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Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

CITIZEN PETITION

The undersigned submits this petition under 21 C.F.R. 10.30 on behalf of a leading provider of opiate addiction treatment services to request under the Food, Drug, and Cosmetic Act (the "FDC Act") and the Controlled Substances Act (the "CSA") that the Commissioner of Food and Drugs (the "Commissioner") take the actions described below with respect to any and all pending new drug applications ("NDAs") for buprenorphine drug products intended for use in the treatment of opiate addiction.

A. ACTIONS REQUESTED

By this petition, the undersigned requests that the Commissioner refrain from entering final approval under section 505 of the FDC Act for any buprenorphine product that has not been presented for review and evaluation before an appropriate FDA advisory committee. The possible marketing of a buprenorphine product for the treatment of opiate addiction raises important scientific, medical, and policy issues that should be vetted before a public advisory committee before any such product is considered for final approval by FDA.

Second, we request that the Commissioner refrain from authorizing the marketing in interstate commerce of any such product without first making a recommendation (through the Assistant Secretary for Health) to the Attorney General to place buprenorphine under a more restrictive level of control. Buprenorphine is currently listed under Schedule V of the CSA, the least restrictive level of control authorized by law for a drug of abuse. The proposed introduction of a tablet-based buprenorphine product, for use in treating opiate addiction, significantly increases the potential for abuse of the drug and, in turn, requires much stricter control under the CSA.

B. STATEMENT OF GROUNDS

1. Background

Bubrenorphine hydrochloride ("buprenorphine") is an opioid agonist drug substance approved for use in the United States for the relief of moderate to severe pain. It is marketed in an injectable dosage form (0.3mg/ml) and is used primarily for inpatient care.

Buprenorphine is a chemical derivative of the narcotic substance thebain,1/ which is controlled by the Drug Enforcement Administration ("DEA") under Schedule II of the CSA, the highest (*i.e.*, most restrictive) level of control for a drug with FDA approved uses. *See* 21 U.S.C. 812(b); 21 C.F.R. 1308.12. Buprenorphine itself is currently controlled under schedule V of the CSA. 21 C.F.R. 1308.15(b).

When administered parenterally, buprenorphine exhibits pharmacologic effects in common with the Schedule II drug substance, morphine. Buprenorphine "exerts its analgesic effect via high affinity binding to μ subclass opiate receptors in the central nervous system." Tab 1, Approved Package Insert for Buprenex®. Although it is generally considered to be a "partial" agonist, FDA has stated that "under the conditions of recommended use it behaves very much like classical μ agonists such as morphine." *Id.* The analgesic potency of buprenorphine, however, is

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1/ The thebain ring is contained within the structure of buprenorphine, resulting in a skeleton much like that of morphine and heroin. *See* 50 FR 8104 (Feb. 28, 1985).

estimated to be 25 to 40 times greater than that of morphine. *See* 53 FR 36886 (Sept. 22, 1988).

As with morphine, buprenorphine has a significant respiratory depressant effect that may occur even within the recommended dosage range. *See* Tab 1, "Warnings: Impaired Respiration." Moreover, use of the drug in combination with benzodiazepines or alcohol can significantly amplify this and other central nervous system effects. As stated in the approved labeling, "[t]here have been reports of respiratory and cardiovascular collapse in patients who received therapeutic doses of diazepam and Burpenex®." *Id.* 2/

For at least the last seven years, the National Institute on Drug Abuse ("NIDA") has been working with a pharmaceutical company, Reckitt & Colman Pharmaceuticals, Inc. ("Reckitt & Colman") under a Cooperative Research and Development Agreement ("CRADA") to develop buprenorphine products for the treatment of opiate dependence. 58 FR 28031 (May 12, 1993) (announcing notice of intent to award NIDA-sponsored CRADA to Reckitt & Colman); *see* Tab 3, NIDA, "Buprenorphine Update: Questions and Answers" (Jan. 29, 2001). As of July 1999, NIDA reported that it had invested more than $25 million in public funds toward the buprenorphine project. Tab 4, Letter from Secretary Shalala to the Honorable John Dingell dated July 14, 1999, at Q.11.

In or about June 1997, Reckitt & Colman submitted an NDA for a buprenorphine product to be marketed under the trade name Subutex® in 2 and 8 mg sublingual tablets. In comparison, the approved dosage strength for Buprenex® is only 0.3 mg, with a maximum recommended dose of 0.6 mg. *See* Tab 1, "Dosage and Administration."

2/ Some have asserted that the risks associated with buprenorphine are mitigated by a "ceiling effect" in high-dose and overdose situations. *Cf.* Tab 2, M. Reynaud *et al.*, "Six deaths linked to concomitant use of buprenorphine and benzodiazepines," 93 *Addiction* 1385, 1386, 1390 (1998) (discussing "the ceiling effect" of buprenorphine but concluding that "the demonstration of potentially lethal effects of the buprenorphine-benzodiazepine association challenges the purported harmlessness of buprenorphine.").

Based on public disclosures by NIDA, it is our understanding that on June 30, 1998, FDA issued an approvable letter for Subutex®. *See* Tab 4 at Q.4. According to NIDA, the 1998 approvable letter raised issues "related to the proposed formulation" for Subutex®. *Id.* The application, however, remains pending at FDA. 3/

In June 1999, Reckitt & Colman submitted a second NDA for a buprenorphine drug product. The second NDA is for a 2 and 8 mg sublingual buprenorphine product in a fixed combination with naloxone hydrochloride, in a 4 to 1 ratio, to be marketed under the trade name Suboxone®. The addition of naloxone – an opioid *antagonist* – is intended to reduce the potential for diversion and abuse associated with a tablet-based form of buprenorphine.

As noted above, buprenorphine exhibits powerful morphine-like effects if administered by injection. The drug itself is easily solubilized and can readily be converted into an injectable dosage form for intravenous administration. Indeed, it has been reported that buprenorphine is abused intravenously by heroin addicted persons in countries where the sublingual tablet is available as an analgesic. Naloxone is known to reverse opiate depression and cause a person addicted to opiates to immediately fall into withdrawal. It is also believed to be much more potent when injected than when taken orally. Thus, the addition of naloxone to buprenorphine is intended to be aversive, to minimize the serious concerns about the introduction a buprenorphine product in a tablet form and the possible IV abuse of the tablet. The Suboxone® NDA, like the Subutex® NDA, remains pending at FDA. 4/

3/ An "approvable letter" is "a written communication to an applicant from FDA stating that the agency will approve the application . . . if specific additional information or material is submitted or specific conditions are met." 21 C.F.R. 314.3. An approvable letter does not constitute approval for purposes of section 505(c) of the FDC Act. *Id.*

4/ In December 1999, the agency issued an "approvable" letter for Suboxone®. And, in January 2000, it was reported that FDA issued a second approvable letter for Subutex®. *See* Tab 5, "Reckitt Suboxone to be First

The maintenance treatment of narcotic addiction has, for at least the last three decades, been subject to strict control and regulation under section 303(g) of the CSA and under extensive federal treatment standards. 21 U.S.C. 823(g). Until January 2001, these standards were contained in regulations maintained by NIDA and FDA under 21 C.F.R. Part 291. The NIDA/FDA regulations effectively limited the maintenance treatment of addiction to comprehensive clinic-based narcotic treatment programs. In January 2001, the Secretary completed the transfer of responsibility for these programs to the Substance Abuse and Mental Health Services Administration (SAMHSA) and finalized a new set of regulations under 42 C.F.R. Part 8 to replace the NIDA/FDA scheme. *See* 66 FR 4076 (Jan. 17, 2001). The new regulations, like the old, contemplate the use of clinic-based programs to oversee the treatment of narcotic addiction.

In October 2000, several months prior to the issuance of the new opioid treatment rules, Congress amended the CSA to allow general practice physicians to undertake the maintenance treatment of narcotic addiction outside the context of full-service programs. Under the new legislation (Pub. L. 106-310), a practitioner who proposes to use a drug *other than* a Schedule II drug may do so, within certain limits, without having to meet the standards established by SAMHSA. Buprenorphine, which is controlled under Schedule V of the CSA would qualify for this exemption or "waiver." Methadone and LAAM, the only two drug products currently approved for the maintenance treatment of opiate addiction, are controlled under Schedule II and would not qualify for the waiver. Thus, under the new legislation, buprenorphine could be the first opiate addiction medication available in community pharmacies for use by general practice physicians.

2. The Need for Advisory Committee Review

The pending buprenorphine NDAs raise important scientific, medical, and policy issues that should be brought before an appropriate FDA advisory committee prior to the agency reaching a final premarket approval decision. *See* 21 C.F.R. 14.5(a) ("An advisory committee is utilized to conduct public hearings on matters of importance that come before FDA, to review

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Anti-Addiction Narcotic Filled in Pharmacy," *F-D-C Reports* ("The Pink Sheet") Oct. 30, 2000.

the issues involved, and to provide advice and recommendations to the Commissioner.").5/

FDA has been a leader in the use of expert advisory committees for several decades. The agency works closely with its advisory committees to ensure that review staff make sound decisions based on good science. Advisory committee meetings also provide one of the few opportunities for the public to participate in the drug approval process. As a former Commissioner explained:

> "Together, this team of advisors delivers a valuable external viewpoint about difficult issues that face the agency," says [former] FDA Commissioner Jane E. Henney, M.D. And its growing emphasis, she says, clearly demonstrates that consumer and patient contributions to the advisory committees are significant. As a result, communications have improved between FDA officials and committee experts, and the public has begun to feel more involved in the agency's decision-making process.

Tab 6, C. Lewis, "Advisory Committees: FDA's Primary Stakeholders Have a Say," *FDA Consumer* (Sept-Oct 2000); *see* 21 C.F.R. 14.1(a)(1) (the agency may convene an advisory committee to hold a public hearing when the Commissioner concludes that it is "in the public interest" for interested persons to present information and their views).

Here, the possible approval of a buprenorphine drug product for use in treating opiate addiction is an action that should not be taken without ample opportunity for public participation. Like other drugs of abuse, such as Oxycontin® and GHB, buprenorphine may pose risks both to the immediate user and to the community. In addition, there are core scientific and medical issues associated with buprenorphine products that should be presented to an advisory committee meeting for careful scrutiny, including:

5/ Applications pending before the Division of Anesthetic, Critical Care, and Addiction Drug Products within the Center for Drug Evaluation and Research ("CDER") generally are presented to the Anesthetic and Life Support Drugs Advisory Committee. An alternative forum would be the Psychopharmacologic Drugs Advisory Committee.

- Does the sponsor's clinical data demonstrate that Subutex® and Suboxone® are safe at the recommended doses, which are orders of magnitude higher than the currently approved dose for buprenorphine? What additional labeling is needed to address safety issues – including respiratory depression and the risks of diversions – associated with the higher dose?

- Do the clinical studies provide substantial evidence of effectiveness? Did the sponsor use an appropriate endpoint? For how long were the patients in the studies expected to remain free of illicit drugs?

- How will buprenorphine products be labeled relative to methadone, the long-established standard for maintenance treatment? For what population or subpopulation will buprenorphine be recommended?

- What is the rationale for approving Subutex®, if the combination product, Suboxone®, is equally effective?

- Has the sponsor demonstrated through adequate tests and studies that the addition of naloxone will, in fact, offset the potential for abuse? Has the stability of naloxone in the combination been demonstrated? If the naloxone degrades at a faster rate than buprenorphine, under conditions of heat, light, and humidity, how will that impact the safety of the drug? What measures must be taken to ensure that drug abusers cannot easily defeat this and other anti-diversionary features?

- Should the drugs be placed under a restricted distribution scheme (21 C.F.R. 314.520) to ensure safe use in what is generally regarded as a difficult patient population (*i.e.*, heroin addicts)? Are "take home" standards needed, and should such standards or requirements be integrated into the final approved labeling?

- What other anti-diversionary measures must be taken to minimize the potential for abuse associated with a solid oral dosage form of buprenorphine?

Given these issues, along with the fact that buprenorphine is described as a drug that will change the "paradigm" of drug abuse treatment, 6/ it would be highly *unusual* were the agency not to seek advisory committee guidance well in advance of reaching a final decision.

Second, an advisory committee meeting will provide an opportunity for FDA to benefit from the independent opinions and recommendations of the Committee members. The pending NDAs have been assembled with substantial support from NIDA, an agency that works very closely with FDA on drug abuse issues. 7/ NIDA itself has made a number of public statements regarding the safety and efficacy of these products, long before FDA has had the chance to consider the data. Indeed, in September 2000, FDA, DEA, and SAMHSA issued a public statement clarifying that buprenorphine is *not* approved for opiate addiction treatment. *See* Tab 7, "Dear Colleague" letter dated Sept. 1, 2000. Given the extensive involvement of a sister-agency in the development of this drug, it is important to bring an independent group of experts into the review process.

Finally, because the original application for buprenorphine has been pending at the agency for more than four years, there is certainly ample time to schedule a meeting. There are, to our knowledge, no "fast track," "accelerated approval," or "priority review" considerations. And, neither of the two advisory committees that would review the pending applications has a full calendar. 8/

6/ *See, e.g.*, 65 FR 25894, 25895 (May 4, 2000).

7/ NIDA and FDA are agencies within the Department of Health and Human Services.

8/ Both committees are chartered to hold at least four meetings per year and, as of December 2001, only one of the committees has a meeting on the calendar in the coming year.

For these reasons, the agency should commit to holding an advisory committee meeting to review the Subutex® and Suboxone® applications before reaching a final approval decision. 9/ If the agency declines to hold such a meeting, it should provide a detailed written explanation as to why it chose not to do so in this instance.

3. The Need for a New Scheduling Analysis

All drugs that are, or have the potential to be, abused in some fashion are subject to control by the Attorney General (and, by delegation of authority, DEA) under the scheduling provisions of the CSA. *See* 21 U.S.C. 811-812. The CSA sets forth five levels of control, with Schedule I being the most restrictive and Schedule V the least restrictive. 21 U.S.C. 812(b). Placement of a particular drug under the one of the five schedules is based primarily on the drug's potential for abuse relative to other controlled drugs and its relative potential for physical or psychological dependence.

The Secretary of the Department of Health and Human Services (and, by delegation of authority, the Assistant Secretary for Health or the "ASH") plays an integral role in scheduling and rescheduling decisions made under the CSA. In particular, before a proceeding may be initiated to schedule a drug, DEA must obtain from the ASH a detailed medical and scientific analysis, along with a recommendation as to the appropriate level of control. *See* 21 U.S.C. 811(b). The analysis, which must be based on the eight factors set forth in section 201(c) of the CSA (21 U.S.C. 811(c)), is generally written by FDA.

Indeed, FDA has been designated as the "lead agency" in carrying out the scheduling responsibilities of the Secretary (and the ASH) under the CSA. *See* 66 FR 20038, n.1 (April 18, 2001). It is FDA's responsibility to keep DEA informed when an application is submitted for a drug that appears to have a potential for abuse. *See* 21 C.F.R. 314.104; *see also* 21 U.S.C. 811(f). And, given FDA's role in the drug approval process, it is not uncommon for the agency on its own initiative to commence a scheduling analysis. Once FDA prepares such an analysis and

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9/ If, in the end, the NDAs are fatally deficient, it would be appropriate for the agency to dispense with the need for a meeting.

recommendation (commonly referred to as an "eight factor analysis"), the document is presented by the Commissioner, with the concurrence of NIDA, to the ASH for transmittal to DEA.

We urge FDA in this instance to prepare a medical and scientific evaluation of buprenorphine, and to recommend the placement of buprenorphine under a much more restrictive level of control than that allowed under Schedule V. We also urge the agency, as it has done in the past, to share its analysis with the public as early in the process as possible. 10/

The abuse potential of a drug substance is dependent on a range of factors, one of which is the ease with which the substance may be diverted for illicit use. The introduction of a tablet dosage form, in itself, is likely to make it easier to divert the drug. For example, for nearly 30 years FDA prohibited the use of solid forms of methadone in narcotic treatment programs, for fear that a solid dosage form (as opposed to an oral solution) will be diverted from programs. 11/

The higher strength of the tablets, when compared with the currently available injectable form (8.0 mg *versus* 0.3 mg) will also significantly change the abuse profile of the drug. From just one 8 mg tablet, an intravenous drug abuser could fashion a solution that is much stronger, both in quantity and concentration, than the currently marketed version of the product. The fact that the NDA sponsor, along with NIDA, has gone to great lengths to develop a combination naloxone product suggests a strong concern about the abuse potential of these tablets.

Finally, and by far the most important consideration, is the proposed distribution of the tablets for use among general practice physicians to treat heroin addicted individuals. No longer will the drug be available

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10/ For example, in April 1998, the agency held an advisory committee meeting to discuss, among other things, a draft eight-factor analysis for the drug tramadol.

11/ The new SAMHSA rules allow for the first time the use of a solid dosage form of methadone. *See* 42 C.F.R. 8.12(h).

primarily as an in-patient analgesic. It will now be widely available for out-patient and "take-home" use among persons who often come into treatment with a history of medical, social, and psychological co-morbidities. Many opiate addicts who undertake treatment exhibit behaviors that are typical of the severely addicted, including deception, exposure to and participation in criminal activity, physiologic and psychological changes, bouts of depression, and a history of social and familial instability. The potential is great that the availability of a morphine-like drug, in a tablet dosage form for use in patient population with a history of drug abuse, will bring with it a significant amount of diversion and abuse. 12/

This marked shift in treatment, and the proposed new use and new dosage form, dramatically changes the abuse liability profile of buprenorphine. Any prior assessment of the likelihood that buprenorphine would be abused, and its relative potential for abuse, is now out-of-date. 13/

For these reasons, we request that FDA prepare – prior to allowing the marketing of a new buprenorphine product14/ – a new eight

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12/ *See, e.g.,* Tab 8, Y. Obadia *et al.*, "Injecting misuse of buprenorphine among French drug users," 96 *Addiction* 267, 269-71 (2001) (finding "substantial misuse" of buprenorphine by injection shortly after the drug was introduced for maintenance treatment and that "injecting misuse of buprenorphine is currently inescapable as soon as buprenorphine is diffused for [drug maintenance treatment].").

13/ The last scheduling decision for buprenorphine was made more than 15 years ago. 50 FR 8104 (Feb. 28, 1985). More recent studies of the drug also suggest that a new analysis is warranted. *See, e.g.,* Tab 2, Tab 8, and Tab 9, Bedi *et al.*, "Abuse Liability of Buprenorphine – A Study Among Experienced Drug Users," 42(1) *Indian J. Physiol Pharmacol* 95, 98 (Jan. 1998) (finding that in a study of six post-detoxified subjects, IM administered buprenorphine caused significant euphoria and was identified as heroin).

14/ Should FDA propose the scheduling of buprenorpine in Schedule II, III, or IV of the CSA, then the sponsor of the drug cannot begin to market the product until after DEA makes a final scheduling decision. *See* FDA Form 356h (requiring NDA sponsors to agree, as a condition of submission, that "If this application applies to a drug product that FDA has proposed for

factor analysis and recommend a much more restrictive level of control. We also ask that the agency share its analysis with the public and, as appropriate, provide an opportunity for public input. The marketing of buprenorphine tablets for use in the treatment of narcotic addiction is a subject of great public concern; substantial public funds have been used to develop the drug and, as discussed, abuse and diversion is likely to have a significant impact on the communities where this drug may be used.

C. ENVIRONMENTAL IMPACT

The actions requested in these comments are not within any of the categories for which an environmental assessment is required pursuant to 21 C.F.R. § 25.22.

D. ECONOMIC IMPACT

Information on the economic impact of this proposal will be submitted if requested by the Commissioner.

E. CERTIFICATION

The undersigned certifies, that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

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scheduling under the [CSA], I agree not to market the product until [DEA] makes a final scheduling decision.").

F. CONCLUSION

On behalf of an interested member of the public, we request that the Commissioner invoke the agency's advisory committee process before approving buprenorphine for use in treating opiate addiction. In addition, we request that FDA prepare a new scheduling analysis for buprenorphine in light of the new dosage form, formulation, and intended use of the drug and share the analysis with the public. Finally, we request that FDA take steps to ensure that buprenorphine products for use in treating opiate addiction are not introduced into interstate commerce until a final scheduling decision by DEA has been reached.

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Enclosures

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