Reckitt Benckiser Pharmaceuticals Inc.

September 25, 2012

BY HAND DELIVERY

Division of Dockets Management
Food and Drug Administration
5630 Fishers Lane, Room 1061 (HFA-305)
Rockville, Maryland 20852

Re: Safety Concerns Regarding Buprenorphine For Opioid Dependence

CITIZEN PETITION

Reckitt Benckiser Pharmaceuticals Inc. ("RBP") submits this petition pursuant to Section 505(b), 505(j), and 505(q) of the Federal Food, Drug, and Cosmetic Act ("FDC Act"), among other provisions of law, to request that the Commissioner of Food and Drugs ("Commissioner") refrain from approving any buprenorphine drug application (whether New Drug Application ("NDA") or Abbreviated New Drug Application ("ANDA")) for opioid dependence treatment until the Food and Drug Administration ("FDA") considers whether such application includes adequate measures to ensure the safe use of buprenorphine, and require all approved applications to contain the same safeguards. As described further below, use of buprenorphine products without these safeguards puts opioid dependent patients and their families at risk.

The approval of Subutex® (buprenorphine HC1) and Suboxone® (buprenorphine HC1-naloxone HC1) for opioid dependence treatment created a pathway to treatment for a historically underserved patient population. However, as a partial μ-opioid agonist, buprenorphine poses risks of diversion, abuse and dependence, especially when prescribed to patients with a history of addiction. Due to these concerns, Suboxone's and Subutex's sponsor, RBP, implemented a comprehensive risk mitigation program ("RiskMAP").

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RBP launched its extensive RiskMAP when Suboxone and Subutex were approved by FDA in 2002. Although the RiskMAP was effective in meaningfully reducing the risks of abuse and diversion, an alarming trend regarding pediatric safety emerged in 2006-2007. Poison control data showed an increasing rate of young children being accidentally exposed to Subutex and Suboxone. RBP took action to address this trend, implementing targeted educational interventions on the risk of pediatric exposure to buprenorphine. RBP also developed Suboxone Film with child-resistant unit-dose packaging to reduce the likelihood of pediatric exposure as well as the number of dosage units exposed if the child-resistant packaging were defeated.

After RBP commenced its pediatric exposure education initiative, the rates of pediatric exposure plateaued. After introduction of buprenorphine film, those rates steeply declined. A recent study by independent experts at the Researched Abuse, Diversion and Addiction-Related Surveillance ("RADARS") System and Venebio Group, LLC further explored the observed association between these measures and the risk of pediatric exposure. Across the study period (fourth quarter 2009 to first quarter 2012) 2,380 unique cases of pediatric exposure in children under the age of 6 were identified, including 536 serious adverse events. The risk of unintentional pediatric exposure in children under 6 years to single entity and combination buprenorphine tablets was 2.5 and 7.8 times greater, respectively, than for buprenorphine combination film. Further, for the most recent quarter measured in 2012, the risk of unintentional pediatric exposures to combination tablets was 8.5 times greater than it was for combination film.

RBP now urges the FDA to recognize the pediatric safety risks posed by buprenorphine marketed for opioid dependence that lacks these safeguards. RBP asks that FDA not approve any buprenorphine application for opioid dependence

without targeted educational interventions on the risk of pediatric exposure because such interventions are important to ensuring pediatric safety. Moreover, RBP asks that FDA not approve any buprenorphine application for opioid dependence without child-resistant unit-dose packaging because evidence shows that such products would be unsafe to young children. Finally, RBP requests FDA not to approve any buprenporhine/naloxone ANDA for opioid dependence treatment until FDA determines whether the reference listed drug ("RLD") for those drugs was discontinued for reasons of safety.

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a. FDA may not approve a buprenorphine NDA for opioid dependence treatment without educational interventions targeted to pediatric exposure risk because the labeling of drugs subject to those NDAs is misleading. 30

b. FDA should not approve a buprenorphine NDA for opioid dependence treatment without targeted educational interventions on

pediatric exposure risks, because the risk-benefit profiles of drugs subject to those NDAs does not favor approval. *33*

c. FDA must deny any buprenorphine ANDA for opioid dependence treatment that lacks targeted educational interventions on pediatric exposure risks because such applications fail to contain the same labeling as the RLD. *34*

d. FDA must deny any buprenorphine ANDA for opioid dependence treatment that lacks educational interventions adopted to reduce the risk of pediatric exposure, because such ANDAs lack the same risk-benefit profile as the RLD. *36*

2. FDA Should Refrain from Approving Applications for Buprenorphine for Opioid Addiction that Lacks Child-Resistant Unit-Dose Packaging. **38**

a. FDA may not approve any buprenorphine NDA for addiction treatment that lacks child-resistant unit-dose packaging because FDA has insufficient information to determine the safety of those drugs. *39*

b. FDA may not approve any buprenorphine NDA for addiction treatment that lacks child-resistant unit-dose packaging because the risk-benefit profile of those drugs does not favor approval. *42*

3. FDA may not approve any buprenorphine/naloxone ANDA for addiction treatment until FDA determines whether the RLD for those drugs was discontinued for reasons of safety **43**

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I. ACTION REQUESTED

A. That FDA refrain from approving any buprenorphine NDA or ANDA for the treatment of opioid addiction that does not include a targeted pediatric exposure education program because those applications are not approvable pursuant to sections 505(b) and (j) of the FDC Act.

B. That FDA refrain from approving applications for buprenorphine for opioid addiction that lacks child-resistant unit-dose packaging.

C. That FDA not approve any buprenorphine/naloxone ANDA for addiction treatment until FDA determines whether the RLD for those drugs was discontinued for reasons of safety.

II. STATEMENT OF GROUNDS

A. FACTUAL BACKGROUND

1. Background and Approval of Buprenorphine

a. Approval of Buprenorphine for Opioid Dependence Significantly Expanded Access to Addiction Treatment

Opioid addiction and abuse is a pervasive public health problem that plagues patients, families, and communities.[1] In 2010, the Substance Abuse and Mental Health Services Administration ("SAMHSA") reported in the National

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[1] Guide to Drug Abuse Epidemiology, Department of Mental Health and Substance Dependence, Noncommunicable Diseases and Mental Health Cluster, World Health Organization (2000), *available at* http://whqlibdoc.who.int/hq/2000/a58352_PartA.pdf. Buprenorphine. Center for Substance Abuse Treatment, Substance Abuse and Mental

Survey on Drug Use and Health, that over 1.9 million Americans suffer from opioid dependence or abuse.[2]

Prior to 2000, patients who suffered from opioid addiction were primarily referred to a narcotic treatment program ("NTP") for opioid maintenance treatment using methadone. Methadone is a Schedule II controlled substance[3] and a full μ-opioid receptor agonist similar to other highly abused opiates such as heroin.[4] To mitigate the risk of diversion associated with prescribing methadone to opioid addicted patients, methadone may only be administered to treat addiction in a facility specially registered by the U.S. Drug Enforcement Administration ("DEA") as a NTP.[5]

Many opioid dependent patients avoided NTPs due to privacy concerns and the perceived stigma attached to those programs rendering methadone an incomplete answer to the demand for opioid addiction treatment.[6] Accordingly, in 2000, Congress sought to improve access to opioid addiction treatment via the Drug Addiction Treatment Act ("DATA"). DATA enabled practitioners who

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2 Substance Abuse and Mental Health Services Administration, Results from the 2010 National Survey on Drug Use and Health: Summary of National Findings, NSDUH Series H-41, HHS Publication No. (SMA) 11-4658, available at http://www.samhsa.gov/data/NSDUH/2k10NSDUH/2k10Results.htm.

3 21 U.S.C. § 812(c) (2010). The U.S. Drug Enforcement Administration ("DEA") places drugs and other substances in a respective schedule according to their relative abuse potential and accepted medical use. For example, Schedule I controlled substances have no currently accepted medical use and a high potential for abuse and, and Schedule II controlled substances have a currently accepted medical use but a higher potential for abuse than Schedule III, IV, or V controlled substances. *Id.* at (b).

4 About Buprenorphine Therapy, U.S. Dep't of Health and Human Services, http://buprenorphine.samhsa.gov/about.html.

5 21 C.F.R. § 1306.07 (2012).

6 Elisa F. Cascade et al., *Prescribing for Buprenorphine in the Treatment of Opioid Addiction*, 4(1) Psychiatry 15, 15-16 (2007).

obtained special training to administer Schedule III, IV, or V controlled substances to a certain number of patients in an office-based setting.[7]

RBP had developed two buprenorphine products for the treatment of opioid addiction: a single-entity buprenorphine product, Subutex, intended for a brief induction stage, and Suboxone, a buprenorphine-naloxone combination drug for post-induction maintenance treatment. Suboxone posed less risk of diversion and abuse than Subutex, because naloxone's μ-opioid antagonist properties will precipitate withdrawal symptoms if used parenterally by a full opioid agonist dependent patient.[8] Suboxone is thus less attractive to drug abusers than Subutex.[9] Prior to these drugs being approved in 2002 by FDA,[10] buprenorphine was rescheduled from Schedule V to Schedule III[11] and they became the first opioid addiction treatments available outside an NTP pursuant to DATA 2000.

The approval of Subutex and Suboxone broke barriers in addiction treatment.[12] For the first time, patients could obtain opioid addiction treatment from their family physicians and take their medication inside the privacy of their own home. Patients who previously avoided treatment due to the stigma and lack of privacy attached to NTPs, finally sought and obtained treatment.[13] Given the

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7 Drug Addiction Treatment Act of 2000, Pub. L. No. 106-310, § 3502, 114 Stat. 1222-7 (2000).

8 Buprenorphine, Center for Substance Abuse Treatment, Substance Abuse and Mental Health Services Administration, US Department of Health and Human Services, About Buprenorphine Therapy, *available at* http://buprenorphine.samhsa.gov/about.html.

9 *Id.*

10 Drugs@FDA, *available at* http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm.

11 67 Fed. Reg. 62,354 (Oct. 7, 2002).

12 Cynthia G. McCormick et al., *Case histories in pharmaceutical risk management*, 105 (Suppl. 1) Drug and Alcohol Dependence S42, S50 (2009).

13 Elisa F. Cascade et al., *supra* n. 6.

devastating impact of opioid addiction on patients and families, the approval of Suboxone and Subutex was a critical step in the advancement of addiction medicine.[14]

b. Suboxone and Subutex Are Associated With Serious Health Risks

Because both Subutex and Suboxone have opioid agonist properties and are indicated to treat opioid addicted patients, these drugs are associated with serious risks of diversion and abuse. Reports indicate that buprenorphine is attractive to drug users and may be abused parenterally.[15] The medical risks of buprenorphine parenteral abuse are similar to the risks associated with other injected substances to include "soft tissue infections, emboli, acute limb ischemia, endocarditis, sepsis, and HIV and Hepatitis C infection."[16]

A significant societal risk associated with buprenorphine diversion is abuse by individuals who are experimenting with illicit drugs, potentially contributing to the occurrence of concomitant drug abuse.[17] Further, as aptly noted by DEA in its rescheduling of buprenorphine, "providing an abusable substance to known drug abusers imparts enhanced risks."[18] Buprenorphine overdose poses medical risks

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14 Guide to Drug Abuse Epidemiology, Department of Mental Health and Substance Dependence, Noncommunicable Diseases and Mental Health Cluster, World Health Organization (2000), *available at* http://whqlibdoc.who.int/hq/2000/a58352_PartA.pdf.

15 Michael A. Yokell, et. al., *Buprenorphine and Buprenorphine/Naloxone Diversion, Misuse, and Illicit Use: An International Review*, 4(1) Curr. Drug Abuse Rev. 28, 32 (2011).

16 *Id.*

17 *Id.*

18 67 Fed. Reg. 62,354,62,357. (Oct. 7, 2002).

comparable to other opioids.[19] Significant respiratory depression and death have occurred in association with buprenorphine, particularly when taken by intravenous route in combination with benzodiazepines or other CNS depressants (including alcohol).[20]

Further, as addressed in Subutex's and Suboxone's labeling, the effects of exposure are particularly acute in young children and can be severe.[21] Similar to other opioids, they include CNS respiratory depression and death.[22] There has also been one case report of onset of acute leukoencephalopathy after buprenorphine intoxication in a two-year-old child.[23] The most serious effects have been reported in children less than two years of age at doses greater than or equal to four milligrams.[24] Because, prior to August 10, 2012, both Subutex and Suboxone were only distributed in 2 mg and 8 mg dosage units, exposures to greater than 2 mgs and less than 8 mgs could only result from the child ingesting multiple 2 mg dosage units.

According to American Association of Poison Control Centers ("AAPCC") data[25] measuring single substance exposures to buprenorphine, meaning no other

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19 *See* Subutex sublingual tablet, NDA 20-732, Risk Evaluation and Mitigation Strategy, Important Safety Information 1, 6 (approved Dec. 2011) (hereinafter "Suboxone Tablet REMS").

20 *Id.*

21 *Id.*

22 Bryan D. Hayes, PharmD et al., *Toxicity of Buprenorphine Overdoses in Children*, 121 Pediatrics e782, e784 (2009).

23 B. Bellot et al., *Acute leukoencephalopathy after buprenorphine intoxication in a 2-year-old child*, 15(4) Eur. J. Pediatr. Neurol. 368 (2011).

24 *Id.*

25 The American Association of Poison Control Centers (AAPCC; http://www.aapcc.org) maintains the national database of information logged by the country's 61 Poison Control Centers (PCCs). Case records in this database are from self-reported calls: they reflect only information provided when the public or healthcare professionals report an actual or

drugs were detected, from 2006 through June 2011, 37% of all exposures involved moderate effect or major effect, including four deaths.[26] In addition, during that same time period, 34% of all exposures to children under 6 resulted in a major or moderate effect, including death.[27]

In August 2010, the first pediatric death attributed solely to buprenorphine was reported to AAPCC.[28] As of June 30, 2011, 3 other deaths had been reported to AAPCC for children under the age of six.[29] In October 2011, the New York Times reported the death of a thirteen-month-old boy who opened a bottle of buprenorphine tablets and ingested them while in his crib.[30] More recently, in

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potential exposure to a substance (e.g., an ingestion, an inhalation, or a topical exposure, etc.), or request information/educational materials. Exposures do not necessarily represent a poisoning or overdose. The AAPCC is not able to completely verify the accuracy of every report made to member centers. Additional exposures may go unreported to PCCs and data referenced from the AAPCC should not be construed to represent the complete incidence of national exposures to any substance(s).

26 Data submitted to NDA 22-410, NDA 20-733, and NDA 20-732.

27 *Id.* AAPCC defines "death" as only death that "was a direct complication of the exposure." Major effect means that the "person exhibited symptoms that were life-threatening or resulted in significant residual disability." Moderate effects means the "exposure was not life-threatening, but some form of treatment was indicated." Minor effect means that "the person exhibited some symptoms, but were minimally bothersome and usually resolved rapidly." American Association of Poison Control Centers, National Poison Data System Report, *available at* http://www.aapcc.org/dnn/LinkClick.aspx?fileticket=WFdNF2cwrMI%3D&tabid=310&mid=728.

28 Data submitted to NDA 22-410, NDA 20-733, and NDA 20-732.

29 *Id.*

30 *Baby Boy Dies; Was Given Pills as a Toy*, N.Y. Times (Oct. 14, 2011), *available at* http://www.nytimes.com/2011/10/15/nyregion/baby-boy-dies-of-Suboxone-overdose.html. *See also*, Kerry A. Schwartz, et. al., *Suboxone (Buprenorphine/Naloxone) Toxicity in Pediatric Patients A Case Report*, 23 Pediatric Emergency Care 651, 651-652 (Sept. 2007) (a report of case studies of pediatric exposures to buprenorphine in young children). It should be noted that AAPCC estimates that it detects only 56%, or just slightly more than half, of poison exposures that occur annually and only 3.5% of poisoning fatalities. Bronstein, A.C., et al., *2007 Annual Report of the American*

August 2012, a local news source reported the hospitalization of a two-year-old child for suspected exposure to Suboxone, after the child's mother reportedly stored the medication in a breath mint container.[31]

c. RBP Adopts a Robust RiskMAP to Address Risks Posed by Subutex and Suboxone

RBP recognized the need to balance the public health benefit of expanded access to addiction treatment and the unique diversion and abuse concerns and medical risks posed by Suboxone and Subutex. Thus, prior to FDA approval, RBP worked closely with FDA, Substance Abuse and Mental Health Services Administration ("SAMHSA"), and DEA to appropriately manage these risks. This collaboration resulted in a comprehensive FDA-approved RiskMAP, which included extensive monitoring, education, and surveillance measures.[32] RBP later adjusted and improved this RiskMAP to address the emergence of pediatric safety concerns stemming from an unanticipated spike in pediatric exposures to buprenorphine.

i. RBP Monitors Buprenorphine Use

As part of its RiskMAP, RBP undertook an expansive monitoring and reporting initiative. RBP monitored and reported instances of individuals who were primarily addicted to buprenorphine, abuse of buprenorphine by opioid-naive individuals, death due to overdose of buprenorphine, and neonatal withdrawal

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Association of Poison Control Centers' National Poison Data System (NPDS), 45 Clinical Toxicology 815 (2007).

31 *See Police: 2-Year-Old Overdosed on Narcotics*, Rtv6theindychannel, (Aug. 22, 2012), *available at* http://www.theindychannel.com/news/31376335/detail.html.

32 Cynthia G. McCormick et al., *supra* n. 12.

from buprenorphine.[33] This monitoring kept RBP apprised of changes in buprenorphine abuse, diversion, misuse and other important safety trends.

Further, as part of its effort to monitor and investigate suspicious orders by customers, RBP established a single distribution center for Subutex and Suboxone.[34] RBP created a new function within the company that focused solely on assisting the distribution facility to establish parameters for detecting, evaluating, and canceling suspicious orders.[35] The Medication Utilization Manager, who performs this function, is further apprised when safety concerns, such as increased incidence of diversion or pediatric exposures arise in geographic regions of the country, so that RBP can target and address those trends.

ii. RBP's Comprehensive Education Materials and Interventions

RBP developed educational materials to emphasize the safe and effective use of buprenorphine for providers, patients, counselors and families.[36] Those materials focused on reinforcing the matrix of care model for addiction treatment and provided information that supported best medical practices.[37] The matrix model emphasizes the importance of integrating all aspects of addiction treatment including relapse prevention, family and group therapy, motivational interviewing,

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33 *Id.*

34 *Id.* Wholesale distributors are required to report to DEA suspicious orders of controlled substances. Suspicious orders include orders of an unusual size, frequency, and orders deviating from a normal pattern. 21 C.F.R. § 1301.74(b).

35 Cynthia G. McCormick et al., *supra* n. 12.

36 *Id.*

37 *Id.*

12-step involvement, and psychological and social support.[38] In addition, RBP emphasized the important role of counseling and other behavioral treatment as a supplement to opioid maintenance to achieve successful outcomes. By educating providers on these important aspects of addiction therapy, RBP contributed to ensuring that patients successfully completed treatment. RBP ensured that education on proper prescribing and the risks of abuse and diversion was a standard component of all promotional materials.[39] RBP also provided unrestricted grants to professional associations authorized by DATA 2000 to train providers on becoming DATA-certified.[40]

RBP utilized several critical educational interventions to ensure risk messages and strategies reached the treatment community. RBP sent teams of field representatives into the community to educate physicians, pharmacists, and counselors on the proper use of Suboxone and Subutex. RBP ensured these field representatives, a.k.a. Clinical Liaisons, were properly trained on the risks of buprenorphine use for opioid maintenance treatment and the role that Suboxone and Subutex treatment play in the overall treatment regimen. RBP also developed websites to reinforce educational messages about the risks of misuse and abuse associated with Subutex and Suboxone, and the importance of treatment being more than just the prescription of a medication.[41]

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38 *See* Ahndrea Weiner, M.S., LMFT, Matrix Model of Outpatient Treatment for Substance Dependence (May 19, 2003), *available at* http://www.ag.state.nd.us/MethSummit/MethTreatment-AhndreaWeiner.pdf

39 Cynthia G. McCormick et al., *supra* n. 12.

40 *Id.*

41 *Id.* By 2011, over 2.6 million unique visitors accessed www.Suboxone.com and www.turntohelp.com. Through these websites, patients and caregivers contemplating or committed to treatment can sign up to receive ongoing treatment support via email

RBP created a Medical Information Unit to field calls from patients and providers about safety issues regarding buprenorphine, including misuse or accidental exposure. These calls are answered by a registered nurse trained on appropriate steps to take in a safety emergency.

RBP also established a team of Field Medical Advisors ("FMAs") to educate providers on best medical practices and ways to decrease risks of diversion and abuse.[42] FMAs have significant experience and/or clinical education in addiction medicine and ensure providers receive important safety information. FMAs' key messages included the importance of early and frequent patient assessments; patient medication dosage limits; the need to educate patients to refrain from misusing, abusing or diverting their medication; and the importance of proper storage of medication. The FMAs also worked closely with the Medication Utilization Manager to evaluate signs of abuse and actively intervene through education and field contact where there was suspected misuse of Suboxone or Subutex.[43]

In addition, RBP initiated an innovative Treatment Advocate Training Program, through which it recruited and trained individuals with prior experience in addiction medicine, called Treatment Advocates ("TAs"). TAs facilitate one-on-one and small group discussions with physicians, pharmacists and other providers on the appropriate use and risks of misuse, abuse, and diversion of buprenorphine. RBP conducts a large number of TA small group discussions each year throughout the country (4,000 between July 2011 and June 2012, alone).

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messages to improve their knowledge of the disease of addiction and steps that can be taken to ensure successful treatment.

42 Cynthia G. McCormick et al., *supra* n. 12, at S50.

43 *Id.* at S50-S51.

RBP contracted with an independent monitoring organization to, among other things, actively survey DATA-qualified physicians and persons enrolled in substance abuse treatment programs on the prevalence of buprenorphine abuse; monitor emergency department visits related to buprenorphine; analyze poison control center and emergency room data for reported buprenorphine exposure cases; monitor internet newsgroups, chat rooms, and blogs discussing buprenorphine in the context of misuse and abuse; and utilize a network of key informants to monitor trends in illegal drug use in their locales and provide street-level surveillance.[44] This monitoring alerted RBP of changes in diversion and abuse trends, new issues of misuse, and other important safety trends so that RBP could appropriately respond and implement new safety initiatives as necessary.

iii. RBP Develops Subutex and Suboxone REMS

In 2007, Congress amended the FDC Act to require Risk Evaluation and Mitigation Strategies ("REMS") for new and existing drugs that posed certain public health risks.[45] FDA required that applicants for drugs subject to RiskMAPs develop a REMS program that included the RiskMAP elements. In response, RBP developed REMS for Suboxone and Subutex while continuing to maintain and improve implementation of its RiskMAP.

Suboxone's and Subutex's REMS are now in place with clear goals and mechanisms to mitigate the risks of unintentional pediatric exposures, accidental overdose, misuse, and abuse, and inform patients of the serious risks associated with use of Suboxone and Subutex. The REMS requires a Medication Guide to be

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44 *Id.* at S51.

45 Food and Drug Administration Amendments Act (FDAAA) of 2007, Pub. L. No. 110-85, Title IX, Subtitle A, Section 901, 121 Stat. 823 (2007), (codified at 21 U.S.C. § 355-1).

dispensed with each Suboxone/Subutex prescription, certain Elements to Assure Safe Use ("ETASU"), and certain monitoring and implementation requirements.[46]

The Subutex and Suboxone REMS Medication Guide educates patients on risks related to use, such as physical dependence and the onset of withdrawal when Suboxone is used parenterally.[47] The ETASU include, among other things, requiring patients to meet certain diagnostic criteria prior to prescribing those medications, the use of an "Appropriate Use Checklist" by providers, and the mailing of educational materials to DATA-certified providers and retail pharmacies.[48] Subutex and Suboxone's REMS ask providers, *inter alia,* to monitor patients' use of their medication through weekly or more frequent visits depending on patient stability and progression in treatment, to assess and reinforce patients' compliance with their medication regimen, and to assess whether the patients' are receiving the appropriate psychosocial support.[49] As part of the REMS implementation, RBP monitors provider compliance with the REMS program through surveys of providers and patients, and monitors health care utilization databases and conducts ongoing surveillance.[50]

RBP's risk mitigation strategies have been successful in improving education on safety risks of buprenorphine use as an opioid maintenance medication. Initial results from RBP's assessments reveal high levels of provider

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46 Subutex sublingual tablet, NDA 20-732, Risk Evaluation and Mitigation Strategy (approved Dec. 2011) (hereinafter "Subutex REMS"); Suboxone Tablet REMS; Suboxone sublingual film, NDA 22-410, Risk Evaluation and Mitigation Strategy (approved Aug. 2010) (hereinafter "Suboxone Film REMS").

47 Suboxone Tablet REMS, Medication Guide at 2.

48 Suboxone Tablet REMS; Suboxone Film REMS; Subutex REMS.

49 *Id.*

50 *Id.*

understanding of the serious risks of misuse and abuse of Suboxone and Subutex, the importance of appropriate use of buprenorphine products for successful opioid dependence treatment, and the role of psychosocial support for safe and effective opioid addiction treatment with buprenorphine.[51]

It 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. RBP's monitoring, educational initiatives, and interventions surely play a large role and RBP's view has always been that the appropriate management of abuse, misuse, and diversion risks since Subutex's and Suboxone's approval is largely attributed to those efforts, including the RiskMAP and REMS, as a whole.

2. RBP Responds to an Alarming Trend in Pediatric Exposure Rates

Despite having a robust RiskMAP in place that successfully reduced the risk of diversion and abuse of Suboxone and Subutex, RBP noticed a disturbing buprenorphine-related safety trend. A report based on data from AAPCC showed 53 exposures to buprenorphine in children under six in 2004.[52] By 2006, the number reported by AAPCC had jumped to 204 exposures among children under the age of six.[53]

RBP responded to this important public safety concern. By June of 2007, RBP had developed materials for an education campaign to inform patients and

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51 *See e.g.* Suboxone sublingual film REMS assessment, submitted to NDA 22-410, (August 2011).

52 Edward W. Boyer, MD, PhD, et al., *Methadone and Buprenorphine Toxicity in Children*, 19 The Amer. Journal on Addictions 89 -95 (Figure 1) (2009).

53 Data submitted to NDA 20-732, 20-733, and 22-410.

providers of the unique risks of pediatric exposure to buprenorphine. Using RBP's educational resources, discussed above, over subsequent months, patients and providers were educated about the increased risks of pediatric exposure, the need for patients to properly store their medication, and the need to seek immediate emergency intervention if an exposure occurred. RBP utilized all available resources in its targeted educational campaign, including outreach by Clinical Liaisons, Field Medical Advisors, and Treatment Advocates. These individuals informed providers of the pediatric safety risks of Suboxone and Subutex and promoted best practices to ensure patients properly stored their medication away from children, and these messages were repeated frequently. Further, in March of 2008, RBP amended its labeling for Suboxone to include a warning that patients should "always store buprenorphine-containing medications safely and out of the reach of children, and destroy any unused medication appropriately."[54]

Even as those targeted educational interventions persisted, rates of pediatric exposure to buprenorphine continued to rise between 2008 and 2009. The number of children under six exposed to buprenorphine products had risen to 431 in 2007, 866 in 2008, and 1318 in 2009 (Figure 1).[55]

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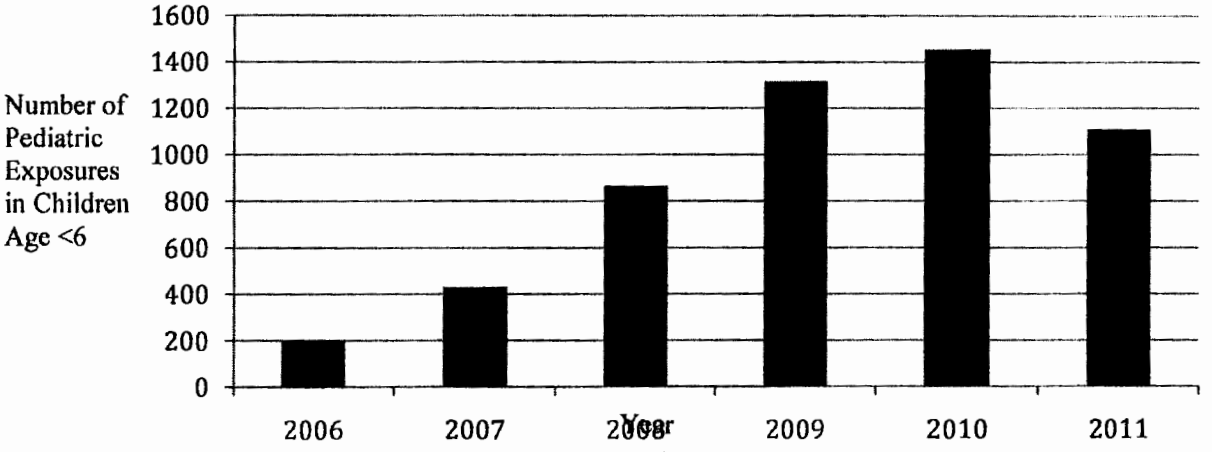
[54] *See* FDA, Drugs@FDA, Suboxone Labeling (2008), *available at* http://www.accessdata.fda.gov/scripts/cder/drugsatfda.

[55] This rise could be explained by the fact that passive educational interventions such as mailings are generally ineffective alone at creating changes in provider behavior and require reinforcement over time through active interventions like RBP's targeted outreach. *See* JM Grimshaw, et al., *Changing Provider Behavior: An Overview of Systematic Reviews of Interventions*, 39 Med. Care II2, 45 (Aug. 2001). In RBP's experience, genuine change in provider and patient behavior requires multiple active interventions.

Figure 1: Trend in Pediatric Exposure to Buprenorphine 2006-2011



Source: Data from AAPCC, submitted to NDA 20-732, NDA 20-733, and NDA 22-410)

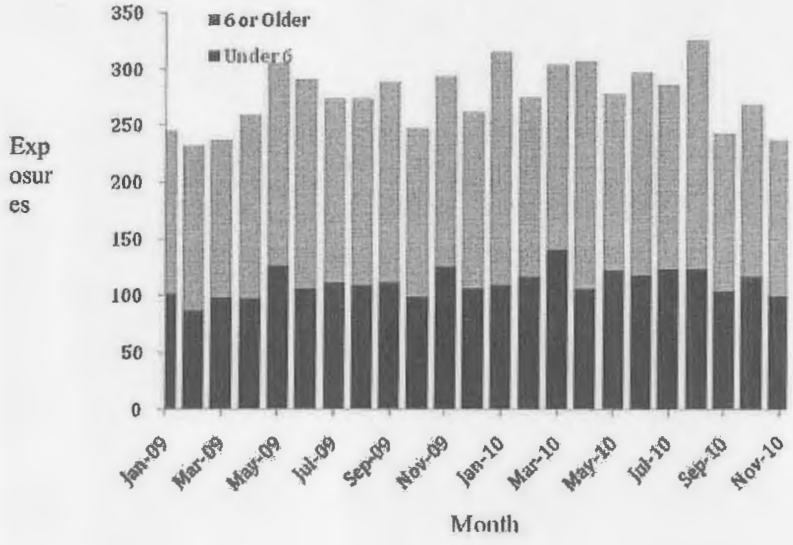
This alarming trend was unforeseen by RBP and FDA. Indeed, the rise in pediatric exposures to buprenorphine was disproportionate to buprenorphine sales. (Figure 2).

Figure 2: Pediatric Exposures to Subutex and Suboxone per Million Dosage Units Distributed

Source: Data Submitted to NDA 20, 732, NDA 20-733, and NDA 22-410)

RBP continued its educational campaign on the risk of pediatric exposures. RBP's educational efforts finally stemmed the rising tide of pediatric exposures. As shown in Figures 1 and 2, the number of exposures in 2010 was only slightly higher than 2009. In August of 2009, RBP began monitoring AAPCC data on a monthly basis to more closely track pediatric exposure rates. This more granular data confirmed that pediatric exposures to buprenorphine had begun to stabilize at the 2009 level (Figure 3).

Figure 3: Plateau in Pediatric Exposures Post Education Initiatives



Source: Data from AAPCC, (submitted to NDA 20-732, NDA 20-733, and NDA 22-410

3. RBP Develops Buprenorphine Film

During the time period of the rise in pediatric exposure rates, RBP had begun development of a buprenorphine product with the potential to decrease the risk of pediatric exposure: Suboxone Film. A primary reason that such a product

was attractive from a risk management standpoint is that each individual Suboxone Film product would be placed inside a child-resistant foil package.[56] This child-resistant unit-dose packaging would inherently reduce the number of dosage units of exposure if a child defeated the child-resistant packaging. That is, it eliminated the risk posed by tablet-bottle packaging that a child, having defeated the child-resistant packaging, would have access to multiple doses of buprenorphine. In addition, packaging Suboxone Film in unit-dose packaging reduced the risk that patients would otherwise repackage their Suboxone in a manner that eliminated its child-resistant feature.[57]

As the New Drug Application ("NDA") for Suboxone Film was being reviewed in May of 2009, RBP proposed to FDA that the labeling should include a strong risk message related to pediatric exposure possibly resulting in death. Specifically, RBP proposed: "Keep out of the reach and sight of children because of the risk of respiratory depression which may potentially be fatal." FDA agreed

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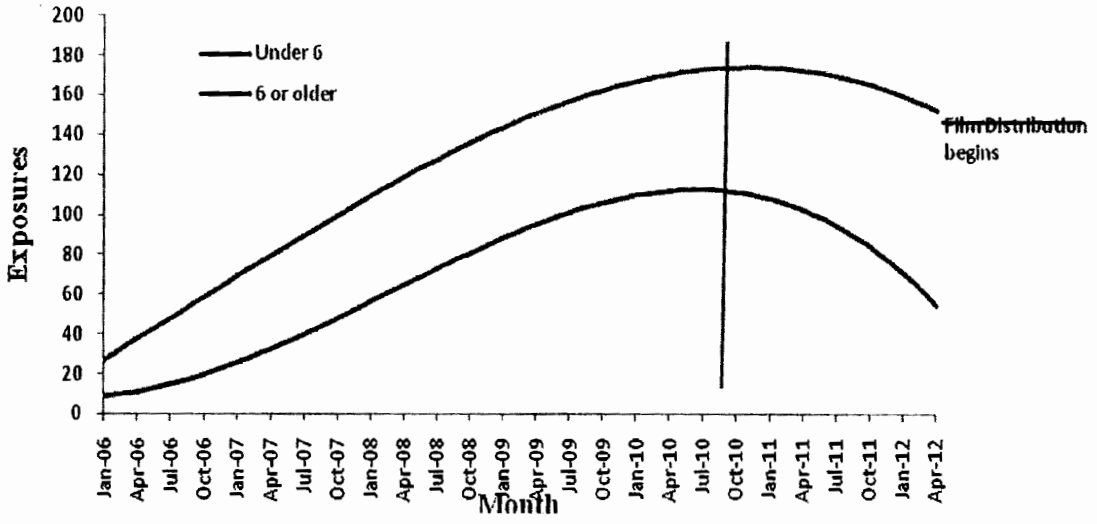
[56] Another way that Suboxone Film contributes to mitigating risk is that as a film dosage form, it can not be crushed and injected, thus reducing the risk of abuse and diversion. In addition, in August 2012, FDA approved two additional strengths of the film product 12mg and 4mg). See FDA, Drugs@FDA, available at: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory#apphist. Because the dose of buprenorphine is titrated, the availability of additional strengths will help prevent the possibility of a patient opening the child-resistant packaging and removing only part of the dose, leaving the remainder in a place that may not prevent pediatric exposure.

[57] This was not the first time that RBP recognized the value of unit-dose packaging of buprenorphine. RBP had been working to develop unit-dose packaging for Suboxone tablets since before the product was first approved for marketing. However, initial efforts to develop unit-dose packaging for Suboxone tablets using peel-push blisters were met with limited success due to technical issues involving the integrity of the tablet when attempting to remove it from the packaging. RBP proceeded with these efforts, but encountered other technical issues, primarily related to the stability of naloxone in certain unit-dose packaging configurations. Although later studies revealed unit-dose packaging of Suboxone may be feasible, RBP focused its resources on the development of Suboxone Film.

that a risk message was needed and required: "Children who accidentally take Suboxone will need emergency medical care. Keep Suboxone out of the reach of children."

FDA approved Suboxone Film in August of 2010. In September of that year, RBP began distribution of Suboxone film with unit-dose child-resistant packaging.[58] By 2011, data from AAPCC had demonstrated a precipitous decline in the number of pediatric exposures to buprenorphine products, even from 2009 levels (Figure 4).

Figure 4: Trend Line of exposures to Suboxone over Time



Source: Data from AAPCC, submitted to NDA 20-732, NDA 20-733, and NDA 22-410

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58 The Consumer Product Safety Commission does not require testing in children who are less than 48 months in age to meet the minimum child-resistant packaging standards. *See* 16 C.F.R. § 1700.20(a)(2). However, RBP conducted special child-resistant packaging testing of Suboxone Film in children ages eighteen to thirty-six months, in part because 100% of child patient deaths due to buprenorphine exposure came from this population. That testing revealed a 0% success rate for children in this age group in defeating the unit-dose child-resistant packaging of Suboxone Film.

4. Recent Study Reveals Decreased Risk of Pediatric Exposure to Buprenorphine in Child-Resistant Unit-Dose Packaging

A recent study by independent experts at the Researched Abuse, Diversion and Addiction-Related Surveillance ("RADARS") System and Venebio Group, LLC further explored the risk of pediatric exposure (hereinafter, "pediatric exposure analysis"). Specifically, that study estimated and compared the frequency of reports of unintentional exposure among children under six to single entity buprenorphine tablets, Suboxone tablets, and Suboxone film; attempted to identify, using a root cause analysis, factors influencing the unintentional pediatric exposure and assessed causality of reported adverse events associated with unintentional pediatric exposure to buprenorphine via an expert physician panel.[59]

The study estimated the relative risk (rate ratio) of unintentional pediatric exposure for the following two comparisons: 1) single-ingredient tablet (generic/Subutex) vs. combination ingredient film (Suboxone film) and 2) combination ingredient only analysis (Suboxone tablet vs. Suboxone film).

A root cause analysis was performed on each of the eligible cases. All potential root causes were recorded, but the Executive Summary focused on causes related to physician/patient education and packaging. Further results related to these and other root cause factors are being reviewed by the expert clinical panel and will be submitted to FDA when complete.

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[59] *See* Exhibit 1: Venebio, Accidental Exposure to Buprenorphine in Children: Focus on the Impact of Product Packaging and Patient/Physician Education: Executive Summary, (Sept. 14, 2012).

A total of 2,380 unique cases of exposure meeting the inclusion criteria were identified (2,337 from the RADARS System Poison Control Program, 40 from RBP Pharmacovigilance Database, and three duplicate cases for which data were merged from the two sources). Of these, 154 (6.5%) cases were associated with single-ingredient tablets, 2,107 (88.5%) cases were associated with combination-ingredient tablets, 118 (5.0%) cases were associated with combination-ingredient film, and one case (<0.1%) was an unspecified buprenorphine exposure.

Across the study period (fourth quarter 2009 through first quarter 2012), mean rates of accidental pediatric exposure to single- and combination-ingredient tablets per 10,000 unique recipients of a dispensed drug (URDD) were 2.51 cases/10,000 URDD (95% CI: 2.12 –2.98) and 6.25 cases/10,000 URDD (95% CI: 5.90 – 6.63), respectively, and mean rates for combination-ingredient film were 0.71 cases/10,000 URDD (95% CI: 0.59 – 0.87).

The risk of unintentional pediatric exposure to single- and combination tablets was 2.5 and 7.8 times higher, respectively, than the risk for combination film. For the most recent quarter (January-March 2012) the risk of unintentional pediatric exposures to single- and combination ingredient tablets was 3.2 and 8.5 times greater than for combination film, respectively.

The case reports reviewed did not provide sufficient information regarding physician/patient education or medication packaging to draw definitive conclusions. However, further analysis is ongoing to ascertain why the rates of pediatric exposure to child-resistant unit-dose packaged buprenorphine film (Suboxone Film) are significantly less than the rates of exposure to buprenorphine

packaged as loose tablets in a bottle, and these data will be submitted to FDA as soon as it is available.

5. RBP Discontinues Marketing of Suboxone Sublingual Tablets Due to Safety Concerns

Review of the pediatric exposure analysis revealed significant safety risks posed by buprenorphine products for opioid dependence in multi-dose packaging. It revealed that the risk of accidental exposure to children under six is 2.5 and 7.8 times greater for multi-dose packaged buprenorphine and buprenorphine/naloxone, respectively, than for unit-dose packaged buprenorphine/naloxone. Based on the ready availability of safer alternatives for opioid dependence treatment through Suboxone Film, on September 18, 2012, RBP notified FDA of its intent to discontinue marketing Suboxone Tablet (NDA 20-733).

B. LEGAL BACKGROUND

One of FDA's most important missions is to ensure the availability of drugs that are both effective and safe. All drugs, whether approved under an NDA or an ANDA, must be shown to be safe. An NDA may not be approved if "upon the basis of the information submitted . . . as part of the application, or upon the basis of any other information . . . with respect to such drug, [there is] insufficient information to determine whether such drug is safe for use . . . ."[60] FDA's regulations indicate that an ANDA product is unsafe, and may not be approved, if there is a "reasonable basis" to conclude that the ANDA raises serious questions

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60 *See* FDC Act §§ 505(d)(4); 21 U.S.C. 505(d)(4).

of safety.[61] FDA has also indicated that the ANDA disapproval standards are consistent with the ANDA withdrawal standards, and FDA may withdraw an ANDA "whenever there is a reasonable basis to conclude that a drug is unsafe even if the agency lacks proof that the drug is unsafe."[62]

To ensure safety, the FDC Act requires FDA not to approve a NDA for a new drug, if, "the [proposed] labeling is false and misleading in any particular."[63] The FDC Act further restricts the introduction of drugs into the marketplace whose labeling is misleading or lacks adequate safety warnings by deeming those drugs misbranded.[64] In addition, FDA may not approve a NDA if "upon the basis of information submitted to him as part of the application, or upon the basis of any other information before him with respect to such drug, he has insufficient information to determine whether such drug is safe for use under the "conditions prescribed recommended, or suggested in the [drug's] proposed labeling."[65]

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61 21 C.F.R. § 314.127(a)(8)(ii) (stating FDA may not approve an ANDA when "there is a reasonable basis to conclude that one or more of the inactive ingredients of the proposed drug or its composition raises serious questions of safety or efficacy.")

62 57 Fed. Reg. 17950, 17969 (April 28, 1992). Approval of an NDA or ANDA may be withdrawn if "new evidence of clinical experience, not contained in the application or not available to FDA until after the application or abbreviated application was approved, or tests by new methods, or tests by methods not deemed reasonably applicable when the application or abbreviated application was approved, evaluated together with the evidence available when the application or abbreviated application was approved, reveal that the drug is not shown to be safe for use under the conditions of use upon the basis of which the application or abbreviated application was approved." 21 C.F.R. § 314.150(a)(2)(ii).

63 FDC Act § 505(d)(7), 21 U.S.C. 355(d)(7); *See also* 21 C.F.R. § 314.125(a)(6).

64 FDC Act § 301(a), 21 U.S.C. § 331(a) (prohibiting the introduction or the delivery for introduction into interstate commerce of any food, drug, device, tobacco product, or cosmetic that is adulterated or misbranded"); § 502(f) (defining misbranded to include inadequate safety warnings).

65 FDC Act § 505(d)(4); 21 U.S.C. 355(d)(4); *See also* 21 C.F.R. § 314.125(a)(4).

Moreover, the FDC Act now requires FDA to "implement a structured risk-benefit assessment" in determining whether to approve a "new drug."[66]

To ensure the safety of generic drugs, FDA may not approve a generic drug application ("ANDA") if the generic drug lacks "sameness" to the reference listed drug ("RLD").[67] As FDA has summarized the applicable statutory and regulatory standards: "The ANDA applicant must identify the listed drug on which it seeks to rely, and, with limited exceptions, the drug product described in the ANDA must contain the same active ingredient, conditions of use, route of administration, dosage form, strength, and (with certain permissible differences) labeling as the listed drug it references."[68] Following the U.S. Supreme Court's decree that the FDC Act "must be given the most harmonious comprehensive meaning possible in light of legislative policy and purpose" FDA has held in the context of ANDA approval, "that the FDC Act could not impose a burden on the agency . . . that would require approval of potentially unsafe drugs."[69]

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66 *See* Food and Drug Administration Safety and Innovation Act, Pub. L. No. 112-144, § 905, 126 Stat. 993, 1092 (2012) (amending FDC Act § 505(d))). Notwithstanding this mandate, FDA has historically employed such an analysis in the approval process. *See* International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, Periodic Benefit-Risk Evaluation Report (PBRER) (Feb. 20, 2012) (stating "[w]hen a drug is approved for marketing, a conclusion has been reached that, when used in accordance with approved product information, its benefits outweigh its risks."), *available at* http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E2C/E2C_R2__Step2.pdf.

67 *See* FDC Act § 505(j); 21 U.S.C. § 355(j); 21 C.F.R. § 314.127.

68 FDA Response to Perrigo Company's Citizen Petition, Docket No. FDA-2011-P-0840, at 2 (May 16, 2012) (emphasis added) (citing FDC Act § (j)(2)(A) and (j)(4), and 21 C.F.R. § 314.94(a)).

69 57 Fed. Reg. 17950, 17969 (April 28, 1992).

Moreover, FDA may not approve an ANDA, if "the reference listed drug has been voluntarily withdrawn from sale and the agency has not determined whether the withdrawal is for safety or effectiveness reasons."[70] In making this determination, FDA will consider the risk benefit profile of the withdrawn drug, including whether the withdrawn drug has any material efficacy advantage over comparable safer drugs.[71]

C. ANALYSIS

1. FDA Should Refrain from Approving any Buprenorphine NDA or ANDA That Does Not Include A Targeted Pediatric Exposure Education Program Because Those Applications Are Not Approvable Pursuant to Sections 505(b) and (j) of the FDC Act.

In response to the rise in accidental pediatric exposures to buprenorphine, RBP implemented a comprehensive pediatric exposure education campaign with specific interventions targeted to educate providers on pediatric exposure risks and the importance of instructing patients to safeguard their buprenorphine. RBP sent teams of personnel into the field to communicate these messages to providers. RBP reinforced these messages through educational materials it mailed directly to providers. RBP further utilized specially trained instructors to hold educational sessions with providers that focused on pediatric exposure risks and the importance of patients' safeguarding their medication. Through their constant persistence and targeted delivery, RBP's measures were critical to ensuring that

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70 21 C.F.R. § 314.127(a)(11).

71 *See* Response to Citizen Petition, FDA to ISTA Pharmaceuticals, FDA Docket No. 2008-p-0368 at 16 (May 11, 2011) (stating, "[e]ven if Bromday were shown to be safer than Xibrom that would not necessarily mean that Xibrom should no longer be considered sufficiently safe. Rather, the Agency would evaluate Xibrom's risks in light of its benefits, including any evidence that showed that Xibrom offers any material efficacy advantage over Bromday").

providers understood risks and took appropriate action. Subsequently, the risks of pediatric exposure to buprenorphine plateaued and eventually declined. RBP has since continued, expanded, and enhanced those efforts. There is certainly more than a reasonable basis to question the safety of a buprenorphine product that is marketed without any of these interventions. The data indicate that without such interventions, unintentional pediatric exposures are very likely to rise. Accordingly, FDA should not approve any NDA or ANDA for buprenorphine for opioid dependence treatment that fails to commit to comparable interventions.

a. FDA may not approve a buprenorphine NDA for opioid dependence treatment without educational interventions targeted to pediatric exposure risk because the labeling of drugs subject to those NDAs is misleading.

The FDC Act makes clear that FDA shall not approve any NDA if, based on the information available to the Agency, the NDA's proposed labeling is false or misleading in any particular.[72] The FDC Act defines labeling broadly to include "all labels and other written, printed, or graphic matter (1) upon any article or any of its containers or wrappers, or (2) accompanying such article."[73] Based on a series of court cases originating in 1948 with *Kordel v. United States*, 335 U.S. 345 (1948) and *United States v. Urbuteit*, 335 U.S. 355 (1948), FDA considers all textually related product information disseminated by the manufacturer to be "labeling" within the meaning of FDC Act § 201(m), even if the product is not distributed with the information.

> Brochures, booklets, mailing pieces, detailing pieces, file cards, bulletins, calendars, price lists, catalogs, house organs, letters, motion picture films, film strips, lantern slides, sound recordings, exhibits,

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72 FDC Act § 505(d)(7); 21 U.S.C. § 355(d)(7); 21 C.F.R. § 314.125(b)(6).
73 FDC Act § 201(m), 21 U.S.C. § 321(m).

> literature, and reprints and similar pieces of printed, audio, or visual matter descriptive of a drug and references published (for example, the "Physicians Desk Reference") for use by medical practitioners, pharmacists, or nurses, containing drug information supplied by the manufacturer, packer, or distributor of the drug and which are disseminated by or on behalf of its manufacturer, packer, or distributor are hereby determined to be labeling as defined in section 201(m) of the act.[74]

Under this standard, there can be little question that RBP's educational campaign would be considered to be part of the labeling for its buprenorphine products.

FDA considers a drug's labeling to be misleading if it omits material facts.[75] Here, a buprenorphine NDA sponsor who fails to ensure the adequate dissemination of the pediatric safety risks of buprenorphine for opioid dependence, omits material information from its labeling that would ensure patients properly safeguard their medication. This renders the labeling of such a drug misleading.

This omission further renders those drugs misbranded.[76] To be sure, in *Ezagui v. Dow Chem. Corp.*, 598 F.2d 727, 733-36 (2d Cir. 1979), the court found that the failure of Park-Davis "to provide adequate warnings of known risks associated with normal use" of Quadrigen, namely the risk of harm posed to infants, rendered the company's labeling in violation of the FDC Act's misbranding provisions.[77]

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74 21 C.F.R. § 202.1(l)(2).

75 FDC Act § 201(n); 21 U.S.C. § 321(n).

76 FDC Act § 502(f)(2); 21 U.S.C. § 352(f)(2) (rendering a drug misbranded if the drug has inadequate safety warnings).

77 *Id.*

FDA has not required conclusive evidence of causation to take action in response to other pediatric safety concerns. In 2006, FDA published its intent to take enforcement action against all drugs containing carbinoxamine that were labeled for use in children less than 2 years of age or marketed as drops for oral administration.[78] In so doing, it noted

> The agency is aware of 21 deaths since 1983 in children under 2 years of age associated with carbinoxamine-containing products. However, in most of those incidents, other active ingredients in the drugs or other factors aside from the drug could have been responsible for the death a causative relationship between exposure to carbinoxamine and death in these infants has not been established. Nevertheless, there is scientific support for the proposition that infants and young children may be more susceptible to experiencing drug-related adverse events, in part due to the normal immaturity of their metabolic pathways.[79]

Likewise, FDA should find that RBP's continuous implementation of targeted educational interventions on pediatric exposure is certainly associated with, and likely contributed to, the plateau and subsequent decline in accidental pediatric exposures. Conclusive proof of causation is not the appropriate standard. Thus, to ensure appropriate safe use of buprenorphine for opioid dependence, FDA should not approve any NDA that does not include these targeted interventions.

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78 Carbinoxamine Products; Enforcement Action Dates, 71 Fed. Reg. 33462-33465, 33463 (June 9, 2006).

79 *Id.*

b. FDA should not approve a buprenorphine NDA for opioid dependence treatment without targeted educational interventions on pediatric exposure risks, because the risk-benefit profiles of drugs subject to those NDAs does not favor approval.

FDA must refuse to approve a NDA if the drug presents unreasonable safety risks.[80] As noted above, Congress recently amended section 505(d) of the FDC Act to require FDA to "implement a structured risk-benefit assessment framework in the new drug approval process to facilitate the balanced consideration of benefits and risks, a consistent and systematic approach to the discussion and regulatory decision-making, and the communication of the benefits and risks of new drugs."[81]

The public health benefits of buprenorphine when used for opioid maintenance are significant. Without buprenorphine, many patients would not have access to addiction treatment. These key benefits must be viewed in light of evidence showing that prior to and during the initial stages of RBP's pediatric exposure educational campaign, pediatric exposures to buprenorphine increased unexpectedly. Moreover, given the vulnerability of the affected population, FDA must give additional weight to the risk of pediatric exposure in the risk-benefit analysis. As FDA recently explained:

> [FDA] is mindful of risks posed to certain vulnerable populations, such as pediatric patients, older patients, and pregnant women.

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80 FDC Act § 505(b); 21 U.S.C. § 355(b).

81 *See* Food and Drug Administration Safety and Innovation Act, Pub. L. No. 112-144, § 905, 126 Stat. 993, 1092 (2012) (amending FDC Act § 505(d))). http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E2C/E2C_R2__Step2.pdf.

Evidence that a drug poses a risk to such populations would more likely weigh in favor of making the safety issue a priority.[82]

FDA should recognize the observed association between RBP's initiatives and improvements in pediatric safety. RBP urges FDA to ensure that the appropriate balance of risk to benefit is achieved for buprenorphine, and not approve any buprenorphine NDA for opioid addiction that fails to include these interventions.

c. *FDA must deny any buprenorphine ANDA for opioid dependence treatment that lacks targeted educational interventions on pediatric exposure risks because such applications fail to contain the same labeling as the RLD.*

With certain exceptions, FDA may not approve an ANDA if the ANDA fails to include the same labeling as the RLD.[83] The FDC Act allows labeling differences that are necessary "because the new [generic] drug and the listed [pioneer] drug are produced or distributed by different manufacturers."[84] The FDA has interpreted this exception to permit changes in labeling because of "differences in expiration date, formulation, bioavailability, or pharmacokinetics, [or] labeling revisions made to comply with current FDA labeling guidelines or other guidance."[85]

Given the association between the decreased rate of pediatric exposures and RBP's campaign on pediatric exposure risks, FDA should not approve a

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82 Food and Drug Administration, Draft Guidance, Classifying Significant Postmarketing Drug Safety Issues, 7 (Mar. 2012).

83 FDC Act § 505(j)(4)(G), 21 U.S.C. § 355(j)(4)(G); 21 C.F.R. § 314.127(a)(4).

84 FDC Act § 505(j)(2)(A)(v); 21 U.S.C. § 355(j)(2)(A)(v).

85 21 C.F.R. § 314.94(a)(8)(iv).

buprenorphine ANDA without these important safeguards. The risks of CNS suppression and death of children are too grave to justify such approval.

In FDA's response to a citizen petition of Accutane, FDA explained that all generic manufacturers of Accutane must adopt all of the essential elements of Accutane's risk – management measures.[86] In particular, CDER Director, Janet Woodcock, stated that "the documents in the [risk management program] are part of the product labeling," and "all generic [Accutane] manufacturers, as part of their labeling for ANDA approval, will have the same educational materials."[87]

If FDA were to permit buprenorphine ANDA sponsors to forgo certain educational interventions on pediatric exposure, to ensure comparable safety profiles of those drugs and the RLD, FDA would then have to consider imposing heightened labeled warnings on the generic drugs. But, FDA has explained that imposing such a requirement frustrates the purpose of the FDC Act.[88]

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86 Letter from Janet Woodcock, FDA, CDER to Accutane at 4 (Nov. 8, 2002).

87 *Id.* In that case, Roche had submitted certain educational materials for its risk management program for Accutane as part of a labeling supplement. RBP's REMS requires it to "take reasonable steps to improve implementation of these elements to meet the goals of the REMS." Suboxone Tablet REMS at 4. RBP's educational efforts are undoubtedly reasonable steps to further the goals of the REMS, but to date, FDA has not specifically made them a part of the REMS. *See also* Transmucosal Immediate Release Fentanyl (TIRF) REMS (June 2012) (initially approved in December 2011 and specifically containing an education program for prescribers and pharmacists that includes education on pediatric exposure), *available at* http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM289730.pdf.

88 Abbreviated New Drug Applications; Proposed Rule, 54 Fed. Reg. 28872, 28884 (July 10, 1989) (stating "FDA does not believe that it would be consistent with the purpose of section 505(j) of the act, which is to assure the marketing of generic drugs that are as safe and effective as their brand-name counterparts, to interpret section 505(j)(2)(a)(v) of the act as permitting the marketing of generic drugs with diminished safety or effectiveness and concomitantly heightened labeled warnings").

Accordingly, FDA must deny any buprenorphine ANDA that fails to include educational interventions comparable to those adopted by RBP to reduce the risk of pediatric exposure to buprenorphine, as such ANDAs lack the same labeling as the RLD.

d. FDA must deny any buprenorphine ANDA for opioid dependence treatment that lacks educational interventions adopted to reduce the risk of pediatric exposure, because such ANDAs lack the same risk-benefit profile as the RLD.

In determining whether to approve a new drug, FDA will consider whether the risks posed by the drug outweigh its potential benefit.[89] FDA has indicated that an ANDA sponsor must demonstrate that the generic drug has the same risk-benefit profile as the RLD, by stating that those drugs have comparable safety risks.[90]

The benefits of buprenorphine as an opioid dependence medication are clear: both Suboxone and Subutex expanded access to addiction treatment for a significantly underserved population of patients.[91] In addition, compared to a full opioid receptor agonist, buprenorphine has reduced diversion concerns due to its partial opioid-receptor agonist properties. Combining buprenorphine and

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89 Food and Drug Administration Safety and Innovation Act, Pub. L. No. 112-144, § 905, 126 Stat. 993, 1092 (2012) (amending FDC Act § 505(d))).

90 *See* Generic Drugs: Questions and Answers?, *available at* http://www.fda.gov/Drugs/ResourcesForYou/Consumers/QuestionsAnswers/ucm100100.htm. (stating "a generic drug is the same as a brand-name drug in dosage, safety, strength, quality, the way it works, the way it is taken and the way it should be used").

91 Gregory B. Collins, MD et al., *Buprenorphine maintenance: a new treatment for opioid dependence*, 74(7) Cleve. Clin. J. Med. 514 (2007).

naloxone in Suboxone provides further public benefit by reducing the risk that the drug will be abused parenterally.[92]

Buprenorphine is, however, a serious drug. It is an opiate that is associated with risks of abuse and diversion. In some cases, particularly when injected and when used in combination with alcohol or benzodiazepines, buprenorphine can be associated with significant adverse events including respiratory failure and death. That risk is even more acute in exposed children due to their lower body weight. FDA must consider the data presented here showing an alarming increase in the rates of pediatric exposure during the five-years following approval, which has only recently reached a plateau and subsequent decline. The plateau and decline are clearly associated with specific interventions RBP took with respect to pediatric safety, thus the most prudent course is to attribute that success to those measures as a whole.

If the safety risks of a generic and innovator must be the same as the RLD, then FDA cannot conclude that buprenorphine marketed without targeted interventions concerning pediatric exposure is the same as buprenorphine marketed with such interventions. The rate of pediatric exposures was increasing before RBP's targeted education campaign took effect, and has only recently plateaued and begun to decline, thus demonstrating the greater safety risks posed by buprenorphine marketed for addiction treatment without educational interventions. FDA cannot permit the marketing of a drug with equal therapeutic

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92 *See* Buprenorphine, Center for Substance Abuse Treatment, Substance Abuse and Mental Health Services Administration, US Department of Health and Human Services, About Buprenorphine Therapy, *available at* http://buprenorphine.samhsa.gov/about.html.

effect, but a substantially greater safety risk, than an otherwise identical competitor, especially where those risks threaten the safety and lives of children.

2. FDA Should Refrain from Approving Applications for Buprenorphine for Opioid Addiction that Lacks Child-Resistant Unit-Dose Packaging.

As summarized above, the pediatric exposure analysis revealed a highly significant statistical difference between the rates of pediatric exposure to multi-dose packaged buprenorphine versus child-resistant, unit-dose packaged buprenorphine for opioid addiction. Indeed, the risk of unintentional pediatric exposures to multi-dose packaged buprenorphine and buprenorphine/naloxone tablets was 2.5 to 7.8 times greater, respectively, than for child-resistant, unit dose packaged buprenorphine/naloxone film. For the most recent quarter measured in 2012, the risk of unintentional pediatric exposure to buprenorphine/naloxone tablet is 8.5 times greater than for buprenorphine/naloxone film. These findings fundamentally alter the inherent risk-benefit profile of certain buprenorphine drugs marketed for opioid dependence treatment.

The child-resistant unit-dose packaging used by RBP may help to reduce pediatric exposure in several ways. First, it could be more difficult for a child to open the foil wrappers than a bottle. Second, even if a child does defeat the unit-dose packaging, the child is only exposed to one dose of the product. Third, adults may be less likely to open multiple unit-doses packages and improperly store several doses together, such as in a container that is not child-resistant.[93]

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[93] Additionally, it is hoped that the recent approval by the FDA of two new strengths of the film product will reduce the likelihood of a patient opening the foil pouch to extract a partial dose, leaving any remaining drug available for unintentional exposures.

a. FDA may not approve any buprenorphine NDA for addiction treatment that lacks child-resistant unit-dose packaging because FDA has insufficient information to determine the safety of those drugs.

As set forth above, the FDC Act requires FDA to refrain from approving an NDA if "upon the basis of information submitted to [it, FDA] has insufficient information to determine whether [the] drug is safe for use" under the conditions set forth in the drug's proposed labeling.[94]

Not surprisingly, FDA has considered abuse and misuse, to include accidental pediatric exposure, part of a drug's conditions of use in ascertaining safety. For example, in 1977 FDA withdrew trichloroethane aerosol due to concerns of "potential CV toxicity" and "deaths from misuse [and] abuse."[95] Later, in 1982, FDA withdrew camphorated oil due to "infant [and] child poisonings"[96] More recently, FDA requested that Purdue voluntarily cease marketing of Palladone® (hydromorphone HC1 extended-release) Capsules, because pharmacokinetic data revealed that co-ingestion of Palladone with alcohol results in an increase in the peak plasma of hydromorphone. Despite having strong labeling warning patients against the risks of taking Palladone with alcohol,

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94 FDC Act § 505(d)(4); 21 U.S.C. § 355(d)(4); *See also* 21 C.F.R. § 314.125(a)(4).

95 Diane K. Wysowski, Ph.D., et al., Adverse Drug Event Surveillance an Drug Withdrawals in the United States, 1969-2002, The Importance of Reporting Suspected Reactions, 175 Archives Internal Medicine 1363, 1366 (June 27, 2005).

96 *Id.*

including a black box warning, FDA found that the likelihood of patients' misuse of the drug altered its risk/benefit profile and ordered the drug's suspension.[97]

Even more directly relevant here, FDA has found that withdrawal of a drug product was necessary because the drug's dosage form rendered it more subject to abuse than effective alternative drugs with different dosage forms. In 1973, FDA withdrew approval of all drug applications for parenteral methamphetamine. The Agency concluded that "the well documented history of abuse of parenteral methamphetamine, together with the severe risks of dependence and the presence of effective alternative drugs, creates an unfavorable balance of risk to benefit."[98]

Here, the conditions of use of buprenorphine that pose serious questions of safety include the failure of patients or family members to safeguard that medication from children. That failure has contributed to many accidental exposures to children, some causing severe adverse events including hospitalization and death. However, the new pediatric exposure analysis indicates that unit-dose packaging

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97 *See Food and Drug Administration, Press Release,* FDA Asks Purdue Pharma to Withdraw Palladone for Safety Reasons (July 13, 2005), *available at* http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2005/ucm108460.htm ; http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm129288.htm; Public Health Advisory: Suspended Marketing of Palladone (hydromorphone hydrochloride, extended-release capsules) (July 13, 2005), *available at* http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/PublicHealthAdvisories/UCM051743; Palladone Package Insert and Medication Guide (Feb. 11, 2005), *available at* http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=894.

98 Opportunity for a Hearing on Proposal to Withdraw Approval of New Drug Applications, 38 Fed. Reg. 4282 (Feb. 12, 1973); Amphetamines for Human Use; Notice of Withdrawal of Approval of New Drug Applications, 38 Fed. Reg. 8290 (Mar. 30, 1973).

may reduce those risks. Specifically, Suboxone Film in child-resistant foil unit-dose packaging was significantly less likely to be exposed to children than Suboxone tablets in standard child-resistant bottles.

Thus, FDA should refrain from approving any buprenorphine NDA without unit-dose packaging, or where the NDA sponsor otherwise fails to submit data demonstrating the drug does not pose comparable safety risks to multi-dose packaged buprenorphine.[99] Without such packaging or data, FDA would have

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[99] RBP recognizes that in *Nutritional Health Alliance v. FDA*, 318 F.3d 92 (2nd Cir. 2003), the court held that FDA lacked the regulatory authority to promulgate a rule requiring unit-dose packaging of a dietary supplement for the sole purpose of reducing the risk of pediatric exposure. *Id.* at 95. The *Nutritional Health* court also opined, in dicta, that FDA lacked regulatory authority from the FDC Act's adulteration and cGMP provisions to require unit-dose packaging for pharmaceutical drugs. *Id.* at 100. The court explained that Congress transferred FDA's authority to regulate child-resistant packaging to the Consumer Product Safety Commission through the Poison Prevention Packaging Act. *Id.* However, several factors distinguish *Nutritional Health* from the present case. First, buprenorphine is a drug, not a dietary supplement, and the requested action is not a rulemaking. Second, that case considered FDA's authority pursuant to entirely distinct statutory sections, section 402 and 351, finding adulteration is "simply unrelated" to "the risk that a product will be used or be misused in an unintended fashion." *Id.* at 101. In contrast, FDA has broad authority to consider a wide range of public health risks pursuant to sections 505 and 505-1. To be sure, FDA has since considered pediatric exposure risks in making that determination. *See* Letter from Gita A. Akhavan Toyserkani, CDER, FDA, to RBP (Aug. 6, 2010) (requiring RBP to include an analysis of pediatric exposure in its REMS assessments); (Transmucosal Immediate Release Fentanyl (TIRF) Risk Evaluation and Mitigation Strategy (REMS)1, 2 (Dec. 2011), *available at* http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM289730.pdf (including "preventing accidental exposure to children" as an express goal); *See also* FDA, Questions and Answers About Onsolis (fentanyl buccal soluble film) (noting the requirement of Onsolis REMS was to "reduce . . . accidental exposure in children.") FDA has required specific packaging for drugs, most notably for Actiq (oral transmucosal fentanyl citrate; NDA 02-747), to help prevent pediatric exposure. Actiq is provided in "a foil pouch composed of PET, Veleron, foil, polyethylene . . . consumer tested for child resistance and requires scissors to open." CDER, Medical Review, Actiq, NDA 20747, 1.4 (1997). In addition, an "ACTIQ Child Safety Kit" is provided "to patients and their caregivers who have children in the home or visiting." Actiq Package Insert 1, 10 *available at*

insufficient information to determine whether approval of those drugs would result in a spike in pediatric exposures, similar to that which occurred for Suboxone and Subutex, after those products were approved.

b. FDA may not approve any buprenorphine NDA for addiction treatment that lacks child-resistant unit-dose packaging because the risk-benefit profile of those drugs does not favor approval.

As set forth above, the FDC Act requires FDA to consider the risk-benefit profile of a drug prior to its approval.[100] FDA has explained that it will consider a broad range of safety risks and benefits in conducting this risk-benefit analysis.[101] FDA cannot approve an application for a drug that poses heightened safety risks unless the drug also provides a meaningful and significant benefit to the public health.

The pediatrics exposure analysis demonstrates the safety risks of buprenorphine for opioid addiction packaged in multi-dose versus unit-dose packaging. It demonstrates that pediatric exposures to buprenorphine soared while Subutex and Suboxone were packaged and marketed in multi-dose packaging.

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http://www.actiq.com/pdf/actiq_package_insert_4_5_07.pdf, . The Child Safety Kit includes: A child-resistant lock used to secure the storage space where ACTIQ is kept, a portable locking pouch, and a child-resistant temporary storage bottle. ACTIQ Medication Guide at 14, *available at http://www.actiq.com/pdf/actiq_package_insert_4_5_07.pdf*. Thus, special packaging, such as unit-dose packaging of buprenorphine for opioid addiction can be required by FDA to protect the public safety. However, to the extent that FDA disagrees, RBP asks that FDA at least require all buprenorphine applications for opioid dependence include data demonstrating that the drug does not pose unreasonable pediatric safety risks, to adequately ensure safe use of those drugs.

100 Food and Drug Administration Safety and Innovation Act, Pub. L. No. 112-144, § 905, 126 Stat. 993, 1092 (2012) (amending FDC Act § 505(d))).

101 Response to Citizen Petition, FDA to ISTA Pharmaceuticals, FDA Docket No. 2008-p-0368 at 3 (May 11, 2011).

FDA must consider this safety risk in assessing the risks of buprenorphine for opioid dependence that is similarly packaged.

Moreover, FDA must also consider the public health benefits of any buprenorphine drug subject to an NDA that poses these risks. In determining those benefits, FDA must consider whether safer alternative treatment exists for the same indication through currently approved drugs. Thus, FDA must consider the fact that Suboxone Film, which is currently approved for opioid addiction treatment, poses a significantly lower risk of pediatric exposure than comparable drugs in unit-dose packaging. In light of these considerations, the risk-benefit profile of any buprenorphine NDA for opioid addiction treatment without child-resistant unit-dose packaging likely renders those NDAs not approvable by FDA.

3. FDA may not approve any buprenorphine/naloxone ANDA for addiction treatment until FDA determines whether the RLD for those drugs was discontinued for reasons of safety.

FDA may refuse to approve an ANDA if the agency determines the RLD was withdrawn from sale for reasons of safety or effectiveness.[102] Before FDA can approve an ANDA, the FDC Act and implementing regulations require the agency to determine whether the RLD has been voluntarily withdrawn from sale for safety or effectiveness reasons.[103]

In this case, there have been thousands of accidental exposures to children causing severe adverse events including hospitalization and death. RBP now has evidence showing that when buprenorphine for opioid addiction is packaged in child-resistant unit-dose, versus multi-dose packaging, the risks of pediatric

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102 21 C.F.R. § 314.127(a)(11); FDC Act § 505(j)(4)(I).
103 21 C.F.R. § 314.161(A)(1).

exposure are significantly reduced. In response to these findings, RBP discontinued marketing of Suboxone tablets (NDA 20-733). RBP concluded that the balance of risk to benefit, in light of readily available safer alternatives (Suboxone Film) justified that discontinuance. FDA must employ a comparable analysis in determining whether ANDAs that list the discontinued drugs are approvable.

FDA recently employed that analysis in determining that Chloromycetin (chloramphenicol) was withdrawn from sale for reasons of safety or efficacy. Specifically, FDA found that "with the approval of additional therapies with less severe adverse drug effects, FDA has determined that the risks associated with Chloromycetin . . . as currently labeled, outweigh the benefits. Most importantly, Chloromycetin may cause a number of adverse reactions, the most serious being bone marrow depression (anemia, thrombocytopenia, and granulocytopenia temporally associate with treatment)."[104] The comparative safety of formulation and packaging differences can also be considered.[105] In addition, a risk-benefit comparison to alternative products can inform FDA's determination of the reasons a product has been discontinued for sale. For example, in response to a recent citizen petition filed by ISTA Pharmaceuticals, Inc., arguing that its once-a-day

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104 FDA, Determination that Chloromycetin (chloramphenicol) Capsules, 250 Milligrams were withdrawn from sale for reasons of safety or effectiveness, 77 Fed. Reg. 135,135 (July 13, 2012). *See also* FDA, Determination That Halflytely and Bisacodyl Tablets Bowel Prep Kit (Containing Two Bisacodyl Delayed Release Tablets, 5 Milligrams) Was Withdrawn from Sale for Reasons of Safety or Effectiveness, 76 Fed. Reg. 51037 (Aug. 17, 2011) (the 5 mg product had "a safety advantage over the 10 mg product because there is less abdominal fullness and cramping . . . .").

105 FDA, Determination That BREVIBLOC (Esmolol Hydrochloride) Injection, 250 Milligrams/Milliliter, 10—Milliliter Ampule, Was Withdrawn from Sale for Reasons of Safety or Effectiveness, 75 Fed. Reg. 24710 (May 5 2010) (taking into account "alternative presentations of the product" in assessing the risk of medication errors).

formula (Bromday) for bromfenac ophthalmic solution was safer than its then withdrawn twice-a-day formula (Xibrom), and thus any ANDA referencing Xibrom must be denied, FDA stated, "[e]ven if Bromday were shown to be safer than Xibrom that would not necessarily mean that Xibrom should no longer be considered sufficiently safe. Rather, the Agency would evaluate Xibrom's risks in light of its benefits, including any evidence that showed Xibrom offers any material efficacy advantage over Bromday."[106]

Suboxone Tablet offers no efficacy advantage over Suboxone Film, but is associated with a significantly higher risk of pediatric exposure. Suboxone Tablet is thus less safe than Suboxone Film, and RBP discontinued marketing it for that reason. FDA must refuse to approve any ANDA referencing Suboxone Tablet (NDA 20-733) until it determines whether RBP's decision was based on reasons of safety.

CONCLUSION

FDA cannot approve an application for a drug if the drug poses unreasonable safety risks. In administering this important responsibility, FDA considers a broad panoply of factors, each of which is aimed at ensuring that unsafe products do not reach the public.

In response to concerns regarding the potential misuse and abuse of buprenorphine for opioid dependence, RBP adopted a robust RiskMAP. Moreover, when pediatric exposure concerns emerged, RBP adjusted its RiskMAP to address those concerns. Today, the risks of accidental pediatric exposure to

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106 Response to Citizen Petition, FDA to ISTA Pharmaceuticals, FDA Docket No. 2008-p-0368 at 16 (May 11, 2011).

buprenorphine have diminished. FDA should consider the observed association of these events and recognize the importance of all of RBP's risk management interventions. Accordingly, to ensure the future safe use of buprenorphine for opioid addiction treatment, FDA should refrain from approving any buprenorphine application for opioid addiction that lacks risk-management interventions comparable to RBP's.

Further, buprenorphine drugs for opioid dependence that fail to contain child-resistant unit-dose packaging pose an unreasonable risk that those products will be exposed to children, potentially causing permanent injury or even death. This reason alone merits denial of any application for those products. In addition, in light of a readily available safer alternative for opioid addiction treatment with buprenorphine, and FDA's historic treatment of products that pose unique risks of misuse, FDA should deny buprenorphine applications for opioid addiction without child-resistant unit-dose packaging that is associated with a reduction in the risk of pediatric exposure to those drugs.

In light of findings from the recent pediatric exposure analysis, RBP has concluded that it is appropriate to discontinue marketing of Suboxone tablet. Accordingly, FDA may not approve any buprenorphine/naloxone ANDA for addiction treatment that references Suboxone tablet (NDA 20-733) until FDA determines whether that drug was discontinued for reasons of safety.

III. ENVIRONMENTAL IMPACT

RBP claims a categorical exclusion from the requirements for an Environmental Assessment under 21 C.F.R. § 25.31(a) because the grant of this Citizen Petition would not have an effect on the environment.

IV. ECONOMIC IMPACT

Information on the economic impact of the action requested by this Citizen Petition will be submitted if requested by FDA.

V. CERTIFICATION

RBP makes the following certification pursuant to FDC Act § 505(q)(1)(H): I certify that, to my best knowledge and belief: (a) this petition includes all information and views upon which the petition relies; (b) this petition includes representative data and/or information known to the petitioner which are unfavorable to the petition; and (c) I have taken reasonable steps to ensure that any representative data and/or information which are unfavorable to the petition were disclosed to me. I further certify that the information upon which I have based the action requested herein first became known to the party on whose behalf this petition is submitted on or about the following date: September 15, 2012. If I received or expect to receive payments, including cash and other forms of consideration, to file this information or its contents, I received or expect to receive those payments from the following persons or organizations: RBP. I verify under penalty of perjury that the foregoing is true and correct as of the date of the submission of this petition.

Respectfully submitted,

Tim Baxter
Global Medical Director
Reckitt Benckiser Pharmaceuticals, Inc.