IN THE UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF VIRGINIA

FEDERAL TRADE COMMISSION,

Petitioner,

v.

RECKITT BENCKISER PHARMACEUTICALS, INC.,

Respondent.

Misc. No. 3:14MC005

PETITION OF THE FEDERAL TRADE COMMISSION FOR AN ORDER ENFORCING CIVIL INVESTIGATIVE DEMAND

Preamble

Pursuant to Section 20 of the Federal Trade Commission Act ("FTC Act"), 15 U.S.C. § 57b-1, the Federal Trade Commission petitions this Court for an Order requiring Respondent, Reckitt Benckiser Pharmaceuticals, Inc. ("Reckitt"), to comply with an FTC civil investigative demand ("CID"). The CID seeks documents and information relevant to an ongoing Commission law enforcement investigation. The Commission issued the CID to determine whether Reckitt had engaged in unfair methods of competition with respect to its branded drug Suboxone. Specifically, the FTC is investigating whether Reckitt abused public regulatory processes, including filing a citizen petition with the U.S. Food and Drug Administration ("FDA") and negotiating with competing manufacturers, to

maintain its monopoly in the market for Suboxone, an opioid addiction treatment distributed through prescription, rather than by clinic-based methods.

The Declaration under penalty of perjury of Daniel Butrymowicz, which verifies the allegations of this Petition, is attached hereto as Petition Exhibit ("Pet. Exh.") 1. Portions of this declaration are filed under temporary seal.[1] Additional exhibits are as follows:

Pet. Exh. 2 Resolution Authorizing Use of Compulsory Process in Nonpublic Investigation (FTC File No. 131 0036);

Pet. Exh. 3 Civil Investigative Demand to Reckitt Benckiser Pharmaceuticals, Inc., June 13, 2013;

Pet. Exh. 4 Correspondence between the Federal Trade Commission and Reckitt, February 28, 2014 to July 24, 2014 [portions of which are filed under temporary seal];

Pet. Exh. 5 Excerpts from Reckitt's Privilege Log, April 28, 2014 [filed under temporary seal];

Pet. Exh. 6 Draft Executive Summary [filed under temporary seal];

Pet. Exh. 7 Reckitt Benckiser Pharmaceuticals, Inc., Citizen Petition re Safety Concerns Regarding Buprenorphine for Opioid Dependence (Docket No. FDA-2012-P-1028) (Sept. 25, 2012); and

Pet. Exh. 8 Letter regarding Docket No. FDA-2012-P-1028 from Janet Woodcock, MD, Director, Center for Drug Evaluation and Research, FDA, to Tim Baxter, Global Medical Director, Reckitt (Feb. 22, 2013).

Petition Allegations

To support this Petition, the Commission alleges the following:

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[1] The Commission is simultaneously filing a motion to seal these and other materials pursuant to Section 4.10(g) of the FTC's Rules of Practice and Procedure ("FTC Rules"), 16 C.F.R. § 4.10(g), and Section 21 of the FTC Act, 15 U.S.C. § 57b-2(b), (d), and (f).

1. The Commission is an administrative agency of the United States government, organized and existing pursuant to the FTC Act, 15 U.S.C. § 41 *et seq.* The Commission is authorized and directed by Section 5(a) of the FTC Act, 15 U.S.C. § 45(a), to prevent the use of unfair methods of competition and unfair or deceptive acts or practices in or affecting commerce.

2. Section 3 of the FTC Act, 15 U.S.C. § 43, empowers the Commission to prosecute any inquiry necessary to its duties in any part of the United States. Section 6 of the Act, 15 U.S.C. § 46, empowers the Commission to gather and compile information concerning, and to investigate from time to time, the organization, business, conduct, practices and management of, any person, partnership or corporation engaged in or whose business affects commerce, with certain exceptions not relevant here. Section 20 of the FTC Act, 15 U.S.C. § 57b-1, empowers the Commission to require by CID the production of documents or other information relating to any Commission law enforcement investigation.

3. This Court has jurisdiction to enforce the Commission's duly issued CID under Section 20(e) of the FTC Act, 15 U.S.C. § 57b-1(e), which provides, in pertinent part:

> Whenever any person fails to comply with any civil investigative demand duly served upon him under this section, or whenever satisfactory copying or reproduction of material requested pursuant to the demand cannot be accomplished and such person refuses to surrender such material, the Commission, through such officers or attorneys as it may designate, may file, in the district court of the United States for any judicial district in which such person resides, is found, or transacts business, and serve upon such person, a petition for an order of such court for the enforcement of this section.

Respondent Reckitt resides, is found, and transacts business in this judicial district. Pet. Exh. 1, ¶ 3.

4. Reckitt is a Virginia corporation headquartered in Richmond, Virginia at 10710 Midlothian Turnpike, Suite 430. It is a wholly owned subsidiary of Reckitt Benckiser Group plc, a British Corporation. Reckitt sells branded pharmaceutical products throughout the United States, including in this district. Pet. Exh. 1, ¶ 3. One of Reckitt's products is the branded drug Suboxone, a combination of buprenorphine and naloxone used to treat opioid addiction. Pet. Exh. 1, ¶ 4.

5. On May 2, 2013, the Commission issued a Resolution Authorizing the Use of Compulsory Process (FTC File No. 131 0036). Pet. Exh. 1, ¶ 12; Pet. Exh. 2. The Commission directed that "any and all compulsory process" available to staff be used to determine whether Reckitt engaged in unfair methods of competition by using "its monopoly position to switch the Suboxone market to a new, non-substitutable form of Suboxone, abusing FDA-mandated negotiations for a single shared [Risk Evaluation and Mitigation Strategy, or REMS,] system, filing a meritless or sham citizen petition with FDA, or any related conduct regarding these or other pharmaceutical products" in violation of Section 5 of the FTC Act, 15 U.S.C. § 45. Pet. Exh. 1, ¶ 12; Pet. Exh. 2.

6. Under the authority of the resolution, FTC staff is investigating, among other matters, three actions taken by Reckitt with respect to Suboxone: (1) whether Reckitt filed a sham citizen petition to protect its monopoly in branded Suboxone by asking the FDA to ban or limit generic versions; (2) whether Reckitt

obstructed FDA-mandated negotiations with its competitors to develop a safety program (known as REMS) for Suboxone and its generic versions, in order to delay entry of generic Suboxone; and (3) whether Reckitt engaged in anticompetitive conduct to switch consumers from a tablet form of Suboxone that is subject to generic competition to a film form that is not. Pet. Exh. 1, ¶¶ 13-16.

7. On June 13, 2013, the Commission issued the CID to Reckitt for documents, data, and interrogatory responses relevant to the conduct under investigation. Pet. Exh. 1, ¶ 18; Pet. Exh. 3. The company produced documents in a rolling production and in December 2013 certified compliance with the CID. Pet. Exh. 1, ¶ 18.

8. Reckitt's certificate of compliance was accompanied by a privilege log by which Reckitt invoked attorney-client privilege for approximately 37,000 documents. Pet. Exh. 1, ¶ 19.

9. After reviewing the log, on February 28, 2014, FTC staff objected to Reckitt's assertion of attorney-client privilege for "thousands of drafts of documents that Reckitt disclosed, or intended to disclose, to third parties," including, but not limited to, "drafts of agreements, exhibits, letters, memoranda, meeting minutes, presentations, press releases, product brochures, product inserts, promotional materials, public relations documents, and reports and their amendments [as well as] e-mails that appear to discuss those drafts." Pet. Exh. 1, ¶ 19; Pet Exh. 4, at 001-002.[2]

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[2] Page references are to three-digit Bates numbers in the lower right corner of

10. Following further discussions with FTC staff, Reckitt produced approximately 13,000 documents that it previously withheld as privileged, with a revised privilege log. Pet. Exh. 4 at 025, 028-029. This supplemental production included documents previously produced by Reckitt, news articles, and final contracts with third parties. However, Reckitt continues to withhold documents and information that it claims reflect attorney-client communications regardless of whether they are drafts of documents that were ultimately published or disclosed to a third party, or are documents and information related to such disclosures. Pet. Exh. 1, ¶ 20; Pet Exh. 4, at 021, 030-037.

11. Reckitt's refusal to produce the withheld documents has materially impeded the Commission's investigation and is contrary to the public interest. Pet. Exh. 1, ¶ 25. Therefore, we respectfully request that this Court enforce the CID and direct Reckitt to produce those otherwise-responsive documents it has improperly withheld as privileged.

12. No previous application for the relief sought herein has been made to this Court or any other.

Prayer for Relief

WHEREFORE, the Commission invokes the aid of this Court and prays:

a. For the immediate issuance of an order directing Reckitt to show cause why it should not comply in full with the CID;

b. For a prompt determination of this matter and an order requiring

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each document.

Reckitt to fully comply with the CID within ten (10) days of such order;

c. For such other relief as the Court deems just and proper.

Respectfully submitted,

STEPHEN WEISSMAN
Deputy Director
Bureau of Competition

BRADLEY S. ALBERT
Deputy Assistant Director

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Dated: August 7, 2014

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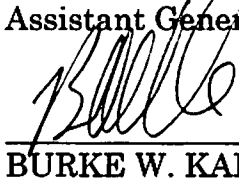

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PETITION EXHIBIT 2

Resolution Authorizing Use of Compulsory Process in Nonpublic Investigation, FTC File No. 131 0036, May 2, 2013

UNITED STATES OF AMERICA
BEFORE THE FEDERAL TRADE COMMISSION

COMMISSIONERS: **Edith Ramirez, Chairwoman**
Julie Brill
Maureen K. Ohlhausen
Joshua D. Wright

RESOLUTION AUTHORIZING USE OF COMPULSORY PROCESS IN NONPUBLIC INVESTIGATION

File No. 131 0036

Nature and Scope of Investigation:

To determine whether Reckitt Benckiser Pharmaceuticals, Inc., or its affiliates, including but not limited to Reckitt Benckiser Group plc, or any other person, has engaged or is engaging in unfair methods of competition in or affecting commerce, in violation of Section 5 of the Federal Trade Commission Act, 15 U.S.C. § 45, as amended, with regard to the pharmaceutical products Suboxone and Subutex, including by using its monopoly position to switch the Suboxone market to a new, non-substitutable form of Suboxone, abusing FDA-mandated negotiations for a single shared REMS system, filing a meritless or sham citizen petition with FDA, or any related conduct regarding these or other pharmaceutical products.

The Federal Trade Commission hereby resolves and directs that any and all compulsory processes available to it be used in connection with this investigation.

Authority to Conduct Investigation:

Sections 6, 9, 10, and 20 of the Federal Trade Commission Act, 15 U.S.C. §§ 46, 49, 50, and 57b-1, as amended; FTC Procedures and Rules of Practice, 16 C.F.R. § 1.1 *et seq.*, and supplements thereto.

By direction of the Commission.

Donald S. Clark
Secretary

Issued: May 2, 2013

PETITION EXHIBIT 3

Civil Investigative Demand to Reckitt Benckiser Pharmaceuticals, Inc., June 13, 2013

United States of America
Federal Trade Commission

CIVIL INVESTIGATIVE DEMAND

1. TO

Reckitt Benckiser Pharmaceuticals, Inc.
c/o Philip A. Proger, Jones Day
51 Louisiana Avene, NW
Washington, DC 20001-2113

This demand is issued pursuant to Section 20 of the Federal Trade Commission Act, 15 U.S.C. § 57b-1, in the course of an investigation to determine whether there is, has been, or may be a violation of any laws administered by the Federal Trade Commission by conduct, activities or proposed action as described in Item 3.

2. ACTION REQUIRED

☐ You are required to appear and testify.

LOCATION OF HEARING	YOUR APPEARANCE WILL BE BEFORE
	DATE AND TIME OF HEARING OR DEPOSITION

☒ You are required to produce all documents described in the attached schedule that are in your possession, custody, or control, and to make them available at your address indicated above for inspection and copying or reproduction at the date and time specified below.

☒ You are required to answer the interrogatories or provide the written report described on the attached schedule. Answer each interrogatory or report separately and fully in writing. Submit your answers or report to the Records Custodian named in Item 4 on or before the date specified below.

DATE AND TIME THE DOCUMENTS MUST BE AVAILABLE

Return date is 30 days from the date the CID is signed. JUL 16 2013

3. SUBJECT OF INVESTIGATION

See attached resolution, FTC File No. 131-0036

4. RECORDS CUSTODIAN/DEPUTY RECORDS CUSTODIAN	5. COMMISSION COUNSEL
Bradley S. Albert, Records Custodian Garth W. Huston, Deputy Records Custodian	Garth W. Huston Daniel W. Butrymowicz

DATE ISSUED	COMMISSIONER'S SIGNATURE
6-13-13	

INSTRUCTIONS AND NOTICES

The delivery of this demand to you by any method prescribed by the Commission's Rules of Practice is legal service and may subject you to a penalty imposed by law for failure to comply. The production of documents or the submission of answers and report in response to this demand must be made under a sworn certificate, in the form printed on the second page of this demand, by the person to whom this demand is directed or, if not a natural person, by a person or persons having knowledge of the facts and circumstances of such production or responsible for answering each interrogatory or report question. This demand does not require approval by OMB under the Paperwork Reduction Act of 1980.

PETITION TO LIMIT OR QUASH

The Commission's Rules of Practice require that any petition to limit or quash this demand be filed within 20 days after service, or, if the return date is less than 20 days after service, prior to the return date. The original and twelve copies of the petition must be filed with the Secretary of the Federal Trade Commission, and one copy should be sent to the Commission Counsel named in Item 5.

YOUR RIGHTS TO REGULATORY ENFORCEMENT FAIRNESS

The FTC has a longstanding commitment to a fair regulatory enforcement environment. If you are a small business (under Small Business Administration standards), you have a right to contact the Small Business Administration's National Ombudsman at 1-888-REGFAIR (1-888-734-3247) or www.sba.gov/ombudsman regarding the fairness of the compliance and enforcement activities of the agency. You should understand, however, that the National Ombudsman cannot change, stop, or delay a federal agency enforcement action.

The FTC strictly forbids retaliatory acts by its employees, and you will not be penalized for expressing a concern about these activities.

TRAVEL EXPENSES

Use the enclosed travel voucher to claim compensation to which you are entitled as a witness for the Commission. The completed travel voucher and this demand should be presented to Commission Counsel for payment. If you are permanently or temporarily living somewhere other than the address on this demand and it would require excessive travel for you to appear, you must get prior approval from Commission Counsel.

A copy of the Commission's Rules of Practice is available online at http://bit.ly/FTCRulesofPractice. Paper copies are available upon request.

Form of Certificate of Compliance*

I/We do certify that all of the documents and information required by the attached Civil Investigative Demand which are in the possession, custody, control, or knowledge of the person to whom the demand is directed have been submitted to a custodian named herein.

If a document responsive to this Civil Investigative Demand has not been submitted, the objections to its submission and the reasons for the objection have been stated.

If an interrogatory or a portion of the request has not been fully answered or a portion of the report has not been completed, the objections to such interrogatory or uncompleted portion and the reasons for the objections have been stated.

Signature _____

Title _____

Sworn to before me this day

_____ _____

_____
Notary Public

_____

*In the event that more than one person is responsible for complying with this demand, the certificate shall identify the documents for which each certifying individual was responsible. In place of a sworn statement, the above certificate of compliance may be supported by an unsworn declaration as provided for by 28 U.S.C. § 1746.

SPECIFICATIONS

SPECIFICATION 1:	Submit one copy of Reckitt Benckiser's organization chart and personnel directory for (1) top-level worldwide and U.S. management; and (2) each of the Company's facilities or divisions involved in any activity relating to Suboxone or any buprenorphine product.
SPECIFICATION 2:	Submit (1) documents sufficient to show the size, structure, and organization of Reckitt Benckiser's branded sales force on a quarterly basis; and (2) documents relating to changes to the size, structure, cost, and organization of Reckitt Benckiser's branded sales force, including all documents summarizing sales force costs and expenditures related to both Suboxone Tablets and Suboxone Film.
SPECIFICATION 3:	For all United States patents and United States patent applications that you claim cover Suboxone products, identify the patent(s) and submit one copy of the patent prosecution history of the patent(s).
SPECIFICATION 4:	Submit all documents relating to the strength, validity, scope, enforceability, or potential infringement of U.S. Patent No. 8,017,150 and any other patent or patent application identified in response to Specification 3.
SPECIFICATION 5:	Submit one copy of each NDA, including any supplements, for Subutex, Suboxone Tablets, and Suboxone Film.
SPECIFICATION 6:	Submit all paragraph IV certifications, and accompanying statements, received by Reckitt Benckiser with respect to the patents listed in FDA's Orange Book for Suboxone, and any other notifications received by Reckitt Benckiser related to a Suboxone ANDA.
SPECIFICATION 7:	Submit all business and brand plans for Suboxone.
SPECIFICATION 8:	Identify all products Reckitt Benckiser believes have competed, currently compete, or may compete in the United States in the next five years with Suboxone.
SPECIFICATION 9:	For every product identified in response to Specification 8, submit all documents showing how, in setting the price for and marketing Suboxone (or determining adjustments to prices such as rebates or discounts) Reckitt Benckiser has considered or factored in the pricing and marketing of such product(s).

SPECIFICATION 10: For Suboxone and all products identified in response to Specification 8, submit on a monthly basis:

A. IMS National Sales Perspective (Retail and Non-Retail) or the equivalent thereof in spreadsheet form, by product form, by manufacturer, and by strength, separately by customer channel, for total sales in dollars, units, and extended units;

B. IMS National Prescription Audit data or the equivalent thereof in spreadsheet form, by product form, by manufacturer, and by strength, separately by customer channel, for newly dispensed prescriptions, refill dispensed prescriptions, total dispensed prescriptions, and for total sales in dollars, units, and extended units; and,

C. all supporting definitions and materials for any IMS data provided.

SPECIFICATION 11: Submit all documents related to competition for the sale of Suboxone and all products identified in response to Specification 8, including but not limited to:

A. documents showing the features, benefits or characteristics of Suboxone relative to other products and/or the functional or economic substitutability between Suboxone and any products identified in response to Specification 8; and

B. documents relating to the actual or projected market shares among Suboxone and any products identified in response to Specification 8.

SPECIFICATION 12: Separately for each strength or version of Suboxone, submit all documents related to Reckitt's Suboxone pricing strategy, including but not limited to documents prepared for any committee or individual responsible for Suboxone pricing, relating to each change in Suboxone's wholesale acquisition cost ("WAC"), or any other changes in Suboxone pricing.

SPECIFICATION 13: For the Company's ten largest PBMs and ten largest managed care organizations, based on units reimbursed of Suboxone Tablets and Suboxone Film, submit all contracts that provide for the terms of Suboxone sales (including pricing, rebates, discounts, or other incentives).

SPECIFICATION 14: Submit all forecasts, draft forecasts, and any communications relating to the forecasts and draft forecasts for sales of Subutex, Suboxone Tablets, and Suboxone Film.

SPECIFICATION 15: Submit all documents discussing the marketing or sale of Suboxone, including but not limited to:

A. business, marketing, advertising, or strategic plans, short-term and long-range strategies and objectives, collaboration plans, and budgets;

B. marketing and promotional materials such as brochures, pamphlets, sales force training materials, talking points, comparisons of Reckitt's Suboxone products to generic buprenorphine products, or any other documents related to marketing or promoting Suboxone;

C. profit & loss or contribution statements for Suboxone, or, if such statements are not prepared, for the smallest applicable unit or division responsible for Suboxone sales for which profit & loss or contribution statements are prepared;

D. documents concerning the actual or projected size, composition, dollar sales, and unit sales of the United States market in which Suboxone is sold;

E. documents presented to management committees, executive committees, or boards of directors relating to the marketing or sale of Suboxone;

F. documents related to the projected or anticipated timing of entry of Generic Suboxone (Tablets or Film) and documents relating to any effect that Generic Suboxone may have or has had on the sales, revenues, prices or profits of Suboxone (Tablets or Film);

G. documents relating to Suboxone's life-cycle management, including but not limited to: (1) documents relating to any reduction, elimination, or increase in promotional support for a Suboxone product; and (2) documents constituting or relating to forecasts, projections, or analyses of the effect of the introduction of other Suboxone products on existing Suboxone products' dollar sales, unit sales, and net sales; and,

H. documents related to plans for line extensions or successor products to Suboxone or other buprenorphine products, including but not limited to Suboxone Injectable. Your response to this sub-section need not include documents of a purely scientific or technical nature relating solely to pharmacokinetic or clinical testing of possible future products, but should include communications to management containing summaries of pharmacokinetic or clinical development of possible future products.

SPECIFICATION 16: Submit all documents relating to:

A. any rebate, return, buy-back, or exchange policies for Suboxone Tablets and/or Suboxone Film, as well as any plans or strategies to destroy or dispose of Suboxone Tablets inventory;

B. plans or strategies to decrease promotional support for Suboxone Tablets, including but not limited to changes in sampling and detailing; and,

C. communications with purchasers or physicians regarding the discontinuance of Suboxone Tablets, as well as any analyses of the cost, timing, or effectiveness of any such plans or strategies.

SPECIFICATION 17: Submit all documents related to Reckitt Benckiser's plans to convert patients or physician prescribing practices from Suboxone Tablets to Suboxone Film, including but not limited to:

A. any comparisons between Suboxone Tablets and Suboxone Film, including but not limited to any analyses of the benefits or advantages of Suboxone Film over Suboxone Tablets or any analyses of the benefits or advantages of Suboxone Tablets over Suboxone Film;

B. plans or strategies to increase or reduce Suboxone prices (for either form);

C. plans or strategies to increase or reduce Suboxone manufacturing output (for either form);

D. plans or strategies to increase or reduce promotional support for Suboxone (for either form);

E. studies concerning physician prescribing habits or patterns relating to either Suboxone Tablets or Suboxone Film; and,

F. analyses of the timing, effectiveness, costs, cost offsets, and diminished profits of any such plans or strategies.

SPECIFICATION 18: Submit all documents related to Reckitt Benckiser's earnings calls, including but not limited to transcripts, presentations, outlines, and notes.

SPECIFICATION 19: Submit all documents planning for or discussing any co-pay card, coupon, discount, or rebate program associated with Suboxone Film, including but not limited to any analyses of the cost, effectiveness, discontinuance, and ROI of such programs.

SPECIFICATION 20: Submit all documents and data analyzing the risks of diversion and abuse for any version of Subutex or Suboxone.

SPECIFICATION 21: For each buprenorphine product produced, marketed, or manufactured by Reckitt Benckiser, including products marketed outside of the United States, submit documents sufficient to show breakage data for that product in each type of packaging in which it is or has been packaged, including but not limited to bottles, blister packaging, or any other form of individual dose packaging.

SPECIFICATION 22: Submit all documents from January 1, 1995 to the present related to Reckitt Benckiser's purchase of, or interest in purchasing the rights to, any other company's buprenorphine product, including but not limited to products that are either in development or already marketed.

SPECIFICATION 23: Submit a copy of each REMS, RiskMAP, or other restricted distribution system through which Reckitt Benckiser distributes or distributed Subutex, Suboxone Tablets, or Suboxone Film.

SPECIFICATION 24: Submit all documents relating to the preparation of Reckitt's REMS for Suboxone Tablets.

SPECIFICATION 25: Submit all documents constituting or relating to any communications with FDA regarding any version of Suboxone or Subutex, including but not limited to any documents relating to a REMS, RiskMAP, or other restricted distribution system for the distribution of Suboxone or Subutex.

SPECIFICATION 26: Submit all documents relating to the effect of any REMS, RiskMAP, or other restricted distribution system on generic competition for Suboxone or Subutex.

SPECIFICATION 27: Submit all documents related to communications between Reckitt Benckiser and any other company regarding that company's current, future, or potential plans to manufacture, market, or distribute branded buprenorphine products, including but not limited to communications with BioDelivery Sciences International, Inc., Orexo AB, or Titan Pharmaceuticals, Inc.

SPECIFICATION 28: Submit all documents related to the negotiations between Reckitt Benckiser and any Suboxone ANDA Filer, including negotiations with the BPMG, regarding the creation or use of an SSRS for the distribution of Suboxone Tablets, including but not limited to:

A. correspondence between Reckitt Benckiser and any Suboxone ANDA Filer, including correspondence with the BPMG;

B. correspondence between Reckitt Benckiser and FDA;

C. internal communications regarding an SSRS for the distribution of Suboxone Tablets;

D. meeting minutes, notes, or other communications regarding SSRS negotiations or Reckitt Benckiser's strategies for SSRS negotiations; and,

E. documents related to the costs or cost savings to Reckitt Benckiser of creating or participating in an SSRS for the distribution of Suboxone Tablets.

SPECIFICATION 29: Submit all documents related to Reckitt Benckiser's potential legal liability resulting from any SSRS for the distribution of Suboxone, including but not limited to any proposed indemnification agreement between Reckitt Benckiser and any Suboxone ANDA Filer.

SPECIFICATION 30: Submit any Non-Disclosure Agreement or any other legal agreement between Reckitt Benckiser and any ANDA filer related to Suboxone.

SPECIFICATION 31: Submit all documents related to the citizen petitions reflected in FDA Docket Nos. 2009-P-0154, 2011-P-0869, and 2012-P-1028, and any other Reckitt Benckiser, Hyman, Phelps, & McNamara, or

MonoSol Rx citizen petitions related to buprenorphine products, and all documents related to the merits of the citizen petitions, including those documents currently not on the public record.

SPECIFICATION 32: Submit all documents regarding the risk of pediatric exposure to Suboxone, including but not limited to scientific studies or studies commissioned by Reckitt Benckiser.

SPECIFICATION 33: Submit all documents related to any communications between Reckitt Benckiser and Monosol Rx regarding Suboxone Film.

SPECIFICATION 34: For each company or consultant Reckitt Benckiser considered or hired to conduct studies, analyses, or other evaluations related to Suboxone or any other buprenorphine product, submit the following:

A. if Reckitt Benckiser issued a Request for Proposal (or similar request for work), a copy of each proposal issued, all responses to the proposal(s), and all communications with those companies who submitted responses;

B. all other communications between Reckitt Benckiser and any company or consultant considered or hired to conduct the studies; and,

C. for any company retained by Reckitt Benckiser to study pediatric exposure or other issues related to the safety of Suboxone products, all contracts and modifications to the contracts, including the scope of the work, and all studies and findings resulting from the contract, including but not limited to all drafts of studies and findings, and any underlying data supplied to or relied upon by the company.

SPECIFICATION 35: From the Suboxone Litigations, submit unredacted versions of all:

A. complaints and answers to counterclaims;

B. interrogatories, requests for admission, interrogatory responses, and responses to requests for admission;

C. court hearing or conference transcripts, including both hearings and conferences conducted in person and by telephone;

D. deposition transcripts;

E. expert reports (with exhibits) prepared by experts retained by Reckitt Benckiser;

F. dispositive motion briefing; and,

G. materials filed by any party with any United States Court of Appeals.

SPECIFICATION 36: Identify all reasons why Reckitt Benckiser purchased the worldwide rights to Temgesic, and describe all reasons why Reckitt Benckiser has not sold Temgesic in the United States.

SPECIFICATION 37: Identify every reason why Reckitt Benckiser sought to convert Suboxone prescriptions from tablet to film form.

SPECIFICATION 38: Separately for each strength, identify the following:

A. every reason why Reckitt Benckiser decided to discontinue manufacturing or distributing Suboxone Tablets;

B. all reasons why Reckitt Benckiser launched Suboxone Tablets in the United States in 30-count bottles but launched Suboxone Tablets in the United Kingdom and Canada in individual blister packaging;

C. every reason why Reckitt Benckiser did not package Suboxone Tablets in individual unit-dose packaging in the United States; and,

D. the name and title of each employee, officer, or director of Reckitt Benckiser, as well as any consultants or other persons retained by Reckitt Benckiser, involved in any decision to discontinue manufacturing or distributing Suboxone Tablets, and identify their roles with respect to the decision.

SPECIFICATION 39: Identify, on a monthly basis, separately for each strength, and separately for each co-pay card, coupon, discount, or rebate program related to Suboxone Film, the total cost of such program.

SPECIFICATION 40: Separately for each past and present NDC code (all digits) for Suboxone, in spreadsheet form, identify:

A. each WAC at which the drug was listed and the corresponding range of dates for which it was listed at that value;

B. the Average Manufacturer's Price ("AMP") by month and quarter;

C. the Average Wholesale Price ("AWP") by month and quarter; and,

D. each NDC code and describe the corresponding product.

SPECIFICATION 41: In spreadsheet form, separately for each dosage form and strength, identify on a monthly basis, in dollars and units:

A. gross and net sales of Suboxone Tablets and Suboxone Film, not including any coupon redemptions, rebates, or discounts;

B. sales net of total Suboxone Film coupon or co-pay redemptions which occurred during the same month;

C. sales net of total Suboxone Tablet coupon or co-pay redemptions which occurred during the same month;

D. sales net of any other rebate or discounts which occurred during the same month; and,

E. promotional expenses, including but not limited to detailing, physician and pharmacist marketing, and medical and other journal advertising.

SPECIFICATION 42: In spreadsheet form, separately for Suboxone Tablets and Suboxone Film, identify on a quarterly basis and an annual basis:

A. gross sales;

B. separately, each significant category of deduction from gross sales including:

1. chargebacks;
2. coupons;
3. discounts;
4. managed care;
5. Medicare;
6. Medicaid; and,
7. other significant deductions, identified separately;

C. net sales;

D. royalties;

E. units sold;

F. cost of goods sold;

G. samples distributed;

H. each significant category of expenses including:

1. promotion expenses;
2. marketing expenses;
3. detailing expenses; and,
4. other significant expenses, identified separately;

I. distribution margin; and,

J. overall margin.

SPECIFICATION 43: In spreadsheet form, for Suboxone Film, identify on a monthly basis and an annual basis:

A. number of co-pay cards redeemed;

B. total dollar amount of the co-pay cards redeemed;

C. separately by the largest 50 third party payors based on units reimbursed:

1. identify the third party payor;
2. number of co-pay cards redeemed; and,
3. total dollar amount of co-pay cards redeemed; and,

D. for cash pay:

1. number of co-pay cards redeemed; and
2. total dollar amount of co-pay cards redeemed.

SPECIFICATION 44: In spreadsheet form, separately for Suboxone Tablets and Suboxone Film, and separately for the largest 50 third party payors based on units reimbursed, identify on a quarterly basis and an annual basis:

A. the third party payor;

B. any associated PBM;

C. rebates paid;

D. units sold;

E. formulary position; and,

F. average patient co-pay/coinsurance amount.

SPECIFICATION 45: Identify any plans Reckitt Benckiser has or had to introduce Suboxone Injectable, or any other New Suboxone, including but not limited to plans to file future supplements to any Suboxone NDA, including:

A. the name and title of each employee, officer, or director of Reckitt Benckiser, as well as any consultants, involved in the decision whether to introduce the new strength or version;

B. the approximate cost and length of time required for obtaining FDA approval;

C. every advantage and disadvantage of the new strength or version relative to previous or current versions of Suboxone;

D. any plans or strategies Reckitt Benckiser has or had to incentivize the purchase or prescription of the new strength or version, including but not limited to any coupon, rebate, or co-pay card programs; and,

E. the approximate date of the expected launch.

SPECIFICATION 46: List, on a monthly basis, separately for each strength, the amount of Suboxone Tablets manufactured by or for Reckitt Benckiser.

SPECIFICATION 47: List, on a monthly basis since 2009, separately for each strength, the number of Suboxone Film strips manufactured by or for Reckitt Benckiser.

SPECIFICATION 48: Separately for each version of Suboxone, describe fully and completely each REMS or RiskMAP currently or formerly in place, including but not limited to:

A. the process through which Reckitt Benckiser distributes Suboxone to a patient;

B. the method by which Reckitt Benckiser tracks Suboxone through the distribution process;

C. the identity of each type of entity involved in the distribution of Suboxone;

D. the process through which each type of entity becomes accepted into the REMS or RiskMAP;

E. any restrictions or limitations to any person's ability to sell, distribute, or use Suboxone; and,

F. the cost to Reckitt Benckiser of creating and/or maintaining any REMS, RiskMAP, or other restricted distribution system for the distribution of Suboxone.

SPECIFICATION 49: For each Reckitt Benckiser employee, officer, director, or agent involved in any way in any decision regarding a REMS, RiskMAP, or other restricted distribution system for Suboxone or Subutex, identify said person's:

A. name, title, division, and responsibilities at Reckitt Benckiser;

B. current employer, by name and address, if said person is no longer employed by Reckitt Benckiser; and,

C. nature and extent of such involvement.

SPECIFICATION 50: Identify every reason why Reckitt Benckiser did not reach an agreement with the Suboxone ANDA Filers as to an SSRS for the distribution of Suboxone Tablets.

SPECIFICATION 51: For each Reckitt Benckiser employee, officer, director, or agent involved in any way in any negotiations with any Suboxone ANDA filers regarding an SSRS for the distribution of Suboxone Tablets, identify said person's:

A. name, title, division, and responsibilities;

B. current employer, by name and address, if said person is no longer employed by Reckitt Benckiser; and,

C. nature and extent of such involvement.

SPECIFICATION 52: Identify and describe any assessment Reckitt Benckiser made related to the merits of any citizen petitions covered by Specification 31, including the names of the individuals responsible for such assessments, and submit the assessment(s).

SPECIFICATION 53: For each instance of communication between Reckitt Benckiser and the FDA relating to the Subutex and Suboxone citizen petitions, identify the following:

A. the date of the communication;

B. the type of the communication;

C. where applicable, the Person(s) who sent the communication, including title and affiliation;

D. where applicable, the Person(s) to whom the communication was addressed, including title and affiliation; and,

E. where applicable, the Person(s) attending the meeting or teleconference, including title and affiliation.

SPECIFICATION 54: Identify the following and submit all documents supporting your response regarding:

A. the date Reckitt Benckiser first became aware of Suboxone or Subutex clinical data indicating a risk of harm from pediatric exposure;

B. each additional piece of evidence relating to pediatric exposure to Suboxone or Subutex of which Reckitt became aware, and the date on which Reckitt Benckiser became aware of each;

C. the date Reckitt Benckiser first communicated internally about discontinuing Suboxone Tablets;

D. the date Reckitt Benckiser determined that it would discontinue selling Suboxone Tablets;

E. the date Reckitt Benckiser stopped producing Suboxone Tablets,

F. the date Reckitt Benckiser discontinued shipping Suboxone Tablets to its distributors;

G. every reason why Reckitt Benckiser did not immediately discontinue Suboxone Tablets after learning of the risks of accidental pediatric exposure;

H. every reason why Reckitt Benckiser did not immediately discontinue Suboxone Tablets upon the launch of Suboxone Film;

I. the date Reckitt Benckiser first communicated internally about filing a citizen petition with the FDA relating to pediatric exposure to Suboxone; and,

J. the date Reckitt Benckiser first started drafting the citizen petition in FDA Docket No. 2012-P-1028.

SPECIFICATION 55: For each Reckitt Benckiser employee, officer, director, or agent involved in any way in any decision regarding the citizen petition in FDA Docket No. 2012-P-1028, identify said person's:

A. name, title, division, and responsibilities at Reckitt Benckiser;

B. current employer, by name and address, if said person is no longer employed by Reckitt Benckiser; and,

C. nature and extent of such involvement.

SPECIFICATION 56: Identify each company, law firm, and consultant Reckitt Benckiser hired to conduct studies, analyses, or other evaluations related to Suboxone or any other buprenorphine product, and identify the type of work each performed for Reckitt Benckiser.

SPECIFICATION 57: Identify all countries in which Reckitt Benckiser markets Subutex or Suboxone. For each country:

A. list the form (tablets, film, other) of each drug available;

B. identify the packaging (i.e., single bottle, blister packing, etc.) for each form of Subutex and/or Suboxone available;

C. identify if and when Reckitt has changed or plans to change the packaging or the form for any Subutex or Suboxone already being sold in that country; and,

D. if Reckitt has changed or plans to change the packaging for any Subutex or Suboxone products sold in any country, state all reasons for the packaging change.

SPECIFICATION 58: For each year from 2009 through the present, identify Reckitt Benckiser's top 25 sales representatives for Suboxone products by volume.

SPECIFICATION 59: For every pharmaceutical company that requested to purchase Suboxone Film from either Reckitt or its wholesalers, identify:

A. the name of the company;

B. the date(s) of the request(s);

C. if applicable, the date Reckitt or its wholesalers sold Suboxone Film pursuant to each request, the amount sold, and the price paid; and,

D. if Reckitt or its wholesalers did not sell Suboxone Film pursuant to any requests, each reason why it did not.

SPECIFICATION 60: Explain whether and under what conditions Reckitt allows its wholesalers or distributors to sell Suboxone to licensed research institutions.

SPECIFICATION 61: Submit all communications from physicians relating to requests for different forms of Suboxone or complaints about ceasing to distribute or manufacture Suboxone Tablets or Subutex.

SPECIFICATION 62: Submit all studies or trials of Suboxone Tablets or Suboxone Film, including but not limited to studies supporting Reckitt's belief that Suboxone Film represents an improvement for patients as compared to Suboxone Tablets.

SPECIFICATION 63: Identify the steps Reckitt Benckiser took to preserve documents related to this CID and the November 30, 2012 Do Not Destroy Letter, and submit one copy of Reckitt Benckiser's document retention policy.

DEFINITIONS

1. The term "ANDA" means abbreviated new drug application, including any amendments or supplements thereto, as defined in Title I of the Drug Price Competition and Patent Term Restoration Act of 1984.

2. The term "agreement" means any oral or written contract, arrangement, or understanding, whether formal or informal, between two or more persons, together with all modifications or amendments thereto.

3. The term "BPMG" means the Buprenorphine Products Manufacturers Group.

4. The term "communication" means any exchange, transfer, or dissemination of information, regardless of the means by which it is accomplished.

5. The terms "discuss" and "discussing" mean in whole or in part constituting, containing, describing, or addressing the designated subject matter, regardless of the length of the treatment or detail of analysis of the subject matter, but not merely referring to the designated subject matter without elaboration. In addition, a document that "discusses" another document includes the other document itself (e.g., a document that "discusses" an agreement or contract includes the agreement or contract itself). Further, these terms include any operating or financial data about the designated subject matter where such data are separately set out as in a chart, listing, table, or graph.

6. The term "document" means all Electronically Stored Information and written, recorded, or graphic material of every kind, prepared by any person, that is in the possession, custody, or control of Reckitt Benckiser. The term "document" includes the complete original document (or a copy thereof if the original is not available), all drafts, whether or not they resulted in a final document, and all copies that differ in any respect from the original, including any notation, underlining, marking, or information not on the original. The term "document" also includes metadata and files, information, or data created or stored in software-as-a-service or cloud-computing. Documents covered by this CID include, but are not limited to, the following: letters; memoranda; presentations; reports; contracts and other agreements; studies; plans; entries in notebooks, calendars and diaries; minutes, records, and transcripts of conferences, meetings, telephone calls or other communications; publications and unpublished speeches or articles; typed and handwritten notes; electronic mail; facsimiles (including the header showing the receipt date and time); tabulations; statements, ledgers, and other records of financial matters or commercial transactions; diagrams, graphs, charts, blueprints, and other drawings; technical plans and specifications; advertising, product labels, and packaging materials; photographs, photocopies, slides, microfilm, microfiche, and other copies or reproductions; film, audio, and video tapes; tape, disk, and other electronic recordings; and computer printouts. Where a document is attached to an email, it must be produced along with that email regardless of whether it has been produced independently.

7. The term "Do Not Destroy Letter" refers to the letter sent on November 30, 2012 from Garth Huston to Javier Rodriguez.

8. The terms "each," "any," and "all" mean "each and every." The terms "and" and "or" have both conjunctive and disjunctive meanings as necessary to bring within the scope of this CID anything that might otherwise be outside its scope. The singular form of a noun or pronoun includes its plural form, and vice versa; and the present tense of any word includes the past tense, and vice versa.

9. The term "Electronically Stored Information" refers to any portion of data found on a computer or other device capable of storing electronic data, where such data is capable of

being manipulated as an entry. "Electronically Stored Information" includes, but is not limited to, e-mail, spreadsheets, databases, word processing documents, images, presentations, application files, executable files, log files, and all other files present on any type of device capable of storing electronic data. Devices capable of storing Electronically Stored Information include, but are not limited to: servers, desktop computers, portable computers, handheld computers, flash memory devices, wireless communication devices, pagers, workstations, minicomputers, mainframes, and any other forms of online or offline storage, whether on or off company premises.

10. The term "FDA" refers to the United States Food and Drug Administration.

11. The term "Generic Suboxone" means any ANDA product which references any Suboxone NDA.

12. The term "identify," when used in reference to a natural person, shall mean to state the person's (1) full name; (2) present or last known residence and telephone number and present or last known business address and telephone number; (3) present or last known employer and job title; and (4) the nature (including job title) and dates of any affiliation, by employment or otherwise, with Reckitt Benckiser. For any person identified, if any of the above information was different during the time period relevant to the CID, supply both the current information and such different information as applies to the time period relevant to the CID. Once a natural person has been identified properly, it shall be sufficient thereafter when identifying that same person to state the name only.

The term "identify," when used in reference to a corporation or other non-natural person, shall mean (1) to state that entity's name; (2) to describe its nature (e.g., corporation, partnership, etc.); (3) to state the location of its principal place of business; and (4) to identify the natural person or persons employed by such entity whose actions on behalf of the entity are responsive to the CID. Once such a person has been identified properly, it shall be sufficient thereafter when identifying that same person to state the name only.

The term "identify," when used in reference to facts, acts, events, occurrences, meetings, or communications, shall mean to describe, with particularity, the fact, act, event, occurrence, meeting, or communication in question, including but not limited to (1) identifying the participants and witnesses of the fact, act, event, occurrence, meeting, or communication; (2) stating the date or dates on which the fact, act, event, occurrence, meeting, or communication took place; (3) stating the location or locations at which the fact, act, event, occurrence, meeting, or communication took place; and (4) providing a description of the substance of the fact, act, event, occurrence, meeting, or communication.

13. The term "NDA" refers to New Drug Application, as defined in Title I of the Drug Price Competition and Patent Term Restoration Act of 1984.

14. The term "New Suboxone" means any future versions or strengths of Suboxone or any similar buprenorphine/naloxone drug that have yet to be approved or released.

15. The term "person" includes Reckitt Benckiser and means any natural person, corporate entity, sole proprietorship, partnership, association, governmental entity, or trust.

16. The term "plan" means a proposal, recommendation, or consideration, whether or not precisely formulated, finalized, authorized, or adopted.

17. The term "purchaser" means an entity with whom Reckitt Benckiser has a contract in place that sets the price for Suboxone sales, including but not limited to wholesalers, distributors, pharmacy benefit managers and health plans.

18. The terms "Reckitt Benckiser," "Reckitt," "RBP," "You," "Your," or "the Company" mean Reckitt Benckiser Pharmaceuticals, Inc., together with its successors, predecessors, divisions, wholly or partially owned subsidiaries, domestic or foreign parents, including Reckitt Benckiser Group, plc, affiliates, partnerships, and joint ventures; and all the directors, officers, employees, consultants, agents, and representatives of the foregoing.

19. The terms "relate" and "relating to" mean, in whole or in part, addressing, analyzing, concerning, constituting, containing, commenting on, discussing, describing, identifying, referring to, reflecting, reporting on, stating, or dealing with.

20. The term "REMS" means a risk evaluation and mitigation strategy adopted with respect to the sale of certain pharmaceutical products, as described in the Food and Drug Administration Amendments Act of 2007, 21 U.S.C., Section 355-1 (2007).

21. The term "ROI" means return on investment.

22. The term "SSRS" means single shared REMS system or program.

23. The term "Suboxone" refers to all dosages of Suboxone Tablets, all dosages of Suboxone Film, and any other buprenorphine/naloxone drug produced by Reckitt Benckiser.

24. The term "Suboxone Tablet" means the drug referenced in FDA New Drug Application number 22-733, including any amendments or supplements thereto.

25. The term "Suboxone Film" means the drug referenced in FDA New Drug Application number 22-410, including any amendments or supplements thereto.

26. The term "Suboxone Injectable" refers to the Suboxone injectable product identified in Shaun Thaxter's July 2012 earnings call presentation titled "Building a sustainable growth business."

27. The term "Suboxone Litigations" means:

    a. *Burlington Drug Company, Inc. v. Reckitt Benckiser Group plc, and Reckitt Benckiser Pharmaceuticals, Inc.*, No. 2-12-CV_282 (D. Vt.); *A.F. of L. – A.G.C. Building Trades Welfare Plan v. Reckitt Benckiser, Inc.*, No. 1:13-cv-43 (D. Vt.

Mar. 11, 2013); *Meijer, Inc. v. Reckitt Benckiser, Inc.*, No. 2:13-cv-1122 (E.D. Pa. Mar. 1, 2013); *Rochester Drug Co-Op, Inc. v. Reckitt Benckiser, Inc.*, No. 2:13-cv-1164 (E.D. Pa. Mar. 5, 2013); *United Food and Commercial Workers Health and Welfare Fund of Northeastern Pennsylvania v. Reckitt Benckiser, Inc.*, No. 1:13-cv-589 (M.D. Pa. Feb. 13, 2013) (Mar. 1, 2013); *Painters District Council No. 30 Health and Welfare Fund v. Reckitt Benckiser, Inc.*, No. 2:13-cv-1455 (D.N.J. Mar. 11, 2013); and *Meridian Plan of Michigan, Inc. v. Reckitt Benckiser Group Plc*, No. 2:13-cv-1594 (E.D. Pa. Mar. 26, 2013); *Mich. Reg'l Council of Carpenters Employee Benefits Fund v. Reckitt Benckiser Inc.*, Case No. 2:13-cv-1808 (E.D. Pa. Apr. 5, 2013); and

b. any other litigation relating to Suboxone or Generic Suboxone between Reckitt and any other party.

28. The term "Subutex" refer to the drug reference in FDA New Drug Application number 20-732, including any amendments or supplements thereto.

INSTRUCTIONS

1. Unless otherwise indicated, each specification in this CID covers documents and information dated, generated, received, or in effect from January 1, 2006, to thirty days before the day when Reckitt Benckiser provides the Commission with its final document submission, the executed certification form, and other compliance-related documents described in Instruction 13 ("Request Period"). Reckitt Benckiser shall preserve documents responsive to the CID created or received after the Request Period until a Commission representative notifies Reckitt Benckiser that the investigation has ended.

2. Except for privileged material, Reckitt Benckiser will produce each responsive document in its entirety by including all attachments and all pages, regardless of whether they directly relate to the specified subject matter. Reckitt Benckiser should submit any appendix, table, or other attachment by either attaching it to the responsive document or clearly marking it to indicate the responsive document to which it corresponds. Attachments must be produced along with the document to which they are attached, regardless of whether they have been produced separately. Except for privileged material, Reckitt Benckiser will not redact, mask, cut, expunge, edit, or delete any responsive document or portion thereof in any manner.

3. Compliance with this CID requires a search of all documents in the possession, custody, or control of Reckitt Benckiser including, without limitation, those documents held by any of Reckitt Benckiser's officers, directors, employees, agents, representatives, or legal counsel, whether or not such documents are on the premises of Reckitt Benckiser. If any person is unwilling to have his or her files searched, or is unwilling to produce responsive documents, Reckitt Benckiser must provide the Commission with the following information as to each such person: his or her name, address, telephone number, and relationship to Reckitt Benckiser. In addition to hard copy documents, the search will include all of Reckitt Benckiser's Electronically Stored Information.

4. Form of Production. Reckitt Benckiser shall submit all documents as instructed below absent written consent signed by a Bureau of Competition Assistant Director.

(a) Documents stored in electronic or hard copy formats in the ordinary course of business shall be submitted in the following electronic format provided that such copies are true, correct, and complete copies of the original documents:

(i) Submit Microsoft Excel, Access, and PowerPoint files in native format with extracted text and applicable metadata and information as described in subparts (a)(iii) and (a)(iv).

(ii) Submit emails in image format with extracted text and the following metadata and information:

Metadata/Document Information	Description
Beginning Bates number	The beginning bates number of the document.
Ending Bates number	The last bates number of the document.
Custodian	The name of the original custodian of the file.
To	Recipient(s) of the email.
From	The person who authored the email.
CC	Person(s) copied on the email.
BCC	Person(s) blind copied on the email.
Subject	Subject line of the email.
Date Sent	Date the email was sent.
Time Sent	Time the email was sent.
Date Received	Date the email was received.
Time Received	Time the email was received.
Attachments	The Document ID of attachment(s).
Mail Folder Path	Location of email in personal folders, subfolders, deleted items or sent items.
Message ID	Microsoft Outlook Message ID or similar value in other message systems.

(iii) Submit email attachments in image format, or native format if the file is one of the types identified in subpart (a)(i), with extracted text and the following metadata and information:

Metadata/Document Information	Description
Beginning Bates number	The beginning bates number of the document.
Ending Bates number	The last bates number of the document.
Custodian	The name of the original custodian of the file.
Parent Email	The Document ID of the parent email.
Modified Date	The date the file was last changed and saved.
Modified Time	The time the file was last changed and saved.
Filename with extension	The name of the file including the extension denoting the application in which the file was created.

Production Link	Relative file path to production media of submitted native files. Example: FTC-001\NATIVE\001\FTC-00003090.xls.
Hash	The Secure Hash Algorithm (SHA) value for the original native file.

(iv) Submit all other electronic documents in image format, or native format if the file is one of the types identified in subpart (a)(i), accompanied by extracted text and the following metadata and information:

Metadata/Document Information	Description
Beginning Bates number	The beginning bates number of the document.
Ending Bates number	The last bates number of the document.
Custodian	The name of the original custodian of the file.
Modified Date	The date the file was last changed and saved.
Modified Time	The time the file was last changed and saved.
Filename with extension	The name of the file including the extension denoting the application in which the file was created.
Originating Path	File path of the file as it resided in its original environment.
Production Link	Relative file path to production media of submitted native files. Example: FTC-001\NATIVE\001\FTC-00003090.xls.
Hash	The Secure Hash Algorithm (SHA) value for the original native file.

(v) Submit documents stored in hard copy in image format accompanied by OCR with the following information:

Metadata/Document Information	Description
Beginning Bates number	The beginning bates number of the document.
Ending Bates number	The last bates number of the document.
Custodian	The name of the original custodian of the file.

(vi) Submit redacted documents in PDF format accompanied by OCR with the metadata and information required by relevant document type in subparts (a)(i) through (a)(v) above. For example, if the redacted file was originally an attachment to an email, provide the metadata and information specified in subpart (a)(iii) above. Additionally, please provide a basis for each privilege claim as detailed in Instruction 7.

(b) Submit data compilations in electronic format, specifically Microsoft Excel spreadsheets or delimited text formats, with all underlying data un-redacted and all underlying formulas and algorithms intact.

(c) If Reckitt Benckiser intends to utilize any de-duplication or email threading software or services when collecting or reviewing information that is stored in the

Company's computer systems or electronic storage media, or if the Company's computer systems contain or utilize such software, Reckitt Benckiser must contact the Commission to determine, with the assistance of the appropriate Commission representative, whether and in what manner Reckitt Benckiser may use such software or services when producing materials in response to this CID.

(d) Produce electronic file and image submissions as follows:

(i) For productions over 10 gigabytes, use IDE, EIDE, and SATA hard disk drives, formatted in Microsoft Windows-compatible, uncompressed data in a USB 2.0 external enclosure;

(ii) For productions under 10 gigabytes, CD-R CD-ROM optical disks formatted to ISO 9660 specifications, DVD-ROM optical disks for Windows-compatible personal computers, and USB 2.0 Flash Drives are acceptable storage formats;

(iii) All documents produced in electronic format shall be scanned for and free of viruses prior to submission. The Commission will return any infected media for replacement, which may affect the timing of Reckitt Benckiser's compliance with this CID; and,

(iv) Encryption of productions using NIST FIPS-compliant cryptographic hardware or software modules, with passwords sent under separate cover, is strongly encouraged.

(e) Each production shall be submitted with a transmittal letter that includes the FTC matter number; production volume name; encryption method/software used; passwords for any password protected files; list of custodians and document identification number range for each; total number of documents; and a list of load file fields in the order in which they are organized in the load file.

5. All documents responsive to this CID:

(a) Shall be produced in complete form, unredacted unless privileged, and in the order in which they appear in the Company's files;

(b) Shall be marked on each page with corporate identification and consecutive document control numbers when produced in image format;

(c) Shall be produced in color where necessary to interpret the document (if the coloring of any document communicates any substantive information, or if black and white photocopying or conversion to TIFF format of any document (e.g., a chart or graph) makes any substantive information contained in the document unintelligible, Reckitt Benckiser must submit the original document, a like-color photocopy, or a JPEG format image);

(d) Shall be accompanied by an affidavit of an officer of Reckitt Benckiser stating that the copies are true, correct, and complete copies of the original documents; and,

(e) Shall be accompanied by an index that identifies (i) the name of each person from whom responsive documents are submitted; and (ii) the corresponding consecutive document control number(s) used to identify that person's documents. The Commission representative will provide a sample index upon request.

6. To the extent that Reckitt Benckiser relies on specific documents in any narrative response to this CID, the Company shall identify each such document by its document control number as part of such narrative response.

7. If Reckitt Benckiser withholds any responsive document or masks or redacts any portion of any responsive document based on a claim of privilege or work-product immunity, the Company must provide the Commission with a log describing the privilege claim and all facts supporting the claim sufficient to comply with Federal Trade Commission Rule of Practice § 2.8A. 16 C.F.R. § 2.8A. For each document withheld, masked, or redacted, the log shall list the following: (a) specific grounds for claim of privilege or immunity, (b) type of document, (c) title, (d) author(s), (e) date, (f) addressees and recipients of the original document or any copy thereof (including persons "cc'd" or "blind cc'd"), (g) a description of the subject matter, with sufficient detail to assess the claim of privilege, (h) a description identifying each attachment to the document, (i) the page length of the document, (j) the relevant specification(s), and (k) for redacted documents, the document control number (as described in Instruction 5). Additionally, for each document withheld under a claim of attorney work-product immunity, the log will list: (l) whether the document was prepared in anticipation of litigation or for trial, (m) the other parties or expected other parties to the litigation and whether that party is adverse, (n) case number, (o) complaint filing date, and (p) court name. For each person listed, the log will include the person's full name, address, job title, and employer or firm; for each non-Company recipient, include such additional description sufficient to show that individual's need to know the information contained in the document. Please denote all attorneys with an asterisk ("*").

The privilege log shall be submitted as a Microsoft Excel or other native file.

An attachment to a document must be entitled to privilege in its own right. If an attachment is responsive and not entitled to privilege in its own right, it must be provided. Reckitt Benckiser must provide all non-privileged portions of any responsive document for which a claim of privilege is asserted, noting where redactions in the document have been made. With respect to documents withheld on grounds of privilege that discuss or describe any U.S. or foreign patent, each individual patent identified in the withheld document must be specified by its patent number.

8. Documents written in a language other than English shall be translated into English, with the English translation attached to the foreign language document.

9. Do not destroy or dispose of documents responsive to this CID, or any other documents relating to the subject matter of this CID. The destruction or disposal of such documents during the pendency of this investigation might constitute a felony in violation of 18 U.S.C. § 1505 and 18 U.S.C. § 1512.

10. Do not produce any Sensitive Personally Identifiable Information ("Sensitive PII") or Sensitive Health Information ("SHI") prior to discussing the information with a Commission representative. If any document responsive to a particular specification contains unresponsive Sensitive PII or SHI, redact the unresponsive Sensitive PII or SHI prior to producing the document. The term "Sensitive PII" means an individual's Social Security Number alone or an individual's name, address or phone number in combination with one or more of the following: date of birth; driver's license number or other state identification number, or a foreign country equivalent; passport number; financial account number; or credit or debit card number. The term "SHI" includes medical records and other individually identifiable health information, whether on paper, in electronic form, or communicated orally. SHI relates to the past, present, or future physical or mental health or condition of an individual, the provision of health care to an individual, or the past, present, or future payment for the provision of health care to an individual.

11. Reckitt Benckiser will provide the Commission with the following: (a) a statement identifying the procedures used to search for electronically stored documents; and (b) a statement identifying the procedures used to search for documents stored in paper format, including for each document custodian, identification of individuals who provided information on the location of responsive documents.

12. Reckitt Benckiser must comply with this CID by submitting all documents and information responsive to it on or before 31 days from the date on which this CID is signed. In addition, when it has completed production, Reckitt Benckiser should also submit the executed and notarized certification form (attached). In order for the Company's response to this CID to be complete, the attached certification form must be executed by the official supervising compliance with this CID, notarized, and submitted along with the responsive materials. Reckitt Benckiser should submit responsive documents to Garth Huston, Federal Trade Commission, Room NJ-7205, 601 New Jersey Ave., NW, Washington, DC 20001.

13. Compliance with this CID requires Reckitt Benckiser to submit to the Commission, on or before 31 days from the date on which this CID is signed, all responsive documents, data, information and the following:

    (a) Executed and notarized certification form, which is included herewith;

(b) Privilege Log according to Instruction 7, if any responsive documents are withheld or redacted;

(c) List of any persons (by name, address, telephone number, and relationship to Reckitt Benckiser) whose files have not been searched according to Instruction 3;

(d) For each document submitted, information sufficient to identify the name of the person from whose files the document was obtained (document custodian), according to Instruction 5; and,

(e) Reckitt Benckiser's Statement of the procedures used by the Company to comply with this CID, according to Instruction 11.

14. If Reckitt Benckiser believes that this CID's specifications can be narrowed consistent with the Commission's need for information, we encourage it to discuss possible modifications with a Commission representative at the earliest possible date. Note that an authorized Commission representative, generally the Bureau of Competition's Assistant Directors, must agree in writing to any modifications to this CID. All inquiries about this CID and modification requests should be directed to Garth Huston at (202) 326-2658.

UNITED STATES OF AMERICA
BEFORE THE FEDERAL TRADE COMMISSION

COMMISSIONERS: **Edith Ramirez, Chairwoman**
Julie Brill
Maureen K. Ohlhausen
Joshua D. Wright

RESOLUTION AUTHORIZING USE OF COMPULSORY PROCESS IN NONPUBLIC INVESTIGATION

File No. 131 0036

Nature and Scope of Investigation:

To determine whether Reckitt Benckiser Pharmaceuticals, Inc., or its affiliates, including but not limited to Reckitt Benckiser Group plc, or any other person, has engaged or is engaging in unfair methods of competition in or affecting commerce, in violation of Section 5 of the Federal Trade Commission Act, 15 U.S.C. § 45, as amended, with regard to the pharmaceutical products Suboxone and Subutex, including by using its monopoly position to switch the Suboxone market to a new, non-substitutable form of Suboxone, abusing FDA-mandated negotiations for a single shared REMS system, filing a meritless or sham citizen petition with FDA, or any related conduct regarding these or other pharmaceutical products.

The Federal Trade Commission hereby resolves and directs that any and all compulsory processes available to it be used in connection with this investigation.

Authority to Conduct Investigation:

Sections 6, 9, 10, and 20 of the Federal Trade Commission Act, 15 U.S.C. §§ 46, 49, 50, and 57b-1, as amended; FTC Procedures and Rules of Practice, 16 C.F.R. § 1.1 *et seq.*, and supplements thereto.

By direction of the Commission.

Donald S. Clark
Secretary

Issued: May 2, 2013

PETITION EXHIBIT 7

Reckitt Benckiser Pharmaceuticals, Inc.,
Citizen Petition re Safety Concerns
Regarding Buprenorphine for Opioid
Dependence,
Docket No. FDA-2012-P-1028,
Sept. 25, 2012

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 HCl) and Suboxone® (buprenorphine HCl-naloxone HCl) 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.

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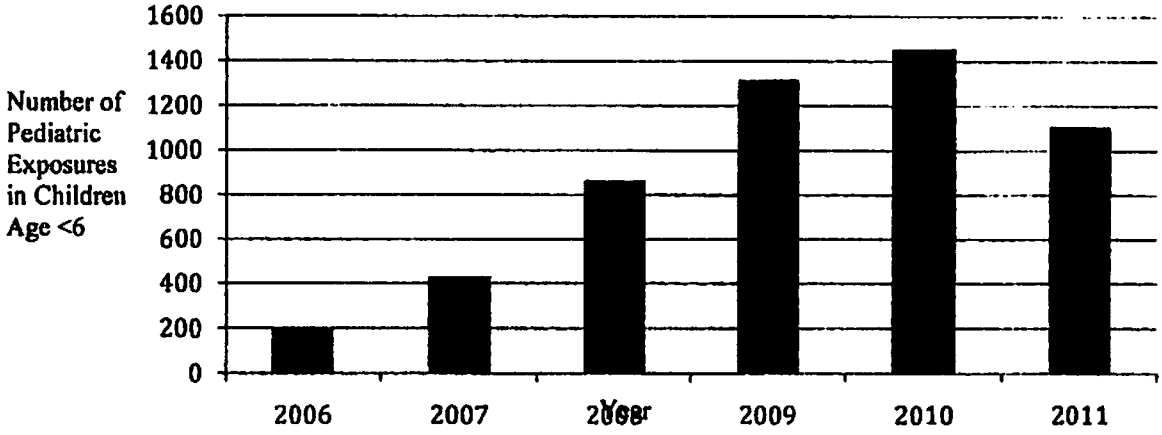
[54] *See* FDA, Drugs@FDA, Suboxone Labeling (2008), *available at* http://www.accessdata.fda.gov/scripts/cder/drugsatfda.

[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



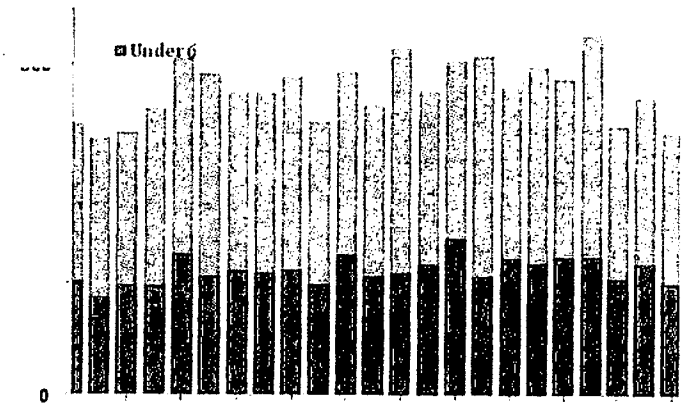
Source: Data from AAPCC, submitted to NDA 20-732, NDA 20-733, and NDA 22-410)

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)

monthly basis to more closely track pediatric exposure rates. This more granular



3. RBP Develops Buprenorphine Film

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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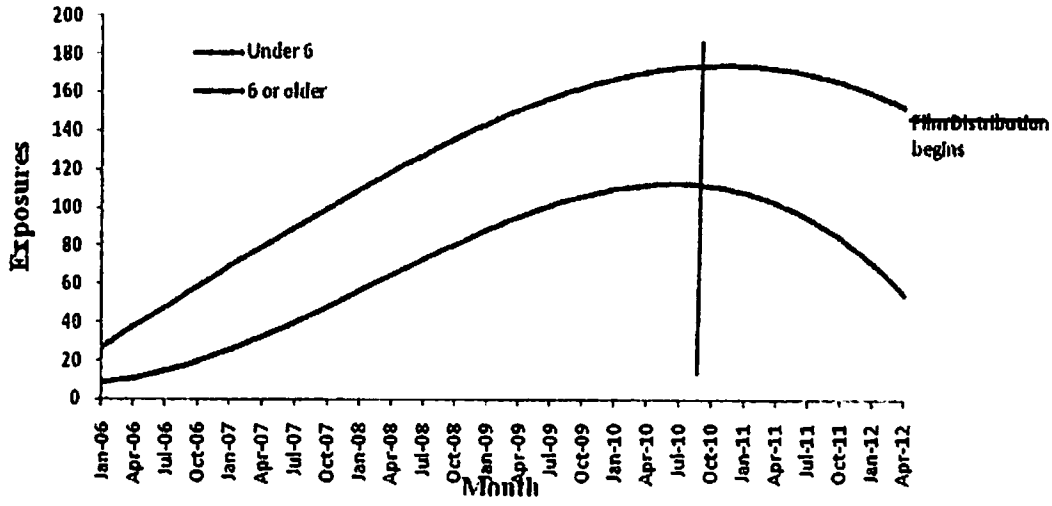
[56] Another way that Suboxone Film contributes to mitigating risk is that as a film dosage form, it can not be crushed and injected, thus reducing the risk of abuse and diversion. In addition, in August 2012, FDA approved two additional strengths of the film product 12mg and 4mg). See FDA, Drugs@FDA, 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

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 HCl 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.

PETITION EXHIBIT 8

Letter regarding Docket No. FDA-2012-P-1028 from Janet Woodcock, MD, Director, Center for Drug Evaluation and Research, FDA, to Tim Baxter, Global Medical Director, Reckitt, Feb. 22, 2013

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
10903 New Hampshire Avenue
Building #51
Silver Spring, MD 20993

FEB 22 2013

Tim Baxter
Global Medical Director
Reckitt Benckiser Pharmaceuticals, Inc.
10710 Midlothian Turnpike, Suite 430
Richmond, VA 23235

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

Dear Mr. Baxter:

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

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

I. BACKGROUND

A. Buprenorphine for Opioid Dependence Treatment

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

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

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

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

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

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

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

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

[4] NDA 20-732.

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

[6] NDA 20-733.

[7] NDA 22-410.

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

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

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

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

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

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

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

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

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

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

[15] McCormick Letter at 4-5.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

B. Legal and Regulatory Framework

1. New Drug Applications

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

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

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

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

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

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

2. Abbreviated New Drug Applications

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

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

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

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

3. Approval of Drug Products with REMS

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

II. DISCUSSION

A. Reckitt Benckiser Petition

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

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

[37] Id.

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

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

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

B. Educational Initiatives and Unit-Dose Packaging

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

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

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

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

1. Educational Measures

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

2. Unit-Dose Packaging

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

C. Discontinuation of SUBOXONE Tablet Product

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

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

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

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

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

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

D. Comments Regarding Anticompetitive Conduct

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

[52] Petition at 23, 11.

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

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

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

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

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

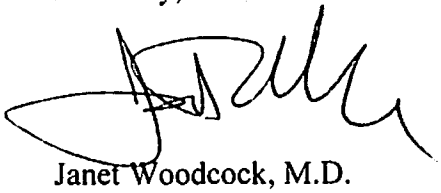
[56] See Actavis Comment at 2; see also generally Amneal Comment at 8; BPMG Comment at 5, 12-13.

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

III. CONCLUSION

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

Sincerely,



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Director
Center for Drug Evaluation and Research