 0.2–1.2 mg (Blaschly, 1973; Judson *et al.*, 1980; Kanof *et al.*, 1991; Peachy and Lei, 1988; Zilm and Sellers, 1978). While addicts that seek treatment may have very high levels of psychological dependence, this data suggest that they may not have high levels of physical dependence on narcotics.

The extent of withdrawal associated with injection of buprenorphine/naloxone combination, should it occur, is directly related to the buprenorphine/naloxone dose and the level of dependence of the subjects. For example, individuals maintained on 30–60 mg of methadone (Strain *et al.*, 1995; Mendelson *et al.*, 1997) or 60–120 mg intramuscular morphine (Mendelson *et al.*, 1996; Fudala *et al.*, 1998; Schuh *et al.*, 1998), opiate doses likely to produce significant physical dependence, experience an unpleasant opioid withdrawal syndrome after injection of low doses of naloxone or buprenorphine/naloxone. Mendelson *et al.* (1999) studied the effects of three intravenous buprenorphine and naloxone combinations on agonist effects and withdrawal signs in 12 opiate-dependent subjects. Following stabilization on a daily dose of 60 mg morphine intramuscularly, subjects were challenged with buprenorphine alone (2 mg intravenously) or in combination with naloxone in ratios of 2:1, 4:1, and 8:1 (1, 0.5, and 0.25 mg of naloxone). Buprenorphine alone did not precipitate withdrawal and produced effects similar to morphine. Dose-dependent increases in withdrawal signs and symptoms and a decrease in opioid agonist effects occurred after all naloxone combinations. At the 4:1 ratio (that which has been chosen for the marketing of the combination product), opioid agonist effects were attenuated by about 50 percent and unpleasant effects were observed for about 30 minutes. These data suggest that injection of the combination buprenorphine/naloxone product has less abuse potential in non-buprenorphine opiate-dependent addicts.

In New Zealand, the only country that has marketed a buprenorphine/naloxone combination product, extensive intravenous abuse of the 0.2 mg buprenorphine tablet among opiate abusers led to the 1991 reformulation of buprenorphine to include 0.17 mg of naloxone. Robinson *et al.* (1993) conducted two separate surveys among narcotic addicts presenting for treatment before and after the launch of the naloxone combination product. In 1990, 81 percent of the patients reported intravenous buprenorphine abuse in the previous 4 weeks, 50 percent reported exclusive use of buprenorphine and 65 percent tested positive for the drug. In 1991, 57 percent reported intravenous abuse of the combination tablet and 43 percent tested positive for the combination. One third of the patients that used the combination product intravenously reported instances of withdrawal symptoms. Only one patient

reported exclusive use (by injection) of buprenorphine/naloxone and experienced no adverse withdrawal effects. The authors concluded that the combination product did act as a deterrent for some drug abusers but did not stop injection practices. In addition, the authors noted that the injection of the combination product would not produce withdrawal symptoms (act as a deterrent) in individuals who were not physically dependent on narcotics or those who were physically dependent on buprenorphine.

Injection of buprenorphine/naloxone in opioid naive individuals, non-dependent opioid abusers or buprenorphine maintained addicts will likely result in opioid agonist effects. For example, intramuscular administration of buprenorphine alone (0.4 and 0.8 mg/70 kg) or in combination with naloxone (0.4 and 0.8 mg/70 kg) was examined in seven non-physically dependent opioid abuser volunteers (Weinhold et al, 1992). In subjective measures of drug effects, buprenorphine alone produced dose dependent increases in "drug liking", "high", and agonist ratings. Administration of 0.4 mg buprenorphine in combination with 0.4 mg naloxone produced positive subjective opiate effects greater than 0.4 mg of buprenorphine alone and a greater percentage of subjects identified the naloxone-buprenorphine combination as an opiate when compared to buprenorphine treatment alone. However, increasing the naloxone concentration to 0.8 mg (twice the concentration of buprenorphine) significantly reduced opioid agonist effects.

In another study with opioid-dependent volunteers stabilized on 8 mg/day sublingual buprenorphine, intravenous buprenorphine (8 mg) with naloxone (4 or 8 mg) produced subjective effects similar to 8 mg sublingual buprenorphine and did not precipitate withdrawal (Harris *et al.*, 2000). Buprenorphine's high affinity for opioid receptors prevents naloxone from displacing buprenorphine already bound to these sites. In some populations of buprenorphine-maintained clients, extremely high intravenous doses of naloxone are required to even partially displace buprenorphine from opioid receptors (Koston *et al.*, 1990).

In non-dependent opioid abusers, sublingual administration of buprenorphine/naloxone (1/0.25, 2/0.5, 4/1, 8/2, 16/4 mg) produced opioid agonist-like effects (Strain *et al.*, 2000).

The data suggest that the buprenorphine/naloxone combination products will likely produce an unpleasant withdrawal when injected by heroin-dependent subjects. However, this combination drug product will not be a serious deterrent to injection by marginally or non-physically dependent users or by individuals stabilized on this medication for addiction treatment (those individuals that will probably have the greatest access to this drug) or by injecting addicts who are abusing and dependent on buprenorphine. In addition, this combination product, taken sublingually, is not a deterrent for abuse by most populations. Studies on snorting and smoking this combination are not available.

One of the many objectives of opioid replacement therapy for addiction treatment is to deter addicts from the continued use of heroin or other opiates. Chronic buprenorphine dosing produces cross-tolerance to other opioids (Jasinski *et al.*, 1978; Bickel *et al.*, 1988) and may limit the magnitude of effects produced by supplemental challenges of other opioids.

In subjects maintained on a sublingual dose of 8 mg/day of buprenorphine, acute supplemental intramuscular doses of buprenorphine (4, 8 and 16 mg) or hydromorphone (9 and 18 mg) administered 16 hours after the buprenorphine daily dose produced opioid agonist effects although there was a lack of graded dose-effects for hydromorphone (Strain *et al.*, 1997). The addition of naloxone to the maintenance dose of buprenorphine does not impart greater blockade (Strain *et al.*, 2002).

In a study to determine what dose of buprenorphine would effectively block the reinforcing effects of intravenous heroin (Comer *et al.*, 2001), both 8 and 16 mg of sublingual buprenorphine maintenance dosing failed to block the effects of 12.5 mg or 25 mg of heroin. These data indicate that buprenorphine maintenance (even at relatively high maintenance doses) may not serve as a deterrent for patients who chose to continue their illicit use of heroin or other opiates.

Buprenorphine has been diverted, trafficked and abused in many countries throughout the world. Starting in the late 1970s, low-dose buprenorphine sublingual tablets and injectable solutions were approved for marketing in many countries. High-dose buprenorphine for narcotic treatment gained marketing approval in France in 1996 and has since been approved in several other countries.

Buprenorphine abuse was detected in many countries soon after it was approved for marketing. The initial profile of low abuse liability and high therapeutic index (safety) fueled decisions that allowed the initial marketing of buprenorphine without any significant restrictions or regulatory controls. Its easy accessibility and acceptability by a wide spectrum of drug abusers, including heroin addicts, resulted in substantial abuse (for example: Levelle *et al.*, 1991; Rainey, 1986; Strang, 1995,1991; Tracqui *et al.*, 1998; Kintz, 2001; Basu, 1998; Robinson *et al.*, 1993; Dore *et al.*, 1997, Singh *et al.*, 1992; Chowdhury *et al.*, 1998). Austria, Australia, Belgium, Germany, France, India, New Zealand, Norway and Sweden have all increased the regulatory controls on buprenorphine. In 1988 the World Health Organization (WHO) recommended that buprenorphine be placed in Schedule III of the Psychotropic Convention. This action was taken by the United Nations in 1989.

A number of factors have contributed to the illicit use of buprenorphine. In areas where heroin has been less available or of low quality, buprenorphine's low cost, easy accessibility, high purity and substantial morphine-like effects have contributed to its popularity on the illicit market. Doctor shopping and forged prescriptions are important sources of this drug and, according to the International Narcotics Control Board (INCB), large quantities of buprenorphine have been trafficked across international borders.

While extensive diversion, trafficking and abuse have been documented for both the sublingual tablets and injectable formulations, the sublingual tablet has a greater appeal to a wider range of drug abusers. The variety of routes of administration may account for this preference. The tablets can be abused by the sublingual route or they can be crushed and snorted or the powder can be solubilized and injected.

In summary, unlike Schedule IV partial mu agonists, buprenorphine is recognized as morphine-like in many drug discrimination studies and produces effects similar to morphine over a wide range of doses. Significant abuse has been documented in many countries although various factors, including the lack of regulatory controls placed on buprenorphine and the scarcity of high purity heroin, have played a role in contributing to this abuse. Buprenorphine's partial agonist effects make buprenorphine less desirable than pure mu agonists in Schedule I or II. The extent to which buprenorphine is able to produce euphoria and "good drug" effects limits its use by opiate tolerant abusers. While buprenorphine can substitute for heroin,

it is rarely preferred over high quality heroin. In addition, the reduced respiratory depressant effects of buprenorphine (as a consequence of its "ceiling effect") imparts greater safety in overdose than other pharmaceutical narcotics controlled in Schedule II.

In reviewing all the data relevant to the abuse potential, including the comments and the DHHS evaluation, the DEA concludes that buprenorphine has an abuse potential less than narcotics in Schedule I or II of the CSA but greater than Schedule IV narcotics.

Dependence Profile of Buprenorphine

In addition to having abuse potential, most drugs controlled under the CSA are capable of producing dependence, either physical (physiological) or psychological. Physical dependence refers to the physiological changes produced by repeated use of a drug that necessitates the continued administration of the drug to prevent a withdrawal syndrome. Psychological dependence refers to the need or craving for a drug that compels an abuser to continue drug use.

Chronic buprenorphine administration is associated with physical dependence (for example see: Jasinski *et al.*, 1978; Kosten *et al.*, 1988, 1990; San *et al.*, 1992; Eissenber *et al.*, 1996). The extent of physical dependence, as measured by an abstinence syndrome, has been characterized as mild to moderate in intensity and of long duration. The profile of withdrawal effects/duration varies with buprenorphine dose, route of administration and duration of chronic use. While some aspects of the abstinence syndrome approach those which occur with pure mu agonists, generally the withdrawal is reported as less intense and may not require pharmaceutical intervention for relief of adverse withdrawal effects.

Jasinski *et al.* (1978) conducted the original clinical abuse liability studies evaluating buprenorphine's abuse potential. Buprenorphine was shown to produce morphine-like subjective, behavioral and physiological effects and morphine-like physical dependence. The abstinence syndrome observed after abrupt withdrawal of chronically administered buprenorphine (8 mg subcutaneous for 60 days) was delayed producing peak Himmelsbach abstinence scores after about two weeks. Peak withdrawal effects were clinically significant but of lesser magnitude than pure mu agonists. Withdrawal effects included loss of appetite, malaise, insomnia, sensitivity of the skin, lacrimation, rhinorrhea, perspiration, gooseflesh, nausea, leg aches and backaches. These effects were variably reported as mild to moderate and clients requested an opiate to alleviate the symptoms.

In another study examining the physical dependence profile of buprenorphine, 19 heroin dependent male subjects were maintained on 8 mg sublingual buprenorphine for 16 days followed by an additional 16 days of daily or every other day dosing of 8 mg (Fudala *et al.*, 1990). Abrupt discontinuation in buprenorphine dosing produced an abstinence syndrome starting within the first 72 hours, peaking within 3 to 5 days and diminishing after 8 to 10 days. Over 50 percent of the participants required therapeutic intervention for withdrawal symptoms.

In a report on the use of Subutex® in France (Ministry of Health of France, 1998), clinicians describe a buprenorphine abstinence syndrome similar to abrupt withdrawal from methadone, characterized by 2 to 3 days of no symptoms followed by 10 days of unpleasant symptoms. Abrupt withdrawal of buprenorphine produced effects approaching that of methadone withdrawal but with periods that were very difficult to bear due to the continual switching between a normal state and a state of withdrawal.

One of the clearest indications of buprenorphine physical dependence potential is data gathered on neonates of buprenorphine maintained mothers (Fisher *et al.*, 2000). Buprenorphine neonatal abstinence syndrome (NAS) was also reported in postmarketing data from Franco. The withdrawal syndrome, including tremor and autonomic hyperreflexia, is generally mild to moderate in severity. Between 1996 and the first six months of 1999, 66 reports of NAS were reported to the manufacturer.

The extent of psychological dependence produced by buprenorphine is largely dependent on its ability to produce pleasurable effects and the desire or need to continue the use of this drug for those effects. High psychological dependence is associated with significant loss of drug use control, escalation of dose, drug seeking behaviors and maladaptive patterns of substance use despite serious negative consequences. In reviewing the psychological dependence profile of buprenorphine, the DEA considered a number of factors including: drug effects, evidence of diversion, trafficking and abuse of buprenorphine, patterns of drug use and physical or psychological problems associated with continued abuse of this drug.

As reviewed earlier, buprenorphine produces significant morphine-like effects over a wide range of doses and in numerous populations of drug abusers. However, buprenorphine's partial agonist activity often results in shallower dose-response curves with reduced maximal amounts of euphoria, drug liking and/or "good drug" effects than many of the pure mu agonists that have been compared to buprenorphine.

Buprenorphine has been extensively diverted, trafficked and abused throughout many countries although those activities have often been fueled by the lack of high purity heroin and limited regulatory controls placed on buprenorphine (Lavelle *et al.*, 1991; Rainey, 1986; Strang, 1995, 1991; Tracqui *et al.*, 1998; Kintz, 2000; Basu, 1998; Robinson *et al.*, 1993; Dore *et al.*, 1997, Singh *et al.*, 1992; Chowdhury *et al.*, 1998). Surveys in several countries show that buprenorphine, along with heroin, temazepam, and amphetamines, ranks among the top drugs most frequently abused (Lavelle *et al.*, 1991; Arditti *et al.*, 1992; Lapeyre-Mestre *et al.*, 1997; Thirion *et al.*, 1999; Shewan *et al.*, 1998; Taylor *et al.*, 1996; Coggans *et al.*, 1991; Barnard *et al.*, 1998). Falsified prescriptions, theft, doctor shopping and street buys have all been identified as sources for buprenorphine.

Buprenorphine use is associated with maladaptive patterns of substance use. In an analysis of 11,186 buprenorphine prescriptions (written in France during 4 months between September through December 1999), 12 percent of the patients received prescriptions from more than two prescribers and 18 percent of the patients were judged as having deviant maintenance treatment with more than two prescribers or more than 20 mg per day of buprenorphine (Thirion *et al.*, 2002). Data provided in a report generated by a multidisciplinary task force (working under an agreement with the Office of the Junior Minister for Health, the General Health Administration and Schering Plough Laboratories) on the use of Subutex® in France noted that the sales of syringes in France remained stable despite the large numbers of individuals in treatment with Subutex®. At the same time, there was a significant reduction in heroin trafficking and heroin-related deaths. As so many heroin addicts were in treatment and being prescribed medications that are not injectable formulations, the sales for injection equipment should have fallen off drastically. That did not occur. Survey data regarding buprenorphine use indicated that between 12 and 31 percent of buprenorphine users crush the buprenorphine tablets and inject

their own medication or diverted medication, often in combination with benzodiazepines (Ministry of Health of France, 1998). Benzodiazepines purportedly enhance and prolong the euphorigenic properties of buprenorphine. These injection practices are associated with the spread of HIV and other communicable diseases as well as serious overdose events. Over 100 deaths in France have been associated high dose buprenorphine injection in combination with benzodiazepines (Tracqui *et al.*, 1998; Kintz, 2001). In another study of 1018 drug injectors in Glasgow during 1993 and 1994, 41 percent of the injectors reported using buprenorphine and, of those, 26 percent reported at least one overdose (Taylor *et al.*, 1996).

A number of case reports involving buprenorphine abuse demonstrate that buprenorphine is associated with a pathological pattern of use, tolerance development and an opiate abstinence syndrome (Quigley *et al.*, 1984; Singh *et al.*, 1992; Basu *et al.*, 1990). Researchers who have compared the toxicologic and psychopathologic characteristics of buprenorphine dependence with those of heroin found no clinically significant differences (Torrens *et al.*, 1993).

The availability and use of high-dose sublingual tablets is a relatively new phenomenon. The ease with which addicts can be detoxified after extended use of buprenorphine at high maintenance doses has not been well established nor is there information regarding continued abstinence after detoxification from long-term, high-dose use/abuse of buprenorphine. The dependence capacity of buprenorphine may be heightened under these conditions.

In summary, buprenorphine produces low to moderate physical dependence. The withdrawal syndrome is of less intensity and longer duration than most narcotics in Schedule I or II of the CSA. Therapeutic intervention may be necessary to help ameliorate some of the withdrawal affects. Buprenorphine abuse is associated with a loss of control, escalation of dose, drug seeking behaviors and maladaptive patterns of substance use. The data suggest that buprenorphine has a relatively high psychological dependence profile although it is generally less reinforcing than heroin and other pure mu agonists.

Answers to Specific Comments Regarding the Proposed Placement of Buprenorphine in Schedule III of the CSA

Comment: The buprenorphine/naloxone product (Suboxone®) should be placed in a lower schedule than the single entity product (Subutex®) when/if approved for use in the United States. This differential scheduling would show the lower abuse potential of the combination product and would encourage physicians to preferentially prescribe the combination product.

Answer: The addition of naloxone to the buprenorphine high dose sublingual tablets may be aversive in physically dependent opiate abusers but it will have little (may reduce agonist effects) or no effect in all other populations of abusers. It does not have significantly less abuse potential. For more information, see section on abuse potential.

A physician with the appropriate training in narcotic addiction treatment (as mandated by the Drug Addiction Treatment Act of 2000) has, or will be provided, information about the merits of prescribing the combination product. Should the buprenorphine sublingual tablets be approved for use in the United States, the physician will, ultimately, write a prescription for Subutex® or Suboxone® based on an informed decision about what he/she feels is the best treatment for the patient.

Comment: Because Buprenex® has been in Schedule V and has not been associated with widespread diversion or abuse, there is no compelling reason to reschedule this medication.

Answer: As a single entity product, Buprenex® has no other active ingredient in its formulation that may mitigate its abuse potential. While no significant abuse of Buprenex® has occurred in the United States (which both FDA and DEA believe is directly related to its limited use in the United States) many countries have experienced significant abuse of low dose buprenorphine in tablet and injectable formulations. Buprenex® does not have less abuse potential than other buprenorphine products.

Comment: Products containing less than 1 mg/ml of buprenorphine should be placed in Schedule V of the CSA.

Answer: Because buprenorphine is significantly more potent than morphine with much greater bioavailability by the injection route of administration, intravenous injection of 0.3 mg of buprenorphine (1 dosage unit of Buprenex®) produces physiological and subjective effects equivalent to 10 mg or more of intravenous morphine (Zacny *et al.*, 1997). Injection of 1 mg/ml buprenorphine would be approximately equivalent to the injection of 20–30 mg of morphine (calculated by extrapolation and considering the shallower dose-response curve). These doses produce significant opiate effects and, if available, are likely to be attractive to most opiate abusers. In addition, as an injectable product, Buprenex® misuse/abuse is associated with possible behavioral risks including shared needles/syringes that contribute to the spread of HIV, hepatitis and other communicable diseases (also review previous comment and answer). There are no provisions in the CSA to schedule narcotic products based solely on the concentration of active ingredient.

Comment: Buprenorphine diversion has been limited to use by out-of-treatment, opioid-dependent, injection drug users.

Answer: While buprenorphine has been primarily abused by injection, data indicates that it has been abused by other routes of administration and other populations of drug abusers. Data from France indicate that a significant percentage of treatment clients (prescribed high dose, single entity product) abuse their own or diverted medication (see discussions on abuse liability and dependence profile).

Comment: Once buprenorphine has been approved for use in opioid substitution treatment, the DEA should study and evaluate abuse over a three-year period in order to more accurately determine whether placement in Schedule III is appropriate.

Answer: Whenever a drug is placed under control in the CSA, the DEA is responsible for monitoring the use of that drug. In addition, the Drug Addiction Treatment Act (DATA) has mandated that DEA monitor the use of Schedule III–V narcotic treatment drugs utilized under DATA.

Comment: The DEA has disregarded data on the development of the naloxone combination product that show significantly less potential for diversion and abuse.

Answer: The DEA is aware that the combination product was specifically developed to deter injection abuse by physically dependent opioid injecting drug abusers. In addition, DEA wants to support and encourage manufacturers to develop products that will reduce the diversion and abuse of legitimate pharmaceuticals. This combination product will inhibit injection by non-buprenorphine dependent addicts and this is a positive outcome. However, after careful examination of all the relevant data regarding the abuse potential of this product in all populations at-risk for abuse (see section on abuse potential), the DEA has concluded that the combination product does not warrant lesser control than other buprenorphine products.

Comment: The DEA has disregarded the additional controls that would be imposed on Subutex® and Suboxone® by the Drug Addiction Treatment Act of 2000 (DATA).

Answer: As part of the review process, both the DEA and the DHHS carefully considered the use of these narcotic treatment drugs within the context of use under DATA. DATA was never intended to be a solitary regulatory piece of legislation and drugs used under this Act must first meet the findings of a Schedule III, IV or V substance as defined in the CSA (21 U.S.C. 812(b)). DATA does not have an impact on the criteria necessary for scheduling under the CSA. The scheduling criteria and procedures remain unchanged and continue to dictate the requirements for the scheduling of buprenorphine as well as any other controlled substance.

Comment: The potential for buprenorphine to be abused, particularly when marketed in high-dose tablets, is consistent with the abuse potential of other Schedule II substances. The partial agonist activity, including safety in overdose, is not supported and, even if true, does not warrant a change from the conclusion that buprenorphine has a high potential for abuse.

Answer: Under certain conditions and in various populations, buprenorphine has a high potential for abuse. Buprenorphine is recognized as morphine-like in many drug discrimination studies and produces effects similar to morphine over a wide range of doses. This data suggests that buprenorphine, if available, would be very attractive to most narcotic abusers (*see* section on abuse potential especially in regard to doses of 2 mg or more). However, the extent to which buprenorphine is able to produce euphoria, "good drug" effects, and respiratory depression is limited by its partial agonist properties. That is, almost uniformly, pure mu agonists are capable of producing greater levels of euphoria and other positive subjective effects than buprenorphine. This is an important issue for a drug-tolerant/dependent narcotic abuser (those likely to be prescribed or have access to high-dose buprenorphine tablets). Buprenorphine may alleviate withdrawal, but may not produce the level of "feel-good" effects that the abuser is seeking. Although buprenorphine is abused by heroin addicts, it is rarely preferred over high quality heroin even when buprenorphine is co-administered with benzodiazepines. The low availability and high cost of high purity heroin compared to the high availability and low cost of buprenorphine have been factors in the high incidence of buprenorphine abuse in many countries. Currently, the availability and purity of heroin across the United States is very high while the price of heroin is relatively low in comparison to the projected cost of buprenorphine tablets.

The DEA cited safety in overdose as an example of buprenorphine's partial agonist activity and as a mitigating factor differentiating the abuse potential of buprenorphine from mu agonists in Schedule II of the CSA. Factor (6) under 811(c) requires that the DEA consider what, if any, risk there is to the public health. The commenter argued that this margin of safety exists only when the drug is taken in a carefully controlled clinical setting without concomitant use of other drugs. In fact, narcotic addicts are likely to abuse benzodiazepines with buprenorphine and often by the injection route—all risk factors for buprenorphine-related deaths. The DEA agrees that the increased safety with respect to diminished respiratory depression may be negated under these circumstances. Data from France regarding buprenorphine-related deaths also supports this conclusion. However, for the initiate to opioid abuse or the non-dependent opioid abuser using buprenorphine, the concurrent injection use of buprenorphine with benzodiazepines is less likely to occur. In addition, accidental death or serious overdose by a child or other family member who ingests the medication of an individual prescribed buprenorphine is also less likely to occur. This is an advantage over drugs like morphine, oxycodone and methadone and a relevant factor that carries considerable significance when weighing public health risks and the need for regulatory scrutiny.

In reviewing all the data relevant to the abuse potential, including the evaluation provided by the DHHS as well as all the comments, the DEA concludes that buprenorphine has an abuse potential less than narcotics in Schedule I or II of the CSA but greater than Schedule IV narcotics. It should be noted that a Schedule III substance can have a relatively high abuse potential. The law (21 U.S.C. 812 (b)(3)) does not have an absolute descriptive term (*i.e.* high, low) relating to the abuse potential of Schedule III substances. However, the abuse potential must be less than Schedule I or II.

Comment: The DEA failed to consider that the illusion of safety may result in greater potential for abuse.

Answer: Prior to completing the final scheduling review document, the DEA received the FDA review document and a scheduling recommendation from the DHHS. The FDA specifically cited this concern in their document and the DEA considered this possibility. Buprenorphine has often been touted as a drug with minimal abuse potential and great safety in overdose. In many countries, these misconceptions have led to less regulatory oversight and freer prescribing practices by physicians resulting in easier access and greater availability of buprenorphine for abuse purposes. See sections on the abuse potential and dependence profile of buprenorphine. The narcotic abuser may view buprenorphine "safety" as a good reason to select buprenorphine over another narcotic or to use greater amounts of buprenorphine without regard to possible overdose.

Comment: Scheduling under the CSA is a relative analysis and depends on aligning a drug with the closest set of comparators. Buprenorphine most closely resembles Schedule II narcotics.

Answer: Scheduling is a relative analysis. The effects produced by buprenorphine were compared to many Schedule II substances and found, under certain conditions, to be similar. However, buprenorphine is a partial agonist and shares some very important properties with other partial agonists in Schedule IV (*i.e.* pentazocine and butorphanol). These partial agonist properties play an important role when comparing buprenorphine effects with pure mu agonist effects. Continued use of all narcotic agonists results in tolerance development, dependence and possible addiction. For the narcotic abuser, escalation of dose, to achieve enhanced effects or to compensate for drug tolerance, will, at some point, be compromised with a partial agonist: the dose-response curve of buprenorphine is more shallow and less linear than mu agonists. This means that buprenorphine may not produce the enhanced effects sought by the chronic drug abuser. In addition, the current data indicates that buprenorphine produces moderate physical dependence and relatively high psychological dependence, not the severe dependence of Schedule II narcotics. Both the DHHS and the DEA have determined that the available data on buprenorphine regarding the abuse potential and dependence profile are most closely aligned to, or defined by, a Schedule III narcotic. For review, please see previous sections on abuse potential and dependence profile found herein.

Comment: Buprenorphine is a gateway drug compounding its public health risks.

Answer: Generally, substances like alcohol, nicotine and marijuana are universally accepted as gateway drugs because data shows that they are often the first drugs used by adolescents and a correlation exists between early experimental use of these substances and an escalation to serious drug abuse problems. One of the at-risk populations for buprenorphine abuse is naïve (inexperienced) opioid abusers (*see* section on abuse potential). Early experimentation with buprenorphine may lead to serious drug abuse problems.

Comment: The DEA has not been consistent in its decision making process and has failed to meet the "non-arbitrary agency requirements." The finding that buprenorphine has a potential for abuse less than Schedule I or II substances is arbitrary and capricious and not supported by underlying administrative record.

Answer: The DEA has not been arbitrary or capricious in the decision making process regarding the abuse potential of buprenorphine. Buprenorphine has a very unique pharmacological profile and produces a range of opioid effects typical of both pure mu agonists and prototypical partial agonists depending on dose, pattern of use, and population taking this drug. Most single entity pure mu agonists are controlled in Schedule I or II of the CSA, while partial agonists, butorphanol and pentazocine, are controlled in Schedule IV. After reviewing all the relevant data, the DEA concluded that buprenorphine's abuse potential is most closely defined by Schedule III (*see* section on abuse potential and answers to previous comments).

Comment: One of the strongest signs that a drug has a high potential for abuse is evidence that it is abused through multiple routes of administration, and that it is used with other drugs of abuse. Among other things, this shows that drug abusers not only like the drug, they are trying to enhance its effects. DEA's finding on the abuse potential of buprenorphine failed to consider and give adequate weight to the evidence on this point.

Answer: The DEA did consider various pharmacological parameters relating to the use of buprenorphine by various routes of administration (*see* section on abuse potential). Drug abusers frequently abuse more than one drug. The reasons for this are varied. Abusers may be trying to enhance the effects of the drug they are using and/or trying to ameliorate some of the unwanted side effects. The DEA believes appropriate weight was placed on this issue.

Comment: DEA's conclusion that buprenorphine most closely resembles a Schedule III drug, with respect to physical and psychological dependence, is contrary to evidence.

Answer: This comment was followed by a number of citations that were taken from the buprenorphine scheduling review documents of both DEA and FDA (those reviews that were conducted prior to the proposal to place buprenorphine in Schedule III). These comments, for the most part, were taken out of context, interpreted differently or weighted differently than by DEA and/or FDA. For example, the statement that buprenorphine produces "morphine-like physical dependence" does not mean that morphine and buprenorphine have the same physical dependence capacity. It does mean that the physiological changes produced by buprenorphine and morphine are similar and they share similar withdrawal signs. The statement that "under most conditions, buprenorphine's physiological and psychological effects are essentially the same as morphine or hydromorphone" means that buprenorphine is capable of producing effects (*i.e.*, miosis, respiratory depression, analgesia, drug euphoria, drug liking and sedation) on a par with morphine and hydromorphone "under most conditions". A more appropriate caveat would be "under many conditions". This was a statement taken out of context and does not mean that these drugs produce the same dependence profile. It is important to note that, in making scheduling decisions, all the available information regarding a substance must be synthesized and weighed. The section on dependence profile found herein does not contain all the data DEA relied upon but does provide a summary of some important data and the rationale used by DEA in concluding that buprenorphine produces moderate physical dependence and relatively high psychological dependence.

Comment: In the absence of sufficient data on physical and psychological dependence, the DEA must give weight to its abuse liability assessment.

Answer: While some data was lacking regarding the dependence profile of long-term use/abuse of high dose buprenorphine, sufficient data is available for making a determination regarding buprenorphine dependence (*see* previous section on dependence profile). In addition, DEA did not find that buprenorphine has an abuse potential consistent with Schedule II.

Comment: Whether buprenorphine will be eligible for office-based use under recently enacted federal legislation is not a relevant factor in the scheduling analysis and DEA erred by considering it.

Answer: In the March 21, 2002, **Federal Register** notice on the proposed rule for buprenorphine scheduling, the DEA made the following statement under a section on consequences of this proposed rule: "The DEA recognizes the need to expand narcotic treatment and this factor was a consideration in proposing Schedule III placement for buprenorphine."

The proposed placement of buprenorphine in Schedule III was not made on the basis of making buprenorphine products available for office-based narcotic treatment. Taken out of context, we recognize that this statement could possibly lead to that interpretation. This statement was meant as a preamble to express DEA's concerns regarding the use of buprenorphine within the context of office-based narcotic treatment. The DEA does recognize the need to expand treatment. As part of our scheduling review, DEA did consider the impact of buprenorphine treatment products used within the context of office-based practice.

The factors for determining the placement of a substance within one of the schedules of controlled substances are specifically laid out in Title 21 U.S.C. 812(b). The manner in which a substance will be used and its availability to the public are among the elements that must be considered in determining a substance's actual or relative potential for abuse (*see* section on abuse potential). The DEA did not consider the need to expand narcotic treatment as a specific factor in determining the placement of buprenorphine under the CSA. Certainly the anticipated use of buprenorphine for addiction treatment was a point of consideration in terms of its possible impact on the relative potential for abuse, however, it was not a determining factor.

Comment: To the extent that DEA considered the placement of buprenorphine under Schedule III, in order to expand access to narcotic treatment (67 FR at 13115), DEA was required to do a complete analysis of the impact of its proposal under the Regulatory Flexibility Act (5 U.S.C. 601 *et seq.*). Among other things, DEA was required to consider the impact of the decision on small businesses, including methadone treatment programs.

Answer: As stated previously, the DEA did not propose placement of

buprenorphine in Schedule III in order to have it available for office based treatment; it was DEA's analysis of the factors laid out in Section 811(c) that resulted in the determination that buprenorphine should be placed in Schedule III.

With respect to the issue of possible economic impact, DEA does not view the placement of buprenorphine into Schedule III as having a direct economic impact on the activities of traditional narcotic treatment programs. As a Schedule III controlled substance, buprenorphine will be equally available to traditional NTP programs as well as office-based treatment providers. The migration of stabilized patients from NTP's to office-based treatment programs will be driven more by the differences in the program requirements and characteristics. The office-based programs may be more attractive to the stabilized patients. As such, DEA stands by its certification that placement of buprenorphine in Schedule III will not have a significant economic impact on a substantial number of small business entities.

Comment: In its concluding statement (of the proposed rule), DEA notes that buprenorphine's abuse potential and dependence profile suggest that there may be significant abuse and diversion of the tablets in the United States. DEA therefore intends to initiate action to increase regulatory control, should that occur. This approach, however, is fundamentally at odds with the approach required under the CSA. The CSA requires DEA to make a reasonable predictive judgment about a drug, and to act proactively to address it. As Congress recognized, the risks associated with drug abuse are too great from a law enforcement and public health perspective to take a reactive posture.

Answer: Sublingual tablets of buprenorphine have not been available in the United States. Both the DEA and FDA relied heavily on foreign experience with these products and no country has marketed a high dose, naloxone-combination product. While drug abuse and addiction are universal problems, the availability of potent narcotic pharmaceuticals and high purity heroin in the United States will likely alter the types of abuse problems experienced with high dose buprenorphine tablets when/if they are approved for marketing. That is, one of the motivators involved in the abuse of buprenorphine in many countries has been the lack of affordable, high purity heroin and fewer, more restrictive controls placed on potent narcotic analgesics. At the same time, narcotic treatment under DATA will be a considerable departure from the more structured Narcotic Treatment Programs of the past decades. Should these products be approved, they will be prescribed by physicians, who may not have extensive experience in dealing with this patient population, and used by addicts, who are likely to abuse/divert their medications. This activity, under DATA, will occur in the absence of enforceable minimal standards of treatment. DEA believes that these conditions increase the likelihood of diversion and abuse of these products.

In light of these uncertainties and in consideration of all the data relevant to buprenorphine's abuse potential and dependence capacity, the DEA has concluded that Schedule III placement and the constraints placed on physicians under the Drug Addiction Treatment Act of 2000 (Pub. L. 106–310) will be sufficient to curb significant abuse problems. However, if our assessment is not correct, the DEA will take appropriate actions.

Comment: The DEA has not presented an adequate basis for the proposed rulemaking. Many of the studies cited by DEA and FDA are not described in sufficient detail. Moreover, some important information from these studies has not been considered by DEA.

Answer: The proposed rule outlines the basic facts. It provides a brief description about the action being proposed, describes buprenorphine as a derivative of thebaine, a partial agonist and its efficacy as an analgesic (with far greater potency than morphine). The two NDAs for buprenorphine products pending at FDA are mentioned with respect to being high-dose sublingual tablets intended for narcotic treatment. The notice outlines an FDA review as part of an NDA process for the proposed treatment drugs. Greater human experience and new scientific data prompted a scheduling review by FDA that resulted in a DHHS rescheduling recommendation. The DEA considered this recommendation and carefully reviewed the FDA scheduling review document (in matters of science and medicine, DHHS findings are binding on DEA). The DEA then conducted a final review and, outlined in the proposed notice, the factors DEA considered in making the decision to propose Schedule III for buprenorphine and all products containing buprenorphine. This was the basis for this proposed rulemaking. Upon request, the DEA did provide the FDA and DEA review documents to interested parties.

In this final rule, the DEA has included summaries of the data DEA relied upon in determining the abuse potential and dependence profile of buprenorphine. However, like most review documents, specific details about all the studies cannot be given. Citations, however, are provided.

This commentator stated that DEA's statements regarding buprenorphine's potency with respect to morphine and the fact that buprenorphine is a derivative of thebaine have no bearing on buprenorphine's abuse potential. As a derivative of thebaine, buprenorphine was originally classified under the CSA as a narcotic. This statement was not made to imply anything with respect to abuse potential. Many substances (*i.e.* opiate antagonists) are derived from thebaine and have no abuse potential. Potency, however, is an element that directly affects the abuse potential. As mentioned in an earlier comment, 1 mg/ml of buprenorphine produces substantial euphoria. If buprenorphine is marketed in 2 and 8 mg tablets, those tablets can be dissolved in water and shared by several opiate abusers (depending on level of narcotic tolerance). The implications of this activity speak directly to the abuse potential and the possible public health risks associated with shared injection equipment.

The DEA did review and consider the information in the literature cited, as well as countless other scientific papers, law enforcement and drug abuse data bases, and law enforcement documents that were not cited.

Comment: The proposed rule has not adequately described the pharmacology of the drug substance buprenorphine or the drug products that would be affected by this rule.

Answer: The section herein on abuse potential reviews the pharmacological profile of buprenorphine. Currently, only one buprenorphine product, Buprenex®, will be affected by this rule. This drug product is an injectable formulation containing 0.3 mg/ml of buprenorphine. It is approved for use for moderate to severe pain management.

Two New Drug Applications (NDA) have been submitted to FDA for high dose sublingual tablets. These potential addiction treatment products include: (1) Subutex®, a mono or single entity buprenorphine product, and (2) Suboxone®, a combination product in a 4:1 ratio of buprenorphine to naloxone. The Subutex® and Suboxone® NDAs remain pending at the FDA. When/if these products are approved for marketing they will also be affected by this rule.

Comment: Many facts cited by the DEA and FDA in their conclusions have been removed from their proper scientific context. This is particularly evident in the description of buprenorphine and in the basis for the DEA conclusion that buprenorphine may cause high psychological dependence.

Answer: Concluding statements rarely provide detail and, by their nature, are brief statements regarding conclusions that are made regarding all the available data. The section on buprenorphine's dependence profile herein and previous comments/answers regarding this issue, provide a detailed discussion of the basis for DEA's conclusions regarding dependence potential.

Comment: The DEA and FDA have not explained why data generated since the original scheduling action for buprenorphine in 1985 would alter the original conclusions that buprenorphine has a low potential for abuse and low potential for physical and psychological dependence.

Answer: The DEA has reviewed all the documents pertaining to the original placement of buprenorphine in Schedule V of the CSA. In 1981, buprenorphine hydrochloride (Buprenex®) was approved for use in the United States as an analgesic. In 1982, the Assistant Secretary of Health recommended that buprenorphine be placed in Schedule V of the CSA. This recommendation was based on findings that buprenorphine had an approved medical use in the United States and that its abuse potential and dependence capacity was low and consistent with Schedule V placement. The DEA published a proposal to place buprenorphine in Schedule V in 1982. This rulemaking was finalized on April 1, 1985 (50 FR 8104) following a hearing requested by Reckitt & Colman (now Reckitt Benckiser), the patent holder and manufacturer for buprenorphine worldwide. The company's objection to the proposal was based on their contention that buprenorphine did not have sufficient potential for abuse to warrant Schedule V placement in the CSA and that buprenorphine should not be classified as a narcotic as defined by the CSA. Data was provided from several countries including West Germany, Australia and New Zealand (where buprenorphine had been available for a limited period of time) showing buprenorphine abuse, diversion and trafficking. In addition, FDA provided testimony at the administrative hearing on buprenorphine regarding the basis for their decision to recommend Schedule V.

In reviewing this data, the science, at that time, relied heavily on preclinical studies that indicated that buprenorphine had minimal abuse potential and dependence producing capacity. While Jasinski's (1978) original clinical abuse liability study was available and considered, more weight was placed on the fact that buprenorphine's partial agonist activity mitigated the development of any serious abuse problems and the belief that this was an exceedingly safe drug in overdose. Clinical use in foreign countries, where it had already been approved for marketing, was limited but did indicate that buprenorphine had some abuse potential. However, as a low-dose, injectable formulation for the treatment of moderate to severe pain, widespread use and availability was not anticipated.

Since that time, the use, abuse and available data have increased. Clinical experience with various dosage forms for both pain management and addiction treatment is now available. In addition, the anticipated use of high-dose buprenorphine tablets with the possibility that they could be prescribed by physicians and used in an office based setting for the treatment of opioid addiction prompted FDA to re-evaluate the status of buprenorphine under the CSA. In reviewing all the available data, both FDA and DEA have concluded that placement in Schedule III as a narcotic is the most appropriate schedule for buprenorphine and products containing buprenorphine.

Comment: DEA and FDA rely heavily on data concerning abuse of buprenorphine in foreign countries that occurred prior to the international control of buprenorphine in 1989 under the 1971 Psychotropic Convention.

Answer: Both DEA and FDA reviewed all the available data that addressed the eight factors that are used as a basis for making a final scheduling decision. Published literature regarding the use, misuse, abuse, diversion and trafficking in buprenorphine was gathered and assessed. Published data about the abuse of any drug often provides a wealth of information including: who is abusing it, how it is being abused, source of the drug and possible street prices, extent or seriousness of the abuse, drug effects, concurrent use of other drugs, and reasons it is sought and abused. Much of this information is timeless and speaks to the ability of a drug to produce certain effects that some humans find pleasurable. Both DEA and FDA considered buprenorphine abuse data within the context of regulatory controls, heroin availability and purity, and availability and use of other pharmaceutical narcotics.

Comment: The DEA and FDA have inadequately described the conditions of use of Subutex® in France and the impact of such use on either the mortality associated with heroin addiction or the frequency of abuse of buprenorphine. It is asserted without supporting data that the conditions of use that will apply to Suboxone® and Subutex®, should they be approved for use in the United States, will inevitably lead to significant abuse of buprenorphine. There is no discussion of how the proposed use of Subutex® in the United States may differ from the use of this product in France. There is not an acknowledgment in the proposed rule that one of the products under development, which is not available in France, contains naloxone to deter intravenous abuse.

Answer: Buprenorphine was first marketed in France in 1987 as a low dose sublingual tablet (Arditti *et al.*, 1992). Between 1992 and 1993, buprenorphine was identified as the third most commonly appearing drug in falsified prescriptions in southwestern France (Baumevielle *et al.*, 1997). In December 1992, the French government instituted special dispensing and prescribing procedures similar to those governing narcotic drugs: buprenorphine was monitored by the French Medical Association; prescriptions were required to be written on a voucher taken from a counterfoil prescription book that was specifically designed for narcotic drugs; and prescriptions could be filled by any pharmacy, but had to be retained by the pharmacist for three years.

In 1996, general practitioners were permitted to prescribe buprenorphine sublingual tablets (Subutex®, 2 and 8 mg) for treating opiate dependence for up to 28 days per prescription. This system of treatment is a considerable departure from previous policy. Prior to 1996, France provided very limited treatment with methadone in state-run clinics (on a per capita basis, France had the lowest narcotic treatment of any European country). The spread of HIV and other communicable diseases by intravenous drug users and the acceptance of various types of narcotic replacement treatment in other countries (methadone, morphine, heroin and low-dose buprenorphine), combined with data suggesting that high-dose buprenorphine was a safer treatment drug, set the stage for France's new policy. When Subutex® was first launched, the street price of an 8 mg sublingual tablet was 100 francs (Auriacombe *et al.*, 1997). More recently

(Dru, 1999), the street price for buprenorphine in Paris was 10 to 15 francs and was reported as being easily accessible on the illicit market. This reduction in street pricing for buprenorphine is likely the result of widespread availability, by licit and illicit means. Because of continuing reports of abuse and diversion, in September 1999, restrictions on dispensing of buprenorphine were tightened to a 7-day supply per prescription.

Information regarding the use of Subutex® in France comes from a variety of sources. One of the first and most comprehensive reports was generated by a multidisciplinary task force (working under an agreement with the Office of the Junior Minister for Health, the General Health Administration and Schering Plough Laboratories) and reported on the early use of Subutex® in France. Data presented in the report suggested that trafficking in heroin and heroin overdose deaths significantly declined in France since Subutex® became available (an estimated 75 percent reduction). However, data also showed that Subutex® use is associated with significant public health risks. The following points were made by the task force:

- The use of benzodiazepines in combination with buprenorphine products is frequently encountered (both self-reports of addicts and studies have verified the frequency of this combination: about 20 to 44 percent of addicts treated with Subutex® also administer benzodiazepines). From February 1996 to October 1997, health officials were aware of 17 deaths associated with this combination.
- Sales of syringes remained stable despite the large numbers of individuals in treatment with Subutex® (50,000 buprenorphine-treated patients in 1997). Addicts reported that they continue to inject, often crushing, dissolving and injecting their buprenorphine tablets as well as other drugs of abuse.
- Survey data indicated that general practitioners were unable to obtain psychological services for their patients, as few psychiatrists want to treat intravenous drug users (less than 1 percent of the psychiatrists were linked to addiction treatment or had experience in treating addiction).
- Subutex® was diverted and abused by a significant percentage of individuals receiving buprenorphine prescriptions: 12 to 31 percent injected their own medication and 2 to 9 percent received multiple prescriptions from 2 or more physicians.
- Young abusers, not yet addicted to narcotics, were using buprenorphine as a "gateway" drug (the degree to which this occurs was unknown).

Recent data regarding Subutex® use in France is provided by Thirion *et al.* (2002), who conducted an analysis of 11,186 buprenorphine prescriptions (written between September through December 1999) to determine how buprenorphine was being used by French practitioners. Eighty five percent of the buprenorphine prescriptions were written by general practitioners who often prescribed for only one or two patients. The mean dose was 11.5 mg/day. Twelve percent of the patients received prescriptions from more than two prescribers and 43 percent of the maintained patients had an associated benzodiazepine prescription, often on the same prescription form. Sixty one percent of the patients had regular follow-up, 21 percent had occasional consultations and 18 percent had deviant maintenance treatment (more than two prescribers or more than 20 mg per day of buprenorphine). The authors concluded that the easy access to maintenance treatment in France is associated with a high risk of buprenorphine abuse.

A number of studies have examined buprenorphine-related deaths in France. In a compilation of the case reports and analysis involving buprenorphine overdoses (29 non-fatal and 20 fatal occurring between February 1996 and October 1997 at the hospitals and forensic laboratories in Strasbourg, France), Tracqui and colleagues (1998) speculated that the high dosage of Subutex® tablets is likely to play a role in the occurrence of accidents in spite of the theoretical "ceiling effect." However, almost all cases involved diverted medication and the use of other psychoactive drugs, especially benzodiazepines. Intravenous injection of the crushed tablet also appears to be a risk factor and was associated with 8 deaths and 10 non-fatal overdoses.

Kintz (2001) reported an additional 117 deaths involving buprenorphine. These fatalities were observed at the Institute of Legal Medicine of Strasbourg from March 1998—July 2000 (39 cases) and at 13 other French forensic centers from mid 1996—March 2000 (78 cases). Eighty two percent of the cases involved males. Needle marks suggesting recent intravenous injection(s) were observed in about half of the subjects. All but one case involved concomitant intake of other psychotropic substances. Benzodiazepines were most commonly found in combination with buprenorphine (91 cases). The author concluded that intravenous injection, concomitant use of CNS depressants (especially benzodiazepines) and high-dose buprenorphine formulation were risk factors in buprenorphine-associated fatalities. He further concluded that the total number of buprenorphine-related deaths in France is probably underestimated due to: (1) The drug is difficult to analyze (low concentration and no readily available immunoassay in France); (2) only some forensic centers responded to the question of fatalities involving buprenorphine; and (3) in numerous cases, an obvious overdose (known drug addict, presence of syringe or packages of Subutex®), no autopsy is requested by the police or a judge.

If approved for use in the United States, the prescription of Subutex® or Suboxone® in an office based setting will be a significant departure from years of regulated narcotic treatment practice. While physicians who want to prescribe these drugs for narcotic treatment must be certified by CSAT and can only treat up to 30 opiate-dependent patients at any given time, other regulatory requirements are less restrictive than those in France.

The above data show a pattern of increased regulatory control measures as a consequence of increasing levels of diversion and abuse. Injection of the Subutex® tablets is a common practice among treatment clients and prescription data indicates that they are also using benzodiazepines. Addiction is a medical disease associated with predictive behaviors that transcend national boundaries. Even in the best treatment programs, recurrent relapse occurs. As stated previously, providing prescriptions of narcotic substances to known drug abusers for the treatment of opiate dependence, in the absence of any enforceable treatment standards, is likely to be related with the diversion and abuse of these medications.

Comment: The additional controls that would be provided by moving buprenorphine to Schedule III are not described and no rationale is provided for the assertion that the Drug Addiction Treatment Act will not provide adequate safeguards for the public health.

Answer: The regulatory controls for those who handle Schedule III narcotics are described later in this final rule. There are some additional regulatory requirements beyond what is required of Schedule V narcotics: prescription refills are limited to 5 refills in 6 months, a permit is required to export this drug, and both manufacturers and distributors must file reports with the DEA. For individuals involved in illicit

activities, trafficking penalties and fines are significantly increased.

The Drug Addiction Treatment Act DATA) does not have an impact on DEA's scheduling responsibilities under the CSA. The scheduling criteria and procedures remain unchanged and continue to dictate the requirements for the scheduling of buprenorphine as well as any other controlled substance.

Comment: The overwhelming scientific and medical evidence demonstrates that buprenorphine should not be rescheduled. If buprenorphine is rescheduled, it should not be placed any higher than Schedule IV.

Answer: Both the DEA and the DHHS have determined that the preponderance of evidence indicates that buprenorphine has an abuse potential and dependence profile consistent with Schedule III of the CSA. The sections on abuse potential and dependence profile and answers to previous comments address this issue.

Conclusion

Relying on the scientific and medical evaluation and scheduling recommendation of the DHHS in accordance with Section 201(b) of the Act (21 U.S.C. 811 (b)), and after a careful consideration of all comments and a final, independent review by the DEA, the Deputy Administrator finds that:

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

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

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

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Regulatory Requirements

Persons who manufacture, distribute, dispense, import, export, store or engage in research with buprenorphine must comply with the following regulatory requirements:

1. *Registration.* Any person who manufactures, distributes, dispenses, imports or exports buprenorphine or engages in research or conducts instructional activities or chemical analysis with respect to this substance must be registered to conduct such activities in accordance with 21 CFR part 1301. Those individuals who are currently registered to handle buprenorphine in Schedule V may continue activities under that registration until approved or denied registration in Schedule III provided such registrant has filed an application for registration in Schedule III with DEA on or before November 6, 2002. Any persons not currently registered and proposing to engage in such activities may not conduct activities with the substance until properly registered in Schedule III.

2. *Security.* Buprenorphine must be manufactured, distributed and stored in accordance with 21 CFR 1301.71, 1301.72(b), (c), and (d), 1301.73, 1301.74, 1301.75(b) and (c) and 1301.76.

3. *Labeling and packaging.* Products manufactured, distributed or dispensed before October 7, 2002 and labeled as Schedule V may be distributed and dispensed until April 7, 2002. Products manufactured, distributed or dispensed after October 7, 2002 shall comply with the requirement of 21 CFR 1302.03–1302.07.

4. *Inventory.* Registrants possessing buprenorphine are required to take inventories pursuant to 21 CFR 1304.03, 1304.04 and 1304.11.

5. *Records and reports.* All registrants must keep records and provide reports pursuant to 21 CFR 1304.03, 1304.04, 1304.21–1304.25 and 1304.33.

6. *Prescriptions.* All prescriptions for buprenorphine or prescriptions for products containing buprenorphine are to be issued pursuant to 21 CFR 1306.03–1306.07 and 1306.21–1306.26.

7. *Importation and Exportation.* All importation and exportation of buprenorphine shall be in compliance with 21 CFR part 1312.

8. *Criminal Liability.* Any activity with buprenorphine not authorized by, or in violation of, the CSA or the Controlled Substances Import and Export Act or the Narcotic Addict Treatment Act of 2000, shall continue to be unlawful on or after October 7, 2002, except as authorized in this rule.

Regulatory Certifications

Regulatory Flexibility Act

The Deputy 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 Deputy 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 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),and redelegated to the Deputy Administrator pursuant to 28 CFR 0.104, the Deputy Administrator hereby amends 21 CFR part 1308 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 amended by revising paragraph (e) to read as follows:

§ 1308.13 Schedule II.

* * * * *

(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.]

* * * * *

3. Section 1308.15(b) is revised to read as follows:

§ 1308.15 Schedule V.

* * * * *

(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]

* * * * *

Dated: October 1, 2002.

John B. Brown, III,

Deputy Administrator.

[FR Doc. 02–25293 Filed 10–4–02; 8:45 am]

BILLING CODE 4410–09–P

DEPARTMENT OF TRANSPORTATION

Federal Highway Administration

23 CFR Part 450

[FHWA Docket No. FHWA–2001–10886]

RIN 2125–AE92

Metropolitan Transportation Planning and Programming

AGENCY: Federal Highway Administration (FHWA), DOT.

DEPARTMENT OF JUSTICE

Drug Enforcement Administration

21 CFR Part 1308

[DEA–200[illegible]]

RIN 1117–AA59

Schedule of Controlled Substances: Placement of Dichloralphenazone into Schedule IV

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

ACTION: Final rule.

SUMMARY: With the issuance of this final rule, the Acting Administrator of the DEA specifically lists the substance dichloralphenazone, including its salts, isomers, and salts of isomers in Schedule IV of the Controlled Substances Act (CSA, 21 U.S.C. 801 et seq.). As a result of this rule, the regulatory controls and criminal sanctions of Schedule IV will be applicable to the manufacture, distribution, dispensing, importation and exportation of dichloralphenazone and products containing dichloralphenazone.

EFFECTIVE DATE: Effective August 16, 2001.

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 Dichloralphenazone?

Dichloralphenazone (also known as dichloralantipyrine) is a compound containing two molecules of chloral hydrate (2,2,2-trichloro-1,1-ethanediol) and one molecule of phenazone (1,2-dihydro-1,5-dimethyl-2-phenyl-3H-pyrazol-3-one); CAS No. 480–30–8. Dichloralphenazone is a sedative typically used in combination with isometheptene mucate and acetaminophen in formulating prescription pharmaceuticals for the relief of tension and vascular headaches. When dichloralphenazone is administered or placed in an aqueous solution (a liquid preparation of any substance dissolved in water) it dissociates to form chloral hydrate and phenazone.

Why Is DEA Issuing This Rulemaking?

Schedule IV controlled substances are listed in 21 CFR 1308.14. Section 1308.14(c) lists 49 depressants, including chloral hydrate, that are Schedule IV controlled substances. The first sentence of 21 CFR 1308.14(c) states that the category of Schedule IV depressants includes "any material, compound, mixture, or preparation which contains any quantity of" the substances listed in the section. Since dichloralphenazone is a compound containing chloral hydrate, it is likewise a Schedule IV depressant.

Since dichloralphenazone has not been recognized as a compound containing chloral hydrate and confusion has existed with regard to its control status, the DEA published a proposed rule in the **Federal Register** on December 11, 2000 (65 FR 77328) to expressly list dichloralphenazone as a Schedule IV depressant. This proposed rule provided 60 days for comments.

Were There Any Comments Regarding the Proposed Rule?

The DEA received two comments regarding the proposal. The Healthcare Distribution Management Association (formerly the National Wholesale Druggists' Association), whose members operate over 200 distribution centers throughout the U.S., requested an additional 30 days from the date of publication of this final rule to comply with security, inventory, recordkeeping and reporting, and importing and exporting requirements for the handling of dichloralphenazone. They felt that moving dichloralphenazone from an uncontrolled status to a controlled status required system and operational changes that could not be implemented immediately upon publication of this final rule. The DEA has no objection to the additional 30 days and is incorporating this change into this final rule.

Elan Pharmaceuticals, manufacturer of Midrin® (a prescription product containing isometheptene, dichloralphenazone and acetaminophen marketed in the U.S. for over 30 years) commented that federal and state authorities have not regulated dichloralphenazone as a Schedule IV substance, physicians and pharmacists have not treated Midrin® as a controlled drug product and major drug compendiums (*Physician's Desk Reference, Merck Index, Drug Facts and Comparisons*) have not identified dichloralphenazone or Midrin® as a controlled substance. In addition they noted that the DEA interpretation that Midrin® is a scheduled drug would likely affect prescribing practices and raise DEA registration, labeling, recordkeeping and reporting issues and create confusion among practitioners and patients. Further, Elan poses that there is little evidence that Midrin® or any other dichloralphenazone product has been misused, abused or diverted. The DEA received a formal request from Elan Pharmaceuticals for an exemption for Midrin® as an exempt non-narcotic prescription product. That request will be evaluated according to 21 CFR 1308.31.

The DEA is aware that dichloralphenazone and products containing this substance have not been identified or treated as controlled substances. The determination that dichloralphenazone is a controlled substance is based, in part, on its status as a compound containing chloral hydrate. In addition, numerous drug abuse emergency room episodes have involved Midrin®. The DEA has made every effort to reduce any confusion on the part of handlers of dichloralphenazone or products containing this substance and chose to expressly list this substance in order to eliminate confusion. The DEA invites any other company to submit a formal request for an exemption from Schedule IV regulation for any dichloralphenazone product. The data submitted under 21 CFR 1308.31 are evaluated to determine if such an exemption is warranted.

What Regulatory Requirements Will Be Applied to Handlers of Dichoralphenazone?

Persons who manufacture, distribute, dispense, import, export, store or engage in research with dichloralphenazone must comply with the following regulatory requirements:

1. *Registration.* Any person who manufactures, distributes, dispenses, imports or exports dichloralphenazone or engages in research or conducts instructional activities or chemical analysis with respect to this preparation must be registered to conduct such activities in accordance with 21 CFR part 1301. Any person who is currently engaged in any of the above activities must submit an application for registration by September 17, 2001 and may continue their activities until the DEA has approved or denied that application.

2. *Disposal of stocks.* Any person who elects not to obtain a Schedule IV registration or is not entitled to such registration must surrender all quantities of currently held dichloralphenazone in accordance with procedures outlined in 21 CFR 1307.21 on or before September 17, 2001, or may transfer all quantities of currently held dichloralphenazone to a person registered under the CSA and authorized to possess Schedule IV control substances on or before

September 17, 2001.

Dichloralphenazone to be surrendered to DEA must be listed on a DEA Form 41, "Inventory of Controlled Substances Surrendered for Destruction." DEA Form 41 and instructions can be obtained from the nearest DEA office.

3. *Security.* Dichloralphenazone must be manufactured, distributed and stored in accordance with 21 CFR 1301.71, 1301.72(b), (c), and (d), 1301.73, 1301.74, 1301.75(b) and (c) and 1301.76 after September 17, 2001.

4. *Labeling and packaging.* All commercial containers of dichloralphenazone that are packaged on or after February 12, 2002 must have the appropriate Schedule IV labeling and packaging as required by 21 CFR 1302.03–1302.07. Commercial containers of dichloralphenazone packaged before February 12, 2002 and not meeting the requirements specified in 21 CFR 1302.03–1302.07 may be distributed until May 13, 2002. On and after May 13, 2002 all commercial containers of dichloralphenazone must bear the CIV labels as specified in 21 CFR 1302.03–1032.07.

5. *Inventory.* Registrants possessing dichloralphenazone are required to take inventories pursuant to 21 CFR 1304.03, 1304.04 and 1304.11 after September 17, 2001.

6. *Records.* All registrants must keep records pursuant to 21 CFR 1304.03, 1304.04 and 1304.21–1304.23 after September 17, 2001.

7. *Prescriptions.* All prescriptions for dichloralphenazone or prescriptions for products containing dichloralphenazone or prescriptions for products containing dichloralphenazone are to be issued pursuant to 21 CFR 1306.03–1306.06 and 1306.21–1306.26. All prescriptions for dichloralphenazone or products containing dichloralphenazone issued on or before October 15, 2001, if authorized for refilling, shall, as of that date, be limited to five refills and shall not be refilled after February 12, 2002.

8. *Importation and Exportation.* All importation and exportation of dichloralphenazone shall be in compliance with 21 CFR part 1312 after September 17, 2001.

9. *Criminal Liability.* Any activity with dichloralphenazone not authorized by, or in violation of, the CSA or the Controlled Substances Import and Export Act shall be unlawful on or after August 16, 2001, except as authorized in this rule.

Regulatory Certifications

Regulatory Flexibility Act

The Acting 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. 601 *et seq.*). It will not have a significant economic impact on a substantial number of small business entities. Most handlers of dichloralphenazone or prescription products containing this substance are already registered to handle controlled substances and are subject to the regulatory requirements of the CSA.

Executive Order 12866

The Acting Administrator further certifies that this 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.

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.

Executive Order 13132

This 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 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 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.

Plain Language Instructions

The Drug Enforcement Administration makes every effort to write clearly. If you have suggestions as to how to improve the clarity of this regulation, call or write Patricia M. Good, Chief, Liaison and Policy Section, Office of Diversion Control, Drug Enforcement Administration, Washington, DC 20537, telephone (202) 307–7297.

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 Acting Administrator hereby rules 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 1308.14 is amended by redesignating the existing paragraphs (c)(15) through (c)(49) as (c)(16) through (c)(50) and by adding a new paragraph (c)(15) to read as follows:

§ 1308.14 Schedule IV.

* * * * *

(c) * * *

(15) Dichloralphenazone—2467.

* * * * *

Dated: August 3, 2001.

William B. Simpkins,

Acting Administrator.

[FR Doc. 01–20579 Filed 8–15–01; 8:45 am]

BILLING CODE 4410–09–M

DEPARTMENT OF JUSTICE

Drug Enforcement Administration

21 CFR Part 1310

[DEA–156FF]

RIN #1117–AA43

Listed Chemicals; Establishment of Non-Regulated Transactions in Anhydrous Hydrogen Chloride

AGENCY: Drug Enforcement Administration (DEA), Justice.

ACTION: Final rule confirmation.

SUMMARY: Effective October 3, 1996, the Comprehensive Methamphetamine

AH #1

BOARD OF PHARMACY
State of North Dakota

John Hoeven, Governor

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House Bill 1146
Senate Judiciary Committee
Wednesday – March 12th, 2003 - 10:00 AM – Fort Lincoln Room

Chairman Traynor, members of the Judiciary Committee, for the record I am Howard C. Anderson, Jr, R.Ph., Executive Director of the North Dakota State Board of Pharmacy.

Thank you for the opportunity to appear before you today. This bill was introduced at the request of the State Board of Pharmacy and contains two drugs which have been rescheduled by the FDA and the DEA. We are now including these in the North Dakota statute to place them in the same schedule in which they have been placed federally.

Page 1 Line 24 places buprenorphine in schedule III of the Controlled Substances Act. I have attached the Federal Register, which explains the federal scheduling.

Page 3 Line 12 places dichloralphenazone in schedule IV of the Controlled Substances Act. I have again attached the Federal Register indicating the federal scheduling.

Thank you,

Howard C. Anderson, Jr, R.Ph.
Executive Director