DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 98N–0148]

International Drug Scheduling; Convention on Psychotropic Substances; Single Convention on Narcotic Drugs; World Health Organization Scheduling Recommendations for Ephedrine, Dihydroetorphine, Remifentanil, and Certain Isomers

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is providing interested persons with the opportunity to submit written comments and to request an informal public meeting concerning recommendations by the World Health Organization (WHO) to impose international manufacturing and distributing restrictions, under international treaties, on certain drug substances. The comments received in response to this notice and/or public meeting will be considered in preparing the U.S. position on these proposals for a meeting of the United Nations Commission on Narcotic Drugs (CND) in Vienna, Austria, in March 1999. This notice is issued under the Controlled Substances Act.

DATES: Written comments by February 10, 1999; written requests for a public meeting and the reasons for such a request by January 26, 1999.

ADDRESSES: Submit written comments to the Dockets Management Branch (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Submit written requests for a public meeting and the reasons for such a request to Nicholas P. Reuter (address below).

FOR FURTHER INFORMATION CONTACT: Nicholas P. Reuter, Office of Health Affairs (HFY–20), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–443–1382, or e-mail: ''nreuter@oc.fda.gov''.

SUPPLEMENTARY INFORMATION:

I. Background

The United States is a party to the 1971 Convention on Psychotropic Substances (the Convention). Section 201(d)(2)(B) of the Controlled Substances Act (the CSA) (21 U.S.C. 811(d)(2)(B)) provides that when the United States is notified under Article 2 of the Convention that the CND proposes to decide whether to add a drug or other substance to one of the schedules of the Convention, transfer a drug or substance from one schedule to another, or delete it from the schedules, the Secretary of State must transmit notice of such information to the Secretary of Health and Human Services (HHS). The Secretary of HHS must then publish a summary of such information in the **Federal Register** and provide opportunity for interested persons to submit comments. The Secretary of HHS shall then evaluate the proposal and furnish a recommendation to the Secretary of State which shall be binding on the representative of the United States in discussions and negotiations relating to the proposal.

As detailed below, the Secretary of State has received two notifications from the Secretary-General of the United Nations (the Secretary-General) regarding substances to be considered for control under the Psychotropic Convention. These notifications reflect the recommendations from the 31st WHO Expert Committee for Drug Dependence (ECDD), which met in June 1998. In the **Federal Register** of March 18, 1998 (63 FR 13258), FDA announced the WHO ECDD review and invited interested persons to submit information for WHO's consideration.

The full text of the notifications from the Secretary-General is provided in section II of this document. Section 201(d)(2)(B) of the CSA requires the Secretary of HHS, after receiving a notification proposing scheduling, to publish a notice in the **Federal Register** to provide the opportunity for interested persons to submit information and comments on the proposed scheduling action.

The United States is also a party to the 1961 Single Convention on Narcotic Drugs. The Secretary of State has received a notification form the Secretary-General regarding substances to be considered for control under this convention. The CSA does not require HHS to publish a summary of such information in the **Federal Register**. Nevertheless, in an effort to provide interested and affected persons an opportunity to submit comments regarding the WHO recommendations for narcotic drugs, the notification regarding these substances is also included in this **Federal Register** notice. The comments will be shared with other relevant agencies to assist the Secretary of State in formulating the U.S. position on the control of these substances. The HHS recommendations are not binding on the representative of the United States in discussions and negotiations relating to the proposal regarding control of substances under the Single Convention.

II. United Nations Notifications

The formal United Nations notifications which identify the drug substances and explain the basis for the recommendations are reproduced below.

A. Notification on l-ephedrine, and d,l ephedrine

Reference: NAR/CL.18/1998 CU 98/215
TLAB/CSSS/303/98
UNDCP 42nd CND
WHO/ECDD 31 (1971C)

The Secretary-General of the United Nations presents his compliments to the Secretary of State of the United States of America and has the honour to inform the Government that the World Health Organization (WHO), pursuant to article 2, paragraphs 1 and 4, of the Convention on Psychotropic Substances of 1971, has notified the Secretary-General by note dated 30 September 1998 that it is of the opinion that (1*RS*2*S*)-2-methylamino-1-phenylpropan-1-ol (also known as *l*-ephedrine) and the racemate (1*RS*2*SR*)-2-methylamino-1-phenylpropan-1-ol (also known as *d*,*l*-ephedrine) should be included in Schedule IV of that Convention.

In accordance with the provisions of article 2, paragraphs 1 and 4, of the Convention, the Secretary-General hereby transmits the text of the notification as annex I to the present note.

The World Health Organization, in connection with the notification has also submitted advance excerpts from the report of the thirty-first meeting of the WHO Expert Committee on Drug Dependence (23–26 June 1998), which reviewed the substance with a view, *inter alia*, to possible international control. The excerpts from that report concerning the substance recommended for scheduling are hereby transmitted as annex II.

In accordance with the provisions of article 2, paragraph 2 of the Convention, the notification from the World Health Organization will be brought to the attention of the Commission on Narcotic Drugs at its next session in March 1999. Any action or decision taken by the Commission with respect to this notification, pursuant to article 2, paragraph 5, of the Convention, will be notified to States Parties in due course. Article 2, paragraph 5, reads as follows:

''The Commission, taking into account the communication from the World Health Organization, whose assessments shall be determinative as to medical and scientific matters, and bearing in mind the economic, social, legal, administrative and other factors it may consider relevant, may add the substance to Schedule I, II, III or IV. The Commission may seek further information form the World Health Organization or from other appropriate sources.''

In order to assist the Commission in reaching a decision, it would be appreciated if an economic, social, legal, administrative or other factors the Government may consider relevant to the possible scheduling of *l*-ephedrine and the racemate could be

communicated at the latest by 4 January 1999 to the Executive Director of the Office for Drug Control and Crime Prevention, c/o Commission and Secretariat Services Section, P.O. Box 500, A–1400 Vienna, Austria, fax: +43–1–26060–5885.
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Note dated 30 September 1998 addressed to the United Nations By the World Health Organization

The World Health Organization presents its compliments to the United Nations and has the honour to transmit, in accordance with Article 2, paragraphs 1 and 4 of the Convention on Psychotropic Substances, 1971, assessments and recommendation of the World Health Organization concerning the proposed inclusion of ephedrine (*l*-ephedrine and its racemate) in Schedule IV of the said Convention, as set forth in Annex hereto.

The World Health Organization avails itself of this opportunity to present to the United Nations the assurance of its highest consideration.
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Ephedrine

1. *Substance identification*

Ephedrine (2-methylamino-1-phenylpropan-1-ol) exists in fours stereoisomeric forms and two corresponding racemic mixtures. They are designated traditionally *l*-ephedrine, *d*-ephedrine and *l*-pseudoephedrine and *d*-pseudoephedrine. *l*-Ephedrine, also designated as (–)-ephedrine, is chemically (1*R*,2*S*)-2-methylamino-1-phenylpropan-1-ol. Racemic ephedrine also designated as *d*,*l*-ephedrine or (±)-ephedrine, is chemically (1*RS*,2*SR*)-2-methylamino-1-phenylpropan-1-ol.

2. *Similarity to known substances and effects on the central nervous system*

Ephedrine is chemically and pharmacologically similar to amphetamines. It is also similar to cathine which is (+)-norpseudoephedrine. Ephedrine is both an α- and β-adrenergic agonist and enhances the release of norepinephrine from sympathetic neurons. In general, ephedrine is viewed as being a less potent central nervous system stimulating agent but a more effective bronchodilator. Ephedrine increases motor activity and mental alertness, and diminishes the sense of fatigue. Ephedrine decreases appetite and promotes weight loss.

3. *Dependence Potential*

In humans with histories of substance abuse, *l*-ephedrine, *d*-amphetamine (INN: dexamfetamine), *d*-methamphetamine (INN: metamfetamine), phenmetrazine, and methylphenidate injected subcutaneously produced similar increases in respiratory rate and blood pressure and similar types of subjective changes, including euphoria. The agents differed in relative potency. In general, amphetamine-like stimulants differed only in relative potencies when given orally. *l*-Ephedrine was five times less potent than amphetamine in producing amphetamine-like subjective and physiological effects in substance abusers, but was more potent than amfepramone (diethylpropion).

In monkeys trained to self-administer cocaine, *l*-ephedrine maintained responding rates greater than saline in substitution tests. In rats trained to discriminate cocaine from placebo, *l*-ephedrine generalized to cocaine – though at a slightly lower rate than *d*-amphetamine. Ephedrine generalized to cocaine and *d*-amphetamine in other drug discrimination studies in rats. In amphetamine-trained monkeys, an oral dose of 10 mg racemic ephedrine was discriminated as amphetamine. In monkeys trained to self-administer cocaine, *l*- and racemic ephedrine had definite reinforcing effects. *d*-Ephedrine was both less efficacious and potent than the *l*-isomer in its ability to generalize to amphetamine.

4. *Actual abuse and/or evidence of likelihood of abuse*

Of the 50 countries which have returned the questionnaire to WHO, ephedrine was available for medical use in 46 countries. Of the 46 countries, the following 12 countries have indicated present or past ephedrine abuse or illicit traffic in ephedrine presumably associated with its abuse: Belgium, Burkina Faso, China, Costa Rica, Germany, Finland, France, Ireland, Sudan, Slovakia, Thailand and USA. Although quantitative information is difficult to obtain, the extent of ephedrine abuse was significant enough for some governments to implement various regulatory controls. The current problem of abuse seems to be particularly serious in certain African countries. When abuse exists, it seems to involve ephedrine single entity products. In addition, in the USA, combination products containing ephedrine in herbal preparations have been abused.

The problem of ephedrine diversion was reported in the material provided by the International Narcotics Control Board, which indicated that few countries served as major supplier of ephedrine to other countries. Often, there is a large gap between the amount required for legitimate use and the amount imported into these countries reflecting diversion for abuse. Some ephedrine, traded in dosage forms, is used as a precursor to synthesize methamphetamine.

5. *Therapeutic usefulness*

Ephedrine is used widely as a bronchodilator in the symptomatic treatment of reversible bronchospasm which may occur in association with asthma, bronchitis, emphysema, and other obstructive pulmonary diseases. Hypotension and shock have been treated with parenteral ephedrine through its actions producing cardiac stimulation and vasoconstriction. Less common indications include obesity, motion sickness and enuresis.

The commonality of ephedrine use as a medicine is indicated by the fact that 92% of the countries which responded to the WHO questionnaire (46/50) indicated therapeutic use of ephedrine. This figure suggests that ephedrine is used therapeutically in many countries in the world. Some of these countries have indicated a large number of pharmaceutical products containing ephedrine on the market, often as combination products.

6. *Recommendation*

On the basis of the available information concerning its pharmacological profile, dependence potential and actual abuse, the public health and social problems associated with the abuse of ephedrine are assessed to be significant. The current problem appears to be particularly serious in certain African countries. On this basis, it is recommended that *l*-ephedrine and the racemate be placed in Schedule IV of the Convention on Psychotropic Substances, 1971. The *d*-isomer, which is significantly less potent than the *l*-isomer, need not be controlled. In making this recommendation, it is noted that ephedrine combination products would be eligible for exemption according to the 1971 Convention.

It is further noted that there are overlapping jurisdictions concerning the 1971 Convention and the 1988 UN Convention Against Illicit Traffic in Narcotic Drugs and Psychotropic Substances, which may make full effective international regulations of ephedrine difficult. The interrelationship and interpretation of these conventions needs clarification by appropriate international bodies, including the International Narcotics Control Board and the World Health Organization. In addition, it is recommended that these bodies develop ways to alert Member States which export pharmaceutical formulations of ephedrine, that these preparations have the potential for abuse and use as a precursor.

B. Notification Regarding the Proposal of the Government of Spain

Reference: NAR/CL.17/1998 CU 98/214
TLAB/CSSS/302/98
UNDCP 42nd CND
WHO/ECDD 31 (1971C)

The Secretary-General of the United Nations presents his compliments to the Secretary of State of the United States of America and has the honour to refer to his note NAR/CL.4/1997 of 28 May 1997, by which he transmitted a notification received from the Government of Spain pursuant to article 2, paragraph 1 of the Convention on Psychotropic Substances, 1971. In its notification the Government of Spain informed the Secretary-General that it was of the opinion that Schedules I and II of the 1971 Convention should be amended to include: (a) isomers, except were expressly excluded, of substances listed in those Schedules, whenever the existence of such isomers is possible; (b) esters and ethers of substance in those Schedules, except where included in another Schedule, whenever the existence of such esters or ethers is possible; (c) salts of those esters, ethers and isomers, under the conditions stated above, whenever the formation of such salts is possible; and (d) a substance resulting from modification of the chemical structure of a substance already in Schedule I or II and which produces pharmacological effects similar to those produces by the original substances.

The Secretary-General also transmitted a copy of that notification to the World Health Organization (WHO), in accordance with the provision of article 2, paragraph 2 of the Convention, for consideration by the thirty-first meeting of the WHO Expert Committee on Drug Dependence in 1988.

In accordance with the provision of article 2, paragraph 4, of the Convention, the World Health Organization has transmitted to the Secretary-General, by a noted dated 30 September 1988, its assessment and recommendation in response to the proposal made by the Government of Spain. Those recommendations read as follows:

(i) WHO does not recommend to amend Schedule I and Schedule II of the 1971 Convention, to extend international controls collectively to esters, ethers, and analogues of controlled substances;

(ii) with regard to isomers, WHO recommends that a phrase could be added for substances in Schedule I of the 1971 Convention. That phrase would read as follows: ''The stereoisomers, unless specifically excepted, of substance in this Schedule, whenever the existence of such stereoisomers is possible within the specific chemical designation'', and

(iii) with regard to stereoisomers of the substances in Schedule II, III and IV of the 1971 Convention, WHO recommends that interpretation guidelines should be developed by the International Narcotic Control Board in collaboration with the World Health Organization, in order to eliminate the confusion arising from inconsistencies in the present nomenclature of the Schedules in the 1971 Convention.

In accordance with the provisions of article 2, paragraphs 1 and 4, of the Convention, the Secretary-General hereby transmits the text of the notification as annex I to the present note.

The World Health Organization, in connection with the notification has also submitted advance excerpts from the report of the thirty-first meeting of the WHO Expert Committee on Drug Dependence (23–26 June 1998), which examined the proposal of the Government of Spain. The excerpts from that report are hereby transmitted as annex II.

In accordance with the provision of article 2, paragraph 2 of the Convention, the notifications from the Government of Spain and from the World Health Organization will be brought to the attention of the Commission on Narcotic Drugs at its next session in March 1999. Any action or decision taken by the Commission with respect to this notification, pursuant to article 2, paragraph 5, of the Convention, will be notified to States Parties in due course. Article 2, paragraph 5, reads as follows:

''The Commission, taking into account the communication from the World Health Organization, whose assessments shall be determinative as to medical and scientific matters, and bearing in mind the economic, social, legal, administrative and other factors it may consider relevant, may add the substance to Schedule I, II, III or IV. The Commission may seek further information form the World Health Organization or from other appropriate sources.''

In order to assist the Commission in reaching a decision, it would be appreciated if an economic, social, legal, administrative or other factors the Government may consider relevant to the recommendations made by the World Health Organization in response to the proposal made by the Government of Spain could be communicated a the latest by 4 January 1999 to the Executive Director of the Office for Drug Control and Crime Prevention, c/o Commission and Secretariat Services Section, P.O. Box 500, A–1400 Vienna, Austria, fax: +43–1–26060–5885.

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Note dated 30 September 1998 addressed to the United Nations By the World Health Organization

The World Health Organization presents its compliments to the United Nations and has the honour to transmit, in accordance with Article 2, paragraphs 1 and 4 of the Convention on Psychotropic Substances, 1971, assessments and recommendation of the World Health Organization, as set forth in Annex hereto, in response to the Note Verbale of 15 May 1997 concerning the proposal by the Government of Spain.

The World Health Organization avails itself of this opportunity to present to the United Nations the assurance of its highest consideration.

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Proposal of the Government of Spain

1. *Outline of the Proposal*

In 1997, the Spanish Government submitted a proposal to the Secretary General of the United Nations to amend the 1971 Convention on Psychotropic Substances by adding to Schedules I and II, the chemical compositions of the isomers, esters and ethers of the psychotropic substances already in these schedules, as well as any modified chemical compounds producing effects similar to those produced by the original substances (hereinafter referred to as ''analogues''). The Spanish proposal also recommends the inclusion of the salts of the substances. However, the question of salts is not addressed in the following section since the salts of the substances listed in these Schedules are already under international control. An in-depth analysis of potential advantages and disadvantages of this proposal has led to the following conclusions.

2. *Assessment and recommendation*

With regard to the scheduling of analogues or ''any modified chemical compounds producing effects similar to those produced by the original substances'', extending controls collectively to these groups of substances which are related to, but potential pharmacologically different from, the substances in the two Schedules may contradict the scheduling procedure stipulated in Article 2 of the 1971 Convention on Psychotropic Substances which requires WHO to evaluate individual problems, such as disagreements among Parties concerning the precise scope of substances under control. The same questions may arise concerning the scheduling of esters and ethers. In addition, the advantages in terms of extended scope of control would be rather limited. Though difficult to evaluation, controlling analogues, esters and ethers is likely to have a negative impact on legitimate industrial and research activities involving these substances.

For these reasons, it is not recommend to amend Schedules I and II of the 1971 Convention to extend international controls collectively to esters, ethers and analogues of controlled substances. It has been noted, however, that criminal activities involving analogues of controlled substances can be controlled at the national level, without extending unnecessary administrative and regulatory controls to these substances used for legitimate industrial and research purposes. In one country, this was achieved by applying only criminal controls to certain specified acts involving analogues. Governments having similar problems with analogues should consider the desirability of adopting similar selective control measures, an option which is not available under the 1971 Convention once analogues have been scheduled.

In some countries, introducing national controls for new analogues synthesized by clandestine laboratories is very difficult. Ideally, a combination of national and international controls should be developed concurrently. There is a need to expedite the critical review of substance brought to the attention of WHO by governments.

With regard to isomers, a useful clarification could be provided by introducing a modified qualifying phrase in the proposal of the Spanish Government into Schedule I. The revised phrase to be added to Schedule I would read as follows (addition underlined):

The *stereo*isomers, unless specifically excepted, of psychotropic substance in this Schedule, whenever the existence of such *stereo*isomers is possible within the specific chemical designation in this Schedule.

This renders the proposal chemically precise and consistent with the current interpretation of the Schedule. Hence the proposal could provide an explicit clarification of the scope of controlled isomers including racemates.

With regard to stereoisomers of the substances in Schedules II, III and IV, the confusion arising from the inconsistencies in the present nomenclature of the Schedules should be clarified by means of interpretation guidelines to be developed by an appropriate international body, such as the International Narcotics Control Board, in collaboration with WHO.

C. Notification on Dihydroetorphine and Remifentanil

Reference: NAR/CL.16/1998 CU 98/213
TLAB/CSSS/301/98
UNDCP 42nd CND
WHO/ECDD 31 (1961C)

The Secretary-General of the United Nations presents his compliments to the

Secretary of State of the United States of America and has the honour to inform the Government that the World Health Organization (WHO), pursuant to article 3, paragraphs 1 and paragraph 3 (iii), of the Single Convention on Narcotic Drugs, 1961, and of that Convention as amended by the 1971 Protocol, has notified the Secretary-General by note dated 30 September 1998 that it is of the opinion that 7,8-dihydro-7-α-[1-(*R*)-hydroxy-1-methylbutyl]-6,14-*endo*-ethanotetrahydrooripavine (also known as dihydroetorphine) and that 1-(2-methoxycarbonylethyl)-4-(phenylpropionylamino)-piperidine-4-carboxylic acid methyl ester (also known as remifentanil) should be included in Schedule I of the Convention.

In accordance with the provisions of article 3, paragraph 2, of the Convention, the Secretary-General hereby transmits the text of the notification as annex I to the present note.

The World Health Organization, in connection with the notification has also submitted advance excerpts from the report of the thirty-first meeting of the WHO Expert Committee on Drug Dependence (23–26 June 1998), which reviewed these substances with a view, *inter alia*, to possible international control. The excerpts from that report concerning the two substances recommend for scheduling, are hereby transmitted as annex II.

In accordance with the provisions of article 3, paragraph 2 of the Convention, the notification from the World Health Organization will be brought to the attention of the Commission on Narcotic Drugs at its next session in March 1999 in accordance with article 3, paragraph (iii), of the Convention.

Article 3, paragraph 3 (iii), reads as follows:

''If the World Health Organization finds that the substance is liable to similar abuse and productive of similar ill effects as the drugs in Schedule I or Schedule II or is convertible into a drug, it shall communicate that finding to the Commission which may, in accordance with the recommendation of the World Health Organization, decide that the substance shall be added to Schedule I or Schedule II.''

Any action or decision taken by the Commission with respect to this notification, pursuant to article 3, paragraph 3 (iii), of the Convention, will be notified to Governments in due course.

11 November 1998
NAR/CL.16/1998
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Annex I

Note dated 30 September 1998 addressed to the United Nations By the World Health Organization

The World Health Organization presents its compliments to the United Nations and has the honour to transmit, in accordance with Article 3, paragraphs 1 and 3 (iii) of the Single Convention on Narcotic Drugs, 1961, as amended by the 1972 Protocol Amending the Single Convention on Narcotic Drugs, 1961, assessments and recommendation of the World Health Organization, as set forth in the annex hereto, concerning the proposed inclusion of dihydroetorphine and remifentanil in Schedule I of the said Convention.

The World Health Organization avails itself of this opportunity to present to the United Nations the assurance of its highest consideration.

11 November 1998
NAR/CL.16/1998
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Dihydroetorphine

1. *Substance identification*

Dihydroetorphine (CAS 14357–76–7) is chemically 7,8-dihydro-7-α-[1-(*R*)-hydroxy-1-methylbutyl]-6,14-*endo*-ethanotetrahydrooripavine.

2. *Similarity to known substances and effects on the central nervous system*

Dihydroetorphine is chemically similar to etorphine, which is in Schedule I of the Single Convention on Narcotic Drugs, 1961. Pharmacologically, animal studies indicate that dihydroetorphine is a highly potent analgesic, with an analgesic efficacy of 6,000 and 11,000 times as potent as morphine in mice and rabbits, respectively. In mice and rabbits, the peak analgesic effect was attained 15 minutes after subcutaneous injection of dihydroetorphine, and the duration of analgesic effect lasted 60–90 minutes, which was shorter than that of morphine (120–150 minutes). Radioligand binding assay indicated that dihydroetorphine is a selective mu-type opioid-receptor agonist.

3. *Dependence Potential*

Animal studies indicated that dihydroetorphine possessed a strong psychological dependence potential, 5,000–10,000 times more potent than morphine in self-administration tests in rats, 500 and 100 times more potent than morphine and heroin in self-administration studies in monkeys, 8,000 and 1,000 times more potent than morphine and heroin in drug discrimination studies in rats, respectively. However, animal studies showed that the physical dependence-producing properties of dihydroetorphine were relatively low. The withdrawal syndromes caused by dihydroetorphine in mice jumping tests were weaker than morphine. In monkey withdrawal precipitation tests and abrupt withdrawal tests, withdrawal syndromes of dihydroetorphine were significantly weaker than those of morphine.

4. *Actual abuse and/or evidence of likelihood of abuse*

Abuse of dihydroetorphine began soon after it was marketed in China in 1992. Although indicated as an analgesic, it was also used as an opiate withdrawal syndrome suppressing agent. Its abuse spread very quickly in the country. Epidemiological studies have shown that there were two reasons for starting to abuse dihydroetorphine – iatrogenic and social. One group of abusers began to use the drug for medical purposes but increased the doses because tolerance developed quickly, and the potent dependence-producing properties of dihydroetorphine played a dominant role in compelling the patient to start abusing the drug. Opiate abusers were another group of people who took the drug as a substitute for heroin because of its stronger psychological dependence-producing properties, cheaper price, and less strict control than heroin.

5. *Therapeutic usefulness*

Dihydroetorphine was registered in China in December 1992 for the relief of acute severe pain. However, it is not useful as a drug for substitution treatment of opioid withdrawal because of short duration of action.

6. *Recommendation*

Dihydroetorphine is a potent mu-type opioid-receptor agonist. Based on its pharmacological properties and dependence potential demonstrated in animal studies, as well as its actual abuse observed in China, it is estimated that dihydroetorphine is liable to similar abuse and productive of similar ill effects as the drugs in Schedule I of the Single Convention on Narcotic Drugs, 1961. It is therefore recommended that dihydroetorphine be placed in Schedule I of this Convention.

Remifentanil (INN)

1. *Substance Identification*

Remifentanil (CAS–132875–61–7), chemically 1-(2-methoxycarbonylethyl)-4-(phenylpropionylamino)-piperidine-4-carboxylic acid methyl ester, is also known as GI 87084X. Remifentanil hydrochloride (CAS–132539–07–2) is also known as GI 87084B. There are no chiral carbon atoms in the molecule; so no stereoisomers or racemates are possible.

2. *Similarity to known substances and effects on the central nervous system*

Remifentanil is classified as a relatively selective mu-type opioid-receptor agonist with a profile similar to fentanyl, alfentanil and sufentanil, but with an ultra-short duration of action. Comparison of potency in *in vitro* binding assays specific for the mu-type opioid receptor has demonstrated similar potencies of remifentanil and fentanyl. Remifentanil's analgesic potency was found as similar to fentanyl, alfentanil and sufentanil in rats, mice and dogs.
In clinical pharmacology studies, remifentanil exhibited properties (including adverse effects) that were similar to other fentanyl analogues. The most serious adverse effects were attributable to its mu-type opioid-receptor agonist properties and included hyptotension, bradycardia, muscle rigidity and respiratory depression.

3. *Dependence potential*

Withdrawal signs developed in rats following cessation of remifentanil administration. Remifentanil substituted for morphine in morphine-dependent withdrawn monkeys. Remifentanil was found reinforcing in self-administration studies in monkeys.
In opiate-experienced nondependent human subjects, the very rapid subjective peak effects of remifentanil were not significantly different from those of fentanyl. In another study involving healthy subjects, euphoria occurred at about the same incidence for remifentanil as for fentanyl and alfentanil.

4. *Actual abuse and/or evidence of likelihood of abuse*

One case of remifentanil abuse and overdose by intra-nasal administration occurred during the clinical study of the drug. Remifentanil had been administered over a period of several weeks, leading to an overdose resulting in loss of consciousness, tachycardia, depressed respiration and seizures. Following emergency room treatment, the patient recovered.

5. *Therapeutic usefulness*

Remifentanil is used as an analgesic during induction and maintenance of general anesthesia, in postoperative anesthesia, and in monitored anesthesia care. Remifentanil has been approved for marketing in 17 countries.

6. *Recommendation*

Remifentanil is a short-acting mu-type opioid-receptor agonist. Based on its pharmacological properties and dependence potential, it is estimated that remifentanil is liable to similar abuse and productive of similar ill effects as the drugs in Schedule I of the Single Convention on Narcotic Drugs, 1961. It is therefore recommended that remifentanil be placed in Schedule I of this Convention.

III. Discussion

Although WHO has made specific scheduling recommendations for each of the drug substances, CND is not obliged to follow the WHO recommendations. Options available to the CND for substances considered for control under the Psychotropic Convention include: (1) Acceptance of the WHO recommendations; (2) acceptance of the recommendations to control but control the drug substance in a schedule other than that recommended; or (3) reject the recommendations entirely.

A. Ephedrine

Ephedrine has been recommended for control in Schedule IV of the Psychotropic Convention. If ephedrine is controlled in Schedule IV, the United States, as a signatory to the Convention would have to determine what additional domestic controls, if any, may be needed to fulfill its obligations.

The Convention requires licenses for manufacturers, distributors, and those entities in the retail trade. In addition, Article 9 of the Convention states that ''[t]he Parties shall require that substances in Schedules II, III and IV be supplied or dispensed for use by individuals pursuant to medical prescription only, except when individuals may lawfully obtain, use, dispense or administer such substances in the duly authorized exercise of therapeutic or scientific functions.'' On the other hand, the WHO notification on ephedrine states that ''in making this recommendation, it is noted that ephedrine combination products would be eligible for exemption according to the 1971 Convention.'' The Psychotropic Convention does not mention ''combinations'' but the term ''preparations'' is defined under Article 1 as ''(i) any solution or mixture, in whatever physical state containing one or more psychotropic substances, or (ii) one or more psychotropic substances in dosage form.'' Under Article 3, paragraphs 2 and 3, a party may exempt a preparation from certain controls under the Convention, including the prescription requirement, if the preparation is compounded in such a way that it presents no, or a negligible, risk of abuse.

Ephedrine is available in the United States as an ingredient in over-the-counter (OTC) bronchodilator products and in certain OTC hemorrhoid treatment products. Importantly, ephedrine has been designated as a listed chemical under the CSA (21 U.S.C. 802(34)) and is subject to regulations under 21 CFR 1309, 1310, and 1313 , which are enforced by the Drug Enforcement Administration. Accordingly, distribution of ephedrine single-entity products and certain transactions involving ephedrine combination products are subject to the recordkeeping, reporting, registration, and import/export notification provisions of the CSA. These controls must be examined to determine whether they enable the United States to fulfil its obligations for ephedrine, should it be controlled under Schedule IV of the Psychotropic Convention. Finally, it should be noted that under Article 2, paragraph 7(d), of the Psychotropic Convention, a party may notify the United Nations that, due to exceptional circumstances, it will elect not to apply all of the provisions required by the Convention.

B. Spanish Proposal on Isomers of Schedule I Substances

WHO has also recommended adding a phrase to Schedule I that would ''clarify'' that stereoisomers of psychotropic substances in Schedule I of the Convention would be considered as Schedule I substances. According to WHO, this is ''chemically precise and consistent with the current interpretations of the Convention * * * [and] could provide an explicit clarification of the scope of controlled isomers including racemates.''

It should be noted that WHO is recommending a change in the wording of the list of substances controlled in Schedule I. A similar change was approved by the Commission on Narcotic Drugs in 1977 which modified the Schedules to state, ''[a]lso under international control are the salts of the substances listed in these Schedules, whenever the existence of such salts is possible.'' Adding such a statement about stereoisomers, as WHO has recommended, should not have a significant impact on the scope of control of psychotropic substances. Domestically, under the CSA, stereoisomers are automatically subject to control when a substance is added to Schedule I.

C. Dihydroetorphine and Remifentanil

Dihydroetorphine is a hydrogenated derivative of etorphine and a potent μ-opioid-receptor agonist used as a short-acting analgesic in China. It is not marketed in the United States, but it is considered a Schedule II narcotic substance under the CSA because it is a thebaine derivative. Remifentanil is a selective μ-opioid-receptor agonist of the fentanyl group. Remifentanil is approved in the Unites States as an anesthetic and is controlled domestically as a narcotic in schedule II of the CSA. As such, no additional controls will be necessary to fulfil U.S. obligations if remifentanil is controlled under Schedule I of the Single Convention.

FDA, on behalf of the Secretary of HHS, invites interested persons to submit comments on the United Nations notifications concerning these drug substances and WHO's recommendations on stereoisomers pursuant to the proposal from the Government of Spain. FDA, in cooperation with the National Institute on Drug Abuse, will consider the comments on behalf of HHS in evaluating the WHO scheduling recommendations. Then, under section 811(d)(2)(B) of the CSA, HHS will recommend to the Secretary of State what position the United States should take when voting on the recommendations at the CND meeting in March 1999. Comments regarding the WHO recommendations for control of substances under the Single Convention will also be forwarded to the relevant agencies for consideration in developing the U.S. position regarding narcotic substances at the CND meeting.

IV. Submission of Comments and Opportunity for Public Meeting

Interested persons may, on or before February 10, 1999, submit to the Dockets Management Branch (address above) written comments regarding this notice. FDA does not presently plan to hold a public meeting. If any person believes that, in addition to its written comments, a public meeting would

contribute to the development of the U.S. position on the substances to be considered for control under the Psychotropic Convention, a request for a public meeting and the reasons for such a request should be sent to Nicholas P. Reuter (address above) on or before January 26, 1999. The short time period for the submission of comments and requests for a public meeting is needed to assure that HHS may, in a timely fashion, carry out the required action and be responsive to the United Nations. Comments are to be identified with the docket number found in brackets in the heading of this document. Received comments may be seen in the Dockets Management Branch (address above) between 9 a.m. and 4 p.m., Monday through Friday.

Dated: January 4, 1999.

William K. Hubbard,

Associate Commissioner for Policy Coordination.

[FR Doc. 99–448 Filed 1–8–99; 8:45 am]

BILLING CODE 4160–01–F

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 99F–0001]

McNeil Specialty Products Co.; Filing of Food Additive Petition

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing that McNeil Specialty Products Company has filed a petition proposing that the food additive regulations be amended to provide for additional uses of sucralose as a general purpose sweetener in food.

DATES: Written comments on the petitioner's environmental assessment by February 10, 1999.

ADDRESSES: Submit written comments to the Dockets Management Branch (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT: Blondell Anderson, Center for Food Safety and Applied Nutrition (HFS–206), Food and Drug Administration, 200 C St. SW., Washington, DC 20204, 202–418–3106.

SUPPLEMENTARY INFORMATION: Under the Federal Food, Drug, and Cosmetic Act (sec. 409(b)(5) (21 U.S.C. 348(b)(5))), notice is given that a food additive petition (FAP 8A4624) has been filed by McNeil Specialty Products Co., 501 George St., New Brunswick, NJ 08903–2400. The petition proposes to amend the food additive regulations in § 172.831 *Sucralose* (21 CFR 172.831) to expand the permitted uses of sucralose to allow as a general purpose sweetener in food.

The potential environmental impact of this action is being reviewed. To encourage public participation consistent with regulations promulgated under the National Environmental Policy Act (40 CFR 1501.4(b)), the agency is placing the environmental assessment submitted with the petition that is the subject of this notice on display at the Dockets Management Branch (address above) for public review and comment. Interested persons may, on or before February 10, 1999, submit to the Dockets Management Branch (address above) written comments. Two copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday. FDA will also place on public display any amendments to, or comments on, the petitioner's environmental assessment without further announcement in the **Federal Register**.

If, based on its review, the agency finds that an environmental impact statement is not required and this petition results in a regulation, the notice of availability of the agency's finding of no significant impact and the evidence supporting that finding will be published with the regulation in the **Federal Register** in accordance with 21 CFR 25.40(c).

Dated: December 23, 1998.

George H. Pauli,

Acting Director, Office of Premarket Approval, Center for Food Safety and Applied Nutrition.

[FR Doc. 99–518 Filed 1–8–99; 8:45 am]

BILLING CODE 4160–01–F

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

Peripheral and Central Nervous System Drugs Advisory Committee Meeting; Cancellation

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is canceling the meeting of the Peripheral and Central Nervous System Drugs Advisory Committee scheduled for January 29, 1999. This meeting was announced in the **Federal Register** of December 23, 1998 (63 FR 71145).

FOR FURTHER INFORMATION CONTACT: Sandra Titus, Center for Drug Evaluation and Research (HFD–21), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–827–7001, or FDA Advisory Committee Information Line 1–800–741–8138 (301–443–0572 in the Washington, DC area), code 12543.

Dated: January 4, 1999.

Michael A. Friedman,

Deputy Commissioner for Operations.

[FR Doc. 99–517 Filed 1–8–99; 8:45 am]

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Substance Abuse and Mental Health Services Administration

Agency Information Collection Activities: Proposed Collection; Comment Request

In compliance with Section 3506(c)(2)(A) of the Paperwork Reduction Act of 1995 concerning opportunity for public comment on proposed collections of information, the Substance Abuse and Mental Health Services Administration will publish periodic summaries of proposed projects. To request more information on the proposed projects or to obtain a copy of the information collection plans, call the SAMHSA Reports Clearance Officer on (301) 443–7978.

Comments are invited on: (a) Whether the proposed collections of information are necessary for the proper performance of the functions of the agency, including whether the information shall have practical utility; (b) the accuracy of the agency's estimate of the burden of the proposed collection of information; (c) ways to enhance the quality, utility, and clarity of the information to be collected; and (d) ways to minimize the burden of the collection of information on respondents, including through the use of automated collection techniques or other forms of information technology.

Proposed Project: Projects for Assistance in Transition from Homelessness (PATH) Annual Report—New—The Center for Mental Health Services awards grants each fiscal year to each of the States, the District of