DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

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Re: Docket No. FDA-2009-P-0154

Dear Dr. Kramer and Mr. Dasgupta:

This letter responds to your citizen petition dated March 6, 2009. The petition requests that the Food and Drug Administration (FDA or the Agency) apply certain standards to generic versions of Subutex (buprenorphine hydrochloride (HCl) sublingual tablets) and Suboxone (buprenorphine HCl and naloxone HCl dihydrate sublingual tablets), which are approved for treating opioid dependence. More specifically, you request that FDA take the following actions:

1. Approve abbreviated new drug applications (ANDAs) for which either Subutex or Suboxone is the reference listed drug (RLD) only if the inactive ingredients in the proposed generic product 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).

2. 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 risks associated with use of the product by injection.

3. Review ANDA 078633, as well as any other ANDAs that reference Subutex or Suboxone as the RLD and 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).

4. Require sponsors of any ANDA that does not meet the requirements set forth in 21 CFR 314.94(a)(9)(iii) to withdraw the product from the market.

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Your petition is based on your concern that generic versions of these products will be approved that would contain talc, an excipient that you assert would make these products particularly dangerous if, contrary to warnings in their labeling, they are injected intravenously by users. Because they are intended to be used by persons with a history of drug abuse, you are concerned that these drugs will be used intravenously by some patients.

We have reviewed your petition and references. As explained in more detail below, we are denying the requests made in your petition.

I. BACKGROUND

A. Subutex and Suboxone

Subutex (buprenorphine HCl sublingual tablets, new drug application (NDA) 020732, approved October 8, 2002) and Suboxone (buprenorphine HCl and naloxone HCl dihydrate sublingual tablets, NDA 020733, approved October 8, 2002) are indicated for the treatment of opioid dependence. Both are uncoated tablets available in 2-milligram (mg) and 8-mg buprenorphine dosage strengths. The active ingredient, buprenorphine, is a partial opioid agonist. It is available at lower doses as an analgesic. Buprenorphine is a Schedule III narcotic under the Controlled Substances Act. Suboxone contains buprenorphine HCl and naloxone HCl dihydrate at a ratio of 4:1 (2 mg/0.5 mg and 8 mg/2 mg) (ratio of free bases). Naloxone is an opioid antagonist. It is present in the product for the purpose of discouraging misuse by injection. Intravenous administration of buprenorphine/naloxone combinations may produce opioid withdrawal effects.

Subutex and Suboxone have combined labeling, as they are intended to be used in sequence by patients. The labeling of Subutex and Suboxone instructs prescribers to initiate treatment with supervised administration. The labeling makes clear that Subutex, which does not contain naloxone, should be limited to supervised use wherever possible. As patients progress, Suboxone is intended to be prescribed for take-home use in appropriately limited quantities.

The combined labeling for these products contains a warning that deaths have occurred when addicts have intravenously misused buprenorphine, usually with benzodiazepines concomitantly.

When Subutex and Suboxone were initially approved, a Risk Management Plan was put in place, designed to ensure safe and effective use of the products. The features of the Risk Management Plan for Subutex and Suboxone include (1) targeted product distribution and sales monitoring; (2) active surveillance for diversion and abuse; and (3) educational programs for patients, physicians, and pharmacists. The Risk Management Plan also references a requirement, legislated under the Drug Abuse Treatment Act of 2000, that Suboxone and Subutex may be prescribed for addiction treatment only by physicians who have met certain requirements (specifically, a minimum of 8 hours of

training) and have obtained the proper waiver from the Drug Enforcement Administration (DEA) by making appropriate notifications to the Substance Abuse and Mental Health Services Administration (SAMHSA).

B. Legal and Regulatory Background

1. Drug Addiction Treatment Act of 2000

The Drug Addiction Treatment Act of 2000 (DATA) permits specially qualified physicians to prescribe narcotic drugs included in Schedules III, IV, and V of the Controlled Substances Act for the treatment of opioid dependence if the drugs have been approved for such use by FDA. Subutex and Suboxone are currently the only drug products containing a Schedule III-listed active ingredient (i.e., buprenorphine) approved for this use by FDA and are the only drug products currently used under the provisions of DATA. Methadone is also approved for the treatment of opioid dependence, but is a Schedule II drug and may be administered for this purpose only in a clinical setting.

2. ANDAs Submitted Under Section 505(j) of the Act[1]

The Drug Price Competition and Patent Term Restoration Act of 1984 (the Hatch-Waxman Amendments) created the statutory provisions governing ANDAs. The Hatch-Waxman Amendments reflect Congress's attempt to balance the need to encourage innovation with the desire to speed the availability of lower-cost alternatives to approved drugs.

To obtain approval, an ANDA applicant is not required to submit evidence to establish the clinical safety and effectiveness of the drug product; instead, an ANDA relies on FDA's previous finding that the RLD[2] is safe and effective. Under the Hatch-Waxman Amendments, to rely on a previous finding of safety and effectiveness, an ANDA applicant must demonstrate, among other things, that its generic drug is bioequivalent to the RLD.[3] In addition, a drug product described in an ANDA generally must contain the same active ingredient;[4] conditions of use;[5] route of administration, dosage form,

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[1] See section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. 355(j)).

[2] A reference listed drug or RLD is "the listed [i.e., approved] drug identified by FDA as the drug product upon which an applicant relies in seeking approval of its abbreviated application" (21 CFR 314.3). RLDs are identified in FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations* (the Orange Book).

[3] See, e.g., section 505(j)(2)(A)(iv) of the Act (requiring "information to show that the new drug is bioequivalent to the listed drug referred to in clause (i) [i.e., listed drug]..."); 21 CFR 314.3 (defining *reference listed drug*); 21 CFR 314.94(a)(7) (requiring, as part of ANDA content and format, information to show that the drug product is bioequivalent to the reference listed drug upon which the applicant relies); 21 CFR 314.127(a)(6)(i) (providing that FDA will refuse to approve an ANDA if information submitted is insufficient to show that the drug product is bioequivalent to the listed drug referred to in the ANDA); and the Orange Book, Introduction at p. x (defining *reference listed drug*).

[4] See, e.g., 21 CFR 314.94(a)(5).

strength;[6] and (with certain permissible differences) labeling[7] as the RLD, unless a petition for certain changes is approved by the Secretary[8] (section 505(j)(2)(A), (j)(2)(C), and (j)(4) of the Act).

An ANDA applicant also must demonstrate that its generic drug product meets approval requirements relating to the chemistry, manufacturing, and controls for the drug product. Under section 505(j)(4)(A) of the Act, an ANDA must be approved by FDA unless it finds, among other things, that "the methods used in, or the facilities and controls used for, the manufacture, processing, and packing of the drug are inadequate to assure and preserve its identity, strength, quality, and purity." In addition, an ANDA applicant must submit generally the same chemistry, manufacturing, and controls (CMC) information as required in an NDA (21 CFR 314.94(a)(9)).

Finally, of most relevance to your petition, an ANDA applicant for a drug labeled for oral administration is generally permitted to use the inactive ingredients of its choice. Nevertheless, FDA will refuse to approve an ANDA if information submitted in the application or any other information available to FDA shows that the inactive ingredients of the drug product are unsafe, or the composition of the drug product is unsafe, under the conditions of use for which the drug is prescribed, recommended, or suggested in its proposed labeling (section 505(j)(4)(H) of the Act and 21 CFR 314.127(a)(8)(i)).

II. ANALYSIS

All four actions requested in the petition invoke our regulation regarding the composition of generic drug products intended for parenteral administration, 21 CFR 314.94(a)(9)(iii). This regulation requires that generally a generic parenteral drug product contain the same inactive ingredients, in the same concentration, as the RLD. An ANDA applicant may, however, seek approval of a generic parenteral drug product that differs from the RLD in preservative, buffer, or antioxidant, provided that the applicant identifies and characterizes the differences and provides information demonstrating that the differences do not affect the safety or efficacy of the proposed drug product.

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[5] See, e.g., 21 CFR 314.94(a)(4).

[6] See, e.g., 21 CFR 314.94(a)(6).

[7] See, e.g., 21 CFR 314.94(a)(8). This regulation permits certain differences in labeling between a generic product and the RLD required because, among other reasons, they are produced by different manufacturers. Permitted differences include the addition of warning statements associated with inactive ingredients. In *Zeneca v. Shalala*, 213 F.3d 161 (4th Cir. 2000) the court held that the permitted labeling differences include the sulfite warning statement required under 21 CFR 201.22 in the case of a generic version of Diprivan (propofol) containing sodium metabisulfite.

[8] An applicant may submit an ANDA for a drug that has a different route of administration, dosage form, or strength from the RLD, or in limited circumstances is a combination drug with one different active ingredient than the RLD, if the applicant has submitted a petition to the Agency (known as a *suitability petition*) requesting permission to file such an application and has received the Agency's approval (see section 505(j)(2)(C) of the Act and 21 CFR 314.93).

As you know, § 314.94(a)(9)(iii) applies to drug products intended for parenteral administration. It does not govern our review of ANDAs seeking approval of drug products intended for oral administration, including those that may be subject to abuse by injection. You have requested that we nonetheless apply the standard set forth in § 314.94(a)(9)(iii) to all ANDAs for which either Subutex or Suboxone is the RLD. We decline to adopt this standard.

The application of § 314.94(a)(9)(iii) to all generic versions of Subutex and Suboxone would be unwarranted. Your petition asserts that talc and certain other excipients are known to be associated with serious health problems when present in drug products intended for oral use that are misused by intravenous injection. The petition includes information supporting this conclusion, particularly with respect to talc. Even accepting that premise, however, it does not follow that the solution is to require all generic versions of these products to contain the same inactive ingredients as the innovator's products. There is no basis to conclude that the inactive ingredients in the innovator products -- lactose, mannitol, corn starch, Povidone K30, citric acid, sodium citrate, FD&C Yellow 6, magnesium stearate, acesulfame-K, and the flavor ingredient(s) present in Subutex and Suboxone -- will necessarily be safer to intravenous drug abusers when administered intravenously than all other inactive ingredients that may be chosen by generic applicants. FDA did not require the sponsor of Subutex and Suboxone to demonstrate the safety of these inactive ingredients when administered intravenously. In fact, there is no particular reason to consider the inactive ingredients used in Subutex and Suboxone as a standard of safety in this regard.

Because the application of § 314.94(a)(9)(iii) is not warranted for the reasons discussed above, we deny the petition's four requested actions, all of which ask us to apply the standard of § 314.94(a)(9)(iii) to generic versions of Subutex and Suboxone.

III. CONCLUSION

For the reasons discussed above, your petition is denied. FDA will not apply the standard of 21 CFR 314.94(a)(9)(iii) to ANDAs that reference Subutex or Suboxone as the RLD.

Sincerely,

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research