Cover Letter: Citizen Petition Requesting a Safety Review of ANDAs for which Subutex or Suboxone is the RLD

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Attn: Lyle Jaffe

06 March 2009

Dear Sir or Madam,

We are writing in follow to Douglas Kramer's conversation with Mr. Lyle Jaffe on February 23 regarding citizen petition FDA-2009-P-0074.

We wish to submit this petition as a replacement to FDA-2009-0074 which was withdrawn pursuant to § 10.30(g) in order to allow the petitioners to make the certifications required for petitions for stay of action under section 505(q) of the Federal Food Drug and Cosmetic Act, in the event that FDA determines that this petition is subject to the requirements of that section. We are taking this step because we believe that the negative public health consequences of using excipients such as talc in generic versions of Subutex or Suboxone are important enough that the petition must be considered on its merits and not rejected on technical grounds.

The petition is similar to, but not identical to, the previous petition. In addition to changes relating to the possibility that FDA may consider this petition subject to the requirements of section 505(q), and minor editorial revisions, we are providing copies of references cited as footnotes and copies of documents marked with an asterisk (*) in 2 files on the accompanying CD. Where we have cited or discussed a document more than once, we have included only a single copy of that document. For documents that are particularly long, we have edited the footnotes to facilitate finding critical information. We hope that

FDA-2009-P 0154-0001 CP

this will facilitate review and assure that we are indeed providing the agency with "all information and views upon which the petition relies" as the certification requires.

We appreciate your assistance in this matter.

Sincerely,

E. Douglas Kramer, MD

Nabarun Dasgupta, MPH

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[redacted]

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Citizen Petition

The undersigned submit this petition under 21 CFR 10.30 on behalf of themselves, as citizens concerned with the health and wellbeing of Injection Drug Users (IDUs), to request that the Commissioner of Food and Drugs take the actions described below with respect to any and all pending, approved or tentatively approved Abbreviated New Drug Applications (ANDAs) for which either Subutex® (buprenorphine) or Suboxone® (buprenorphine plus naloxone) is the Reference Listed Drug (RLD).

The petitioners are concerned that at least one generic formulation of Subutex approved in the United Kingdom contains talc, an excipient not present in the RLD that makes it less safe than the RLD when injected. This generic formulation also contains excipients in addition to talc that are not present in the innovator. We are concerned that talc and other excipients would not be assessed for their safety when used by injection if such an ANDA were evaluated by FDA as merely an oral or sublingual generic drug. It is not acceptable that the health of drug users seeking treatment be compromised should the agency fail to hold ANDAs for these products to the standards for inactive ingredients required for a parenteral drug product.

Actions Requested

That FDA only approve an Abbreviated New Drug Application (ANDA) for which either Subutex or Suboxone is the Reference Listed Drug (RLD) where the inactive ingredients in the

proposed generic meet the requirements for a generic version of a drug product intended for parenteral use as defined in 21 CFR 314.94 (a)(9)(iii).

That FDA permit only those changes to the inactive ingredients in a Subutex or Suboxone ANDA as allowed under 21 CFR 314.94 (a)(9)(iii) for which the applicant provides information that the proposed change would not increase the risk of use of the product by injection.

That FDA review ANDA 078633, and any other Subutex or Suboxone ANDAs that may have been approved or tentatively approved, to determine whether these ANDAs meet the requirements set forth in 21 CFR 314.94 (a)(9)(iii).

> That FDA require sponsors of any ANDA that does not meet the requirements set forth in 21 CFR 314.94 (a)(9)(iii), and that therefore may contain excipients which have not been shown to be safe when used by injection, withdraw the product from the market.

Statement of Grounds

Summary

FDA is required to consider the safety of inactive ingredients in its evaluation of ANDAs. Moreover, in the case of generic pharmaceuticals intended for intravenous administration, generic drugs are required to contain the same inactive ingredients in the same proportion as the RLD. Intravenous injection of certain pharmaceutical excipients intended for oral use, most notably talc or cellulose, is known to be associated with serious health problems such as chronic granulomatous pulmonary disease, pulmonary fibrosis, and pulmonary hypertension. FDA recognizes the seriousness of these problems and requires a bolded statement concerning the hazards of injection of pharmaceutical excipients in the Drug Abuse and Dependence section of the labeling of many controlled-release oral opioids that contain talc. This statement is not included in the labeling of controlled-release oral opioids that do not contain talc, and is not found in the labeling of Subutex and Suboxone. These two drugs similarly do not contain talc and have not been associated with these problems even though they are routinely used for therapeutic purposes in persons who inject drugs, in accordance with the Drug Addiction Treatment Act of 2000, and are acknowledged to be dosage forms that are injected.

FDA and DEA carefully considered the injection use of buprenorphine in the review, approval and scheduling of Subutex and Suboxone, and the labeling of these products includes appropriate warnings related to the specific hazards of use of Subutex and Suboxone by injection. It is likely that generic versions will also be injected. However, additional warnings would need to be considered for formulations that did not meet the requirements of a generic drug intended for intravenous administration and would clearly be required for formulations that contained excipients unsuitable for intravenous administration such as talc. Changes to safety labeling are not permitted under generic drug regulations.

FDA has the regulatory authority to take the actions requested. It has authority to regulate labeling of both new drugs and generic drugs. FDA has determined in its review and approval of Subutex and Suboxone that the hazards of injection of these products must be labeled. FDA has the authority to withdraw the approval of an abbreviated application. Even if FDA determined in

this instance that it did not have the authority to require that generic versions of Subutex and Suboxone meet the regulatory standards for generic drugs intended for intravenous administration, it is not precluded from requesting sponsors to take this action on a voluntary basis and should do so immediately if a safety review demonstrates that an ANDA Subutex or Suboxone product fails to meet the standards set forth in 21 CFR 314.94 (a)(9)(iii). It is not acceptable that the health of drug users seeking treatment be compromised should the agency fail to hold generics to the standards for inactive ingredients required for a parenteral drug product.

The sponsor of Subutex and Suboxone does not claim any patents on the formulation of these products in the Orange Book. Therefore, it is reasonable to expect that generic formulations of Subutex and Suboxone that met the requirements for generic drugs intended for intravenous administration could be developed without unwarranted delay.

I. FDA is required to consider the safety of inactive ingredients in its evaluation of Abbreviated New Drug Applications; generic versions of pharmaceuticals intended for intravenous administration are required to contain the same inactive ingredients in the same proportion as the RLD

Under 21 CFR 314.94* paragraph (a)(7)(i) (Content and format of an abbreviated application), an abbreviated application must provide "Information that shows that the drug product is bioequivalent to the reference listed drug upon which the applicant relies." However, such demonstration is not sufficient for approval because paragraph (a)(9)(ii) requires that "an applicant shall identify and characterize the inactive ingredients in the proposed drug product and provide information demonstrating that such inactive ingredients do not affect the safety of the proposed drug product." In particular, paragraph (a)(9)(iii) requires that "generally, a drug product intended for parenteral use shall contain the same inactive ingredients and in the same concentration as the reference listed drug" and, that when differences exist, "the applicant identifies and characterizes the differences and provides information demonstrating that the differences do not affect the safety of the proposed drug product."

II. Injection of certain pharmaceutical excipients, most notably talc or cellulose, is known to be associated with serious health problems such as chronic granulomatous pulmonary disease, pulmonary fibrosis, and pulmonary hypertension. FDA recognizes the seriousness of these problems and includes appropriate specific warnings, even when the population receiving the products is at low risk of injection. If Subutex or Suboxone presented these specific risks, in a population at high risk for drug injection, labeling would be required.

It is clear that bioequivalence is necessary but not sufficient grounds for FDA to approve an ANDA. The safety of inactive ingredients must also be considered. This is critical in the case of generic buprenorphine for the treatment of opioid dependence. By definition, persons with opioid dependence are unable to control their opioid use and the use of opioids by injection is prevalent

in this population. Reducing the negative consequences of injection drug use is a major goal of substitution treatment.[1]

The negative health consequences, particularly lung disease, of injecting pharmaceuticals intended for oral administration have been well known for many years[2,3,4]. Excipients most commonly associated with pulmonary problems are insoluble substances such as talc and cellulose. Although other excipients, including starch, are rarely identified in tissues of IDUs at autopsy, starch does not commonly elicit a foreign body inflammatory response[5], perhaps because it is rapidly cleared by the body[6]. The petitioners are not aware of reports of lung disease involving soluble excipients commonly found in heroin[7] such as quinine, lactose or mannitol. This may explain the observation that pulmonary symptoms may be worse in persons who inject pharmaceuticals.[8]

FDA has clearly recognized the importance of excipients such as talc as a cause of medical morbidity among persons who inject pharmaceuticals intended for oral administration. For example, the DRUG ABUSE AND ADDICTION Section of the labeling of OxyContin® includes the following:

> **With parenteral abuse, the tablet excipients, especially talc, can be expected to result in local tissue necrosis, infection, pulmonary granulomas, and increased risk of endocarditis and valvular heart injury[9].** [Emphais in the original.]

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[1] Substitution maintenance therapy in the management of opioid dependence and HIV/AIDS prevention : position paper / World Health Organization, United Nations Office on Drugs and Crime, UNAIDS. http://whqlibdoc.who.int/unaids/2004/9241591153_eng.pdf. Accessed 04 December 2008.

[2] Glassroth J, Adams GD, Schnoll S. The impact of substance abuse on the respiratory system. Chest. 1987 Apr;91(4):596-602.

[3] On 30 September 2008, search of Pubmed for
(("talc"[MeSH Terms] OR "talc"[All Fields]) OR ("cellulose"[MeSH Terms] OR "cellulose"[All Fields])) AND ("substance-related disorders"[MeSH Terms] OR ("substance-related"[All Fields] AND "disorders"[All Fields]) OR "substance-related disorders"[All Fields] OR ("drug"[All Fields] AND "abuse"[All Fields]) OR "drug abuse"[All Fields])

yielded 173 citations many of which describe serious health consequences clearly related to systemic talc or cellulose, exposure, dating back to the 1960s. Although other types exposures, including reports of occupational exposures, are included in these results, injection users of oral pharmaceuticals are clearly a major risk group. The hazards identified included conditions known to be serious and associated with fatal outcomes such as chronic granulomatous pulmonary disease, pulmonary fibrosis, pulmonary hypertension and cor pulmonale.

[4] Itkonen J, Schnoll S, Daghestani A, Glassroth J. Accelerated development of pulmonary complications due to illicit intravenous use of pentazocine and tripelennamine. Am J Med. 1984 Apr;76(4):617-22.

[5] Kringsholm B, Christoffersen P. The nature and the occurrence of birefringent material in different organs in fatal drug addiction. Forensic Sci Int. 1987 May-Jun;34(1-2):53-62.

[6] Lamb D, Roberts G. Starch and talc emboli in drug addicts' lungs. J Clin Pathol. 1972 Oct;25(10):876-81.

[7] Cunningham EE, Venuto RC, Zielezny MA. Adulterants in heroin/cocaine: implications concerning heroin-associated nephropathy. Drug Alcohol Depend. 1984 Sep;14(1):19-22.

[8] Itkonen J, Schnoll S, Daghestani A, Glassroth J. Accelerated development of pulmonary complications due to illicit intravenous use of pentazocine and tripelennamine. Am J Med. 1984 Apr;76(4):617-22.

[9] http://www.fda.gov/cder/foi/label/2008/020553s059lbl.pdf Accessed 04 December 2008

A similar bolded statement is included in the labeling of other controlled-release oral opioids which contain talc (see, for example, the labels for Avinza®*, Kadian®*, MS Contin®*) but not Oramorph SR®* (which contains other excipients but not talc). It is clear that FDA has determined that a warning concerning an expected serious risk such as talc-associated pulmonary disease would be essential to provide to physicians who prescribe opioids even when the population receiving treatment is at low risk for injecting the product[10].

Unlike oral controlled-release opioids, Subutex and Suboxone are intended to be used in a population at elevated risk for drug injection, compared to pain patients. If the risk of expected serious toxicity presented by excipients such as talc existed for sublingual buprenorphine products, it would be essential to label the products accordingly. The omission of such a warning from the labeling of Subutex and Suboxone is appropriate only because these products do not contain talc or cellulose and, therefore, do not present this risk.

III. Pulmonary problems associated with the injection of talc or cellulose have not been reported with Subutex or Suboxone; any changes to the formulation of generic versions of Subutex or Suboxone must be evaluated for safety.

Neither Subutex nor Suboxone contain talc or cellulose, and serious pulmonary disease attributable to the parenteral administration of these excipients have not been reported in over a decade of outpatient Subutex use (and injection) in France[11] and in over 5 years of use of Subutex and Suboxone in the US under the Drug Addiction Treatment Act (DATA)*, despite the vulnerability of the population to complications from injection drug use. Given the safety of Subutex and Suboxone in this regard, there is no justification for allowing changes to the composition of the dosage forms without data justifying the safety of doing so.

IV. The non-medical use of buprenorphine by injection, including the injection of buprenorphine-naloxone combinations, was well documented before buprenorphine was approved in the US.

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[10] The petitioners note that it appears not all generic controlled release opioids that contain talc as an excipient have the appropriate warning and that other safety warnings common to this class of products may also be missing from generic labeling. For example, the petitioners were able to find labeling for a 100 mg dosage unit of a controlled release morphine sulfate product that contains talc, and appears to be a generic version of MS Contin, but whose labeling (on the dailymed web site which is supposed represent the "FDA official PDF" of the labeling) has not been updated to include the talc warning*. Labeling for this product also does not include the black box warning that a 100 mg dose strength is for use in opioid tolerant patients only. This is all the more concerning since the Public Assessment Report for the UK approval of generic Subutex (http://www.mhra.gov.uk/home/groups/pl-a/documents/websiteresources/con018234.pdf*) makes no mention of the possible additional hazard of the use of talc as an excipient in this product, and no mention of the possible safety impact of other changes to the formulation on the safety of the product for use in substitution treatment, where the use of the product by injection is expected. The discrepant safety labeling of branded and generic controlled release oral opioid products, and the possibility that a similar discrepancy in the safety labeling may have occurred in the review and tentative approval of ANDA 078633 (whose labeling is not yet posted on Drugs@FDA), prompted this petition to request a safety review of Subutex and Suboxone ANDAs to assure that all such products are held to the requirements for a generic version of a drug product intended for parenteral use as defined in 21 CFR 314.94 (a)(9)(iii).

[11] As of 24 September 2008 there are 2 reports in PubMed from France describing local cutaneous reactions to starch apparently related to buprenorphine injection. Each abstract describes only a single patient.

The non-medical use of buprenorphine has been well documented for many years. All dosage forms of buprenorphine have been implicated. For example, sublingual analgesic (i.e., low) doses of buprenorphine have been injected in Australia, New Zealand, Germany, the UK, Finland, Ireland, Italy and Spain[12]. More recently, parenteral analgesic dosage forms have been used non-medically by injection in India[13]. Subutex tablets containing 2 or 8 mg of buprenorphine have been reported to be injected by French IDUs[14,15].

A buprenorphine-naloxone combination tablet for analgesic use was introduced in New Zealand on April 1, 1991. The product contained 0.2 mg buprenorphine and 0.17 mg of naloxone (nearly 4 times more naloxone relative to buprenorphine than the formulation of Suboxone which is currently approved in the US and elsewhere for the treatment of opioid dependence). Robinson et al.[16] surveyed drug users presenting for treatment in Wellington, New Zealand concerning drug use before and after this product was launched. Although the street price of buprenorphine-naloxone was less than for buprenorphine alone, the combination product was still routinely injected.

The agency was well aware of these international experiences concerning the non-medical injection use of buprenorphine[17],[18], and this information figured prominently in the approval and scheduling of Subutex and Suboxone.

V. The labeling of Subutex and Suboxone does not restrict the use of buprenorphine in drug injecting populations

According to the labeling of Subutex and Suboxone, these products are approved subject to the provisions of The Drug Addiction Treatment Act (DATA) of 2000 and amendments. DATA allows any physician certified under the Act to prescribe drugs for the treatment of opioid dependence that are controlled in schedules III to V of the Controlled Substances Act (CSA), including Subutex and Suboxone, for the treatment of opioid dependence for up to 100 patients in office-based practice. There is no requirement under DATA that the administration of buprenorphine be supervised or that treatment of IDUs with buprenorphine be restricted compared to patients who do not inject drugs. Since information indicates that only 13% of

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[12] WHO Expert Committee on Drug Dependence, 25th Report. WHO Technical Report Series, 775 Geneva 1989. See discussion of buprenorphine in section 4.2 of the report.

[13] Kumar MS, Mudaliar S, Thyagarajan SP, Kumar S, Selvanayagam A, Daniels D. Rapid assessment and response to injecting drug use in Madras, south India. Int J Drug Policy. 2000 Mar 1;11(1-2):83-98. (Note: section 3.6 of this report identifies the dosage form involved as ampoules, a parenteral dosage form).

[14] Obadia Y, Perrin V, Feroni I, Vlahov D, Moatti JP. Injecting misuse of buprenorphine among French drug users. Addiction. 2001 Feb;96(2):267-72.

[15] Vidal-Trecan G, Varescon I, Nabet N, Boissonnas A. Intravenous use of prescribed sublingual buprenorphine tablets by drug users receiving maintenance therapy in France. Drug Alcohol Depend. 2003 Mar 1;69(2):175-81.

[16] : Robinson GM, Dukes PD, Robinson BJ, Cooke RR, Mahoney GN. The misuse of buprenorphine and a buprenorphine-naloxone combination in Wellington, New Zealand. Drug Alcohol Depend. 1993 Jun;33(1):81-6.

[17] See Abuse Liability Review, NDA 20-733 dated October 7, 1999 by Michael Klein, PhD

[18] 67 FR 194 62354-62370, Schedules of Controlled Substances: Rescheduling of Buprenorphine From Schedule V to Schedule III. Final Rule, October 7, 2002. This document includes numerous references to foreign data on buprenorphine including the statement that "Both the DEA and FDA relied heavily on foreign experience with these products..."

patients are seen by a physician more than 4 times in the first month of treatment,[19] it is of paramount importance that the drug products used in office based practice be as safe as possible.

VI. Persons who inject drugs commonly receive substitution treatment in the US, including treatment with Subutex and Suboxone.

Drug injection is a common occurrence in individuals with opioid dependence, and the lifetime prevalence of drug injection is substantial in populations eligible for treatment under DATA. Among facilities reporting admissions to TEDS, in 2005, 63% of heroin users and 12% of users of other opioids reported their usual route of administration as injection[20]. Among enrollees to methadone maintenance programs in the United States, 78% of patients identifying heroin as their primary drug reported injecting it, and 33% of prescription opioid users reported injecting their primary drug[21]. In a trial by Fiellin et al.[22] 32% of persons treated with buprenorphine-naloxone had a history of intravenous drug use. Among 125 buprenorphine abuse cases reported by the RADARS® System poison centers at the 2008 SAMHSA buprenorphine summit, between 25 and 30% involved parenteral administration and 7% described chronic buprenorphine abuse[23]. These data indicate that a substantial number of persons in the US treated with (or otherwise obtaining) either Subutex or Suboxone are at risk to inject it.

VII. FDA and DEA carefully considered the injection use of buprenorphine in the review, approval and scheduling of Subutex and Suboxone

As discussed above, the agency was well aware of the international experiences concerning the non-medical injection use of buprenorphine.

With respect to Suboxone, in particular, the agency was well aware of the limited impact this formulation might have on the extent of injection of buprenorphine in some populations. For example, in commenting on the report by Robinson concerning the non-medical use of buprenorphine in New Zealand, mentioned above, FDA's Abuse Liability Review States:

> Because of the high receptor affinity of Bu, it was never predicted that injecting Bu-Nx would be aversive in those dependent solely

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[19] http://www.buprenorphine.samhsa.gov/presentations/Clark.pdf Accessed 9/23/2008. (Distribution of physician visits is described on page 45)

[20] Substance Abuse and Mental Health Services Administration, Offi ce of Applied Studies. Treatment Episode Data Set (TEDS): 1995-2005. National Admissions to Substance Abuse Treatment Services, DASIS Series: S-37, DHHS Publication No. (SMA) 07-4234, Rockville, MD, 2007. (see table 3.4)

[21] Rosenblum A, Parrino M, Schnoll SH, Fong C, Maxwell C, Cleland CM, Magura S, Haddox JD. Prescription opioid abuse among enrollees into methadone maintenance treatment.Drug Alcohol Depend. 2007 Sep 6;90(1):64-71. Epub 2007 Mar 26.

[22] Fiellin DA, Pantalon MV, Chawarski MC, Moore BA, Sullivan LE, O'Connor PG, Schottenfeld RS. Counseling plus buprenorphine-naloxone maintenance therapy for opioid dependence. N Engl J Med. 2006 Jul 27;355(4):365-74.

[23] http://www.buprenorphine.samhsa.gov/presentations/Dasgupta.pdf Accessed 9/23/2008. (See page 16 and 17).

> on Bu (or Bu-Nx). It was anticipated that users might largely confine their use to Bu or Bu-Nx, which was not the case[24].

From the Division Director's Memo, entitled "Division Director's Review of NDA and Basis for Action,[25]" it is clear that

- FDA considered both the intravenous use of Subutex that occurs in France and the overall public health impact of the product in that country when it approved Subutex and Suboxone in the US[26].
- FDA was aware of the limited effect the addition of naloxone may have on the intravenous use of buprenorphine when it approved Suboxone[27].
- FDA did not expect Suboxone to prevent injection of buprenorphine, but hoped merely to deter it.[28]

VIII. The labeling of Subutex and Suboxone includes appropriate product-specific warnings related to the use of Subutex and Suboxone by injection

FDA rightly considered the risk of injection of buprenorphine so important that the hazard of injecting it is noted prominently in the first warning in the labeling* for these products:

> **WARNINGS**
>
> **Respiratory Depression:**
>
> Significant respiratory depression has been associated with buprenorphine, particularly by the intravenous route. A number of deaths have occurred when addicts have intravenously misused buprenorphine, usually with benzodiazepines concomitantly. Deaths have also been reported in association with concomitant administration of buprenorphine with other depressants such as alcohol or other opioids. Patients should be warned of the potential

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[24] See Abuse Liability Review, NDA 20-733 dated October 7, 1999 by Michael Klein, PhD, page 13. Document provided as Reference 17.
[25] "Division Director's Review of NDA and Basis for Action", Cynthia McCormick, 10/8/02
[26] Indeed, the division director recognized that "on balance, even given the experience of abuse and diversion of buprenorphine in France, the availability of the pure SUBUTEX formulation has been associated with a reduction overall in the mortality rate associated with heroin addiction in France." See Reference 25, section "Risks and Benefits" page 10.
[27] The division director articulated the limited conclusion that "The review team has determined that the abuse of buprenorphine by the intravenous route may be reduced based on theoretical clinical grounds with the addition of naloxone." See Reference 25, section "Clinical Safety—Abuse Liability and the Fixed-Combination Prescription Drug Regulation," page 6.
[28] In discussing possible advantages over existing therapies, the memo describes Suboxone saying "and, with the addition of naloxone, it is hoped, a deterrent to intravenous abuse." See Reference 25, section "Background," page 1.

danger of the self-administration of benzodiazepines or other depressants while under treatment with SUBUTEX or SUBOXONE.

Given the agency's explicit anticipation that both Subutex and Suboxone would be used by injection, inclusion of this warning is entirely consistent with requirements for safety labeling.[29]

IX. Subutex and Suboxone are appropriately labeled concerning the risks of use of these products by injection; however, safety labeling of ANDAs that did not meet the criteria specified in 21 CFR 314.94 (a)(9)(iii) would need to be evaluated regarding the need to include additional warnings; changing the safety labeling of a drug in this way is not compatible with ANDA regulations.

Safety labeling requirements spelled out in 21 CFR 201.57(c)(6)* do not require labeling of hazards that are purely theoretical. Thus it is appropriate that at the conclusion of its review of data in support of Subutex and Suboxone, including many years of international data concerning the injection of buprenorphine, that the agency determined that the only warning necessary concerning the hazards of injecting buprenorphine is the warning quoted above concerning respiratory depression.

However, it would be essential to provide warning in the labeling of the known hazards associated with the injection of excipients such as talc or cellulose, if these were present in the innovator, since use of these excipients would clearly increase the risk of unsupervised administration as contemplated under DATA. The FDA has clearly (albeit inconsistently) determined that the specific injection hazard of products containing talc must be labeled, even when the patients prescribed the products are at low risk for injecting them. Therefore, ANDAs for Subutex or Suboxone that did not meet the requirements of 21 CFR 314.94 (a)(9)(iii) would need to have their excipients evaluated for safety when injected and might require additional safety labeling compared to the innovator products. Such changes are not permissible under 21 CFR 314.94 (a)(8)(iv). [30]

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[29] Specifically, 21 CFR 201.57(c)(6) requires that the warnings and precautions section of the label: "must describe clinically significant adverse reactions (including any that are potentially fatal, are serious even if infrequent, or can be prevented or mitigated through appropriate use of the drug), other potential safety hazards (including those that are expected for the pharmacological class or those resulting from drug/drug interactions), limitations in use imposed by them (e.g., avoiding certain concomitant therapy), and steps that should be taken if they occur (e.g., dosage modification). The frequency of all clinically significant adverse reactions and the approximate mortality and morbidity rates for patients experiencing the reaction, if known and necessary for the safe and effective use of the drug, must be expressed as provided under paragraph (c)(7) of this section. In accordance with §§ 314.70 and 601.12 of this chapter, the labeling must be revised to include a warning about a clinically significant hazard as soon as there is reasonable evidence of a causal association with a drug; a causal relationship need not have been definitely established. A specific warning relating to a use not provided for under the "Indications and Usage" section may be required by FDA in accordance with sections 201(n) and 502(a) of the act if the drug is commonly prescribed for a disease or condition and such usage is associated with a clinically significant risk or hazard."

[30] Specifically, 21 CFR 314.94 (a)(8)(iv) requires that: "Labeling (including the container label, package insert, and, if applicable, Medication Guide) proposed for the drug product must be the same as the labeling approved for the reference listed drug, except for changes required because of differences approved under a petition filed under § 314.93* or because the drug product and the reference listed drug are produced or distributed by different manufacturers. Such differences between the applicant's proposed labeling and labeling approved for the reference

X. The addition of naloxone to buprenorphine (Suboxone) is not a sufficient deterrent to the injection of buprenorphine to preclude the need for labeling of additional hazards presented by alternative formulations.

Injection of Suboxone has been reported from Finland[31], and Australia[32]. As noted in the Australian report, the injection of Suboxone appeared in the 2006 annual national survey of IDUs concerning drug use in the past 6 months; however, Suboxone was only added to the Australian Pharmaceutical Benefits Scheme in April 2006 and interviews for the Survey were conducted between June and August 2006. As discussed above, injection of buprenorphine in the US (where Suboxone is predominant form of buprenorphine prescribed under DATA[33]) has also been reported.[34]

The extent of injection of Suboxone is not surprising. In 1978, Jasinski[35] reported that doses of naloxone up to 4 mg did not precipitate withdrawal in persons with primary dependence on buprenorphine. In 1996, Eissenberg[36] reported that IM challenges of 3 and 10 mg naloxone produced opioid withdrawal but that challenges with lower doses (0.3 and 1 mg) did not produce withdrawal in opioid dependent subjects who had undergone a 2-week outpatient stabilization on 8 mg per day of sublingual buprenorphine. In 2001, Stoller[37] reported dose-related opioid withdrawal in persons with low levels of opioid physical dependence receiving IM buprenorphine-naloxone who had an opioid response to 8 mg of IM buprenorphine. However, they did not begin to see a withdrawal response until a dose of 4 mg buprenorphine and 1 mg naloxone had been administered. Since low doses of buprenorphine (i.e., approximately 1 mg) have been used by injection, use of a buprenorphine naloxone combination in the treatment of opioid dependence will not, by itself, reduce the risks of buprenorphine injection to the point where warning of specific hazards associated with injection use is not required.

Therefore, it is essential that all formulations of buprenorphine minimize the risk of injection-related complications. The formulations of Subutex and Suboxone do minimize the risk of serious morbidities such as chronic granulomatous pulmonary disease, pulmonary fibrosis, and

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listed drug may include differences in expiration date, formulation, bioavailability, or pharmacokinetics, labeling revisions made to comply with current FDA labeling guidelines or other guidance, or omission of an indication or other aspect of labeling protected by patent or accorded exclusivity under section 505(j)(4)(D) of the act." Note that safety-related changes are not contemplated under 21 CFR 314.93.

[31] Alho H, Sinclair D, Vuori E, Holopainen A. Abuse liability of buprenorphine-naloxone tablets in untreated IV drug users. Drug Alcohol Depend. 2007 Apr 17;88(1):75-8. Epub 2006 Oct 19.

[32] S. O'Brien, E. Black, L. Degenhardt, A. Roxburgh, G. Campbell, B. de Graaff, J. Fetherston, R. Jenkinson, S. Kinner, C. Moon and N. White AUSTRALIAN DRUG TRENDS 2006 Findings from the Illicit Drug Reporting System (IDRS) NDARC Monograph No. 60.
http://ndarc.med.unsw.edu.au/NDARCWeb.nsf/resources/Mono_7/$file/Mono.60.pdf. Accessed 9/23/2008 See sections 8.2 and 8.3 of this report provided as Reference 32.

[33] http://www.buprenorphine.samhsa.gov/presentations/Clark.pdf Accessed 9/23/2008. (See Reference 19, page 26)

[34] http://www.buprenorphine.samhsa.gov/presentations/Dasgupta.pdf Accessed 9/23/2008 (See Reference 23)

[35] Jasinski DR, Pevnick JS, Griffith JD.Human pharmacology and abuse potential of the analgesic buprenorphine: a potential agent for treating narcotic addiction.Arch Gen Psychiatry. 1978 Apr;35(4):501-16.

[36] Eissenberg T, Greenwald MK, Johnson RE, Liebson IA, Bigelow GE, Stitzer ML. Buprenorphine's physical dependence potential: antagonist-precipitated withdrawal in humans. J Pharmacol Exp Ther. 1996 Feb;276(2):449-59.

[37] Stoller KB, Bigelow GE, Walsh SL, Strain EC. Effects of buprenorphine/naloxone in opioid-dependent humans. Psychopharmacology (Berl). 2001 Mar;154(3):230-42.

pulmonary hypertension by not using excipients such as talc or cellulose. The record clearly demonstrates that FDA appropriately considered and labeled the specific risks of injection of Subutex and Suboxone in its approval of these products (see above). It is not acceptable that the health of drug users seeking treatment be compromised should the agency fail to hold generics to the standards for inactive ingredients required for a parenteral drug product.

XI. FDA has the regulatory authority necessary to take the requested actions

It may be argued by those opposed to this petition that FDA does not have authority to regulate the non-medical use of drugs, and that the injection use of Subutex and Suboxone is clearly such a non-medical use. Such an argument is without merit. As discussed above, FDA clearly has the necessary authority to regulate the safety of generic drugs and to regulate drug safety labeling. Since Subutex and Suboxone are products intended for use in a population with a high prevalence of drug injection, and specific warnings about drug injection are included in current labeling, FDA has already determined that warnings about particular hazards associated with injection must be included in labeling. FDA clearly considered the medical consequences of injection of buprenorphine during its review and approval of Subutex and Suboxone and labeled these products appropriately. FDAs findings concerning the public health impact of injection of buprenorphine were clearly central to its approval decision. Therefore any changes in the formulation of generic buprenorphine that have the potential to affect its safety in drug injecting populations and must be evaluated before these products are approved.

The petitioners are health care professionals, not attorneys. As such, we take no position on the authority the FDA should best use to accomplish the actions requested by the petition. We note, however, that even if FDA were to determine that it lacked the authority to require the actions requested, the agency is not prevented from asking sponsors to take the requested actions on a voluntary basis. FDA is well aware that many of the drugs listed in 63 FR 54082* for inclusion in 21 CFR 216.24 ("Drug products withdrawn or removed from the market for reasons of safety or effectiveness") were, in fact, removed "voluntarily" from marketing by their sponsors.

XII. It is reasonable to expect that sublingual dosage forms could be developed that meet the requirements of 21 CFR 314.94 paragraph (a)(9)(iii) since the sponsor of the RLDs claims no patents on the formulations of these products.

As listed in APPROVED DRUG PRODUCTS WITH THERAPEUTIC EQUIVALENCE EVALUATIONS (the "Orange Book" http://www.fda.gov/cder/ob/default.htm), Subutex and Suboxone are the Reference Listed Drug (RLD) for buprenorphine and buprenorphine naloxone for the treatment of opioid dependence. The period of non-patent exclusivity for both Subutex and Suboxone expires on October 8, 2009, and there are no unexpired patents on either product listed in the Orange Book.

Since there are no patents protecting the RLDs, it is reasonable to expect that generic versions of Subutex and Suboxone could be developed that comply with 21 CFR 314.94 paragraph (a)(9)(iii) and do not compromise patient safety (by using insoluble excipients such as talc or cellulose), without unwarranted delay in the availability of generic versions of these products.

XIII. It is unacceptable to ask patients seeking treatment for opioid dependence to accept the added risks of generic formulations of Subutex or Suboxone that do not meet the requirements set forth in 21 CFR 314.94 (a)(9)(iii)

Buprenorphine is the first opioid approved for use in the substitution treatment of opioid dependence that is safe enough in overdose to allow its widespread use in primary care. Ready access to buprenorphine played a critical role in the reduction of heroin overdose mortality in France.[38] In 2006, The WHO Expert Committee on Drug Dependence declined to recommend increasing the international control of buprenorphine, in part because of the importance of access to buprenorphine to efforts to control HIV[39].Therefore, availability of buprenorphine in the US has the potential to play a major role in addressing the two most serious public health problems facing persons with opioid dependence.

The opportunities that substitution treatment with Subutex and Suboxone present for improved outcome in the treatment of opioid dependence must not be compromised by the unwarranted approval of generic versions of these products that present unnecessary risks, whether labeled or not, that may undermine the confidence of patients and physicians in the safety of these products. Therefore, it is essential for FDA to ensure that all generic versions of Subutex and Suboxone meet the requirements for generic products intended for intravenous administration as described in 21 CFR 314.94 paragraph (a)(9)(iii). Such an evaluation must be conducted for all proposed generics, including those that have been tentatively approved.

Environmental Impact

The petitioners believe that the actions requested do not require preparation of an environmental assessment.

Economic Impact

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

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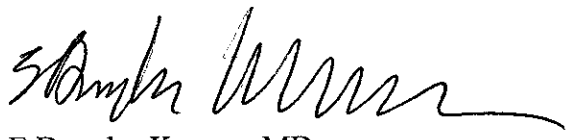
[38] Emmanuelli J, Desenclos JC. Harm reduction interventions, behaviours and associated health outcomes in France, 1996-2003. Addiction. 2005 Nov;100(11):1690-700.

[39] WHO Expert Committee on Drug Dependence, 34th Report. World Health Organ Tech Rep Ser. 942. 2006. See section 2.2.1 of this report for discussion of buprenorphine.

Certification

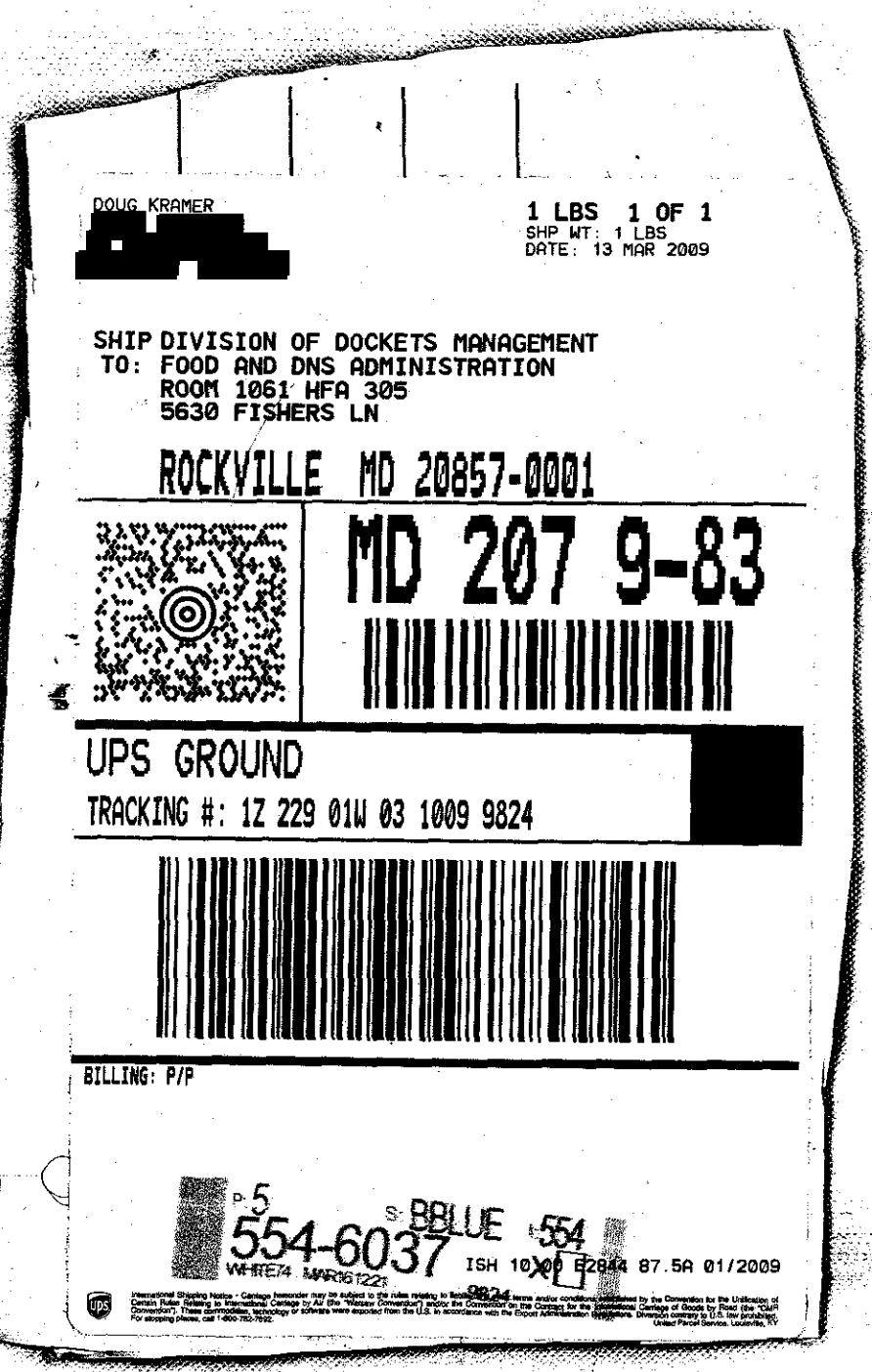
I certify that, to my best knowledge and belief: (a) this petition includes all information and views upon which the petition relies; (b) this petition includes representative data and/or information known to the petitioner which are unfavorable to the petition; and (c) I have taken reasonable steps to ensure that any representative data and/or information which are unfavorable to the petition were disclosed to me. I further certify that the information upon which I have based the action requested herein first became known to the party on whose behalf this petition is submitted on or about the following date: 15 September 2008 [in the blank space, provide the date on which such information first became known to such party]. If I received or expect to receive payments, including cash and other forms of consideration, to file this information or its contents, I received or expect to receive those payments from the following persons or organizations: **NONE—NO PAYMENTS OR OTHER CONSIDERATIONS RECEIVED OR EXPECTED FROM ANY PERSONS OR ORGANIZATIONS** [in the blank space, provide the names of such persons or organizations]. I verify under penalty of perjury that the foregoing is true and correct as of the date of the submission of this petition.



E Douglas Kramer, MD

I certify that, to my best knowledge and belief: (a) this petition includes all information and views upon which the petition relies; (b) this petition includes representative data and/or information known to the petitioner which are unfavorable to the petition; and (c) I have taken reasonable steps to ensure that any representative data and/or information which are unfavorable to the petition were disclosed to me. I further certify that the information upon which I have based the action requested herein first became known to the party on whose behalf this petition is submitted on or about the following date: 15 September 2008 [in the blank space, provide the date on which such information first became known to such party]. If I received or expect to receive payments, including cash and other forms of consideration, to file this information or its contents, I received or expect to receive those payments from the following persons or organizations: **NONE—NO PAYMENTS OR OTHER CONSIDERATIONS RECEIVED OR EXPECTED FROM ANY PERSONS OR ORGANIZATIONS** [in the blank space, provide the names of such persons or organizations]. I verify under penalty of perjury that the foregoing is true and correct as of the date of the submission of this petition.

Nabarun Dasgupta, MPH



DOUG KRAMER
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