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DIRECT DIAL (202) 737-4293

January 13, 2006

BY MESSENGER

Dockets Management Branch
Food and Drug Administration
5630 Fishers Lane
Room 1061 (HFA-305)
Rockville, Maryland 20852

Re: Comments to FDA Docket 2005N-0479

Dear Dockets Management Branch,

On January 12, 2006 we filed the attached comments to FDA Docket 2005N-0479 by electronic submission per FDA's Federal Register notice, 70 Fed. Reg. 73,775 (Dec. 13, 2005). It is our understanding that Ms. Jenny Butler is out of the office until, at least, next Wednesday, January 18, 2006. We also understand that Ms. Butler is the only person at Dockets with access to comments filed via email. Therefore we are providing these paper copies today with hopes they will be logged into your docketing system sooner to allow dissemination to the public as soon as possible.

If you have any questions, please do not hesitate to contact me.

Sincerely,

John A. Gilbert, Jr.

2005N-0479

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JAG/cld
Attachments

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DIRECT DIAL (202) 737-4280

January 12, 2006

Division of Dockets Management
Food and Drug Administration
5630 Fishers Lane
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Rockville, MD 20852

Re: Docket No. 2005N-0479, International Drug Scheduling; Convention on Psychotropic Substances; Single Convention on Narcotic Drugs ... Buprenorphine ... 70 Fed. Reg. 73,775 (Dec. 13, 2005).

On behalf of Purdue Pharma L.P. and Schering-Plough Corporation, this comment responds to the call for information in the Federal Register Notice published on Tuesday, December 13, 2005, by the Food and Drug Administration (FDA). FDA's request comes in response to a questionnaire from WHO inviting "interested persons to submit comments concerning abuse potential, actual abuse, medical usefulness, trafficking, and impact of scheduling changes on availability for medical use of nine drug substances."[1] This comment concerns buprenorphine, a partial μ-opioid agonist that is currently controlled

1 70 Fed. Reg. 73,755.

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internationally in Schedule III of the 1971 Convention. The responders, Purdue Pharma L.P. and Schering-Plough Corporation, each has an interest in buprenorphine as a medicine important in the treatment of pain and opioid dependence.

According to *Guidelines for the WHO review of psychoactive dependence-producing substances for international control* (*Guidelines*),[2] the WHO Secretariat is to request information from governments concerning substances undergoing critical review for purposes of international control under the 1961 and 1971 Conventions.[3] The timeframe established by WHO and FDA for public comment is entirely inadequate for a complete and well-drafted presentation of the relevant data. Moreover, the proposed manner with which WHO would review buprenorphine violates the agency's own *Guidelines.* We urge FDA to consider carefully the role it has taken in this process. The United States should not be a mere conduit for WHO actions that are palpably violative of the *Guidelines*. We urge our government to address this matter with WHO and, if WHO will not respond appropriately, then our government should take the matter to the members of the Executive Board of the World Health Assembly when next it meets. Our government must object strongly to the breaches of established procedure and insist that proper procedure be followed when the Expert Committee on Drug Dependence (ECDD) reviews buprenorphine or any other substance. It is essential that the US take a strong position in support of the established procedures for international control. They must be followed if

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2 Guidelines for the WHO review of dependence-producing psychoactive substances for international control, (*Guidelines*) WHO/EDM/QSM/2000.5. Reprinted from document EB105/2000/REC/1, ANNEX 9, with appendices.

3 *Guidelines*, paragraph 16.

recommendations for international control are to be consistent with the intent of the Conventions.

Following is a summary of the responder's comments on three important issues: 1) WHO's violation of the *Guidelines* in proposing to make a "final decision" on buprenorphine at this time; 2) the negative effect on medical availability of buprenorphine that will result from placing buprenorphine under Schedule I of the Single Convention; and 3) the lack of data demonstrating that nonmedical use of buprenorphine is a serious problem despite increasing use in opioid addiction treatment.

I. WHO's Breach of Established Guidelines will Deny an Appropriate Scientific and Medical Review of Buprenorphine

A. WHO's Current Review of Buprenorphine Violates the *Guidelines*

WHO's current request for information on buprenorphine asks only the following: If buprenorphine is transferred from Schedule III of the Convention on Psychotropic Substances, 1971, to Schedule I of the Single Convention on Narcotic Drugs, 1961, would its availability for medical use will be affected, and how would its availability be affected?[4] Yet, in a letter to Dr. William Steiger of HHS, WHO characterizes the planned review of buprenorphine in March 2006 as a "final decision."[5] We do not understand what this means. The report from the last ECDD meeting, where buprenorphine was given a critical

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4 70 Fed. Reg. at 73,778.

5 Letter from Dr. Vladimir K. Lepakhin, Assistant Director-General, Health Technology and Pharmaceuticals, to Dr. William R. Steiger, Special Assistant to the Secretary for International Affairs, Office of Global Health Affairs (Nov. 16, 2005).

review, concluded with a decision not to change the schedule.[6] The procedure dictated by the *Guidelines* makes no reference to "final decisions." Nor is there any provision that allows the WHO legal department the authority to prescribe decisions as "a legal matter," as is asserted in the WHO letter to Dr. Steiger.

The usual procedure by which ECDD is to make recommendations is that there be a pre-review, then a critical review. Specifically, the *Guidelines* state:

> *Critical Review*
> *15. Critical review is conducted by the Expert Committee in any of the following cases: (1) there has been notification from a Party to the 1961 or the 1971 Convention concerning the scheduling of a substance; (2) there has been an explicit request from CND to review a substance; (3) pre-review of a substance has resulted in a recommendation for critical review as indicated in paragraph 13 above; (4) information is brought to WHO's attention that a substance is clandestinely manufactured, of especially serious risk to public health and society, and of no recognized therapeutic use by any Member State. If therapeutic use of the substance is confirmed subsequently by any Member State in respect of case (4), the substance shall be subjected to a pre-review.*[7]

The *Guidelines* say nothing about a "final decision" procedure. Further, as we review paragraph 15, we find no justification under the conditions of that paragraph for there to be any further review of buprenorphine at this time. There is no provision for a kind of rolling decision-making process for scheduling in which one ECDD can delegate

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6 **WHO ECDD, Thirty-Third Report at 10 (2003), *available at* http://www.unicri.it/min.san.bollettino/altre/915-en.pdf.**

7 *Guidelines*, paragraph 15.

decisions, based on the deliberations of that ECDD, to a future ECDD. The reason the rules do not grant this authority is obvious: the medical and scientific data used by a prior committee are outdated by the time the next ECDD meets. As noted below, this is especially true in the case of buprenorphine. Good science does not allow the kind of decisions upon which the "final decision" procedure would rest.

There is no reasoned basis for why WHO has posed the single, two-part question about the impact of a scheduling change without requesting data on the most current medical and scientific information available concerning buprenorphine. Even the answer to the questions about medical availability will to some extent be affected by the degree of necessity, etc. that attends buprenorphine as a medicine. For example, since the critical review in 2002 WHO itself has sought to have buprenorphine accorded essential drug status. Surely WHO does not wish to have decisions made in 2006 based on data from 2002; that would not include full consideration of the reasons for buprenorphine's placement on the essential drug list and the impact of changes in control on the availability of an essential medicine. That would be inconsistent with good medical and scientific practice.

In fact, the *Guidelines* are quite specific concerning the nature of the data used for ECDD's decision-making. In paragraph 17, WHO is instructed: "[t]o help ensure that all material submitted to the Expert Committee is up to date, the Secretary of the Committee will circulate the agenda of the next meeting to ... collaborating information sources."[8] Further, the ECDD is instructed: "[i]f, for any reason, the Expert Committee bases its

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8 *Guidelines*, paragraph 17.

assessment on limited data, it would need to provide full justification for reaching conclusions on incomplete data."[9] In this case, there can be no justification for ignoring the current data relating to buprenorphine. The inexplicable failure to ask the proper range of questions concerning buprenorphine will, for that reason alone, make it impossible for the ECDD to consider buprenorphine properly at the March 2006 meeting.

The workings of the ECDD have been considered by the Executive Board of the World Health Assembly; the *Guidelines* are the result of that consideration. If WHO is free to ignore the direction of the Executive Board, then deleterious uncertainty will be injected into the process, and member states will no longer value the decisions that are made by WHO and, ultimately, the Commission on Narcotic Drugs (CND).

B. A Scheduling Decision on Buprenorphine Based on the 2002 Critical Review will be Deficient

1. The 2002 Critical Review Misinterpreted the Guidelines and the Conclusions of the 25th ECDD

If the 34th ECDD only considers the 2002 Critical Review and other information provided to the 33rd ECDD, their decisions will be based on inaccurate and incomplete information concerning the *Guidelines* and findings of the 25th ECDD.

The 2002 Critical Review, as considered by the 33rd ECDD, mistakenly stated that 1) the *Guidelines* do not require that control under the 1961 Convention is considered first and separately from control under the 1971 Convention and, 2) the 25th ECDD misinterpreted the *Guidelines* and erred in its evaluation of buprenorphine. The 2002

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9 *Guidelines*, paragraph 20.

Critical Review presented the committee the following incorrect interpretation of the *Guidelines*:

> *As indicated in section 1 F, the main question for the Expert Committee to address is whether buprenorphine should be reclassified as a narcotic drug or it should remain a psychotropic substance as judged by the 1988 Committee. The scheduling requirement under the 1961 Convention is that the substance is "liable to similar abuse and productive of similar ill effects" as those already under its control. The Guidelines re-state this as "morphine-like", "cocaine-like" or "cannabis-like". In the case of buprenorphine, therefore, the question boils down to "how similar to morphine does buprenorphine have to be for it to be judged 'morphine-like'?" Since no specific guidance is available in the Guidelines, there is a need to work out an interpretation guideline to address this question.*
>
> *If any substance that cannot be scheduled under the 1961 Convention could be scheduled under the 1971 Convention, the applicability of the 1961 Convention to a substance could be determined independently, without considering the applicability of the 1971 Convention. This was apparently the view of the 1988 Committee which, without considering the applicability of the 1971 Convention, chose to apply the 1971 Convention to buprenorphine after concluding that the drug was not "morphine-like". In reality, however, the 1971 Convention also specifies the nature of the substance that can be controlled as a psychotropic substance in terms of CNS effects and dependence liability or similarity to psychotropic substances already under control. Therefore, the 1988 Committee was not correct in its process of considering the question. In other words, whether a substance is "morphine-like" or not is a relative question to be judged in relation both to its similarity to a narcotic drug as well as to a psychotropic substance, when the drug under review has considerable similarity to both narcotic drugs and psychotropic substances. It is therefore necessary to examine the applicability of the 1971 Convention to buprenorphine, and re-examine the applicability of the 1961 Convention to it.*[10]

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10 WHO, 33rd ECDD, Critical Review of Psychoactive Substances ("2002 Critical Review), QSM/ECDD33/4, Annex 3, page 2 (Sept. 2002).

Thus, the 33rd ECDD was incorrectly informed that for certain classes of psychoactive substances (i.e., those that have considerable similarity to both narcotic drugs and psychotropic substances) the determination of which Convention is appropriate for purposes of international control is a relative question based on the similarity of the substance to both narcotic drugs and psychotropic substances. Historically, the 1971 Convention was intended to control those psychoactive substances that did not meet criteria for control under the 1961 Convention, but nonetheless warranted international control. Therefore, as the *Guidelines* clearly indicate, the applicability of the 1961 Convention is considered first. The possible applicability of the 1971 Convention is considered only after it has been decided that the 1961 Convention does not apply; the *Guidelines* state:

> *33. The Expert Committee, when deciding whether to recommend international control after completion of its discussions, first decides, with regard to the 1961 Convention, whether the substance has morphine-like, cocaine-like, or cannabis-like effects or is convertible into a scheduled substance having such effects. If so, it then determines, in accordance with Article 3, paragraph 3(iii) of that Convention, if the substance: (1) is liable to similar abuse and productive of similar ill-effects as the substances in Schedule I or Schedule II; or (2) is convertible into a substance already in Schedule I or Schedule II.*
>
> . . .
>
> *37. If the Expert Committee finds that the psychoactive substance does not meet the criteria described in paragraph 33 and cannot therefore be appropriately controlled under the 1961 Convention, it makes its recommendations in terms of the 1971 Convention.*[11]

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11 *Guidelines*, paragraphs 33,37.

The advice given to the 33rd ECDD in the 2002 Critical Review was erroneous when it said that the 25th ECDD "was not correct in its process of considering the question."[12] In fact, expressly following paragraph 37 of the *Guidelines*, the 25th ECDD report states the 1961 Convention "categorizes substances having certain specific characteristics, and substances that act dissimilarly cannot be scheduled under it."[13] The 25th ECDD report goes on to state that: "[t]he Committee carefully examined the texts of the two existing international conventions for drug control and analyzed the pharmacological characteristics of six agonist-antagonist substances."[14] The 25th ECDD report also makes clear that it considered the applicability of the 1961 Convention to buprenorphine. The report states:

> *The Committee concluded, on the basis of information currently available, that none of the six agonist-antagonists opioids considered at the meeting was appropriate for control under the terms of the Single Convention on Narcotic Drugs, 1961.*[15]

In making its recommendations concerning buprenorphine, the 25th ECDD was clearly aware of the development of buprenorphine as a treatment for opioid dependence. The Committee reported "the degree of seriousness of the public health and social problems associated with the abuse of this drug was not found to be great in terms of the numbers of individuals involved and the impact of the abuse on their well-being."[16] However, it was also clearly aware that "problems of considerably greater magnitude may develop as its

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12 2002 Critical Review, Annex 3, page 2.

13 WHO, ECDD Twenty-Fifth Report, at 21 (1989).

14 Id. at 16.

15 Id. at 21.

16 Id. at 23.

reinforcing effects and ability to suppress opioid withdrawal symptoms become better known to those already abusing opioids such as heroin."[17] It was, in fact, the potential for such problems that led the committee to conclude that buprenorphine warranted international control. Nonetheless, the committee reiterated its view that "on the basis of current understanding of opioid pharmacology as outlined in section 4.1.2, the differences between the partial mu agonist buprenorphine and such prototypic mu agonists as heroin, morphine and methadone warrant the use of the Convention on Psychotropic Substances, 1971 for the control of buprenorphine."[18]

The guidance given to the 33rd ECDD should not be used again. The decision making process of the 25th ECDD was correct.

2. There have been Significant Developments in Medical Use of Buprenorphine Since 2002

The WHO questionnaire does not request any new information on the medical use of buprenorphine or whether there have been any indications of abuse. Again, if the 34th ECDD relies on the 2002 Critical Review, the committee will consider incomplete data on buprenorphine.

For example, since 2002 there has been an increase in the medical use of buprenorphine in the United States following the approval of buprenorphine for substitution treatment for opioid dependence. Specifically, the approved use of buprenorphine in office-based treatment has resulted in an increase in the number of patients who seek out

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17 Id. at 24.

18 Id.

treatment. As discussed more fully in Section III, this increased use has not led to a significant problem of abuse or misuse, further demonstrating that buprenorphine is different from morphine and other narcotics in regard to the potential for abuse.

3. The 2002 Critical Review does not Consider the Importance of Buprenorphine in the Prevention and Treatment of HIV among Drug Users

The 2002 Critical Review makes no mention of the role of buprenorphine in control of HIV/AIDS. In its 1995 report INCB expressed concern that nonmedical use of buprenorphine was contributing to the spread of HIV and AIDS in India, Bangladesh and Nepal.[19] This concern was a major reason for the INCB to recommend moving buprenorphine to Schedule I of the 1961 Convention. The spread of HIV is a critical public health issue. However, buprenorphine, along with methadone, is, in fact, central to the effort to control HIV/AIDS in opioid dependent populations. It is for this reason that HIV/AIDS was prominently mentioned in the decision by the 14th WHO Expert Committee on the Selection and Use of Essential Medicines to add these drugs to the WHO model list in 2005.

It is unacceptable, therefore, for the 34th ECDD to consider the 2002 Critical Review document which did not attempt to evaluate the role of buprenorphine in the treatment of drug users who have contracted or are at risk for HIV/AIDS. Such an omission makes it impossible for the ECDD to recommend control of buprenorphine in either the 1961 or 1971 Conventions. Both Conventions require consideration of the public health impact of scheduling decisions. Given what is known about the impact of international drug control

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19 Report of the International Narcotics Control Board for 1995, E/INCB/1995/1, at paragraph 285 (1995).

on the availability of medicines, it is not possible to control buprenorphine without consideration of the practical impact of control of buprenorphine on the spread of HIV/AIDS.

II. Transferring Buprenorphine from Schedule III of the 1971 Convention to Schedule I of the 1961 Convention will Adversely Affect its Availability for Medical Use in the United States.

Transferring buprenorphine from its current position in Schedule III of the 1971 Convention to Schedule I of the 1961 Convention will have a serious negative impact on its availability for medical use. There are several reasons for this.

A. The Controlled Substances Act (CSA) Limits the Drugs Available for use in Substitution Treatment in Primary Care in the United States.

Because of the critical unmet medical need for treatment of addiction in the United States, the U.S. Congress passed the Drug Addiction Treatment Act of 2000 ("DATA") which allows specially trained and certified physicians to treat a limited number of addicts in office-based treatment — but only for drugs in Schedule III – V.[20] Thus, drugs such as morphine or methadone, that are controlled in Schedule II, are not available for use in such treatment under the DATA. The Drug Enforcement Administration (DEA) rescheduled buprenorphine to Schedule III of the CSA,[21] which ensured that it would be available for use under the DATA. Such action is consistent with its current level of international

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20 Codified at 21 U.S.C. § 823(g).

21 Schedules of Controlled Substances: Rescheduling of Buprenorphine From Schedule V to Schedule III, 67 Fed. Reg. 62,354 (Oct. 7, 2002).

control — in Schedule III of the 1971 Convention. Thus, buprenorphine is the first and only agonist drug eligible for office-based use as Congress intended.

Rescheduling buprenorphine to the Single Convention could result in a requirement that the US place all buprenorphine products in Schedule II—which would completely eliminate use of Subutex and Suboxone from office-based addiction treatment.

B. Differential Scheduling of Buprenorphine and Drugs Containing Buprenorphine would be Necessary to Protect the Availability of Buprenorphine in the US

DEA has stated that rescheduling of Subutex, Suboxone and Buprenex will not be required for the US to meet its obligations under the 1961 Convention.[22] However, DEA has acknowledged that rescheduling of buprenorphine to the 1961 Convention would at a minimum require control of bulk buprenorphine in Schedule II of the CSA.[23] DEA's proposal to reschedule buprenorphine to Schedule III in 2000 did not distinguish between the abuse potential of bulk buprenorphine, Subutex, Suboxone and other buprenorphine products such as Buprenex.[24] If there is no difference in the abuse potential between these different buprenorphine-containing products and bulk buprenorphine from the perspective of US law, it is unclear whether DEA could scientifically and medically justify differential scheduling if challenged by opponents of buprenorphine's use in the treatment of addicts.

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22 See Response of the United States to the WHO Questionnaire for Review of Dependence-Producing Psychoactive Substances by the 33rd Expert Committee on Drug Dependence (hereinafter "2002 U.S. Response") at 12-13 (May 17, 2002).

23 Id.

24 67 Fed. Reg. 62,354.

Based on the prior rulemakings scheduling buprenorphine, there is a real concern that some individuals would oppose differential scheduling even without a scientific and medical basis for doing so. For example, in comments filed with the DEA on the 2000 rescheduling of buprenorphine in 2000, one comment, from a physician affiliated with the largest methadone substitution program in the country warned DEA to carefully consider the financial conflicts of persons submitting comments, noting that "[clinic] owners and staff may well have interests that would be adversely affected" by the wider availability of buprenorphine.[25] Another comment was from a law firm that contended that all buprenorphine products should be placed in Schedule II. The same law firm has filed objections to the approval of Subutex and Suboxone without restrictions similar to those placed on methadone substitution on behalf of "a leading provider of opiate addiction treatment services."[26]

It is worth noting that recently, in its decision to control butorphanol, DEA refused to control only the single-entity nasal spray formulation, and placed all products containing this drug in the same schedule as the bulk substance.[27] Therefore, while it is true that dextroproxyphene bulk and finished dosage forms are differentially scheduled,[28] there

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25 Letter from Robert Newman, M.D., Director, Continuum Health Partners, to the DEA (May 23, 2002).

26 Comments of Hogan & Hartson LLP, dated May 22, 2002, filed in response to DEA proposed rule, 67 Fed. Reg. 13114 (Mar. 21, 2002).

27 Schedules of Controlled Substances; Placement of Butorphanol Into Schedule IV, 62 Fed. Reg. 51,370 (Oct. 1, 1997).

28 21 C.F.R. §§ 1308.12 and 14.

remains a concern about differentially scheduling buprenorphine if the drug is rescheduled to Schedule I of the Single Convention.

If it is not possible to differentially schedule single entity buprenorphine drug products from the bulk drug substance in the U.S., individuals will be denied access to buprenorphine in primary care. Such a development would be particularly detrimental to the well-being of pregnant drug users.

C. NIDA has Expressed Concern that Moving Buprenorphine to the 1961 Convention Would Curtail its Medical Use in the U.S.

NIDA has expressed concern that rescheduling in the U.S. as a result of international rescheduling to the 1961 Convention would have a substantial negative impact on the use of buprenorphine in the treatment of addiction.[29] NIDA is rightly concerned that states will impose additional restrictions on buprenorphine if they perceive that it is similar to methadone based on its level of scheduled control. As the Institute of Medicine (IOM) has pointed out, history shows that unwarranted, excessive regulation is clearly something that states have done to opioid dependence treatment with methadone in the past.[30]

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29 2002 U.S. Response at 12-13.

30 Federal Regulation of Methadone Treatment, Richard A. Rettig and Adam Yarmolinski, Editors Committee on Federal Regulation of Methadone Treatment, Institute of Medicine, National Academy Press, Washington D.C., (1995 IOM Report).

D. International Control of Drugs Negatively Influences their Availability for Medical Purposes

Although the U.S. has made substantial progress in recent years in providing adequate access to morphine-like drugs for analgesia, the IOM has pointed out that the restrictions on the use of methadone for substitution treatment are beyond those necessary for medical reasons.[31] Yet the effect of these restrictions is very clear: half of the patients who participated in NIDA's office-based treatment trial had not been in treatment before and were unlikely to seek treatment in methadone clinics. The post-approval evaluation of buprenorphine office-based treatment in the U.S.[32] has shown that a number of those receiving buprenorphine have not previously been in treatment for their illness. This evaluation has also shown that even the much-reduced regulatory burden associated with buprenorphine use under DATA is still a significant deterrent to some physicians using this therapy.[33] Yet, the availability of buprenorphine for the treatment of addiction via physicians' office is becoming increasingly successful. There are almost 10,000 physicians who have been trained in the use of buprenorphine, approximately 6,800 who have received

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31 "[T]here is no compelling *medical* reason, in the committee's view, for regulating methadone differently from all other medications approved by FDA, including schedule II controlled substances." 1995 IOM Report at 4. (Emphasis in the original.)

32 McLeod CC, Kissin WB, Stanton, A, Sonnefeld J. 30-day outcomes for buprenorphine patients treated by a national sample of qualified physicians. Findings from SAMHSA/CSAT's Evaluation of the Buprenorphine Waiver Program. Poster Presented at The College on Problems of Drug Dependence. June 20, 2005.

33 Stanton A, McLeod C, Kissin W, Sonnefeld J, Luckey J. Results from SAMHSA/CSAT's Evaluation of the Buprenorphine Waiver Program. The College on Problems of Drug Dependence. June 20, 2005.

waivers to prescribe it, and about 4,500 currently prescribing buprenorphine to treat addiction.[34] As of March 2005, it was estimated that more than 100,000 patients had been inducted. It is important that more than half of the physicians prescribing buprenorphine had no previous experience providing medication assisted treatment.

The different conditions under which methadone and buprenorphine may be used for substitution treatment in the U.S. are directly related to their domestic control, the extent of which is critically determined by the control of these substances in Schedule I of the 1961 Convention and Schedule III of the 1971 Convention, respectively.

Similarly, it is clear from INCB statistics that the use of full-opioid agonists controlled in Schedule I of the 1961 Convention is uniformly less than the use of drugs such as codeine and dextropropoxyphene, which are controlled in Schedule II of the 1961 Convention. The reason for this is not that codeine is more medically useful than morphine. Rather, it is that preparations of drugs in Schedule II of the 1961 Convention are listed in Schedule III of that Convention and, therefore, have fewer restrictions on their medical use.

The impact of differential scheduling of morphine-like and codeine-like drugs in the U.S. is clear. Single entity hydrocodone is controlled to the same extent as morphine. No single entity hydrocodone-containing pharmaceuticals are in medical use. On the other hand, hydrocodone preparations that include ingredients such as acetaminophen are

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34 Personal Communication with Robert Lubran, MPH, Director of the Division of Pharmacologic Therapies within SAMHSA's Center for Substance Abuse Treatment (CSAT), Department of Health and Human Services, January 2006.

controlled to a lesser extent than morphine. In 2004, there were 92,719,975 prescriptions for these products — far exceeding the 12,118,687 prescriptions for oxycodone-acetaminophen combination products with similar medical indication.[35] Also, largest number of prescriptions in the United States are hydrocodone preparations.

As the above discussion shows, there is a clear link between the international control status of buprenorphine and its control under the CSA. The extent to which moving buprenorphine to Schedule I of the 1961 Convention would affect patient care in the U.S. is, at best, uncertain, but would clearly be adverse to patient care.

The U.S. response to the questionnaire must make clear to WHO that there is a direct link between international scheduling decisions and the resulting domestic scheduling. It must also make clear that there are substantial differences in medical availability between controlled drugs and uncontrolled drugs and between drugs controlled in Schedules III and IV of the 1971 Convention on one hand and drugs controlled in Schedule I of the 1961 Convention on the other hand. It is unacceptable that an expert committee charged with making key recommendations regarding the availability of critical medicines such as buprenorphine would not be apprised of this information.

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35 See The Top 300 Prescriptions for 2004 by Numbers of U.S. Prescriptions Dispensed, available at http://www.rxlist.com/top200.htm. Accessed January 7, 2006.

III. Buprenorphine Abuse is not a Serious Problem in the U.S.

In its response to the WHO Questionnaire for the 2002 critical review of buprenorphine, the U.S. indicated that there was "little abuse" of the currently marketed buprenorphine products and that DEA had not seen any evidence that abuse was increasing.[36] The U.S. also noted that the rescheduling of buprenorphine from Schedule V to III was not based on "an escalation in abuse of buprenorphine" but only in anticipation of approval of new formulations.[37]

Although the FDA notice has not provided sufficient time for a review of all relevant data, a cursory review of the data from the Drug Abuse Warning Network (DAWN), the National Forensic Laboratory Information System (NFLIS) and reference to sources such as the National Association of Drug Diversion Investigators (NADDI) indicate that little has changed since 2002; abuse of buprenorphine is not a serious problem in the U.S. This is true despite buprenorphine's use in a highly vulnerable population, that is, opioid addicts. A recent study referenced in the New England Journal of Medicine indicates that "there has been very little abuse of buprenorphine since its launch for the treatment of opioid addiction in the first quarter of 2003."[38] These findings are contrary to the concerns expressed by DEA and FDA that approval of new formulations would necessarily result in

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36 2002 U.S. Response at 10.

37 Id. at 8.

38 Potential for Abuse of Buprenorphine in Office-Based Treatment of Opioid Dependence, Letter to the New England Journal of Medicine, Theodore J. Cicero, Ph.D. and James A. Inciardi, Ph.D., October 27, 2005.

increased abuse.[39] Any consideration by the 34th ECDD to reschedule buprenorphine without a complete review of these and other data is deficient.

A. Drug Abuse Warning Network (DAWN) Data

Given the increasing use of buprenorphine in the office-based treatment for addiction in the U.S., the relatively low number of DAWN cases and seizures are encouraging in that they suggest that the therapeutic benefit associated with buprenorphine far outweighs the risk of abuse even in a vulnerable population.

DAWN is a measure of the consequences associated with the abuse of drugs. The DAWN data system utilized since 2002 classifies cases based upon a decision tree in which the type of cases is assigned hierarchically. The hierarchy is as follows:

- Suicide attempt
- Seeking Detox
- Alcohol only (age < 21)
- Adverse Reaction
- Overmedication
- Malicious poisoning
- Accidental Ingestion
- Other

There are several definitions that are important for the discussion of buprenorphine in the context of the DAWN data. These definitions are "Overmedication" and "Other." The DAWN ED Reference Guide defines "Overmedication" as patients who took more than the recommended dose of a prescription or OTC drug or dietary supplement. This includes, but

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39 Id. at 10.

is not limited to, the following reasons: patients who forgot they had already taken a dose; those who took extra dose(s) to make up for a missed dose; and patients who took more medication because their symptoms did not subside with the recommended dose. This case type includes patients who took more than the recommended dose for recreational or abuse purposes. Illicit drugs are not included in this case type.

The DAWN ED Reference Guide further defines "Other" as all other drugs and substances not classified above. This category includes all other cases in which drug dependence, abuse, withdrawal, suicidal ideation or gesture, recreational use, or reason unknown (patient comatose) caused or contributed to the ED visit.

The data presented in the tables below are from DAWN for buprenorphine for the period January 1, 2003 to December 28, 2005. An examination of the DAWN data for this period shows that there were a total of 355 cases associated with the use of buprenorphine for this period. This is a very small number of cases especially since this drug is primarily used in a highly vulnerable population (Table 1).

Table 1
Distribution of Opioid Analgesic and Buprenorphine Cases in DAWN 2003-2005

Drug	N
Hydrocodone Combination	25,473
Oxycodone Combinations	23,793
Methadone	18,123
Codeine/Combinations	6,064
Fentanyl	3,188
Hydromorphone	2,143
Buprenorphine	355

Further examination of the unweighted buprenorphine reports in DAWN indicates a total of 349 reports for this period. Fifty-five percent of the cases were male and about half (49.8%) were age 35 or older. Other (48.4%), Adverse Reaction (22.9%), Seeking Detox (19.2%), and Overmedication (7.4%) were the most prevalent types of cases, while Withdrawal (37%), Other (34.7%), Digestive Problems (24.1%), Seeking Detox (18.9%), Psychiatric Condition (13.8%), Overdose (13.2%), and Altered Mental Status (11.5%) account for the majority of the complaints (Table 2).

Table 2
Distribution of Combined Unweighted Buprenorphine New DAWN Cases by Selected Variables for the period 2003-December 28, 2005

Variable	Number	Percent
N	349	
Gender		
Male	193	55.3
Female	155	44.5
Age		
0-20	22	6.3
21-34	153	43.8
35-44	94	26.9
45-54	57	16.3
55+	23	6.6
Type of Case		
Suicide Attempt	2	0.6
Seeking Detox	67	19.2
Adverse Reaction	80	22.9
Overmedication	26	7.4
Malicious Poisoning	0	0

Accidental Ingestion	5	1.4
Other	169	48.4
Chief Complaint		
Overdose	46	13.2
Intoxication	9	2.6
Seizures	3	0.9
Altered Mental Status	40	11.5
Psychiatric Condition	48	13.8
Withdrawal	129	37.0
Seek/Detox	66	18.9
Accident/injury/assault	7	2.0
Abscess/cellulitis/skin/tissue	22	6.3
Chest Pain	11	3.2
Respiratory problems	26	7.4
Digestive Problems	84	24.1
Other	121	34.7
Total Complaints	612	
Complaints/Case	1.8	

The DAWN data also suggest that even among the low number of buprenorphine reports in DAWN, buprenorphine may be being used as a form of self-treatment rather than for abuse purposes. DAWN collects eight different case type with "Other" representing drug abuse. Over the period from January 2003 to December 28, 2005, a total of 349 cases associated with buprenorphine were reported. Of these, 169 (48.4%) were classified as "Other" and the primary complaint was withdrawal. This is unlike other drugs such as oxycodone and codeine where the cases classified as "Other" included a higher rate of the complaint being for "Overdose." (Tables 3 and 4).

Table 3
Comparison of Selected Characteristics between Buprenorphine Cases Classified as Overmedication or Other in New DAWN January 1, 2003-December 28, 2005

	Overmedication		Other	
Variable	Number	%	Number	%
N	26		169	
Gender				
Male	17	65.3	96	56.8
Female	9	34.7	73	43.2
Age				
0-20	0	0	12	7.1
21-34	10	38.5	78	46.2
35-44	6	23.1	46	27.2
45-54	7	26.7	24	14.2
55+	3	11.5	9	5.3
Chief Complaint				
Overdose	18	69.2	14	8.3
Intoxication	3	11.5	4	2.4
Seizures	0	0	1	0.6
Altered Mental Status	8	30.8	20	11.8
Psychiatric Condition	5	19.2	29	17.2
Withdrawal	2	7.7	95	56.2
Seek/Detox	0	0	0	0
Accident/injury/assault	0	0	5	3.0
Abscess/cellulitis/skin/tissue	1	3.8	5	3.0
Chest Pain	0	0	6	3.6
Respiratory problems	1	3.8	14	8.3
Digestive Problems	1	3.8	52	30.8
Other	5	19.2	59	34.9
Total Complaints	44		304	
Complaints/Case	1.7		1.8	

Table 4
Comparison of Selected Characteristics between Cases Classified as Overmedication or Other for Codeine/Combinations and Oxycodone/Combinations for the Period 2003-2004

	Codeine Combinations				Oxycodone Combinations			
	Overmedication		Other		Overmedication		Other	
Variable	Number	%	Number	%	Number	%	Number	%
N	877		585		2,481		4,223	
Gender								
Male	278	51	298	51	1,139	46**	2,515	60
Female	285	49	285	49	1,338	54	1,706	40
Age								
0-20	163	19	100	17	160	6**	460	11
21-34	278	32	169	29	618	25**	1,509	36
35-44	178	20**	157	27	617	25**	1,166	28
45-54	150	17	107	18	590	24**	752	18
55+	104	12	50	9	490	20**	334	8
Chief Complaint								
Overdose	714	81**	229	37	1,857	75**	946	22
Intoxication	45	5**	58	10	153	6**	330	8
Seizures	6	<1	10	2	22	1	83	2
Altered Mental Status	223	25	123	21	764	31**	704	17
Psychiatric Condition	152	17**	119	20	285	11**	826	20
Withdrawal	4	<1**	44	8	36	1**	1,423	3

								4
Seek/Detox	3	<1**	7	1	7	<1	117	3
Accident/injury/assault	14	2**	30	5	60	2**	154	4
Abscess/cellulitis/skin/tissue	9	1*	17	3	27	1**	112	3
Chest Pain	15	2*	21	4	36	1**	176	4
Respiratory problems	15	2*	24	4	100	4**	186	4
Digestive Problems	62	7*	63	11	99	4**	558	13
Other	143	16	156	27	408	16**	1,056	25
Total Complaints	1405		901		3,854		6,671	
Complaints/Case	1.6		1.5		1.5		1.6	

* $p<0.05$ **$p<0.01$

In sum, given the increasing use of buprenorphine in a highly vulnerable population the actual number of DAWN cases is relatively low and shows that buprenorphine abuse is not a serious problem.

B. National Forensic Laboratory Information System (NFLIS)

The data on seizures as reported in the NFLIS database also confirm that there is little abuse of buprenorphine in the U.S. In 2002, the U.S. reported to WHO that there was no evidence of clandestine manufacture of buprenorphine and forensic laboratory seizure data showed very few seizures of buprenorphine injectable products.[40]

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40 2002 U.S. Response at 11.

NFLIS is a computerized database of analyzed drug exhibits from state and local forensic laboratories that was developed by the Research Triangle Institute under contract to the DEA in 1997. The system began reporting data in 1998. By September 30, 2001, 145 of the estimated 276 state and local labs that perform solid dosage drug analysis had been recruited into NFLIS. As of March 2005, the system had grown to include 41 state systems and 81 local or municipal laboratory systems representing 244 individual labs. These labs analyze nearly 71% of the nation's estimated 1.2 million annual state and local drug cases. Data from the System to Retrieve Information from Drug Evidence (STRIDE) are now included in the NFLIS database.

NFLIS results are made available through quarterly and annual reports. These reports provide statistically representative national and regional estimates for the most frequently identified drugs. National case estimates for the most common identified drugs are also presented in the reports. These reports also include findings on major drug categories such as narcotic analgesics, benzodiazepines, club drugs, anabolic steroids, and stimulants. These data are presented in section 2 of the report, and unlike the national estimates which are based on a national sample of laboratories; this section includes data submitted by all participating labs that reported 6 or more months during the year. Also included in the report are data on drug combinations, drug purity for heroin and cocaine, and some city data for the top 4 drugs. A major strength of the NFLIS is its size, which renders it somewhat less susceptible to variations in police activity than STRIDE.

Data were reviewed for buprenorphine for the years 2000 through 2004.[41] Although data for the year 2000 are published, the systems were still in the implementation phase and are not useful for trends.[42] Nonetheless, a review of the data for the year 2000 indicates that even among the 7,680 narcotic analgesics, buprenorphine accounted for 8 cases or approximately 0.1%. Data for the years 2000 - 2004 were obtained from published reports. NFLIS data were examined for pharmaceutical opioids, and buprenorphine for 2000 through 2004. Data are presented as a percentage of total analgesics. If the drugs are also included in the top 25, they are noted. While, as noted above, trends can be analyzed for the period 2002 - 2004, changes in the proportion of drug mentions over time can be assessed for the previous years.

In general, analgesics represent a fraction of all seizures in 2000 - 2004. Cannabis, cocaine, methamphetamine and heroin account for more than 84 percent of all seizures. The remainder of the top 25, including hydrocodone, oxycodone, methadone, codeine, morphine and propoxyphene account for an additional 8.6 percent of total seizures.

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41 2000 – 2004 NFLIS Annual Reports, located at www.deadiversion.usdoj.gov/nflis/index.html.

42 Differences in regional trends may also "reflect different drug enforcement priorities and laboratory policies that can influence the types of drugs submitted to an analyzed by laboratories." A potential example of the impact of lab policies is found in the 2002 Annual Report section on drug combinations. Of the 11,519 drugs items containing two or more substances that were reported, 9 percent or 1,037 contained hydrocodone and acetaminophen. Based on the unweighted data from all reporting labs this should have been closer to 9,500. It is likely that once the hydrocodone was found the lab, especially smaller labs, didn't proceed with further analysis to identify acetaminophen.

Buprenorphine became available for the office-based treatment of addiction in 2003. In 2003, there were nine seizures of buprenorphine. In 2004, despite steadily increasing utilization, there were only 148 seizures. This represents only 0.4% of analgesic seizures and 0.01% of all seizures.

C. National Association of Drug Diversion Investigators (NADDI)

The trends noted by the DAWN data and the NFLIS seizure data appear to be consistent with the observations of drug diversion investigators. For example, in November 2005, the State of Florida was deciding whether to schedule buprenorphine consistent with the federal schedule.[43] An inquiry was made with NADDI. Although only a few responses were received, none indicated a problem with buprenorphine abuse. Agents for Florida concluded that "some abuse has been seen but not to any great extent." There was also an observation that the drug has a slow onset and a different action than opioids that makes it a poor choice for abuse. Another investigator commented that the drug was not found on Internet websites and that it appeared to not be a drug that opioid abusers would seek out.

Data from these various sources, including queries to the NADDI, suggest that the abuse of buprenorphine, despite its availability in a highly vulnerable population, is low. Given the increasing use of buprenorphine in the office-based treatment of addiction, the relatively low number of DAWN cases and seizures are encouraging in that they suggest that the therapeutic benefit associated with buprenorphine far outweighs the risk of abuse even in a vulnerable population.

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43 E-Mails received from NADDI, November 2005.

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In conclusion, the WHO's review of buprenorphine violates the *Guidelines*, and its hastily called meeting of the ECDD ensures that the ECDD will not consider the most relevant scientific and medical information on buprenorphine. Rescheduling of buprenorphine will negatively affect the availability of the drug in the United States for office-based treatment of opioid addiction. Finally, despite limited time to review US data on buprenorphine, it is clear from several sources that there is a lack of significant abuse of buprenorphine, even given increased use by high risk populations.

On behalf of Purdue Pharma, L.P. and Schering-Plough Corporation, we request that the U.S. object to WHO's plan to have the March 2006 ECDD consider a review of buprenorphine. Such objections should be brought to the attention of the members of the Executive Board of the World Health Assembly.

Sincerely,

for

James R. Phelps