Reckitt Benckiser Pharmaceuticals Inc.

November 16, 2012

Dockets Management Branch
Food and Drug Administration
5630 Fisher's Lane, Room 1061 (HFA-305)
Rockville, MD 20852

Re Docket No. FDA-2012-P-1028

Dear Sir or Madam:

On September 25, 2012, Reckitt Benckiser Pharmaceuticals Inc. (RBP) submitted a citizen petition requesting that the Food and Drug Administration (FDA) refrain from approving any application for buprenorphine – a product with known serious risks – for opioid dependence treatment that lacks a targeted pediatric exposure education program and child-resistant unit-dose packaging. The petition includes data, which had come to RBP's attention on September 14, 2012, regarding the risk of pediatric exposure to buprenorphine. The unavoidable conclusion from this data, coupled with the availability of a safer child-resistant unit-dose packaged buprenorphine/naloxone product, led RBP to discontinue marketing buprenorphine tablets (NDA # 20-733).

On October 22, 2012, Amneal Pharmaceuticals, LLC (Amneal) submitted a comment to RBP's citizen petition which contains numerous mischaracterizations of facts related to, and unrelated to, the citizen petition.[1] Amneal's comment, however, fails to include any evidence to rebut the data-driven safety conclusions that led to the petition being filed and RBP to discontinue marketing buprenorphine/naloxone tablets. This approach by Amneal demonstrates a lack of understanding of the statutory basis for in-office treatment of patients addicted to opioids. This is consistent with our interactions with Amneal over the past year and illustrates Amneal's lack of interest in learning about the public health risks inherent in making this product available to patients pursuant to DATA 2000. Moreover, Amneal has stated its desire to execute the minimum possible risk mitigation activities that might satisfy FDA.

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[1] RBP seeks to spare the FDA from any further waste of Agency resources and so has not provided a point-by-point refutation of these mischaracterizations or an accurate history of the single-shared REMS development discussions. Should the Agency be interested in this sort of analysis RBP would be happy to provide it. We believe that the record is clear and irrefutably contrary to many of Amneal's allegations.

RBP filed the citizen petition on the basis of public health concerns regarding pediatric exposure. This public health concern is supported by validated pediatric safety data (*i.e.*, the Executive Summary attached to the citizen petition) that was made available to RBP on September 14, 2012. Amneal states in its comment, as if it somehow discredits the data, that both RBP and FDA were aware of the risk of pediatric exposure to buprenorphine even before buprenorphine was approved. RBP does not deny that this is true. In fact, it was this awareness, coupled with a concern for patient safety, that led RBP to proactively develop a new formulation and why RBP has been vigilant in tracking trends in pediatric exposure and seeking data to determine how best to reduce that risk. Amneal's comment is not correct when it asserts that RBP was aware of the validated pediatric safety data contained in the citizen petition for an extended period of time – unless, of course, eleven (11) calendar days is an extended period of time.

As explained in the citizen petition, the film product was developed in part as a response to RBP's expectation that child-resistant unit-dose packaging would reduce the risk of children being exposed to harmful doses of buprenorphine. That FDA, at the time of initial approval of the film product, did not find the then-theoretical benefits of unit-dose packaging sufficient to include them in the risk evaluation and mitigation strategy (REMS) is irrelevant to RBP's decision to discontinue marketing the tablet and also irrelevant to FDA's view of the newly-submitted data that support what had once been just a theory. As RBP noted in the citizen petition, the first pediatric death associated with a buprenorphine tablet product occurred in June 2010 and was not reported to RBP until October 2012, which was after the film product was approved. Before September of this year, RBP (and perhaps even FDA) strongly suspected that a child-resistant individually wrapped film product could be safer than multiple tablets in containers with child-resistant closures. As RBP gained experience with both products, its belief in the inherent safety advantage of the film product became stronger and it sought to obtain empirical data that would determine whether, in fact, its theoretically and anecdotally driven concerns were warranted. The very first summary analysis of these data was then submitted to FDA without delay. That same information led RBP to discontinue marketing buprenorphine/naloxone tablets.

Amneal's comment never addresses the valid public health issue raised in the citizen petition: namely, that there is approximately a 9-fold difference between film and tablets in terms of the risk of pediatric exposure. RBP is aware of no evidence to the contrary, and Amneal provides none. Instead, Amneal attempts to ignore or trivialize this finding. Amneal first complains that it does not have access to "data, case notes, or actual analysis" (comment at 10). Next, after acknowledging that it does not have access to data/analyses that it claims to need, Amneal states that these data represent merely a "safety signal" that needs to be "confirmed" by further study (id.). Amneal is silent

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regarding how many additional pediatric exposures and subsequent deaths to buprenorphine it would find acceptable while such confirmation is being carried out. Finally, Amneal argues that the data and analyses (that it has not seen) do not support RBP's actions. Furthermore, Amneal's comment necessarily highlights Amneal's complete lack of experience in evaluating RADARS data, and understanding regarding how such data typically are collected or presented (id. at 11). While Amneal would be waiting for further analysis, guidance, clarity, confirmation, or instructions from FDA, the pediatric population undeniably would be at risk of additional exposures and possible deaths. RBP took the only appropriate action in light of the information available, and it did not need to repeat the study authors' careful examination of the underlying data to make that decision.[2]

Amneal's assertion that the approximate 9-fold difference in pediatric exposure rates is related to a difference in time on the market between tablets and film (id. at 11) is unfounded and not supported by data. Amneal may not understand that the rate of pediatric exposure in the analysis was adjusted for availability of the product in the market. Amneal also appears to suggest that no regulatory action be taken until such time as details regarding pediatric exposures to opioids are reported to its satisfaction despite the incontrovertible fact that there is an approximate 9-fold difference in the risk of pediatric exposure between film and tablet. RBP does not believe that the difference in risk of pediatric exposure is going to disappear while Amneal quibbles over how case report data are collected or analyzed.[3] Accordingly, RBP chose to discontinue marketing the product presenting the greater risk without awaiting definitive proof as to which features contributed to that risk.

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[2] The authors of the study are Drs. Richard Dart, Eric Lavonas, Becki Bucher-Bartelson, and Jody Green, and Ms. Kimberly Brown, from the Rocky Mountain Poison and Drug Center, Denver Health and Hospital Authority, which operates the Researched Abuse, Diversion, and Addiction-Related Surveillance (RADARS) System. The other authors are Dr. William Banner (Oklahoma Poison Center and Integris Baptist Medical Center), Pamela Bradt (The Degge Group), and Pradeep Rajan, and Lenn Murrelle from the Venebio Group, LLC. The qualifications and experience of these authors are beyond reproach.

[3] In fact, the risk of unintentional pediatric exposure to buprenorphine and buprenorphine/naloxone tablets seems to be increasing over time. According to the data presented in the Executive Summary, the risk of unintentional pediatric exposure to buprenorphine and buprenorphine/naloxone tablets was 2.5 and 7.8 times higher, respectively, than the risk for combination film over the entire time of observation. While for the first quarter of 2012, (the most recent quarter observed) the risk of unintentional pediatric exposures to buprenorphine and buprenorphine/naloxone tablets increased to 3.2 and 8.5 times greater than for buprenorphine/naloxone film, respectively.

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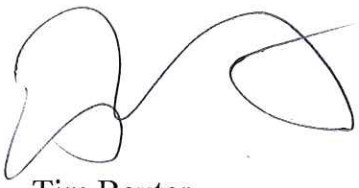
Amneal similarly fails to address the fact that the pediatric deaths at issue have been associated with tablets and that all deaths reported to RBP were received after approval and launch of the film formulation. The tablet product is associated with a much higher risk of pediatric exposure, and exposure necessarily precedes death. RBP attaches to this comment documentation about an additional pediatric death that was reported to and confirmed by RBP after the citizen petition was submitted.[4] This pediatric death was similarly associated with the tablet formulation. Contrary to Amneal's unsupported characterizations and speculations, the desire to avoid even a single additional such report in the future is the primary reason that RBP has discontinued marketing the buprenorphine/naloxone tablet.

* * *

Amneal's comment requests that FDA reject RBP's citizen petition before the agency has even had a chance to consider its merits.[5] In support of this request, Amneal alleges that the citizen petition and RBP's discontinuance of marketing buprenorphine/naloxone tablets is attributable to an economic motive, not a safety motive. This allegation, of course, ignores Amneal's economic motive in this case. That the parties seeking FDA intervention stand to benefit from a particular outcome does not minimize the legitimacy of their concerns.

By its inability to discuss, or perhaps even understand the safety findings reported in the citizen petition, by its emphasis on conjecture as an antidote to data, by inviting FDA to focus only on RBP's possible economic motives while ignoring Amneal's own, Amneal only highlights its lack of interest in understanding and managing the serious public health risks associated with buprenorphine tablets.

Respectfully submitted,



Tim Baxter
Global Medical Director
Reckitt Benckiser Pharmaceuticals Inc.

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[4] The details of the autopsy have been redacted from RB-45309-2012.

[5] Amneal also questions why RBP continues to make the tablets available during the period it is discontinuing marketing the tablets. Amneal seems unconcerned about the devastating effect on patients and the treatment community that would be caused by a precipitous removal, and ignores the mandatory 6-month notice period required under section 506C of the FDC Act.

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ATTACHMENT

U.S. Department of Health and Human Services
Food and Drug Administration

Reckitt Benckiser

Form Approved: OMB No. 0910-0291 Expires: 12/31/2011
Phase Forward FDA Facsimile Approval: 07/12/2006

MEDWATCH

FORM FDA 3500A (01/09)

Mfr report #	RB-45309-2012
UF/Importer Report #	
	FDA Use Only

A. PATIENT INFORMATION

1. Patient Identifier	2. Age at Time of Event: / Date of Birth:	3. Sex	4. Weight
LS In confidence	or 12 months	☑ Female ☐ Male	29.0 lbs or kgs

B. ADVERSE EVENT OR PRODUCT PROBLEM

1. ☑ Adverse Event and/or ☐ Product Problem *(e.g., defects/ malfunctions)*

2. Outcomes Attributed to Adverse Event *(Check all that apply)*
- ☑ Death: 05/08/2012 *(mm/dd/yyyy)*
- ☑ Life-threatening
- ☐ Hospitalization - initial or prolonged
- ☐ Required Intervention to Prevent Permanent Impairment/Damage (Devices)
- ☐ Disability or Permanent Damage
- ☐ Congenital Anomaly/Birth Defect
- ☑ Other Serious (Important Medical Events)

3. Date of Event *(mm/dd/yyyy)*	4. Date of This Report *(mm/dd/yyyy)*
05/??/2012	11/08/2012

5. Describe Event or Problem

Report No. 1 received from a news reporter via Email on 27-Sep-2012:

Inquest jury: 1-year-old died from accidental drug overdose; Pantagraph.com, 26-Sep-2012

This news article states a 1-year-old girl died accidentally of a drug overdose. The child was found unresponsive in her bed by her father on 08-May-2012 around 5:30 am.
The child reportedly suffered from allergies and was given an allergy medication (unknown clarification, unknown dosing) and a pain reliever (no further clarification given, unable to code) before she went to bed. It was reported she had trouble staying awake during her dinner.

The father admitted to obtaining a (cont.)

6. Relevant Tests/Laboratory Data, Including Dates

(Tabularized lab data is appended.)

7. Other Relevant History, Including Preexisting Medical Conditions *(e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)*

Relevant History:
The patient's past medical history included APNEA[Apnoea].

Concomitant disease(s):
The patient's present medical condition (cont.)

Submission of a report does not constitute an admission that medical personnel, user facility, importer, distributor, manufacturer or product caused or contributed to the event.

3500A Facsimile

C. SUSPECT PRODUCT(S)

1. Name *(Give labeled strength & mfr/labeler)*
#1 Suboxone
#2 Allergy medication (None)

2. Dose, Frequency & Route Used	3. Therapy Dates *(if unknown, give duration)* from/to (or best estimate)
#1 (Unknown (cont.)	#1 (05/??/2012 (cont.)
#2 (Unknown (cont.)	#2 (Unknown)

4. Diagnosis for Use *(Indication)*	5. Event Abated After Use Stopped or Dose Reduced?
#1 Accidental drug (cont.)	#1 ☐ Yes ☐ No ☐ Doesn't Apply
#2 Multiple allergies	#2 ☐ Yes ☐ No ☐ Doesn't Apply

6. Lot #	7. Exp. Date	8. Event Reappeared After Reintroduction
#1 Unknown	#1	#1 ☐ Yes ☐ No ☐ Doesn't Apply
#2	#2	#2 ☐ Yes ☐ No ☐ Doesn't Apply

9. NDC# or Unique ID

10. Concomitant Medical Products and Therapy Dates *(Exclude treatment of event)*

G. ALL MANUFACTURERS

1. Contact Office - Name/Address *(and Manufacturing Site for Devices)*
Dr. T. Baxter, Reckitt Benckiser Pharmaceuticals Inc., 10710 Midlothian Turnpike, Richmond, VA 23235 United States

2. Phone Number: 804-423-7088

3. Report Source (Check all that apply)
- ☐ Foreign
- ☐ Study
- ☐ Literature
- ☑ Consumer
- ☑ Health Professional
- ☐ User Facility
- ☐ Company Representative
- ☐ Distributor
- ☐ Other:

4. Date Received by Manufacturer (mm/dd/yyyy): 09/27/2012

5. (A)NDA # 20-733
IND #
STN #
PMA/ 510(k) #

6. If IND, Give Protocol #

7. Type of Report *(Check all that apply)*
- ☐ 5-day ☐ 30-day
- ☐ 7-day ☐ Periodic
- ☐ 10-day ☑ Initial
- ☑ 15-day ☐ Follow-up #

Combination Product ☐ Yes
Pre-1938 ☐ Yes
OTC Product ☐ Yes

9. Manufacturer Report Number: RB-45309-2012

8. Adverse Event Term(s): Accidental drug intake by child (cont.)

E. INITIAL REPORTER

1. Name and Address: Anonymized, United States

Phone #

2. Health Professional?	3. Occupation	4. Initial Reporter Also Sent Report to FDA
☑ Yes ☐ No	(cont.)	☐ Yes ☐ No ☑ Unk.

B5. Describe event or problem (continued)

prescription for Suboxone (tablets). He is accused of allowing the child access to Suboxone (tablets).

The coroner said observations during the autopsy pointed to a potential drug overdose. Toxicology reports turned up evidence of what the coroner described as fatal concentrations of Suboxone. The amount of the narcotic degested by the child and recorded in blood tests was 13.1 nanograms per milliliter according to the coroner.

No further information is known at this time.

Lot number was unknown.
Reporter causality is unknown.

Further information concerning autospy and toxicology reports has been requested from the Coroner's office.
This case was linked to case no. RB-45308-2012 (same reporter).

Report No. 2 received from a Coroner's Forensic Pathologist via follow-up letter on 22-Oct-2012:
Necropsy Report of the Coroner's Forensic Pathologist to the Coroner of McLean County, Illinois
Case No. N-12-206: Name: LJ: Female: 1 year Race: White
Date of Death: 08-May-2012: Date of Autopsy: 09-May-2012
Examined by: J. Scott Denton, MD: Assistant: William Belcher

The examination is performed at the McLean County Coroner's Office regional Autopsy Facility, Bloomington, Illinois, under the authority of Coroner Beth Kimmerling.

External Examination:

REDACTED

Cause of Death Opinion:

This 1 year old, white female child, died from buprenorphine intoxication. Buprenorphine and norbuprenorphine were present in both her blood and liver tissues at reported fatal concentrations. Her father recently began narcotic substitution therapy with buprenorphine.

The child's laboratory tests showed the following results; Liver tissue indicated: positive for norbuprenorphine at a concentration of 6.9 ng/g and positive for buprenorphine at a concentration of 16.2 ng/g. Sodium was 130 mmol/l, potassium 16.4 mmol/l, chloride 116 mmol/l, glucose 0 mg/dL, urea nitrogen 22 mg/dL and creatinine was measured at 0.0 mg/dL. Blood test indicated Norbuprenorphine positive, Norbuprenorphine, Quant: 11.7 ng/ml. Blood test indicated Buprenorphine positive, Buprenorphine, Quant: 13.1 ng/ml. Blood test indicated Naloxone: positive. Blood test indicated Analgesics; positive. The remaining laboratory test were negative and are in the lab data section.

Infant's medical history included past resolved apnea and allergies.

The previously reported adverse event of accidental drug overdose has been deleted from this case after receiving the information for report No. 2.

Lot number was not known. No further information was provided. No other causality assessments were provided. Permission for follow-up was not granted. This case will be closed.

B7. Other relevant history (continued)

includes ALLERGIES[Multiple allergies].

C2. Dose, frequency and route used for suspect product #1 (continued)

dosing details Unknown)

C3. Therapy dates/durations used for suspect product #1 (continued)

to 05/??/2012)

C4. Diagnosis for use (Indication) for suspect product #1 (continued)

intake by child

C2. Dose, frequency and route used for suspect product #2 (continued)

dosing details Unknown)

E3. Initial Reporter occupation (continued)

Coroner's Forensic Pathologist

G8. Adverse event terms (continued)

Somnolence
Unresponsive to stimuli
Toxicity to various agents

MedWatch: Tests/laboratory data

Reckitt Benckiser
Mfr Report #: RB-45309-2012

B6. Lab Data

Panel	Test	Results	Units	Low Normal	High Normal	Normal?	Test Date
Blood test							
	Acetone	Negative	n/a				08/10/2012
	Alcohol	Negative	n/a				08/10/2012
	Amphetamines	Negative	n/a				08/10/2012
	Analgesics	Positive	n/a				08/10/2012
	Anesthetics	Negative	n/a				08/10/2012
	Antibiotics	Negative	n/a				08/10/2012
	Anticonvulsants	Negative	n/a				08/10/2012
	Antidepressants	Negative	n/a				08/10/2012
	Antihistamines	Negative	n/a				08/10/2012
	Antipsychotics	Negative	n/a				08/10/2012
	Barbiturates	Negative	n/a				08/10/2012
	Benzodiazepines	Negative	n/a				08/10/2012
	Buprenorphine	13.1	ng/ml			Elevated	08/10/2012
	Cannabinoids	Negative	n/a				08/10/2012
	Cardiovascular agents	Negative	n/a				08/10/2012
	Cocaine/metabolites	Negative	n/a				08/10/2012
	Endocrine agents	Negative	n/a				08/10/2012
	Ethanol	Negative	n/a				08/10/2012
	Fentanyl	Negative	n/a				08/10/2012
	Gastroenterology agents	Negative	n/a				08/10/2012
	Isopropanol	Negative	n/a				08/10/2012
	Methadone/metabolite	Negative	n/a				08/10/2012
	Methanol	Negative	n/a				08/10/2012
	Naloxone	Positive	n/a				08/10/2012
	Narcotics	Negative	n/a				08/10/2012
	Neurology agents	Negative	n/a				08/10/2012
	Norbuprenorphine	11.7	ng/ml				08/10/2012
	Opiates	Negative	n/a				08/10/2012
	Phencyclidine	Negative	n/a				08/10/2012
	Propoxyphene/metabolite	Negative	n/a				08/10/2012
	Sedatives/Hypnotics	Negative	n/a				08/10/2012
	Stimulants	Negative	n/a				08/10/2012
	Urology agents	Negative	n/a				08/10/2012
Electrolytes							
	Chloride	116	mmol/l				08/10/2012

MedWatch: Tests/laboratory data

Reckitt Benckiser
Mfr Report #: RB-45309-2012

B6. Lab Data

Panel	Test	Results	Units	Low Normal	High Normal	Normal?	Test Date
Electrolytes							
	Creatinine	0	mg/dl				08/10/2012
	Glucose	0	mg/dl				08/10/2012
	Potassium	16.4	mmol/l				08/10/2012
	Sodium	130	mmol/l				08/10/2012
	Urea nitrogen	22	mg/dl				08/10/2012
Liver tissue test							
	Acetaminophen	Negative	n/a				08/10/2012
	Buprenorphine	16.2	ng/g				08/10/2012
	Cetirizine	Unsuitable - test cancelled due to interference	n/a				08/10/2012
	Norbuprenorphine	6.9	ng/g				08/10/2012

PANTAGRAPH.COM

Inquest jury: 1-year-old died from accidental drug overdose

15 HOURS AGO • BY EDITH BRADY-LUNNY | EBLUNNY@PANTAGRAPH.COM

BLOOMINGTON — A 1-year-old girl died accidentally of a drug overdose, a McLean County inquest jury ruled Thursday.

Laina Stevenson was found unresponsive in her bed by her father, Martin Stevenson, around 5:30 a.m. May 8 after the child's twin sister woke up crying, according to information given to the inquest panel by Coroner Beth Kimmerling.

Stevenson, 25, faces felony charges for endangering the health of a child resulting in a death. He is accused of allowing the child access to Suboxone, a drug prescribed to treat opiate dependency.

He was arrested Aug. 15 and remains in jail in lieu of $50,025.

The coroner said observations during the autopsy pointed to a potential drug overdose. Toxicology reports returned in August turned up evidence of what Kimmerling described as "fatal concentrations" of Suboxone.

Normal Police Det. Nicole Bruno testified that Stevenson and his wife Marta told authorities the children suffered from allergies and were given an allergy medication and a pain reliever before they went to bed. They also reported that Laina had trouble staying awake during her dinner.

Martin Stevenson admitted to a drug relapse days before the child's death and to obtaining a prescription for Suboxone.

According to Bruno, the father initially said he took half a pill in the morning but later said he took an entire pill. Stevenson said no pills were missing and the mother told police she saw one-half of a pill in the bottle when she checked it around 9 p.m., said the detective.

The amount of the narcotic digested by the child and recorded in blood tests — 13.1 nanograms per milliliter — surpassed the 8.4 nanograms per milliliter considered fatal in adults, said the coroner.

"It's not a fragment or a crumb — we're talking somewhere along a half or a whole pill," Kimmerling said of the drug.

During his last interview with police in August, Stevenson stopped answering questions and asked for an attorney, said Bruno.

Marta Stevenson was shocked and distraught to hear that the child had ingested

Suboxone and had no explanation, according to police.

The couple's surviving twin and a 9-year-old daughter remain with their mother, Bruno told the jurors.

The jury deliberated about 30 minutes before returning its ruling.