DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
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FEB 22 2013

Tim Baxter
Global Medical Director
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10710 Midlothian Turnpike, Suite 430
Richmond, VA 23235

Re: Docket No. FDA-2012-P-1028

Dear Mr. Baxter:

This letter responds to Reckitt Benckiser's (Reckitt) citizen petition received on September 25, 2012 (Petition). In the Petition, Reckitt requests that the Food and Drug Administration (FDA or Agency) refuse to approve any drug application (whether new drug application (NDA) or abbreviated new drug application (ANDA)) for a buprenorphine product to treat opioid dependence unless the application includes targeted educational interventions addressing the risk of accidental pediatric exposure. It also requests that we refuse to approve applications for buprenorphine products to treat opioid dependence unless they include child-resistant unit-dose packaging (Petition at 2-3). Finally, the Petition asks that FDA refuse to approve any ANDAs for buprenorphine hydrochloride (HCl)/naloxone HCl products for opioid dependence until the Agency determines whether the reference listed drug (RLD)[1] for these products was discontinued for safety reasons (Petition at 3).

FDA has carefully considered the information submitted in the Petition and other relevant data available to the Agency. Based on our review of these materials and for the reasons described below, the Petition is denied.

I. BACKGROUND

A. Buprenorphine for Opioid Dependence Treatment

Buprenorphine was developed as a treatment for opioid dependence because certain of its pharmacological properties suggested it could serve as a safer alternative to methadone.[2] Specifically, a "ceiling effect" exists for buprenorphine's euphorigenic effects, which scientists predicted would make it unattractive as a drug of abuse.[3] A ceiling was also observed for

[1] A "listed" drug is a drug that FDA has approved. A "reference listed drug" is an approved drug that is referenced by an ANDA applicant as a basis for approval of that ANDA.
[2] Methadone was approved for the treatment of opioid dependence in 1972.
[3] Opioid agonists create euphorigenic effects by activating brain receptors. Buprenorphine is a partial opioid agonist, and the euphorigenic effects of buprenorphine are understood to reach a "ceiling" at moderate doses,

respiratory depressant effects, suggesting that accidental overdose deaths (either in the treatment setting or as a result of abuse) would be less common with buprenorphine than with methadone or other full opioid agonists.

Reckitt holds NDAs for SUBUTEX[4] (a sublingual tablet version of buprenorphine HCl indicated for opioid dependence treatment and preferred for use in the induction stage) and SUBOXONE (a combination buprenorphine HCl/naloxone HCl[5] product indicated for maintenance treatment of opioid dependence and available in both sublingual tablet[6] and sublingual film[7] form). FDA approved Reckitt's NDAs for SUBUTEX and SUBOXONE tablets in October of 2002, and its NDA for SUBOXONE film in August of 2010. SUBUTEX and SUBOXONE tablets have been sold in multi-dose containers in the United States since their approval in 2002, while SUBOXONE film has always been sold in unit-dose packaging.

Reckitt has discontinued marketing SUBUTEX tablets; however, there are currently three approved generic versions on the market.[8] There were, until today, no approved generic versions of SUBOXONE, which is the most commonly prescribed buprenorphine product for opioid dependent patients. Two ANDAs for SUBOXONE tablet products have been approved today. SUBOXONE tablets were subject to orphan drug exclusivity which expired on October 8, 2009; they are not subject to any unexpired patents listed in the Orange Book.[9] Orphan drug exclusivity for SUBOXONE film is scheduled to expire on August 30, 2013; in addition, Reckitt has listed a patent in the Orange Book for SUBOXONE film, which will expire in September 2023.

At the time the NDAs for SUBUTEX and SUBOXONE tablets were approved, it was recognized, contrary to earlier expectations, that buprenorphine can produce dependence, and that withdrawal symptoms occur when it is discontinued. There was also sufficient evidence of abuse and diversion of buprenorphine in foreign countries to support placing it into Schedule III of the Controlled Substances Act.

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beyond which increasing doses of the drug do not produce the increased effect that would result from full opioid agonists (like methadone, heroin, and oxycodone). In addition, when a partial agonist displaces a full agonist at the receptor, the relative reduction in receptor activation can produce withdrawal effects. Individuals dependent on full agonists may therefore experience sudden and severe symptoms of withdrawal if they use buprenorphine. This was predicted to serve as a further deterrent to abuse of buprenorphine.

Buprenorphine also has a long duration of action at the receptor. As a result, once on a stable dose, a buprenorphine patient is not expected to experience the alternating highs and lows that can impair daily functioning for users of full opioid agonists, but rather a more stable agonist effect that approximates normality. Finally, buprenorphine is thought to block full opioid full agonists from achieving their full effects, and thus to further deter abuse of these substances for buprenorphine patients.

[4] NDA 20-732.

[5] The naloxone added to SUBOXONE is intended to add an additional measure of abuse deterrence by causing more severe withdrawal if the product is crushed and injected by someone dependent on full opioid agonists.

[6] NDA 20-733.

[7] NDA 22-410.

[8] ANDA 90-360 (held by Barr); ANDA 90-622 (held by Ethypharm); and ANDA 78-633 (held by Roxane).

[9] (FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations*).

The prescription of SUBUTEX and SUBOXONE is also subject to the Drug Addiction Treatment Act of 2000 (DATA 2000).[10] DATA 2000 established a system in which qualifying physicians can prescribe Schedule III, IV, and V opioid medications for opioid dependence treatment outside the opioid treatment program (OTP) setting if the medications are approved by FDA for this indication – thereby eliminating significant barriers to medication-assisted opioid dependence treatment. Buprenorphine's Schedule III status means that, unlike methadone, which is in Schedule II, it can be prescribed by physicians outside of an OTP. SUBUTEX and SUBOXONE are currently the only drug products that qualify under the DATA 2000 framework for opioid dependence prescription treatment in an office-based setting.

DATA 2000 requires that physicians prescribing qualifying drugs for opioid dependence treatment outside the OTP setting satisfy minimum training requirements relating to the special concerns associated with opioid addiction treatment.[11] In addition, as part of the SUBUTEX and SUBOXONE NDA approvals, FDA required a Risk Mitigation Action Plan (RiskMAP) to address the risks of abuse and misuse associated with these products.[12] The RiskMAP included targeted product distribution and sales monitoring, active surveillance for diversion and abuse, and educational programs for patients, physicians, and pharmacists, among other measures.[13] The RiskMAP did not include heightened messaging specifically about accidental pediatric exposure, which had not been identified as a particular safety concern prior to approval.[14]

As part of the surveillance program, Reckitt was required to monitor a variety of sources of information about the abuse and misuse of its products, including the Toxic Exposure Surveillance System (TESS, now the National Poisoning Data System (NPDS), a database of calls to poison control centers).[15] In connection with this surveillance program, in December of 2006, Reckitt received recommendations from an external group of epidemiologists, clinical researchers, and treatment practitioners regarding the risk of accidental exposure to

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[10] 21 U.S.C. 823(g).

[11] 21 U.S.C. 823(g)(2)(G).

[12] Title IX, Subtitle A, section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) amended the Federal Food, Drug & Cosmetic Act (FD&C Act) to give FDA the authority to require a Risk Evaluation and Mitigation Strategy (REMS) when necessary to ensure that the benefits of a drug outweigh its risks. The RiskMAP that had been in effect for SUBUTEX and SUBOXONE tablets prior to the passage of FDAAA was not deemed to be an approved REMS. The Agency subsequently determined under Section 505-1 of the FD&C Act (21 U.S.C. 355-1) that the RiskMAP in place for SUBUTEX and SUBOXONE tablets should be replaced with a REMS program based on new safety information which showed an increase in misuse and abuse of these products since 2002.

[13] Letter to Alan Young, Director of Regulatory Affairs, Reckitt Benckiser, from Cynthia G. McCormick, M.D., Director, Division of Anesthetic, Critical Care, and Addiction Drug Products, Office of Drug Evaluation II, Center for Drug Evaluation and Research, FDA (October 8, 2002) (summarizing RiskMAP elements), available at http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2002/20732,20733ltr.pdf (McCormick Letter).

[14] See id. and educational brochures for physicians, pharmacists and patients required under the SUBUTEX and SUBOXONE tablet RiskMAP, available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2002/20-733_Subutex_Prntlbl.pdf (at 25-49).

[15] McCormick Letter at 4-5.

buprenorphine products.[16] On the basis of poison control center data showing that nearly a third of buprenorphine-related exposures involved children under 6, this group recommended that Reckitt develop a strategy to address the unintentional ingestion of buprenorphine products by children.[17] Subsequently, Reckitt began incorporating additional messaging about the need for safe storage into some of the materials it distributed to patients and physicians outside the requirements of the RiskMAP program.[18]

Reckitt also began developing a new formulation of SUBOXONE, the tablet form of which was (as indicated above) scheduled to have its exclusivity expire in October of 2009.[19] On October 20, 2008, Reckitt submitted an NDA for SUBOXONE sublingual film, which included unit-dose packaging.[20] In reviewing the NDA, FDA concluded that a REMS was necessary to ensure that the benefits of the drug outweigh the risks; specifically, to mitigate the drug's risks of abuse and misuse, and that both the REMS and labeling for SUBOXONE film should include increased warnings and counseling relating to the risk of accidental pediatric exposure.[21] The educational materials that FDA required were designed based on materials from both the original RiskMAP for SUBUTEX and SUBOXONE, and from materials that Reckitt had previously been distributing voluntarily outside its approved RiskMAP for these products.

The elements to assure safe use (ETASU)[22] established as part of the REMS for SUBOXONE film included important new requirements relating to accidental pediatric exposure. The ETASU require that brochures sent to physicians and pharmacists communicate the importance of keeping SUBOXONE out of reach of children and warn of the potentially fatal consequences of pediatric ingestion.[23] These materials advise that if a child is exposed to SUBOXONE, medical attention should be sought immediately.[24] The REMS also requires distribution to each patient

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[16] Reckitt Benckiser Pharmaceuticals, Subutex and Suboxone – Requested Report of Risk Management Program Educational Activities at 9 (submitted February 13, 2008).
[17] Id.
[18] Id.
[19] Both SUBUTEX and SUBOXONE tablets received seven years of orphan drug exclusivity upon approval.
[20] According to the Petition (at 22, n. 57), Reckitt had attempted to develop unit-dose packaging for its tablet buprenorphine products over the years, but experienced technical difficulties and elected to focus its resources on the development of a new dosage form instead. Reckitt sells buprenorphine tablet products outside of the United States in unit-dose packaging.
[21] In its August 2009 Complete Response Letter to Reckitt's NDA for SUBOXONE film (available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022410Orig1s000OtherActionLtr.pdf.), FDA informed Reckitt that its proposed REMS was insufficient to ensure that the benefits of the drug outweighed its risks, including with respect to accidental exposure in children, and provided Reckitt with a list of REMS elements that would be required for approval in order to mitigate these risks.
[22] See section 505-1(f)(3) of the FD&C Act.
[23] SUBOXONE sublingual film, NDA 22-410, Risk Evaluation and Mitigation Strategy (approved August 30, 2010), available at http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM227949.pdf (SUBOXONE sublingual film REMS) at 1-2; REMS Instruction Letter to Prescribers; REMS Introductory Letter to Pharmacists; Physician Brochure, *Important Information for Physicians - Frequently Asked Questions*; Pharmacist Brochure, *Important Information for Pharmacists - Frequently Asked Questions.*
[24] Id.

of a Medication Guide[25] with a prominently placed boxed warning at the beginning of the document stating:

> **IMPORTANT:**
>
> Keep SUBOXONE in a secure place away from children. Accidental use by a child is a medical emergency and can result in death. If a child accidentally uses SUBOXONE, get emergency help right away.[26]

The ETASU also require that, before the drug is dispensed, the risks in the labeling and Medication Guide, which include pediatric exposure risks, be discussed with patients, and that safe storage practices be explained and reviewed.[27] The REMS requires prescribers to document these discussions, and requires the sponsor to distribute an Appropriate Use Checklist (which Reckitt had previously circulated outside of the RiskMAP) to reinforce these and other best prescribing practices.[28]

The sponsor must also monitor compliance with the requirements to document safe use conditions when prescribing and dispensing this drug through surveys of patients and prescribers, evaluations of healthcare utilization databases, and ongoing surveillance (including via the internet, national databases, and surveys conducted at substance abuse treatment programs).[29] It must also monitor and evaluate the implementation of the ETASU and is required to take reasonable steps to improve implementation of these elements to meet the goals of the REMS.[30] The sponsor is also required to ensure that patients are monitored to ensure safe use of the drug and to prevent abuse and misuse.[31] REMS essentially identical to the one required for SUBOXONE film were approved for SUBUTEX and SUBOXONE tablets in December of 2011.[32]

In addition to the risk mitigation strategies imposed via the REMS, FDA required the labeling for SUBOXONE film to emphasize the risk of accidental pediatric exposure, including by addition of the following warning:

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[25] See section 505-1(e) of the FD&C Act.
[26] SUBOXONE sublingual film, NDA 22-410, Medication Guide, available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/022410s006s007mg.pdf
[27] SUBOXONE sublingual film REMS at 1-2.
[28] Id. at 2-3; Appropriate Use Checklist.
[29] SUBOXONE sublingual film REMS at 4; see also generally section 505-1(f)(4) of the FD&C Act.
[30] Id.
[31] Id. at 3.
[32] SUBOXONE sublingual tablet, NDA 20-733, Risk Evaluation and Mitigation Strategy (approved December 22, 2011), available at http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM285895.pdf; SUBUTEX sublingual tablet, NDA 20-732, Risk Evaluation and Mitigation Strategy (approved December 22, 2011), available at http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM285897.pdf.

Unintentional Pediatric Exposure

Buprenorphine can cause severe, possibly fatal, respiratory depression in children who are accidentally exposed to it. Store buprenorphine-containing medications safely out of the sight and reach of children and destroy any unused medication appropriately. *[see Disposal of Unused SUBOXONE Sublingual Film (17.2)].*

FDA also required the addition to the labeling of patient counseling on the importance of safe storage, the potentially fatal consequences of pediatric exposure, and the need for prompt medical attention if a child was exposed to the drug.[33] These labeling changes were subsequently approved for SUBUTEX and SUBOXONE tablets as well.[34]

Since approval of the SUBOXONE film REMS in 2010 (and subsequent approval of the same REMS for SUBOXONE and SUBUTEX tablets in 2011), Reckitt has not proposed any revisions to the REMS for these products to further address the risk of accidental pediatric exposure. In its August 30, 2012, combined REMS assessment for these products, which contained poison control center data and information gathered from surveys of patients and prescribers through that time, Reckitt stated that the REMS for SUBOXONE had been successfully implemented and that it was not proposing any changes.

On September 18, 2012, Reckitt submitted a letter to FDA's Office of Drug Shortages indicating its intention to discontinue marketing SUBOXONE tablets within 6 months because of its concerns about pediatric exposure to this product.[35]

B. Legal and Regulatory Framework

1. New Drug Applications

Under the FD&C Act, sponsors seeking to market a new drug generally must first submit an application to FDA for approval. An NDA contains, among other things, extensive scientific and clinical data demonstrating the safety and effectiveness of the drug (see sections 505(a) and (b) of the FD&C Act, 21 U.S.C. 355(a) and (b)). Under section 505(b)(2) of the FD&C Act, a sponsor may submit an application for approval that relies, at least in part, on investigations that were not conducted by or for the applicant and to which the applicant does not have a right of

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[33] FDA used the previously-approved labeling for SUBUTEX and SUBOXONE tablets as a template, but also updated and reorganized the labeling using the Physician Labeling Rule (PLR) format. In addition to incorporating new information about accidental pediatric exposure and affording new prominence to these safety messages, the PLR format provided additional clarity to the manner in which these messages were communicated. See SUBOXONE sublingual film labeling (originally approved August 30, 2010), available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/022410s000lbl.pdf; (original) SUBOXONE sublingual tablet labeling (approved October 8, 2002), available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2002/20732,20733lbl.pdf.

[34] SUBUTEX supplemental NDA (sNDA) 20-732 S-006 and S-007 (approved December 22, 2011); SUBOXONE sNDA 20-733 S-007 and S-008 (approved December 22, 2011)

[35] Letter to FDA, Office of Drug Shortage, from Ju Yang, Ph.D., Global Director, Regulatory Affairs, Reckitt Benckiser Pharmaceuticals Inc. (September 18, 2012).

reference. A 505(b)(2) application, like any NDA, must contain information adequate to show that the drug is safe and effective and must include data necessary to support the safety and effectiveness of any aspects of the proposed drug product that represent modifications to or changes from the listed drug on which it relies.

If, based on the information submitted with the application or any other information before the Agency, FDA has insufficient information to determine whether the drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling, the Agency will refuse to approve the NDA (section 505(d) of the FD&C Act). FDA will also refuse to approve an NDA if the proposed labeling is false or misleading in any particular (id.). Failure to include adequate warnings about safe use may also result in a drug product being deemed misbranded (section 502(f) of the FD&C Act). The FD&C Act prohibits the introduction (or delivery for introduction) into interstate commerce of any misbranded drug (section 301(a) of the FD&C Act (21 U.S.C. 331)).

2. Abbreviated New Drug Applications

The ANDA approval process established by the Drug Price Competition and Patent Term Restoration Act of 1984 (the Hatch-Waxman Amendments) is set forth in section 505(j) of the FD&C Act. To obtain approval, an ANDA applicant is not required to submit evidence establishing the clinical safety and effectiveness of the drug product; instead, an ANDA relies on FDA's previous finding that the RLD is safe and effective. To rely on a previous finding of safety and effectiveness, an ANDA applicant must demonstrate, among other things, that its drug product is bioequivalent to the RLD (section 505(j)(2)(A)(iv) of the FD&C Act).

In addition, an ANDA must contain, with certain exceptions, information to show that the proposed drug has the same active ingredient(s), indications for use, route of administration, dosage form, strength, and labeling as the RLD (section 505(j)(2)(A) of the FD&C Act). Section 505(j)(2)(A)(v) of the FD&C Act sets forth the permissible exceptions to the requirement that labeling be the same, providing that an ANDA must contain:

> information to show that the labeling proposed for the new drug is the same as the labeling approved for the listed drug...except for changes required because of differences approved under a petition filed under subparagraph (C) or because the new drug and the listed drug are produced or distributed by different manufacturers.

Section 505(j)(2)(A)(v) of the FD&C Act. FDA will not approve an ANDA lacking such a demonstration (section 505(j)(4)(G) of the FD&C Act). If the RLD has been voluntarily withdrawn from sale, FDA may not approve an ANDA referencing it until it determines whether the withdrawal was for reasons of safety or efficacy (21 CFR 314.161(A)(1)).

3. *Approval of Drug Products with REMS*

Section 505-1(a)(1) of the FD&C Act authorizes FDA to require applicants[36] to submit a proposed REMS when FDA has determined that a REMS is necessary to ensure that the benefits of a drug outweigh its risks. A REMS is a required risk management plan that uses risk minimization strategies beyond routine professional labeling (such as Medication Guides, patient package inserts, and/or communication plans) to ensure that the benefits of a drug outweigh its risks. In addition, FDA may require certain "elements to assure safe use" (ETASU) when additional elements are necessary to mitigate the risks associated with a drug (section 505-1(f)(3) of the FD&C Act). ETASU may include, for example, requirements that healthcare providers who prescribe the drug have particular training or experience, that patients using the drug be monitored, or that the drug be dispensed to patients with evidence or other documentation of safe use conditions.[37] If a listed drug is subject to a REMS, ANDAs referencing it must have the same Medication Guide if there is one[38] and the same or comparable ETASU (section 505-1(i)(1) of the FD&C Act).

II. DISCUSSION

A. Reckitt Benckiser Petition

The Petition indicates that, in 2006 and 2007, poison control center data began to show an increasing rate of pediatric exposure to buprenorphine products (Petition at 2). The Petition states that Reckitt took a number of actions to address this issue, including implementing targeted educational interventions on the risk of pediatric exposure and developing SUBOXONE film in unit-dose packaging (id.). The Petition contends that after Reckitt implemented its education initiative, rates of pediatric exposure plateaued, and that after the film (which uses unit-dose packaging) was introduced, exposure rates steeply declined (id.). The Petition relies on a recent study conducted by the Researched Abuse, Diversion and Addiction-Related Surveillance (RADARS) System and Venebio Group, which states that between the fourth quarter of 2009 and the first quarter of 2012, the rates of accidental exposure in children under 6 to buprenorphine or buprenorphine/naloxone tablets were 2.5 and 7.8 times greater respectively than to buprenorphine/naloxone film. For the first quarter of 2012, the most recent measured, the Petition states that the rate of pediatric exposure to buprenorphine/naloxone tablets was 8.5 times greater than for the film (id.).

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[36] Section 505-1 of the FD&C Act applies to any application for approval of a prescription drug submitted under section 505(b) or (j) of the FD&C Act (thus including both NDAs, including NDAs submitted under section 505(b)(2), and ANDAs submitted under 505(j)), as well as applications submitted under section 351 of the Public Health Service Act.

[37] Id.

[38] Medication Guides, which are part of approved labeling (see 21 CFR 208), are subject to the FD&C Act's same labeling requirement. We note that Medication Guides may also be part of a REMS (see section 505-1(e)(2) of the FD&C Act).

The Petition therefore requests that we refuse to approve any drug application for a buprenorphine product to treat opioid dependence unless the application includes targeted educational interventions addressing the risk of accidental pediatric exposure and child-resistant unit-dose packaging (Petition at 2-3). In support of these requests, it argues that Reckitt's educational campaign on accidental pediatric exposure is part of its labeling, and that the failure to require comparable educational interventions would render the labeling of buprenorphine NDAs for opioid dependence misleading, and the drugs themselves misbranded (Petition at 30-32). The Petition states, in addition, that the risk-benefit profile of buprenorphine NDAs for opioid dependence lacking targeted educational interventions on accidental pediatric exposure does not favor approval (Petition at 33-34). With respect to ANDAs, it argues that FDA may not approve a buprenorphine ANDA for opioid dependence treatment lacking targeted educational interventions on pediatric exposure risks because such applications would not have either the same labeling as the RLD (Petition at 34-36) or the same risk-benefit profile as the RLD (Petition at 36-38).

The Petition asserts, in addition, that FDA should refrain from approving buprenorphine NDAs for opioid dependence treatment without child-resistant unit-dose packaging (unless the applicant submits data showing that the proposed drug does not pose safety risks comparable to multi-dose packaged buprenorphine) because FDA does not have sufficient information to determine the safety of such drugs (Petition at 39-42). It states that the risk-benefit profile of such NDAs would not favor approval (Petition at 42-43). Finally, it asks that FDA refuse to approve any ANDAs for buprenorphine HCl/naloxone HCl products for opioid dependence until the Agency determines whether the RLD was discontinued for safety reasons (Petition at 3).

B. Educational Initiatives and Unit-Dose Packaging

While Reckitt requests that we refuse to approve any drug applications for buprenorphine products for opioid dependence that lack targeted educational interventions and unit-dose packaging, the Petition is not supported by evidence that these measures (rather than others undertaken to address this issue) caused the decline in accidental pediatric exposures. Both the Petition and the Executive Summary of the RADARS study[39] submitted in support of it acknowledge that the impact of educational interventions and packaging on the decline in pediatric exposure was not evaluated, and that definitive conclusions about these measures could not be reached (see, e.g., Petition at 25 ("the case reports reviewed did not provide sufficient information regarding physician/patient education or medication packaging to draw definitive conclusions"); Executive Summary at 5 ("Overall there was insufficient information in the case narratives from Poison Centers and the RBPPV database to determine whether physician/patient education influences the risk of unintentional pediatric exposure" and "The Poison Center reports (representing >98% of cases analyzed herein) that we reviewed did not include information regarding physician/patient education") and at 6 ("While there was insufficient information available on the use of physician/patient education to make definitive conclusions regarding its

[39] Accidental Exposure to Buprenorphine in Children: Executive Summary (Prepared September 14, 2012), Exhibit to Reckitt Citizen Petition (Executive Summary).

influence, further analysis of the data is ongoing to understand the impact of packaging on unintentional pediatric exposures").

FDA reviewed several additional data sources in an attempt to substantiate the Petition's claims (including FDA's Adverse Event Reporting System (FAERS) database, the National Electronic Injury Surveillance System Cooperative Adverse Drug Event Surveillance Project (NEISS CADES) database, poison control center data, medical literature, news media, and reports from foreign regulatory entities[40]). While these sources appeared to verify a downward trend in accidental pediatric exposures to buprenorphine products,[41] the cause of this decline (i.e., whether it resulted from packaging changes, educational measures, introduction of a new dosage form, or other factors) could not be verified using these data sources.

1. Educational Measures

The timing of the decline in accidental pediatric exposures (which, according to the Petition at 20, began in 2011) suggests that the implementation of the labeling warning, REMS, and Medication Guide for SUBOXONE film in 2010, with new messages relating to accidental pediatric exposure, likely also contributed to the reduction in the rate of accidental pediatric exposure. The Petition itself acknowledges (at 18) that "[i]t is not possible to determine what part of these impressive results are attributable to RBP's REMS, and what part are attributable to RBP's other risk mitigation efforts." A single type of educational intervention, therefore, has not been isolated as having contributed to the reduction.

As described above, the REMS and labeling currently approved for SUBUTEX and SUBOXONE contain increased and more prominent warnings about the risks of accidental pediatric exposure, and impose new patient counseling requirements designed to reinforce the

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[40] FDA queried regulatory agencies in Australia (Therapeutic Goods Administration), Canada (Health Canada), New Zealand (Medicines and Medical Devices Safety Authority), Singapore (Health Sciences Authority), and Europe (European Medicines Agency) to understand their experience with buprenorphine tablets and buprenorphine/naloxone tablets and film.

[41] FDA agrees that American Association of Poison Control Center (AAPCC) data showed an upward trend in accidental pediatric exposure rates as measured by calls to poison control centers with a subsequent plateau in these calls starting in or after 2009. These trends were similar to trends in emergency department (ED) visits for pediatric buprenorphine exposure in NEISS-CADES reviewed by FDA. However, FDA was not able to determine using NEISS-CADES data if the plateau in accidental pediatric exposures identified in AAPCC data began in 2009 or afterwards.

In the two-year period 2008/2009, a total of 1,916 ED visits due to accidental buprenorphine ingestion in children younger than age 6 years were projected nationally and 2,998 ED visits were projected for 2010/2011. An estimated 1,918 ED visits for buprenorphine exposure were projected nationally in 2010, but in 2011, the projected number of ED visits fell below 1,200. NEISS-CADES standards require (among other things) a minimum of 1200 projected ED visits for a national estimate to be considered stable. Nevertheless, these data suggest that 2010 may have been the peak year, and reinforces the observed decline in accidental pediatric exposure beginning in 2011 in poison control center data. (We note that the NEISS-CADES ED data are subject to some additional limitations, including wide confidence intervals. These estimates were not adjusted for changes in drug utilization).

importance of safe storage of these products away from children. These materials were designed using not only educational pieces from the original RiskMAP for these products, but also an Appropriate Use Checklist for documentation of safe use conditions and clinical monitoring of each patient that had previously been implemented voluntarily by Reckitt outside of the RiskMAP.

FDA believes these measures, among others, have contributed to substantially reducing the prevalence in the addiction treatment community of the notion that buprenorphine products are not dangerous in overdose or subject to abuse and diversion. The increased understanding of these risks and of the importance of close monitoring of patients on buprenorphine therapy has likely also played a role in reducing accidental pediatric exposure.[42]

In short, FDA has determined that the data do not support a conclusion that the additional educational interventions described by Reckitt over and above those required by the existing REMS are necessary to ensure that the benefits of these products outweigh the risks. Nevertheless, FDA will review any NDAs for buprenorphine products for opioid dependence treatment and determine, based on the specifics of each application, whether approval is appropriate[43] and what measures are necessary to mitigate attendant risks, including those of accidental pediatric exposure.[44] To the extent such NDAs present similar risks of accidental pediatric exposure, FDA will rely on the experience it has gained in developing the labeling warnings and REMS elements (including Medication Guides) addressing this risk for Reckitt's buprenorphine products in developing appropriate risk mitigation measures for these products. We will also continue to be informed by data gathered on these risks via the required monitoring and reporting through the REMS and other sources.

Educational interventions that are not required under the SUBUTEX or SUBOXONE REMS or labeling also would not be required of ANDAs referencing these products. As described above,

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[42] It is possible that buprenorphine's unique pharmacology (which initially contributed to underestimation by many of the risk of diversion associated with this drug) and the initial lack of clear labeling information on how to manage overdose at the time of approval (since remedied) also increased the likelihood that any one accidental exposure resulted in a call to a poison control center, thus inflating the numerator in studies based on poison control center data when compared to drugs for which the pharmacology and management of overdose were well-understood. Intervening efforts to educate the medical community about the product's pharmacology may improve the comparability of event rate numerators across data sources in these kinds of analyses.

[43] We note that, were evidence to show that the exposure-related risks associated with buprenorphine use were too great to permit unsupervised use, refusal to approve buprenorphine products for opioid dependence is not the only remedy available to FDA. DATA 2000, which permits the use of qualifying opioid treatment products outside the OTP setting, also provides for the making of an "adverse determination" about qualifying drugs (21 U.S.C. 823(g)(2)(C)(ii)). An adverse determination results in the imposition of additional standards relating to either the quantity of the drug that can be provided for unsupervised use or the qualifications of prescribing physicians (id.). Were the exposure-related risks of a particular buprenorphine product too great, FDA could seek such an adverse determination for the product (and, for example, recommend its restriction to the OTP setting) rather than simply refusing to approve it.

[44] Each potential buprenorphine product for opioid dependence submitted for approval in an NDA could utilize a different formulation, dosage form, etc., and each of these features could impact accidental pediatric exposure (and what additional measures are necessary in terms of risk mitigation).

the ANDA review process set forth in the FD&C Act is designed to ensure that ANDAs have the same risk-benefit profile as the RLD. It does so by requiring ANDA applicants to demonstrate that the proposed drug is bioequivalent to the RLD and that it has the same active ingredient(s), indications for use, route of administration, dosage form, strength, and labeling as the RLD (section 505(j)(2)(A) of the FD&C Act). If an RLD is subject to a REMS, ANDAs referencing it are subject to the same Medication Guide and the same or comparable ETASU (sections 505-1(i)(1) and (j)(2)(A)(v) of the FD&C Act). The FD&C Act does not require that ANDA holders implement activities and/or distribute materials that FDA has concluded are not required for the safe and effective use of the listed product.

All generic buprenorphine products for opioid dependence treatment will be required to utilize a REMS that contains comparable[45] requirements to those in place for the listed drugs, which FDA has concluded are, together with required labeling warnings, adequate to mitigate the accidental pediatric exposure risks associated with these products. To the extent Reckitt engages in voluntary educational activities and/or distributes materials which are not part of either its REMS or its labeling, implementation of these activities and/or distribution of these materials are not required of ANDAs referencing these drugs. Contrary to the Petition (at 34-36), the "same labeling" rule does not support Reckitt's claims. The FD&C Act requires that labeling for an ANDA be the same as the labeling "approved for the listed drug" (section 505(j)(2)(A)(v) and (4)(G)). Materials distributed voluntarily by Reckitt that have not been approved by FDA do not constitute "approved labeling," and are therefore not subject to the FD&C Act's same labeling requirement.

As noted above, however, the REMS for buprenorphine products for opioid dependence treatment require continued monitoring and assessment of the effectiveness of the mitigation measures currently in place to address accidental pediatric exposure. If FDA determines that further educational interventions are necessary to mitigate this risk, additional measures will be required for the RLD, and the same or comparable measures will be required of referencing ANDAs. Should Reckitt obtain data showing that a particular educational intervention that is not currently part of the REMS or labeling is necessary for the safe use of these products, such data should be submitted to the applicable NDAs.[46]

2. Unit-Dose Packaging

The Petition also argues that FDA should refrain from approving NDAs for buprenorphine products for opioid dependence treatment that do not include child-resistant[47] unit-dose

[45] FDA has (pursuant to section 505-1(i)(1)(B)(i) of the FD&C Act) waived the requirement that ANDAs referencing SUBUTEX and SUBOXONE use a single, shared system under section 505-1(f) with the listed drugs. This waiver was granted because FDA determined that the statutory criteria in section 505-1(i) of the FD&C Act were met. When a waiver is granted, ANDAs may be subject to different but comparable aspects of the ETASU for the RLDs (section 505-1(i)(1)(B)).

[46] This data should be submitted as either a REMS modification supplement or REMS correspondence or, if one is imminent, as part of a REMS assessment.

[47] Regulations promulgated by the Consumer Product Safety Commission under the Poison Prevention Packaging Act (PPPA), require all controlled drugs for oral use, which include buprenorphine-containing tablets, to be

packaging (unless the applicant submits data demonstrating that the proposed drug does not pose safety risks comparable to multi-dose packaged buprenorphine) because FDA does not have sufficient information to determine the safety of such drugs (Petition at 39-42). It also states that the risk-benefit profile of such NDAs would not favor approval (Petition at 42-43).

As indicated above, FDA has concluded that the current risk mitigation measures for buprenorphine products for opioid dependence treatment are adequate to address the risk of accidental pediatric exposure to these products. Reckitt has not provided evidence demonstrating that the use of unit-dose packaging (rather than labeling changes, REMS modifications, dosage form or other changes) caused the decline in accidental pediatric exposure. In addition, certain of the assumptions underlying Reckitt's argument in favor of unit-dose packaging are unsupported. The Petition states, for example, that the most serious exposure effects have been reported in children under 2 at doses greater than or equal to 4 milligrams (mg) (Petition at 10).[48] The Petition argues that exposure to amounts of buprenorphine greater than 2 mgs and less than 8 mg can only be caused by ingestion of multiple 2 mg dosage units because, prior to August 2012, the only commercially available strengths of buprenorphine were 2 mg and 8 mg tablets or film strips (id.).

Data reviewed by FDA (including from FAERS, NEISS CADES case reports, and from drug usage survey data) confirm, however, that patients take and are prescribed partial doses of buprenorphine, that they split their tablets before using them and save partial tablets for later use, and that some cases of pediatric exposure involve exposure to partial tablets or partial film strips.[49] Pediatric ingestion of multiple 2 mg dosage units is therefore not the only way to achieve exposure to amounts between 2 and 8 mg. Accidental exposure to partial doses of buprenorphine would not be prevented by unit-dose packaging.

In addition, based on the available data, it appears that the practice of removing buprenorphine products from their packaging and storing them outside of their intended packaging can and does occur with all three buprenorphine products for opioid dependence. Such storage practices also likely contribute to accidental pediatric exposure. We do not know the rate at which this unsafe practice occurs, whether it differs between packaging configurations, or whether the risk of harm once the product is repackaged is the same for all buprenorphine oral products. [50]

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dispensed by pharmacies in child-resistant containers (except where an exemption is requested by the prescriber or purchaser) (16 CFR 1700.14(a)(4), 1700.15(a)-(c); 15 U.S.C. 1473(b)). As a result, we expect in most cases that, regardless of whether unit-dose or multi-dose packaging is in place, patients will receive buprenorphine tablets in pharmacy-supplied child-resistant containers.

[48] No data was provided in the Petition for FDA to evaluate the validity of this assertion.

[49] Data reviewed by FDA on drug usage from survey data confirm that patients are prescribed partial doses of buprenorphine. As indicated above, to achieve partial doses of buprenorphine, patients may split their tablets or films before use and save the remaining quantity for later use. Although the number of pediatric ingestions that occur following the splitting of tablets and film is unknown, pediatric exposure data from FAERS and NEISS-CADES indicates that some cases of pediatric exposure involve exposure to partial tablets or partial film strips.

[49] NEISS-CADES reported during 2004 -2011 and FAERS reported during 2006-2012

[50] Reckitt suggests (at 38, n. 93) that the risk posed by improper storage of partial dosage units may be mitigated by the recent approval of 4 mg and 8 mg strengths of the SUBOXONE film, which it hopes will help reduce the

Finally, the RADARS study and supporting documentation do not provide data about how much buprenorphine was involved in each instance of exposure (i.e., whether exposure involved a single film or tablet or more/less). Nevertheless, in the cases for which FDA was able to find data, exposure to partial or single doses of buprenorphine, rather than to multiple doses, appears to predominate. To understand the potential benefit of unit-dose packaging (which could limit to one dose the quantity ingested if packaging is defeated by a child), FDA evaluated the narratives of cases reported to NEISS-CADES and FAERS in an attempt to determine the amount of drug ingested with each exposure. FDA evaluated the narratives of 187 such cases. Approximately a quarter of these cases did not include estimates of the quantity ingested; however, for the three quarters of cases that did provide this information, most (112 out of 131) cases involved ingestion of less than or equal to one tablet or film. Only a small number of the cases for which this information was available (19 of 131) involved ingestion of a quantity greater than one tablet or film.

Although child resistant unit-dose packaging could provide additional deterrence to accidental pediatric exposure, many products which are potentially harmful to children are distributed without unit-dose packaging. While FDA welcomes and encourages sponsors to utilize unit-dose packaging for their oral buprenorphine products, we do not believe the data at this time support refusing to approve applications that lack such packaging. We will, however, refer this matter to the Consumer Product Safety Commission (CPSC), so that the CPSC can determine if it believes specific standards for buprenorphine products should be developed under the PPPA. We will also, as indicated above, continue to monitor data relating to accidental pediatric exposure to buprenorphine products. Should data show that additional measures are necessary to mitigate this risk, we will take appropriate regulatory action at that time.

C. Discontinuation of SUBOXONE Tablet Product

The Petition also asks FDA to refuse to approve any ANDAs for buprenorphine HCl/naloxone HCl products for opioid dependence until the Agency determines whether the RLD for these products was discontinued for safety reasons (Petition at 3). FDA regulations require that a determination as to whether a listed drug was voluntarily withdrawn from sale for safety or effectiveness reasons be made by the Agency prior to approving an ANDA referring to the listed drug.[51] Reckitt's buprenorphine HCl/naloxone HCl products (SUBOXONE tablets and film), however, have not been withdrawn from sale. While Reckitt has declared its intention to withdraw SUBOXONE tablets from sale in the future, our understanding is that this product

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practice of partial dosing and mitigate the risk of pediatric exposures in households where patients use less than a full film strip to achieve a given dose. Reckitt has provided no data to support this view, however, and FDA is not convinced that the commercial availability of these strengths will eliminate the practice of using partial doses for a variety of reasons. Some patients/providers may be motivated to use partial amounts of a higher strength of the film to achieve a given dose if doing so reduces the cost per dose of the drug for patients or third-party payers. Others may need to adjust their dosage for clinical reasons using the supply they have on hand. In any case, the practice of splitting tablets or film may be expected to continue.

[51] 21 CFR 314.161(A)(1).

continues to be shipped and sold. Accordingly, a determination as to whether it was withdrawn from sale for reasons of safety is not required at this time in order to approve ANDAs referencing this product.

Nevertheless, the Agency has determined, on the basis of the data available, that withdrawal of SUBOXONE tablets is not necessary for reasons of safety. The RADARS study on which the Petition relies does not add substantial new information to the data reviewed in connection with the SUBOXONE film NDA, which led to REMS requirements and labeling modifications for both the film and tablet products to address this issue. In fact, this data suggests an encouraging downward trend in accidental pediatric exposure that could be attributed to a variety of factors, as discussed above. These include improvements in labeling to provide clearer messages about the risks and additional information about management of overdose, letters to prescribers and pharmacists informing them of product risks, including of accidental pediatric exposure, Medication Guides provided to patients emphasizing the risk of accidental pediatric exposure, and a physician checklist that directs physicians to review this topic with patients. All of these educational efforts are expected to continue to have a favorable impact on rates of accidental pediatric exposure. As discussed above, until these messages were disseminated (whether via Reckitt's voluntary educational interventions or through the current approved REMS), many prescribers, pharmacists, and patients held the mistaken impression that buprenorphine was not dangerous in terms of abuse or overdose. This seems to be a situation in which educational efforts had the potential to be particularly effective.

Reckitt's own actions also undermine, to some extent, its claims with respect to the severity of this safety issue. Notwithstanding the availability of data showing (according to the Petition) an increasing rate of accidental pediatric exposure through at least the first part of 2010, and the first report of a pediatric death in June of 2010,[52] Reckitt did not seek to discontinue marketing of the tablet in multi-dose containers for more than two years. As recently as August 2012, Reckitt indicated to FDA its view that the SUBOXONE REMS, which is designed to mitigate the risks associated with that drug, had been successfully implemented and that it was not proposing any changes. The timing of Reckitt's September 2012 announcement that it would discontinue marketing of the tablet product because of pediatric exposure issues, given its close alignment with the period in which generic competition for this product was expected to begin,[53] cannot be ignored.

D. Comments Regarding Anticompetitive Conduct

Several commenters assert that FDA should deny Reckitt's Petition under section 505(q)(1)(E) of the FD&C Act, which permits denial when a petition "was submitted with the primary purpose of delaying the approval of an application and the petition does not on its face raise valid

[52] Petition at 23, 11.

[53] Reckitt had access to information about the timing of ANDAs for SUBOXONE tablets as a result of efforts to secure its participation in a single shared REMS for this product.

scientific or regulatory issues."[54] Commenters claim the Petition is part of a pattern of anticompetitive behavior on Reckitt's part intended to delay approval of generic versions of its products that includes, for example, its lack of cooperation with the efforts of FDA and potential generic competitors to negotiate a single shared REMS with its buprenorphine products.[55] Commenters emphasize that Reckitt, while arguing that the marketing of generic versions of SUBOXONE tablets in multi-dose packaging presents a risk to children, has continued to market its own SUBOXONE tablet product in multi-dose packaging, suggesting that its arguments on this point are no more than an effort to avoid generic competition.[56] Commenters argue that Reckitt's activities indicate an effort to maintain its monopoly on the tablet version of SUBOXONE as long as it can while it switches consumers to the film version of the product, [57] which is subject to statutory exclusivity and for which Reckitt claims patent protection.

FDA is not denying Reckitt's Petition pursuant to section 505(q)(1)(E) of the FD&C Act. The Agency has, however, referred this matter to the Federal Trade Commission, which has the administrative tools and the expertise to investigate and address anticompetitive business practices.

[54] See Comment of Actavis Inc. (January 31, 2013) (Actavis Comment); Comment of Buprenorphine Products Manufacturers Group (February 1, 2013) (BPMG Comment); Comment of Amneal Pharmaceuticals LLC (February 4, 2013) (Amneal Comment). We note that FDA also received comments on the Petition from Reckitt, the American Society of Addiction Medicine, and Dr. Hallam Gugelmann. Because Reckitt and Dr. Gugelmann failed to verify their comments under section 505(q)(1)(I) of the FD&C Act, FDA is not permitted to accept these comments for review. We have reviewed these comments, however, and nothing in them would change the decisions reached by FDA in this response.

[55] See Actavis Comment at 2-3, 8; BPMG Comment at 1-3, 19-20; Amneal Comment at 2-8.

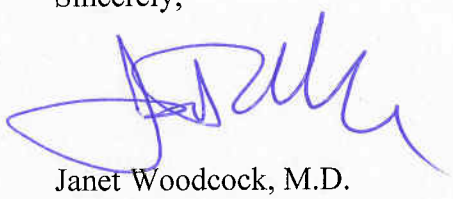
[56] See Actavis Comment at 2; see also generally Amneal Comment at 8; BPMG Comment at 5, 12-13.

[57] See Amneal Comment at 2 ("RBP's petition is the latest chapter in a sophisticated, strategic campaign to preserve RBP's multi-billion dollar Suboxone monopoly by (1) preventing or delaying approval of generic versions of Suboxone Tablets, and (2) transitioning Suboxone patients to a patent protected film dosage form."); BPMG Comment at 15-16; Actavis Comment at 2-3.

III. CONCLUSION

For the reasons described above, Reckitt's request that FDA refuse to approve any drug application for a buprenorphine product for opioid dependence treatment unless the application includes targeted educational interventions addressing accidental pediatric exposure (beyond what is required by the approved REMS and labeling for these products) is denied. Reckitt's request that we refuse to approve applications for such products unless they include child-resistant, unit-dose packaging (or safety data showing a superior risk profile to SUBOXONE tablets) is also denied. Reckitt's request that the Agency not approve any ANDAs for buprenorphine HCl/naloxone HCl products prior to determining whether these products were discontinued for safety reasons is also denied.

Sincerely,



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