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June 7, 2007

Food and Drug Administration
Dockets Management Branch
Room 1-23
12420 Parklawn Dr
Rockville, MD 20857
301-827-6860

CITIZEN PETITION

The Undersigned submit this petition in quadruple to address appropriate modifications to 21 CFR Part 291, 42 CFR Part 8 in accordance with 21 CFR Part 10.30. The Methadone related deaths and cases of diversion have risen astronomically since SAMHSA has been responsible for overseeing OTP's.

This petition is on behalf of the victims and those yet to be victims of methadone. We are the concerned citizens, family members, and friends of those who have died at the hands of uninformed doctors, hospitals, and methadone.

A. ACTION REQUESTED

We are asking government agencies to enact stricter guidelines in prescribing methadone for any reason. It must be mandatory that all doctors be certified and trained in the pharmacology of methadone; inpatient stays must be required during induction to methadone; all staff must be extensively trained in monitoring methadone patients for symptoms of toxicity. Clinic patients should be tested weekly for legal and illegal drugs that are taken with methadone to get "high" or experience "euphoria", such as benzodiazepines, alcohol, cocaine, heroin, marijuana etc... and face severe consequences or mandatory detoxification from the methadone program after 3 dirty urines. Selling of take home doses must result in termination from methadone program permanently throughout the U.S. When presenting inebriated at clinic, clinic should also document such activity as well as prevent client from driving. Take home doses for all patients receiving methadone should be eliminated thus preventing the risk of diversion or precautions such as pill safe should be implemented. http://www.thepillsafe.com/

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B. STATEMENT OF GROUNDS

We (the families of methadone victims) are requesting new laws surrounding who can prescribe methadone, clinic rules and regulations, as well as stiffer penalties for those caught selling their take home doses. The whole methadone maintenance system needs an overhauling. We cannot continue to allow a legal medication to be killing more people than the illegal drugs. Our government cannot be allowed to use tax dollars to fund their legal drug dealing operations.

Methadone is now the #2 Killer Drug in the U.S. This is a legal drug that has been thought to be safe for the past 40 years. Only recently when its use became approved for pain management patients has the cardio toxic risks emerged. Previously, methadone has been used exclusively for replacement therapy for heroin patients and death was thought to be an effect of the accumulation of many years of drug abuse. With the surge in pain medication misuse and abuse, more patients are being referred to methadone clinics and physicians treating pain who believe the myth that methadone is safer or non addictive because of its use with weaning addicts from heroin. Methadone is more addictive then any other pain medication including heroin because of its extremely long half life, cardio toxic risks, numerous fatal drug interactions, dosages based on tolerance, and small margin of error. Up until November 2006, the government and pharmaceutical companies have been suppressing the numerous health and fatality risks related to methadone.

- There are between 800,000 & 900,000 (some statistics give different numbers) heroin addicts in the U.S and 1,881 people died from heroin in the U.S. in 2004.

- There are 200,000 people on methadone for drug treatment and an undetermined number of people on it for pain, but even if we double the 200,000 and assume it's 400,000 total people on methadone, there were 3,849 deaths in 2004.

- Methadone looks like the "gold standard" but is killing more than heroin, the drug its supposed to save people from!

- Every day 10.9 people die from methadone (according to 2004 stats).

Current statistics show that nearly 4,000 people a year die from methadone. These deaths are mostly happening to pain management and detoxification patients' within the first 10 days of taking initial dose. Most of these deaths are related to methadone prescribed with other medications that react as additives with the methadone. Diversion of methadone is a serious problem because it lands this most deadly drug on the streets. Statistics also state that methadone is contributing to more deaths nationwide then heroin and is second only to cocaine deaths.

The potential of abuse, diversion, and overdose to new patients being prescribed methadone is overwhelming. The unique properties of methadone, its long half life, and

its negative interaction with numerous drugs make it an optimal choice as a last result treatment for chronic pain and addiction.

Full statement of grounds continued on attached page.

C. ENVIROMENTAL IMPACT

The Petitioner claims a categorical exclusion under 21 CFR 25. 31.

D. ECONOMIC IMPACT

The petitioner does not believe with would be applicable as shifting responsibility back to the FDA would place methadone under the proper regulatory agency with other opioid and scheduled drugs.

E. CERTIFIATION

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 know to the petitioner which are unfavorable to the petition.

Sincerely

Melissa Zuppardi
President
HAMRD, Inc. (Helping America Reduce Methadone Deaths)
65 Montowese St
Branford, CT 06405

enc: Attachments

Methadone is an opiate that was first introduced after World War II as an alternative to morphine. Methadone was originally thought to be less addictive because of its extremely long half life. Today, methadone is used as an analgesic for pain management and more popularly as replacement therapy for heroin and other opiate addictions. According to Wikipedia 2006, "methadone is chemically unlike morphine or heroin, methadone also acts on the opioid receptors and thus produces many of the same effects...methadone has a slow metabolism and very high lipid solubility, making it longer lasting than morphine-based drugs." Methadone is also one of the cheapest of the opiates landing it as a preferred drug for insurance companies consequently making doctors more apt to prescribe it to patients.

Methadone is fat soluble and is primarily stored in the liver and secondarily in other body tissues such as lungs, kidney, and spleen. Methadone is difficult to detect in blood because it's mainly stored in these organs and the transfer between body organs and blood is slower according to Australian Government Department of Health and Ageing (2003). The elimination half-life of methadone ranges from 24-36 hours but may deviate from 4 to 91 hours depending on how it metabolizes in the individual body chemistry of each patient and due to the fact of other drug interactions that may be taking place. The Center for Substance Abuse Treatment, Methadone-Associated Mortality: Background Briefing Report (~~2004)~~ states that "because of the long half-life, achieving steady-state serum methadone levels (SML's) - in which drug elimination is in balance with the amount of drug remaining in the body - requires, on average, from 4 to 5 days, although it can take much longer in some individuals... After each dose, the SML, typically reaches a peak in 3 to 4 hours (with a range of 1 to 5 hours), although individual physiologic responses differ for a variety of reasons."

Methadone has many uses but only recently has become more popular for pain management and recreation. Methadone was initially created as an opiate analgesic but became accepted as an agonist agent in heroin addicts. Its effectiveness is in replacement of heroin in the opioid receptors in the brain of the addict to eliminate painful withdrawals and reduce cravings. Methadone essentially replaces an illegal short acting drug (heroin) with a legal long acting drug (methadone) to help reduce crime, and decrease spread of blood borne diseases associated with illicit drug use while enabling the individual to pursue a healthy lifestyle and contribute as a productive member of society.

In an article from George Mason University , Maia Szalavitz (2006) attributes the recent rise in Methadone being prescribed for pain management to the deaths and addiction potential of OxyContin. Pressure, from the DEA, along with media forced physicians to look for a safer but effective alternative to OxyContin therefore resulting in prescriptions for the widely used Methadone. Methadone has been primarily successful in its treatment of heroin addiction. Methadone has been extensively researched and is believed less addictive because of its longer half-life duration then other opiates used to treat pain. Opiates have historically been used for recreation to achieve the "high" associated with the release of endorphins creating a euphoric sensation. This feeling of euphoria has led many people to abuse opiates by not taking them as prescribed resulting in continued use and consequently dependence and finally addiction. Methadone seems to be an appropriate substitution of other more popular opiates that are abused because of its delayed narcotic effect and lack of the typical "high". The Charleston Gazette (2006) states that "researchers found that opioid painkillers caused 91 percent more deaths in 2002 than four years before – far more than heroin or cocaine, according to death certificates". With those astounding statistics it stands to reason why medical professionals are looking for a safer approach at treating chronic pain.

Since methadone has been more recently used for non-addicts; methadone sales (not including methadone for drug treatment) have risen 175 percent, more than any other opioid sold according to The Charleston Gazette (2006) Methadone mortality rates have increased, with increased methadone sales. The Charleston Gazette (2006) reports a new analysis done by the Centers for Disease Control and Prevention found the number of Americans who have died from overdoses of methadone increased 213 percent between 1999 and 2002. Methadone advocates and pharmaceutical companies attribute this increase to illegally obtained and diverted methadone pills almost exclusively from pain management recipients and not methadone clinics. Research indicates the majority of deaths occur during the induction phase

of methadone, in patients with prescriptions or beginning a maintenance program.

Induction to methadone poses the most significant risks to patients because methadone doses are frequently increased rapidly, while many patients have not yet achieved the levels of tolerance to physiologically combat fatal respiratory depression. Karch and Stephens (2000) state that most deaths occur during the first few weeks of treatment.

"The conversion of methadone to the metabolite EDDP is mediated by liver microsomes, mainly CYP3A4 and possibly CYP2C9 and CYP2C19. Methadone induces hepatic production of these microsomal enzymes, accelerating the metabolism of methadone in chronic users. The enzyme systems will not have been induced in new opiate users who will thus take longer to clear methadone from their bodies, placing them at greater risk of overdose. If other drugs are misused, or if prescription drugs are taken, the picture is further complicated since these drugs can induce, inhibit or compete for the same microsomal enzymes".

A National Assessment of Methadone-Associated Mortality: Background Briefing Report states (2004) that the increased death rate during induction is attributed to the intricacy of the opioid dependence status of new patients...since methadone is dosed primarily on tolerance level of the individual, physicians must rely on the patient's evaluation of their usage. (The National Assessment of Methadone-Associated Mortality 2004) New opioid users take longer to clear methadone from their systems which exposes them to increased overdose risk. New users starting methadone in excess of their actual tolerance level can suffer overdose and death. Physicians must weigh the risk vs. benefit when prescribing methadone between therapeutic (reduce withdrawals) and toxic (overdose) effects of methadone. Oral methadone as low as 20mg can be fatal in a new patient after several days of treatment because of methadone's extended half-life; half of the previous day's dose is in the patients system and accumulates in the body. The Australian Government Department of Health and Ageing (2003) reccomends that the methadone dose not be increased for at least the first 3 days of treatment unless there are clear signs of withdrawal at the time of peak effect; dose increments of 5-10mg every 3 days subject to assessment; and limiting total weekly increase to 20mg. The report also advises that patients should be observed daily prior to dosing and at least 2-4 hours post dosage. Opioid tolerance is a complex process of neuroadaptation and even experienced users can experience methadone toxicity resulting in respiratory depression (Leavitt 2003). Leavitt also states that death related to methadone intoxication during induction is 7-fold greater than patients threat of death prior to entering MMT and virtually 98 times greater for new patients than for patients who have been effectively receiving treatment for over two weeks...death usually occurs in the first 3-10 days after of initial dosage. Deaths take place several hours after dose at peak SML's while patient is at home in bed or at detoxification sleeping which is why dosages should be taken in the morning and patient constantly monitored. The Australian Government Department of Health and Ageing (2003) attributes the causation of death in early treatment to the slow onset of action and long half life which can be vastly deceptive, with toxic effects becoming apparent many hours after ingestion. Deaths most commonly take place on third or fourth day of treatment because methadone levels rise steadily with each additional prescribed amount. It is imperative that patients be monitored extensively with any means necessary during induction to avoid the inevitable consequence of death as a result of dosing errors or concomitant use of other drugs that may prove lethal combined with methadone. Because many patients are inducted onto methadone for the purpose of easing withdrawal symptoms it's difficult for the patient and staff to differentiate if what they are experiencing are the toxic effects of methadone or withdrawals associated with an inadequate dose of methadone, at which time the dose may raised and prove fatal to the patient.

One way to avoid overdosing patients is blood testing to determine if SML's are in the appropriate range. Researchers have proposed this diagnostic tool as a means to aid physicians in determining suitable dosing. Researchers have attempted to find a correlation between trough (low = steady state) and peak (high = 2-4 hours after dosing) methadone levels in the blood. Leavitt (2003) writes "Payte and colleagues (2003) have emphasized that the ratio between peak and trough SML measures can be most clinically useful. The peak SML occurring at roughly 2 to 4 hours post-dosing should be no more than twice the trough level.

This would provide an optimal peak-to-ratio of 2 or less". Even though the peak and trough levels may not correlate it is still the best clinical indication doctors may have that a patient has been overmedicated. During an overdose, peak SML would occur along with corresponding overdose signs and symptoms observed in the patient. It is crucial that all patients receiving methadone be sufficiently observed and tested prior to dosing to determine if any concomitant medications are present in the patients system that pose a threat to the metabolizing of methadone.

Many patients receiving MMT for addiction and pain management have other comorbid disorders that require additional medications for stabilization and quality of life. Various medications pose a serious threat to the patient taking methadone even when the individual drug is virtually harmless when take alone. Many researchers have attributed methadone related death to the "poison cocktail" consisting of methadone, benzodiazepines, alcohol, other psychotropic medications, and additional opioids. Benzodiazepines are a Central Nervous System depressant and react as an additive to methadone consequently inducing fatal respiratory depression, hypoxia, and sometimes pulmonary edema. Bruce Goldberger a forensic toxicologist whose laboratory performs drug analyses for medical examiners in 35 Florida counties describes how methadone related deaths occur by lowering blood pressure and heart rate and slows respiration...respiratory failure is the most common cause of methadone-related deaths (Nordlie 2002). Doctors and patients are encouraged to carefully review all of the prescribed medications prior to consenting to methadone treatment. Patients need to be aware of eminent danger that combining even the most "harmless" medication may possess lethal synergistic and additive effects. Surprisingly the Black Box warnings for methadone do not caution against the serious risk of drug interactions (S. O'Leary personal communication, Sept. 9, 2006).

Statistics overwhelmingly indicate more precautions need to be taken to insure this epidemic does not continue. Three studies, including one by the CDC, link the rise in methadone prescriptions sales with the increase in deaths from methadone painkillers (pill form), not methadone (liquid) obtained from drug treatment clinics (Finn and Tuckwiller 2006). Robert Lubran, director of the division of pharmacologic therapies at the U.S. Substance Abuse and Mental Health Services Administration states "I think that physicians who are prescribing methadone for analgesia may not be as completely aware of some of the properties of methadone that create a potential for harm" (associated press 2006). Researchers believe that patients taking methadone for pain relief are at an increased risk for overdose because the pain-killing effects wear off in 12 hours but the drug remains in the body for several more hours (Join Together 2003). This additional threat is posed to opioid naïve patients that may be drowsy and subsequently take an additional pill forgetting their last dose. Joseph Haddock, an analyst for the Justice Department's National Drug Intelligence Center, said "Methadone is probably one of the very few drugs that I've seen doctors almost kill patients with... it's that hard to use when you first start to use" (Belluck 2003). The FDA regulations 21 CFR 291 and SAMHSA 42 CFR Part 8, state that appropriately licensed and certified physicians may prescribe methadone and other narcotic drugs for treatment of pain, however the new Federal regulations do not permit physicians to treat opiate addiction with narcotic drugs. Only an Opioid Agonist Treatment Program possessing a current, valid certification from SAMHSA can be considered qualified by the Secretary under section 303(g)(1) of the Controlled Substances Act (21 U.S.C. 823 (g)(1) to be registered to dispense opioid drugs in the treatment of opioid addiction.

iversion of methadone pills should be a foremost public health concern. Diversion of this unpredictable medication lands methadone on the street and the hands of unsuspecting users. According to Federal regulations methadone maintenance patients for addiction treatment must earn their take home doses. However, many seasoned addicts are well aware of the Federal restrictions pertaining to addiction treatment professionals and not for physicians for pain treatment; addicts will then "doctor-shop" in order to get multiple prescriptions of methadone and other opiates to use and/or sell on the street. Because many physicians treating chronic pain are not specially trained in addiction or methadone therapy remain under the assumption that methadone is less dangerous and addictive due to its long onset and chemical duration; this misconception leads doctors to prescribe liberal amounts of methadone

to pain management patients, making diversion more apt to occur.

All patients regardless of whether using methadone for pain relief or addiction recovery must be appropriately assessed for methadone maintenance and only considered for MMT as a last resort.

Physicians must safeguard the public and patients when dispensing medications with such addictive and deadly potential. In addition to the above assessment recommendations from the Federal Register Department of Health and Human Services U.S. Federal government has established Patient admission criteria under 42 CFR part 8.12 (e) (2001). A patient must be determined sufficient for MMT and meet the medical criteria listed in the DSM-IV, that a person is currently addicted to an opioid drug, and that person became addicted at least 1 year before admission for treatment (this requirement may be waived for patients released from penal institution, pregnant women, and previously treated patients). It is also required that a patient provides written consent to maintenance treatment and all relevant facts concerning use of the opioid drug have been explained to the patient. Many patients entering MMT through a detoxification program or under the influence of narcotics may be disoriented and not capable of making informed decisions based on the risks associated with methadone. Substance abusers seek instant gratification and if proposed with a solution to end painful withdrawal symptoms many in the grip of addiction and withdrawal will choose the drug, regardless of the risk posed. Doctors must be armed with adequate knowledge about the patient and the drug to be able to assist patients in the decision making process and be prudent with prescriptions that endanger lives; methadone must not be used as a band-aid for addiction. The Federal Register, in section (f)Required Services, paragraph (2) states each patient is required to undergo a complete, fully documented physical evaluation by a program physician or primary care physician before admission to the OTP (Opiate Treatment Programs).

For physicians who are not well-versed in the dangers associated with methadone toxicity by way of overmedication and concomitant drugs would essentially dose patients according to the FDA approved labeling instructions. Finn and Tuckwiller (2006) write that the "usual adult dosage" according to the package insert is "2.5 mg to 10 mg every three or four hours as necessary...for pain relief." An unqualified doctor prescribing methadone might assume a patient could theoretically take up to 80 mg of methadone a day. Studies say that 50 mg a day or less could kill a patient not used to strong painkillers. Another disturbing detail is that in 2001, a doctor from a federally funded research institute discovered methadone could cause problems with heart rhythms that could prove to be fatal. Charleston Gazette (2006). Raymond Woosley at the University of Arizona's Center for Education and Research on Therapeutics also found that methadone can cause cardiac arrhythmia, which may lead to blackouts and sudden death....Woosley reports that methadone patients dying suddenly emerged soon after it began being used for addiction treatment, "but they were drug addicts, and everyone blamed drug abuse for the deaths" (Charleston Gazette 2006). It's ironic that the strongest supporters of methadone besides the pharmaceutical companies happen to be the addicts and patients who are being exploited and victimized by those benefiting the most by this drug.

In 2003 methadone contributed to 2,992 deaths nationwide according to data reported by Finn and Tuckwiller (2006). In a reply to Finn and Tuckwiller, regarding the increase in deaths and potentially dangerous labeling on methadone, Suzan Cruzan (FDA spokeswoman) stated "The mortality rate associated with untreated opioid addiction is extremely high and the effect of placing a 'boxed warning'; regarding the potential cardiotoxicity was determined to have a potentially negative impact on appropriate treatment of these patients". The government did take notice after the 2003 record number of deaths associated with methadone and the Bush administration responded by gathering the top experts on drug overdoses, doctors, researchers, and medical examiners, as well as representatives from the federal Drug Enforcement Administration, Food and Drug Administration, and Substance Abuse and Mental Health Association. Finn and Tuckwiller (2006) report "the man hired to research and write the report based on the conference, as well as background paper for conference participants, was Stewart B. Leavitt, an addiction specialist whose work is funded by the makers of methadone".

Stewart B. Leavitt PhD served as researcher/writer for A National Assessment of Methadone-Associated Mortality: Background Briefing Report from the U.S. Department of Health and Human Services. Stewart B Leavitt also writes Addiction Treatment Forum Methadone Dosing & Safety in the Treatment of Opioid Addiction which is funded by Mallinckrodt, Inc. a manufacturer of methadone.

PETITION

I petition the FDA, U.S. Department of Health and Human Services, DEA , SAMHSA, and the media to take notice on behalf of victims of methadone and those that are yet to become victims and make changes to prevent any more unnecessary deaths. Hire a team of independent researchers not funded by pharmaceutical companies; a person or group of people that stand to gain no financial benefit on the outcome of the studies. All doctors need mandatory training regarding the effects of methadone and concomitant medications. No matter how diversion of methadone takes place it poses a threat to public safety and this medication should never leave a facility or pain management clinic and neither should the patient without being closely monitored during the first 2-4 hours after dosage.

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