ERRATUM #1

To FDA Briefing Document Joint Meeting of Psychopharmacologic Drugs Advisory Committee and Drug Safety and Risk Management Advisory Committee

October 31, 2017

ERRATA to FDA Briefing Document
Joint Meeting of Psychopharmacologic Drugs Advisory Committee
and Drug Safety and Risk Management Advisory Committee
October 31, 2017

1. The following tables replace the corresponding tables on Page 56 in the background document:

Table 21: Baseline medical history distribution in Phase 3 studies

	Phase 3 DB (13-0001)						Phase 3 Open-label (13-0003)							
	PBO		RBP300/100 mg		RBP 300/300		De novo 300/Flex		PBO Roll-over 300/Flex		RBP 100 Roll-over 300/Flex		RBP 300 Roll over 300/Flex	
	N=100		N=203		N=201		N=412		N=32		N=112		N=113	
Preferred term	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Drug abuse	88	88%	169	83%	162	81%	363	88%	29	91%	90	80%	92	81%
Hypertension	12	12%	32	16%	31	15%	49	12%	8	25%	20	18%	17	15%
Hepatitis C	10	10%	32	16%	24	12%	60	15%	4	13%	20	18%	18	16%
Depression	14	14%	28	14%	23	11%	60	15%	7	22%	14	13%	12	11%
Drug dependence	11	11%	25	12%	31	15%	46	11%	3	9%	17	15%	16	14%
Back pain	13	13%	31	15%	32	16%	40	10%	5	16%	14	13%	13	12%
Anxiety	10	10%	23	11%	22	11%	44	11%	4	13%	7	6%	9	8%
Insomnia	6	6%	23	11%	27	13%	40	10%	2	6%	8	7%	11	10%
Asthma	6	6%	12	6%	16	8%	35	8%	1	3%	3	3%	10	9%
Seasonal allergy	10	10%	11	5%	17	8%	16	4%	3	9%	7	6%	10	9%

Table 22: Baseline BMI group distribution in Phase 3 studies

	Phase 3 DB (13-0001)						Phase 3 Open-label (13-0003)							
	PBO		RBP300/100 mg		RBP 300/300		De novo 300/Flex		PBO Roll-over 300/Flex		RBP 100 Roll-over 300/Flex		RBP 300 Roll over 300/Flex	
	N=100		N=203		N=201		N=412		N=32		N=112		N=113	
BMI group	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
> 0 to < 18.5	3	3%	6	3%	2	1%	9	2%	0	0%	4	4%	4	4%
>= 18.5 to < 25	46	46%	99	49%	88	44%	206	50%	14	44%	50	45%	46	41%
>= 25 to < 30	32	32%	66	33%	55	27%	122	30%	10	31%	38	34%	29	26%
>= 30	19	19%	32	16%	56	28%	75	18%	8	25%	20	18%	34	30%

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2. The following table replace the corresponding table on Page 64 in the background document:

Table 26: TEAEs leading to drug discontinuation in Phase 3 studies

Table 6.9: TEAEs leading to drug discontinuations In Phase III studies																
	Phase III DB (13-0001)						Phase III Open label (13-0003)									
	PBO		RBP300/100		RBP 300/300		De novo 300/Flex		PBO Roll-over		RBP 100 Roll-over		RBP 300 Roll over		Total	
Preferred term	N=100		N=203		N=201		N=412		N=32		N=112		N=113		N=916	
Any TEAEs	**2**	**2%**	**7**	**3%**	**10**	**5%**	**12**	**3%**	**1**	**3%**	**0**	**0%**	**3**	**3%**	**35**	**3.82%**
Drug withdrawal syndrome	1	1%	2	1%	0	0%	3	1%	0	0%	0	0%	0	0%	6	1%
Aspartate aminotransferase increased	0	0%	0	0%	2	1%	1	<1%	0	0%	0	0%	0	0%	3	<1%
Sedation	0	0%	1	<1%	1	0%	0	0%	0	0%	0	0%	1	1%	3	<1%
Constipation	0	0%	1	<1%	0	0%	1	<1%	0	0%	0	0%	0	0%	2	<1%
Liver function test increased	0	0%	0	0%	1	<1%	1	<1%	0	0%	0	0%	0	0%	2	<1%
Nausea	0	0%	0	0%	1	<1%	1	<1%	0	0%	0	0%	0	0%	2	<1%
Somnolence	0	0%	0	0%	1	<1%	1	<1%	0	0%	0	0%	0	0%	2	<1%
Accidental overdose	0	0%	0	0%	0	0%	1	<1%	0	0%	0	0%	0	0%	1	<1%
Alanine aminotransferase increased	0	0%	0	0%	1	<1%	0	0%	0	0%	0	0%	0	0%	1	<1%
Diabetes mellitus	0	0%	0	0%	0	0%	1	<1%	0	0%	0	0%	0	0%	1	<1%
Extradural abscess	1	1%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	1	<1%
Formication	0	0%	0	0%	1	<1%	0	0%	0	0%	0	0%	0	0%	1	<1%
Gallbladder perforation	0	0%	0	0%	0	0%	1	<1%	0	0%	0	0%	0	0%	1	<1%
Gamma-glutamyltransferase increased	0	0%	0	0%	1	<1%	0	0%	0	0%	0	0%	0	0%	1	<1%
Gun shot wound	0	0%	0	0%	1	<1%	0	0%	0	0%	0	0%	0	0%	1	<1%
Hepatitis C	0	0%	0	0%	1	<1%	0	0%	0	0%	0	0%	0	0%	1	<1%
Injection site pain	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	1	1%	1	<1%
Injection site reaction	0	0%	0	0%	0	0%	1	<1%	0	0%	0	0%	0	0%	1	<1%
Injection site swelling	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	1	1%	1	<1%
Injection site ulcer	0	0%	0	0%	1	<1%	0	0%	0	0%	0	0%	0	0%	1	<1%
Lymphadenitis	0	0%	1	<1%	0	0%	0	0%	0	0%	0	0%	0	0%	1	<1%
Migraine	0	0%	0	0%	0	0%	0	0%	1	3%	0	0%	0	0%	1	<1%
Neutrophil count decreased	0	0%	0	0%	1	<1%	0	0%	0	0%	0	0%	0	0%	1	<1%
Pulmonary embolism	0	0%	1	<1%	0	0%	0	0%	0	0%	0	0%	0	0%	1	<1%

Rash	0	0%	1	<1%	0	0%	0	0%	0	0%	0	0%	0	0%	1	<1%
Vomiting	0	0%	0	0%	1	<1%	0	0%	0	0%	0	0%	0	0%	1	<1%
Weight decreased	**0**	**0%**	**0**	**0%**	**0**	**0%**	**0**	**0%**	**0**	**0%**	**0**	**0%**	**1**	**1%**	**1**	**<1%**

3. The following table replace the corresponding tables on Page 65 in the background document:

Table 27: TEAEs leading to drug dose reduction in Phase 3 open-label study (13-0003)

Table 6.10: TEAEs leading to drug dose reduction in Phase III Open label study (13-0003)										
	De novo 300/Flex		**PBO Roll-over**		**RBP 100 Roll-over**		**RBP 300 Roll over**		**Total**	
	N=412		**N=32**		**N=112**		**N=113**		**N=669**	
Preferred term	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Any TEAEs	**29**	**7%**	**4**	**13%**	**5**	**4%**	**8**	**7%**	**46**	**7%**
Alanine aminotransferase increased	5	1%	0	0%	0	0%	1	1%	6	1%
Sedation	2	0%	0	0%	2	2%	3	3%	7	1%
Constipation	4	1%	0	0%	0	0%	1	1%	5	1%
Fatigue	2	0%	1	3%	1	1%	0	0%	4	1%
Aspartate aminotransferase increased	3	1%	0	0%	0	0%	1	1%	4	1%
Nausea	3	1%	0	0%	0	0%	1	1%	4	1%
Gamma-glutamyl transferase increased	1	0%	0	0%	1	1%	0	0%	2	<1%
Headache	3	1%	0	0%	0	0%	0	0%	3	0%
Lethargy	2	0%	0	0%	0	0%	1	1%	3	0%
Somnolence	3	1%	0	0%	0	0%	0	0%	3	0%
Hepatic enzyme increased	1	0%	1	3%	0	0%	0	0%	2	0%
Hepatic function abnormal	2	0%	0	0%	0	0%	0	0%	2	0%
Injection site pain	1	0%	1	3%	0	0%	0	0%	2	0%
Insomnia	2	0%	0	0%	0	0%	0	0%	2	0%
Decreased appetite	0	0%	0	0%	1	1%	0	0%	1	0%
Dizziness	0	0%	0	0%	0	0%	1	1%	1	0%

Erectile dysfunction	0	0%	1	3%	0	0%	0	0%	1	0%
Euphoric mood	1	0%	0	0%	0	0%	0	0%	1	0%
Flushing	0	0%	0	0%	0	0%	1	1%	1	0%
Hypersomnia	1	0%	0	0%	0	0%	0	0%	1	0%
Migraine	1	0%	0	0%	0	0%	0	0%	1	0%
Muscle twitching	0	0%	1	3%	0	0%	0	0%	1	0%
Vomiting	1	0%	0	0%	0	0%	0	0%	1	0%

4. The following table replaces the corresponding table on Page 67 in the background document:

Table 29: Common TEAEs more than 2% occurrence in RBP-6000 treatment group in Phase 3 studies

Table 6.12: Common TEAEs more than 2% occurrence in RBP-6000 group in pooled Phase III studies								
	Phase III DB study (13-0001)						**Phase III OL study (13-0003)**	
	PBO		**RBP 300/100 mg**		**RBP 300/300 mg**		**RBP 300/Flex**	
	N=100		**N=203**		**N=201**		**N=444**	
Preferred term	**N**	%	N	%	N	%	N	%
Constipation	0	0%	19	9%	16	8%	50	11%
Insomnia	11	11%	13	6%	17	9%	27	6%
Headache	6	6%	19	9%	17	9%	35	8%
Nausea	5	5%	18	9%	16	8%	38	9%
Vomiting	4	4%	19	9%	11	6%	19	4%
Injection site pain	3	3%	10	5%	12	6%	35	5%
Injection site pruritus	4	4%	13	6%	19	9%	18	3%
Fatigue	3	3%	8	4%	12	6%	20	5%
Nasopharyngitis	1	1%	11	5%	10	5%	24	5%
Upper respiratory tract infection	1	1%	15	7%	12	6%	19	4%
Anxiety	5	5%	10	5%	8	4%	14	3%
Drug withdrawal syndrome	6	6%	90	4%	7	0%	10	2%
Injection site erythema	0	0%	9	4%	6	3%	21	3%
Back pain	3	3%	8	4%	6	3%	16	4%
Toothache	1	1%	8	4%	5	2%	16	4%

Somnolence	0	0%	10	5%	4	2%	13	3%
Diarrhoea	5	5%	5	2.5%	5	3%	7	2%
Aspartate aminotransferase increased	0	0%	7	3%	9	4%	10	1%
Gamma-glutamyltransferase increased	1	1%	6	3%	8	4%	11	2%
Pain	4	4%	3	2%	5	2%	9	2%
Arthralgia	3	3%	4	2%	3	2%	12	3%
Urinary tract infection	0	0%	4	2%	5	3%	12	3%
Blood creatine phosphokinase increased	1	1%	11	5%	5	2%	8	1%
Alanine aminotransferase increased	0	0%	2	1%	10	5%	10	1%
Pain in extremity	0	0%	1	0%	4	2%	12	3%
Hyperhidrosis	0	0%	4	2%	4	3%	7	2%
Weight increased	0	0%	2	1%	7	3%	8	2%
Decreased appetite	3	3%	1	0%	3	2%	8	2%
Tooth abscess	0	0%	8	4%	5	3%	1	0%
Gastroenteritis viral	0	0%	3	1%	5	2%	5	1%

5. The following table replaces the corresponding table on Page 70 in the background document:

Table 30: TEAEs related to injection site injuries in Phase 3 studies

Table 6.13: TEAEs related to injection site injuries

		Phase III DB (13-0001)						Phase III Open label (13-0003)							
		PBO		RBP300/100		RBP 300/300		e novo 300/Fle		PBO Roll-over		0 Roll-over 30		300 Roll over 300/	
		N=100		N=203		N=201		N=412		N=32		N=112		N=113	
AE Severity	*Preferred term*	N	%	N	%	N	%	N	%	N	%	N	%	N	%
	Any TEAEs	**9**	**9%**	**24**	**11.8%**	**37**	**18.4%**	**58**	**14.0%**	**2**	**6.25%**	**13**	**11.6%**	**6**	**5.30%**
MILD	Injection site bruising	0	0%	1	0.9%	2	1%	1	0%	0	0%	0	0%	0	0%
MILD	Injection site discomfort	0	0%	1	0%	0	0%	2	.4%	0	0%	0	0%	0	0%
MILD	Injection site erythema	0	0%	7	3.4%	3	1.4%	16	3.8%	0	0%	4	3.5%	1	.8%
MILD	Injection site haematoma	0	0%	0	0%	0	0%	1	0%	0	0%	0	0%	0	0%
MILD	Injection site infection	0	0%	0	0%	0	0%	1	0.2%	0	0%	0	0%	0	0%
MILD	Injection site inflammation	1	1%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
MILD	Injection site mass	0	0%	0	0%	1	0%	0	0%	0	0%	0	0%	0	0%
MILD	Injection site nodule	0	0%	0	0%	1	0%	0	0%	0	0%	0	0%	0	0%
MILD	Injection site pain	1	1%	7	3%	10	4.9%	20	4.8%	1	3%	2	1.7%	2	1.7%
MILD	Injection site pruritus	3	3%	7	3.4%	11	5%	14	3%	1	3%	6	5%	2	1.7%
MILD	Injection site swelling	0	0%	1	0%	1	0%	1	0%	0	0%	1	0.8%	1	.8%
MILD	Injection site warmth	0	0%	1	0%	0	0%	0	0%	0	0%	0	0%	0	0%
MODERATE	Injection site cellulitis	0	0%	0	0%	0	0%	1	0.2%	0	0%	0	0%	0	0%
MODERATE	Injection site dermatitis	0	0%	0	0%	0	0%	0	0%	0	0%	1	.8%	0	0%
MODERATE	Injection site discomfort	0	0%	0	0%	1	0%	1	0%	0	0%	0	0%	0	0%
MODERATE	Injection site erythema	0	0%	2	0.9%	3	1%	4	0.9%	0	0%	0	0%	0	0%
MODERATE	Injection site induration	0	0%	1	0%	1	0%	1	0%	0	0%	0	0%	0	0%
MODERATE	Injection site oedema	0	0%	0	0%	1	0%	0	0%	0	0%	0	0%	0	0%
MODERATE	Injection site infection	1	1%	0	0%	1	.4%	1	0.2%	0	0%	0	0%	0	0%
MODERATE	Injection site pain	2	2%	3	1%	2	0.9%	9	2.1%	1	3%	0	0%	2	1.7%
MODERATE	Injection site pruritus	1	1%	4	1.9%	7	3%	3	.7%	0	0%	0	0%	0	0%
MODERATE	Injection site rash	0	0%	0	0%	1	0%	0	0%	0	0%	0	0%	0	0%
MODERATE	Injection site reaction	0	0%	0	0%	0	0%	1	0%	0	0%	3	2.6%	0	0%
MODERATE	Injection site swelling	0	0%	1	0%	0	0%	0	0%	0	0%	0	0%	0	0%

MODERATE	Injection site ulcer	0	0%	0	0%	1	0%	0	0%	0	0%	0	0%	0	0%
SEVERE	Injection site pruritus	0	0%	0	0%	1	0%	0	0%	0	0%	0	0%	0	0%
SEVERE	Injection site cellulitis	0	0%	0	0%	0	0%	1	0.2%	0	0%	0	0%	0	0%

6. The following table replaces the corresponding table on Page 71 in the background document:

Table 31: TEAEs related to injection site injuries by action on study treatment in Phase 3 studies

Table 6.14: TEAEs with injection site injuries by action on study treatment in pooled phase III study

		Phase III DB study (13-0001)						Phase III OL study (13-0003)	
		PBO		RBP-6000 300/100 mg		RBP-6000 300/300 mg		RBP-6000 300/Flex	
		N=100		N=203		N=201		N=444	
Actions on study treatment	***Preferred term***	**N**	%	N	%	N	%	N	%
DOSE REDUCED	**Injection site pain**	**0**	**0%**	**0**	**0%**	**0**	**0%**	**1**	**0%**
DRUG WITHDRAWN	**Injection site reaction**	**0**	**0%**	**0**	**0%**	**0**	**0%**	**1**	**0%**
DRUG WITHDRAWN	**Injection site pain**	**0**	**0%**	**0**	**0%**	**1**	**0%**	**0**	**0%**
DRUG WITHDRAWN	**Injection site swelling**	**0**	**0%**	**0**	**0%**	**1**	**0%**	**0**	**0%**
DRUG WITHDRAWN	**Injection site ulcer**	**0**	**0%**	**0**	**0%**	**1**	**0%**	**0**	**0%**

ERRATUM #2

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1. Page 98: The count of deaths involving buprenorphine in the Summary table should be changed from 3 deaths in 2012 to 5 deaths, and from 14 total deaths in 2010-2015 to 16 total deaths. The Summary table should have a footnote indicating that all deaths were for children <6 years old. The corrected table is as follows:

Summary table: Total exposure calls to poison control centers, emergency department visits, and deaths involving buprenorphine or buprenorphine-naloxone, children ≤10 years of age, 2010-2015

Measure	2010	2011	2012	2013	2014	2015	Total
Calls for unintentional general exposure to buprenorphine (AAPCC-NPDS)							
Count	1,540	1,177	1,094	891	985	1,040	6,727
Age-specific call rate per 1 million census population	34.45	26.39	24.59	20.02	22.13	23.36	25.16
ED visits for unsupervised buprenorphine ingestions (NEISS-CADES)							
Projected estimate [95% CI]	3,095 [1,887-4,304]		2,142 [1,115-3,170]		2,136 [958-3,314]		7,374 [4,492-10,256]
Age-specific ED visit rate per 1 million census population	34.7 [21.1-48.2]		24.1 [12.5-35.6]		24.0 [10.8-37.2]		27.6 [16.8-38.4]
Deaths involving buprenorphine (NVSS-M linked with death certificate literal text)*							
Count	3	4	5	2	2	Not assessed	16

Age specific rates: 0-10 year olds from US 2010 Census population

* All deaths were of children <6 years old.

2. Page 106: The first paragraph should be changed from:

"**Table 4** summarizes the number of deaths involving buprenorphine among children ≤10 years old from 2010 through 2014. There were 14 deaths identified, of which 13 (92.9%) were among children <6 years old. Eleven (78.6%) deaths only involved buprenorphine or buprenorphine/naloxone. Only three (21.4%) of the 14 deaths were not due to pediatric accidental exposures to buprenorphine because they were homicides; no suicides involving buprenorphine were identified. The annual number of deaths did not vary much during the study period, despite improvements in the reporting of specific drugs on death certificates[12] and an overarching increase in total deaths[13] during the study period."

to: "From 2010 through 2014, all 16 deaths involving buprenorphine were among children < 6 years old (**Table 4**); no deaths involving buprenorphine were identified for children 6 to 10 years old. Eleven (68.8%) deaths only involved buprenorphine or buprenorphine/naloxone. Only three (18.8%) of the 16 deaths were not due to pediatric accidental exposures to buprenorphine because they were

homicides; no suicides involving buprenorphine were identified. The annual number of deaths did not vary much during the study period, despite improvements in the reporting of specific drugs on death certificates[12] and an overarching increase in total deaths[13] during the study period."

3. Page 106: Table 4 should be changed from:

Table 4: Deaths involving buprenorphine among children ≤10, NVSS-M linked with death certificate literal text, 2010-2014

	2010	2011	2012	2013	2014	Total
Total deaths	3	4	3	2	2	14
Children <6 years old	3	4	2	2	2	13
Children 6-10 years old	0	0	1	0	0	1
Involvement of other drug(s)	1	0	1	1	0	3
Children < 6 years old	1	0	0	1	0	2
Children 6-10 years old	0	0	1	0	0	1

to:

Table 4: Deaths involving buprenorphine among children <6, NVSS-M linked with death certificate literal text, 2010-2014

	2010	2011	2012	2013	2014	Total
Total deaths	3	4	5	2	2	16
Involvement of other drug(s)	1	0	3	1	0	5

4. Page 106: The first sentence in the second to last paragraph should be changed from: "…and deaths from NVSS-M with buprenorphine involvement (92.9%) involved children <6 years of age" to "…and deaths from NVSS-M with buprenorphine involvement (100%) involved children <6 years of age."

5. Page 107. The first sentence of the third paragraph should be changed from "The number of deaths involving buprenorphine among children ≤10 years of age was steady…" to "The number of deaths involving buprenorphine among children <6 years of age was steady…"