The following is a list of action items.

ACTION: The Sponsor will submit the information about the characterization of the impurities to the Division.

ACTION: The Sponsor will clarify the COA listed in the meeting package for the Suboxone extract used in the pre-clinical studies on impurities.

ACTION: The Sponsor agreed to send in a request for another meeting prior to the next submission.

ACTION: The Sponsor will provide the appropriate data for acceptance criteria for the drug product tests.

ACTION: The Sponsor will provide the appropriate data on individual degradation products.

ACTION: The Sponsor will provide the acceptance criteria for individual degradation products. The Sponsor has improved their identification and monitoring process.

ACTION: The Sponsor will provide the test and acceptance criteria for individual tablet dissolution. In the submission the data were reported as mean data but the individual tablet data are available.

ACTION: The Sponsor will provide data to cross correlate the different degradation products found in Subutex and Suboxone.

ACTION: The Sponsor will provide identification of the site of packaging used for drug product stability batches and the proposed commercial drug product packaging site.

ACTION: No agreement was reached on a PK study design and this issue will need to be resolved by telecon or another meeting.

ACTION: The Sponsor will submit a summary of all the stability studies conducted on the drug product (manufacturing site, packaging, formulation, storage conditions, etc.).

The meeting adjourned at ~12:30 PM

NOTE: The Sponsor provided a package of their overheads used during the meeting.

APPEARS THIS WAY

/s/

Sara Shepherd
3/13/01 08:57:35 AM

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: January 25, 2001

To: Director, Division of Anesthetic, Critical Care, and Addiction Drug Products (HFD-170)

Through: Deborah B. Leiderman, MD, MA
Director, Controlled Substance Staff (HFD-009)

From: Michael Klein, Ph.D.
Controlled Substance Staff (HFD-009)

Subject: Controlled Substance Staff Proposals on Scheduling and Risk Management for Buprenorphine and Buprenorphine-Naloxone Sublingual Tablets (NDA #20-732 & 20-733)

The purpose of this memo is to summarize the basis for the proposal to reschedule buprenorphine under the Controlled Substances Act (CSA) to Schedule III and to reschedule the combination products of buprenorphine-naloxone to Schedule IV. Rescheduling will occur soon after approval of NDAs 20-732 and 20-733, and prior to marketing. For the purposes of CSA scheduling, buprenorphine is defined as the drug substance and all possible products, mixtures and combinations, except for approved drug products that contain buprenorphine and naloxone. CSS additionally proposes that a Risk Management Program be developed to ensure safe use of the buprenorphine-containing drugs.

DRUG SCHEDULING & RISK MANAGEMENT PROPOSALS

The criteria for listing a drug in a CSA schedule derive from an assessment of its relative abuse and dependence potential properties. A drug listed in Schedule III must have a potential for abuse less than drugs in Schedules I and II and must produce moderate or low physical dependence or high psychological dependence. A drug in Schedule IV has a lower potential for abuse than drugs in Schedule III and produces limited physical or psychological dependence. Sublingual buprenorphine tablets produce predominantly opiate agonist effects with little or no contributing antagonist effect of naloxone. By contrast, buprenorphine combined with naloxone and parenterally administered to opioid-dependent individuals may precipitate a withdrawal syndrome. Actual abuse documented from France, New Zealand, and other countries largely involves opiate addicts extracting and injecting the active ingredient of the buprenorphine tablets. Therefore, if this pattern repeats in the United States, the addition of antagonist to buprenorphine would be expected to reduce its intravenous abuse, although other routes for the "street addict" to abuse the drug would not be significantly affected.

In addition to listing buprenorphine in more restrictive CSA schedules, a Risk Management Program (RMP) is needed and needs to be part of the NDAs. Such a program will ensure safe use of buprenorphine and prevent abuse by other at-risk populations, including the drug naïve individual and non-dependent intravenous opioid abuser. Features of the Program should include the following:

1. A post-marketing surveillance plan for diversion and safety
2. Development of —
3. Voluntary restriction of take-home medication
4. An —
5. Educational material to be distributed to patients, doctors, pharmacies
6. A plan to monitor signals for off-label use
7. 1-800 number to report diversion
8. A Dear Pharmacy/Healthcare letter
9. A plan for physician/pharmacist interaction
10. Monitoring of existing databases to provide periodic updates to FDA

ABUSE AND DEPENDENCE POTENTIAL

The evaluation of buprenorphine considers the profile of effects related to (1) abuse potential and (2) physical dependence capability.

Buprenorphine has high affinity for, and slow dissociation from, the mu-opioid receptor. Buprenorphine produces a typical opioid-like spectrum of effects. These include euphoria, drug liking, pupillary constriction, respiratory depression and sedation. In both preclinical and clinical studies, buprenorphine manifests a shallower dose response curve and "ceiling effect" for many actions compared to pure agonists such as morphine (C-II) and hydromorphone (C-II). Buprenorphine is thus considered a partial opioid agonist.

The withdrawal syndrome that develops after continued use is typical of opioids and is evidence of the capacity of buprenorphine to produce physical dependence. The intensity of the withdrawal syndrome has been evaluated by clinical investigators to vary from moderately severe to moderate to mild. Drug craving has been reported after discontinuing use of buprenorphine, which has in some patients resulted in the need to resume use of heroin. This craving is indicative of psychophysiological dependence. Individuals dependent on buprenorphine can easily return to heroin use and vice versa. Twenty percent of newborns born to mothers in treatment with buprenorphine substitution for opiate dependence have exhibited a narcotic abstinence syndrome (NAS) severe enough to require treatment. For mothers maintained on methadone (C-II), 60-80% NAS of varying severity was reported.

The presence of the opiate antagonist, naloxone, in the combination product is expected to reduce its abuse. The antagonist may diminish the euphoria produced by buprenorphine. Withdrawal in opiate dependent individuals may be precipitated, if the drug combination is

parenterally administered. Dependence production is thus limited in this at-risk population. Naloxone administered by the sublingual route is not bioavailable.

MORBIDITY AND MORTALITY

In France, sublingual buprenorphine has been available by prescription. During the first three years of marketing, approximately — individuals were treated with the drug for heroin addiction. More than 100 buprenorphine-related deaths were reported. The deaths involved individuals who were not in treatment for addiction, but who obtained the drug through diversion. Most cases involved diverted medication and concomitant use of other psychoactive drugs, especially benzodiazepines. Risks associated with misuse of the tablet form of buprenorphine were primarily by intravenous injection.

Benzodiazepines ranked first in association, (present in 91 observations, of which 64 were nordiazepam). There were 37 cases involving neuroleptics, of which 26 were with cyamemazine. Eighteen cases (8 with tricyclics and 10 SSRI's) were with antidepressants. Concomitant use of other narcotics was observed with morphine (12 cases), codeine (2 cases), methadone (4 cases), meperidine (1 case) and *dextro*-propoxyphene (4 cases). There were 4 reported fatalities involving ethanol and buprenorphine.

ACTUAL ABUSE

Numerous articles have been published in the scientific literature on buprenorphine abuse. Thus far, in the United States, buprenorphine has been marketed as a Schedule V, injectable product (0.3 mg/mL). Abuse of the injectable formulation has been low, because of limited marketing and availability. Parenteral formulations are not available to patient populations to the same extent as are oral, sublingual, or transdermal formulations. Many national governments have increased the regulatory controls on buprenorphine as a result of abuse and diversion. The reports from other countries need to be examined in relation to how the new drug products will be marketed in the United States. The proposed additional CSA restrictions and Risk Management Program will offer deterrents to abuse, diversion, overdose, and deaths, which differ from the manner in which buprenorphine has been marketed elsewhere after approval.

Buprenorphine was first marketed in France in 1987 as an analgesic. Its approval for treatment of opiate addiction followed in 1996. Abuse and diversion was identified soon after it first became available. Due to misuse of the sublingual form, special narcotic restrictions on the prescribing and dispensing of buprenorphine in treating pain were instituted in December 1992. Prescriptions had to be written on a voucher taken from a counterfoil prescription book that was specifically designed for narcotic drugs and monitored by the French Medical Association. Records had to be retained by the pharmacist for 3 years. The prescription could be filled by any pharmacy. As of 1996, general practitioners were permitted to prescribe the buprenorphine tablets for treating opiate dependence for up to 28 days per prescription, by use of the counterfoil prescription book. Doses prescribed were in the range of 4 to 16 mg/day. In September 20,

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