

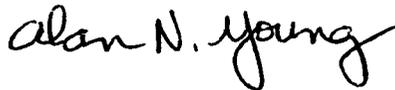
Responses to all items are provided here. Under separate cover we will be sending a test data set of the Case Report Tabulations to assure that you are able to read the data in that format.

The agency alerted Reckitt & Colman to the likelihood that the Biopharmaceutics reviewer would have additional questions in the next week. The agency requested, and Reckitt & Colman agreed to submit, 1 desk copy of NDA 20-733, Volumes 1.4, 1.5 and 1.168.

The requested desk copies of NDA 20-733, Volumes 1.4, 1.5 and 1.168 are enclosed.

Please do not hesitate to call if you have any questions.

Sincerely,

A handwritten signature in black ink that reads "Alan N. Young". The signature is written in a cursive style with a large, stylized "Y" and "N".

Alan Young
Director, Regulatory Affairs

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**ATTACHMENT 1:
Ownership of Data**

CMC	
Buprenorphine HCl	R&C own the data
Naloxone HCl	Right of reference to DMF DMF
Suboxone tablets	R&C own the data
Subutex tablets	R&C own the data
Buprenorphine Solutions	Right resulting from NIH CRADA
Non-clinical Pharmacology and Toxicology	
Buprenorphine study report data	R&C own the data
Buprenorphine + naloxone study report data	R&C own the data
Publications	In Public Domain
Human Pharmacokinetics and Bioavailability	
CR95/001	Right resulting from NIH CRADA
CR97/007	Right resulting from NIH CRADA
CR96/009	Right resulting from NIH CRADA
CR96/012	Right resulting from NIH CRADA
CR94/001	Right resulting from NIH CRADA
CR87/027	R&C own the data
CR92/111	Right resulting from NIH CRADA
CR96/016	Right resulting from NIH CRADA
CR92/108	Right resulting from NIH CRADA
CR91/080	Right resulting from NIH CRADA
NONMEM#1	Right resulting from NIH CRADA
NONMEM#2	Right resulting from NIH CRADA
NONMEM#3	Right resulting from NIH CRADA
CR94/006	Right resulting from NIH CRADA
Publications	In Public Domain
Dissolution studies	R&C own the data
<u>CYP 450 studies</u>	
Publications	In Public Domain
Study by Sellers (6.F.3.6.8)	R&C own the data
Clinical Pharmacology	
Pharmacokinetic studies	As above
CR93/005	Right resulting from NIH CRADA
CR93/004	Right resulting from NIH CRADA
CR94/003	Right resulting from NIH CRADA
CR92/110	Right resulting from NIH CRADA
Publications	In Public Domain
Controlled Clinical Trials	
CR96/013 + CR96/014 (#1008)	Right resulting from NIH CRADA
CR92/102	Right resulting from NIH CRADA
CR96/004 (Italy)	Right of use with permission of investigators
CR96/003 (Switzerland)	Right of use with permission of investigators

CR96/001 (Austria)	In Public Domain
CR97/008	Right resulting from NIH CRADA
CR96/005 (Australia)	Joint ownership of R&C, _____ and Investigators
CR96/015 (UK)	R&C own the data
CR88/130	Right resulting from NIH CRADA
CR97/004	Right resulting from NIH CRADA
CR96/002 (Spain)	Right of use with permission of investigators
CR92/099	Right resulting from NIH CRADA
CR92/100	Right resulting from NIH CRADA
Publications	In Public Domain
Uncontrolled Clinical Trials	
CR94/005	Right of use with permission of investigators
CR90/001	Right of reference under R&C and Schering-Plough agreement
CR98/001 (Australia)	Right of use with permission of investigators
Publications	In Public Domain
Other Studies and Information	
RC980118 (Neonatal withdrawal)	Right of reference under R&C and Schering-Plough agreement
CR96/006 (SPESUB, France)	Right of reference under R&C and Schering-Plough agreement
8.F.6.5.1 (Subutex, French AEs)	Right of reference under R&C and Schering-Plough agreement
8.F.6.5.2 (Low dose buprenorphine products)	R&C own the data
8.F.6.5.3 (Deaths, low dose buprenorphine products)	R&C own the data
Publications	In Public Domain
Other items	
Summary of Effectiveness	R&C own the data
Integrated Summary of Safety	Joint ownership of R&C and NIDA under CRADA
Drug Abuse Liability Package	R&C own the data

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ATTACHMENT 2:

Location of Suboxone Data Tabulations in NDA 20-733

Domain	Study	NDA Section	NDA Volume	Page(s)
CR96/013: Suboxone v Subutex v Placebo CR96/014: Suboxone			93 to 112	
Demographics	CR96/013 CR96/014	14.2.2.1 14.2.2.6	96 96	55 to 110
Concomitant Medications	CR96/013 CR96/014	14.2.3.2 14.2.3.4 14.2.3.6	97 98 99 99	41 to 70 1 to end 1 to 461 464 to end
Medical History	CR96/013 CR96/014	14.2.2.8 14.2.2.13	96 96	243 to 323 329 to end
Drug Exposure	CR96/013 CR96/014	14.2.3.1 14.2.3.3 14.2.3.5	97 98 99	2 to 40 1 to end 462 to 463
Disposition	CR96/013 CR96/014	14.2.1.1 14.2.1.2 14.2.1.3	96 96 96	3 to 15 16 to 32 33 to 34
Efficacy Results	CR96/013	14.2.4	100	1 to 301
Adverse Events	CR96/013 CR96/014	14.2.5.1 14.2.5.10 14.2.5.19	100 101 102 105	303 to 364 1 to end 1 to end 188 to 191
Biochemistry	CR96/013 CR96/014	14.2.5.2 14.2.5.3 14.2.5.11 14.2.5.12 14.2.5.20 14.2.5.21	100 100 103 103 105 105	365 to 385 386 to 406 1 to 102 103 to 205 192 to 193 194 to 195
Hematology	CR96/013 CR96/014	14.2.5.4 14.2.5.13 14.2.5.22	100 104 105	407 to 427 206 to 308 196 to 197
Urinalysis	CR96/013 CR96/014	14.2.5.5 14.2.5.14 14.2.5.22	100 104 105	428 to 448 309 to 411 194 to 195
ECG	CR96/013 CR96/014	14.2.5.18 14.2.5.27 14.2.5.27	100 105 105	499 to end 136 to 187 206 to 208
Vital Signs	CR96/013 CR96/014	14.2.5.7 14.2.5.16 14.2.5.25	100 105 105	459 to 479 1 to 106 202 to 203
Physical Exam	CR96/013 CR96/014	14.2.5.9 14.2.5.17 14.2.5.26	100 105 105	480 to 498 107 to 135 204 to 205
CR95/002: Suboxone		All listings	145	

ATTACHMENT 3:

**The Effects of Gender, and Ethnicity on the Effectiveness of
Suboxone and Subutex Tablets**

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8.G.6.2 The effects of Gender and Ethnicity on the Effectiveness of Suboxone and Subutex Tablets.

The effects of gender, and ethnicity on the effectiveness of Suboxone (and Subutex) tablets has been determined in study CR96/013, the Pivotal Multicenter Efficacy/Safety Trial of Suboxone for the Treatment of Opiate Dependence

Study CR96/013
Section 8.D.2.1.1
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Study Site / Investigators

Phase 1 of Study 1008A was a randomized, placebo controlled, double blind study intended to demonstrate the safety and efficacy of 4-weeks treatment with Suboxone sublingual tablets. Matched Subutex (mono buprenorphine) tablets were included as an active control and matched placebo tablets as a non-active control.

Phase 2 of Study 1008A and Study 1008B offered continued open label treatment of Suboxone for up to a total of 52 weeks, including at-home use. The treatment environment is distinct from current practices and therefore individuals targeted for participation were those who were not presently enrolled in an opiate-substitution treatment program for reasons of choice, eligibility, or availability of services. The study investigators and the study sites are shown in Table 1.

**Table 1. Listing of Site Investigators and Their Affiliations
Study 1008A and Study 1008B**

Site No.	Site Investigators	Affiliation	
Study 1008A			
539	Eugene Somoza, MD	VAMC	Cincinnati, OH
578	Usha Malkerneker, MD	VAMC	Hines, IL
630	Paul Casadonte, MD	VAMC	New York, NY
642	Laura McNicholas, MD, PhD	VAMC	Philadelphia, PA
662	Donald J. Tusel, MD	VAMC	San Francisco, CA
689	Susan Stine, MD, PhD	VAMC	West Haven, CT
691	Walter Ling, MD	VAMC	West Los Angeles, CA
750	John A. Renner, Jr., MD	VAMC	Boston, MA
Study 1008B			
512	Joe Liberto, MD	VAMC	Baltimore, MD
546	Richard Douyou, MD	VAMC	Miami, FL
629	Marcos Fe-Bornstein, MD	VAMC	New Orleans, LA
672	Erick Santos, MD	VAMC	San Juan, PR

Study Design

The study is a multicenter, clinical trial conducted in two phases. The first, 4-week phase of Study 1008A was conducted at eight sites as a randomized, placebo controlled, double blind efficacy assessment. Subjects were to be randomly assigned to one of three treatment groups: 16mg Suboxone per day, 16mg Subutex per day or placebo. Subjects returned to the clinic daily (Monday through Friday) for dosing, urine collection, and safety and efficacy assessments. Take-home medication was provided for weekends and public holidays. A follow-up visit was to occur approximately 30 days after subject terminated from or completed the protocol. Drug was administered as sublingual tablets. Subjects completing the 4-week efficacy phase (Study 1008A, phase 1) were given the opportunity to continue into a second 48-week phase so that additional safety data could be collected on Suboxone tablets (only); these subjects retained their original study number and the original treatment assignment was not unblinded.

The second phase of the study (phase 2 of Study 1008A, and Study 1008B conducted at four additional sites) was a 48- and 52-week, respectively, open label safety assessment of Suboxone, in doses up to 24 mg per day. After 2 weeks of treatment in this phase, at the discretion of the investigators, subjects could be seen weekly for dispensing of take-home supplies and evaluated for safety. Adverse events were recorded at each subject visit and clinical laboratory studies were obtained monthly. Approximately 30 days after the subject discontinued or completed the protocol, he/she was contacted for brief questioning.

Disposition of Subjects

Study subjects were recruited from the population of opiate-dependent individuals. Efforts were to be made to have women comprise at least one third of the total number of subjects enrolled. A total of 451 subjects were screened from which 326 were randomized to treatment: 110 subjects to receive the combination therapy (buprenorphine/naloxone), 106 subjects to receive monotherapy (buprenorphine), and 110 subjects to receive placebo. Three subjects, one in each group were not dosed. Therefore the intent-to-treat efficacy sample comprised 323 subjects, 109 combination, 105 monotherapy and 109 placebo. A summary of subject disposition in the 4 week efficacy study is shown in Table 2.

Table 2. Summary of Subject Disposition by Treatment Group and Reason for Discontinuation in Double Blind Phase of Study 1008A

	Number of Subjects (N=326)			
	Combination	Monotherapy	Placebo	Total
Subject Disposition				
Screened				451
Randomized to treatment	110	106	110	326
Not dosed	1	1	1	3
Intent-to-treat (Efficacy)	109	105	109	323
Enrolled at time of study closure (Unable to complete because efficacy study ended)	11	4	12	27
Full efficacy population	98	101	97	296
Completed	82 (84%)	86 (85%)	75 (77%)	243 (82%)
Discontinued	16 (16%)	15 (15%)	22 (23%)	53 (18%)
Reason for Discontinuation				
Poor Response	0	0	1	1
Adverse event	3	2	0	5
Failure to return to clinic	7	4	5	16
Failure to return to clinic Greater than 7 days)	4	1	8	13
Incarceration	2	0	1	3
Attendance difficulties (e.g. moved)	0	1	3	4
Administrative discharge	0	0	0	4
Other (including Subject's choice)	0	5	2	7

* These subjects subsequently returned to the clinic and received treatment during the open label safety phase of the study

For the 296 subjects who were not affected by the early closure of the study, retention in the study was high; 243 subjects (82%) completed and 53 (18%) discontinued. Five of these subjects discontinued due to adverse events. Three of them were receiving buprenorphine/naloxone combination therapy; their adverse events included nausea,

vomiting, and withdrawal symptoms (1 subject); withdrawal symptoms alone (1 subject); and irritability, headache, and decreased appetite (1 subject). The remaining two subjects received buprenorphine monotherapy and experienced nausea (1 subject) and sedation and dizziness (1 subject).

Demographics and Drug Use History

All subjects enrolled in the efficacy study were opiate-dependent and had used heroin for a median duration of 84 months (range 3 to 468 months) at the time of entry into the study (Table 3). The majority of subjects were white men in their mid-thirties. Their mean age was 37.6 years. Of the 323 subjects in the efficacy study, 64.7% were men and 35.3% were women. None of the women were pregnant at study entry. Over half (61.0%) of the subjects were White, 28.5% were Black, 7.1% were Hispanic, 1.2% were Native American, and 2.2% were Asian or Pacific Islander. There were no statistically significant differences in any baseline characteristic between treatment groups.

Table 3. Baseline Demographics (Study 1008A Phase 1)

	Overall total	Combination	Monotherapy	Placebo
NUMBER SUBJECTS	323	109	105	109
MEAN AGE	37.6	38.1	37.1	38.1
(Range)	(19-60)	(19-59)	(19-57)	(19-60)
GENDER				
Male	209 (64.7%)	68 (62.4%)	70 (66.7%)	71 (65.1%)
Female	114 (35.3%)	41 (37.6%)	35 (33.3%)	38 (34.9%)
RACE				
White - Non Hispanic	197 (61.0%)	65 (59.6%)	62 (59.0%)	70 (64.2%)
Black - Non Hispanic	92 (28.5%)	32 (29.4%)	35 (33.3%)	25 (22.9%)
Hispanic	23 (7.1%)	8 (7.3%)	6 (5.7%)	9 (8.3%)
Native American	4 (1.2%)	2 (1.8%)	0 (0.0%)	2 (1.8%)
Asian/Pacific Islander	7 (2.2%)	2 (1.8%)	2 (1.9%)	3 (2.8%)
HEIGHT, inches (SE)	67.7 (0.4)	68.3 (0.3)	68.0 (0.4)	68.0 (0.2)
Range	59-76	59-75	53-76	53-76
WEIGHT, lbs (SE)	159.4 (2.9)	161.9 (2.9)**	167.0 (3.5)	162.8 (1.8)**
Range	107-254	104-272	109-273	104-273
MEDIAN DURATION OF HEROIN ABUSE, months	84	84	84	84
Range	6-396	3-420	6-468	3-468

*Calculated based on data from 104 subjects treated with buprenorphine monotherapy for a total of 322 subjects in all treatment groups

**Calculated based on data from 103 subjects treated with buprenorphine monotherapy for a total of 321 subjects in all treatment groups

Induction

Induction onto Suboxone was not attempted directly but was achieved using mono buprenorphine tablets on Day 1 (1 x 8mg tablet) and Day 2 (16mg, 2 x 8mg tablets). Patients in the Suboxone group were transferred to 16mg Suboxone (2 x 8mg tablets) on Day 3 and retained on the dose for the next 4 weeks. Patients in the monotherapy group continued on that medication. Placebo group patients were inducted with matching placebo tablets and remained on this study medication throughout the 4 week trial.

Dosing and Compliance

Retention in the 4-week efficacy study, in terms of subjects attending clinic visits for dosing, was good; a total of 243 of 296 of subjects (82%) who had the opportunity to complete the

efficacy study before it was stopped, did so. During the efficacy study, the mean buprenorphine dose received by subjects in the combination therapy and monotherapy groups was approximately 14.5 mg/day and 14.1 mg/day, respectively.

Efficacy Evaluation: Urine Tests Negative for Opiates

There were two primary efficacy parameters: the number of opiate negative urine samples and opiate craving score values. It was hypothesized that buprenorphine treatment with combination or monotherapy tablets would give rise to an increased number of opiate negative urine samples and would reduce opiate craving scores. All baseline urine samples were presumed positive and were not analyzed. Each subject in Study 1008A was to provide 12 on-treatment urine samples during the 4-week efficacy study. All missing urine tests were considered "positive" for opiates.

Patients treated with Suboxone or Subutex tablets had a statistically significantly higher percentage of urine samples that were negative for opiates than patients treated with placebo tablets (Table 4).

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Table 4. Mean Percent (SE) Urine Samples Negative for Opiates by Treatment Group for Subjects in the Efficacy Study.

Treatment Group	N	Mean Percent (SE)	P-value vs Placebo [†]
Buprenorphine/naloxone	109	17.8 (2.3)	<0.0001
Buprenorphine	105	20.7 (2.8)	<0.0001
Placebo	109	5.8 (1.7)	-
Total	323	14.7 (1.4)	-

[†]Two-way ANOVA

When results were evaluated by center, results were consistent with each center displaying a higher percentage of clean urine samples for combination therapy and monotherapy than the placebo (Table 5). There was a statistically significant effect of center but the treatment-by-center interaction was not significant (p=0.96).

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Table 5. Urine samples negative for opiates at the 8 Centers

Center	Combination Therapy		Monotherapy		Placebo		All Subjects	
	N	Mean (SE)	N	Mean (SE)	N	Mean (SE)	N	Mean (SE)
Boston	16	12.4 (4.4)	15	16.8 (5.5)	16	2.7 (1.7)	47	10.5 (2.5)
Cincinnati	16	32.9 (7.4)	16	36.9 (9.9)	16	18.0 (6.4)	48	29.2 (4.7)
Hines	15	23.9 (7.2)	13	25.3 (8.1)	13	3.4 (1.6)	41	17.9 (3.9)
New York	16	11.5 (4.3)	14	15.2 (5.6)	16	0.0 (0.0)	46	8.6 (2.4)
Philadelphia	12	19.4 (8.9)	13	17.9 (8.2)	12	8.3 (8.3)	37	15.3 (4.8)
San Francisco	13	3.5 (1.9)	12	17.4 (7.5)	14	0.0 (0.0)	39	6.5 (2.6)
West Haven	9	19.1 (8.2)	9	27.5 (11.5)	9	12.0 (10.0)	27	19.5 (5.7)
West LA	12	18.9 (6.5)	13	7.5 (5.1)	13	4.2 (3.0)	38	10.0 (3.0)
All Subjects	109	17.8 (2.3)	105	20.7 (2.8)	109	5.8 (1.7)	323	14.7 (1.4)

There was no significant effect of age, gender or ethnicity on the percentage of clean urine samples, nor was there a significant interaction between these variables and treatment. Urine samples negative for opiates summarized by gender are shown in Table 6. Urine samples negative for opiates summarized by ethnicity are shown in Table 7.

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Table 6. Summary statistics of opiate negative urines, by gender

Gender	Combination Therapy		Monotherapy		Placebo		All Subjects	
	N	Mean (SE)	N	Mean (SE)	N	Mean (SE)	N	Mean (SE)
Male	68	16.5 (2.8)	70	21.3 (3.5)	71	5.6 (2.1)	209	14.4 (1.7)
Female	41	20.0 (4.0)	35	19.4 (4.6)	38	6.3 (2.8)	114	15.2 (2.3)
All Subjects	109	17.8 (2.3)	105	20.7 (2.8)	109	5.8 (1.7)	323	14.7 (1.4)

Table 7. Summary statistics of opiate negative urines, by ethnicity

Ethnicity	Combination Therapy		Monotherapy		Placebo		All Subjects	
	N	Mean (SE)	N	Mean (SE)	N	Mean (SE)	N	Mean (SE)
White	65	17.4 (3.1)	62	20.5 (3.5)	70	6.9 (2.4)	197	14.7 (1.8)
Black	32	18.9 (4.2)	35	22.3 (5.5)	25	4.1 (2.4)	92	16.2 (2.7)
Other	12	17.0 (6.4)	8	14.8 (8.9)	14	3.7 (2.6)	34	11.0 (3.3)
All Subjects	109	17.8 (2.3)	105	20.7 (2.8)	109	5.8 (1.7)	323	14.7 (1.4)

Efficacy Evaluation: Opiate Craving

Upon entry into the efficacy study, opiate craving was moderate (mean scores 62.4 to 65.6) and reflect no apparent differences between treatment groups. There was a steady decline in mean craving scores following treatment with buprenorphine in both treatment groups: at Week 4 the mean score in the combination therapy group was 29.8 and 33.0 in the monotherapy group (Table 8). There was a smaller change in opiate craving in the placebo-treated group, with a mean Week 4 craving score of 55.1. The trend differed statistically significantly among the treatment groups ($p < 0.0001$), thus the treatment effect was examined by week. At each week after baseline, the craving score in the combination therapy group was significantly lower than that in the placebo group ($p < 0.0001$), as was the score in the monotherapy group ($p < 0.0001$).

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Table 8. Opiate Craving Score Adjusted Means (SE) by Treatment Group and Follow-up Period for Subjects in the Efficacy Study

Week	Combination Therapy		Monotherapy		Placebo	
	N	Mean (SE)	N	Mean (SE)	N	Mean (SE)
Baseline	109	62.4 (2.6)	104	63.3 (2.7)	109	65.6 (2.4)
1	108	44.4 (2.2)	104	45.7 (2.3)	107	60.5 (2.2)
2	98	33.8 (2.4)	93	33.2 (2.6)	100	57.0 (2.3)
3	95	30.2 (2.6)	89	35.6 (2.8)	90	54.4 (2.6)
4	86	29.8 (2.8)	86	33.0 (3.0)	79	55.1 (2.8)

Combination therapy vs. Placebo: $p < 0.0001$, repeated measures ANOVA, verified with split-plot analysis
Monotherapy vs. Placebo: $p < 0.0001$, repeated measures ANOVA, verified with split-plot analysis

No significant interactions between treatment and center, age, gender or ethnicity on craving scores were detected, as shown in Tables 9 (Center), 10 (Gender), and 11 (Ethnicity).

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Table 9. Opiate Craving Score Adjusted Means (SE) from the 8 Centers, by Treatment Group and Follow-up Period for Subjects in the Efficacy Study

Center	Week	Combination Therapy		Monotherapy		Placebo		All Subjects	
		N	Mean (SE)	N	Mean (SE)	N	Mean (SE)	N	Mean (SE)
Boston	Baseline	16	69.1 (6.6)	15	72.7 (6.5)	16	71.1 (5.5)	47	70.9 (3.5)
	1	16	52.8 (5.8)	15	42.1 (5.3)	16	55.4 (6.3)	47	50.3 (3.4)
	2	15	38.2 (6.7)	13	37.5 (7.2)	13	56.2 (5.6)	41	43.7 (3.9)
	3	15	40.3 (7.7)	13	35.0 (7.8)	13	49.1 (5.9)	41	41.4 (4.2)
	4	13	38.5 (7.3)	13	27.4 (6.5)	11	51.2 (6.1)	37	38.4 (4.1)
Cincinnati	Baseline	16	73.3 (5.6)	16	70.9 (6.6)	16	71.6 (5.7)	48	71.9 (3.4)
	1	16	52.8 (4.8)	16	44.2 (6.9)	16	67.2 (4.7)	48	54.7 (3.4)
	2	16	44.2 (6.2)	16	37.6 (7.2)	16	64.0 (4.8)	48	48.6 (3.8)
	3	16	42.9 (6.5)	15	38.7 (7.5)	16	66.5 (5.1)	47	49.6 (4.0)
	4	15	43.7 (6.6)	15	39.5 (7.4)	15	64.4 (4.8)	45	49.2 (3.9)
Hines	Baseline	15	68.3 (8.0)	13	77.8 (7.6)	13	75.7 (6.0)	41	73.7 (4.2)
	1	15	42.3 (5.3)	13	41.0 (8.1)	13	63.3 (7.1)	41	48.5 (4.1)
	2	13	32.9 (5.4)	12	28.9 (7.4)	13	61.6 (6.1)	38	41.5 (4.3)
	3	12	24.0 (5.8)	13	35.3 (8.3)	12	62.7 (6.9)	37	40.5 (4.8)
	4	11	22.2 (6.0)	13	35.8 (8.9)	11	65.0 (8.1)	35	40.7 (5.4)
New York	Baseline	16	52.9 (7.0)	14	50.8 (6.4)	16	48.8 (7.2)	46	50.8 (3.9)
	1	16	35.1 (7.4)	14	48.3 (6.3)	15	56.6 (7.0)	45	46.4 (4.1)
	2	14	32.8 (8.5)	14	34.2 (6.6)	14	50.9 (8.3)	42	39.3 (4.6)
	3	12	27.3 (9.3)	13	39.2 (7.5)	12	46.0 (10.1)	37	37.6 (5.2)
	4	12	31.5 (10.2)	13	36.0 (8.6)	10	51.6 (11.3)	35	38.9 (5.7)
Philadelphia	Baseline	12	48.8 (8.8)	13	55.5 (7.4)	12	60.2 (7.7)	37	54.8 (4.5)
	1	12	38.4 (6.0)	13	40.4 (5.1)	12	53.7 (7.4)	37	44.1 (3.7)
	2	12	22.2 (5.2)	12	25.4 (4.0)	12	48.4 (7.7)	36	32.0 (3.8)
	3	11	17.9 (4.1)	11	25.1 (4.4)	12	46.9 (8.6)	34	30.5 (4.1)
	4	9	14.1 (4.8)	10	20.6 (5.3)	11	50.0 (9.3)	30	29.4 (4.9)
San Francisco	Baseline	13	56.9 (7.3)	12	70.8 (7.7)	14	66.4 (6.5)	39	64.6 (4.1)
	1	13	45.7 (7.5)	12	56.8 (7.9)	14	64.4 (5.3)	39	55.8 (4.0)
	2	10	38.1 (9.3)	10	35.7 (10.4)	13	67.2 (5.4)	33	48.8 (5.3)
	3	10	34.7 (8.9)	10	35.7 (9.7)	11	58.9 (6.5)	31	43.6 (5.1)
	4	9	31.5 (8.6)	10	36.8 (10.2)	9	55.1 (7.5)	28	41.0 (5.4)
West Haven	Baseline	9	64.4 (5.6)	9	64.2 (6.1)	9	70.0 (6.4)	27	66.2 (3.4)
	1	9	35.4 (7.5)	9	51.6 (7.5)	9	60.3 (4.9)	27	49.1 (4.3)
	2	8	27.7 (7.0)	6	32.0 (11.5)	8	47.7 (5.4)	22	36.1 (4.7)
	3	8	24.0 (6.5)	6	33.4 (12.2)	6	51.0 (6.9)	20	34.9 (5.3)
	4	7	27.3 (8.3)	6	27.3 (12.7)	5	48.0 (8.6)	18	33.0 (5.9)
West LA	Baseline	12	62.6 (7.2)	12	40.1 (8.1)	13	63.4 (7.5)	37	55.6 (4.6)
	1	11	48.4 (5.1)	12	44.1 (5.9)	12	63.1 (6.8)	35	52.0 (3.7)
	2	10	27.4 (3.1)	10	32.0 (7.2)	11	54.3 (7.5)	31	38.4 (4.2)
	3	11	21.0 (6.3)	8	40.9 (9.0)	8	46.6 (7.7)	27	34.5 (4.7)
	4	10	18.5 (7.2)	6	36.4 (10.2)	7	44.2 (5.7)	23	31.0 (4.9)
All Subjects	Baseline	109	62.4 (2.6)	104	63.3 (2.7)	109	65.6 (2.4)	322	63.8 (1.5)
	1	108	44.4 (2.2)	104	45.7 (2.3)	107	60.5 (2.2)	319	50.2 (1.4)
	2	98	33.8 (2.4)	93	33.2 (2.6)	100	57.0 (2.3)	291	41.6 (1.6)
	3	95	30.2 (2.6)	89	35.6 (2.8)	90	54.4 (2.6)	274	39.9 (1.7)
	4	86	29.8 (2.8)	86	33.0 (3.0)	79	55.1 (2.8)	251	38.9 (1.8)

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Table 10. Summary statistics of mean adjusted opiate craving scores, by gender

Gender	Week	Combination Therapy		Monotherapy		Placebo		All Subjects	
		N	Mean (SE)	N	Mean (SE)	N	Mean (SE)	N	Mean (SE)
Male	Baseline	68	59.9 (3.1)	69	60.1 (3.4)	71	63.0 (3.0)	208	61.0 (1.8)
	1	68	43.2 (3.0)	69	43.8 (2.8)	70	59.0 (2.7)	207	48.8 (1.7)
	2	61	35.4 (3.3)	62	32.3 (3.1)	63	54.9 (2.9)	186	41.0 (1.9)
	3	60	32.8 (3.4)	59	34.2 (3.5)	56	51.0 (3.2)	175	39.1 (2.0)
	4	56	32.1 (3.7)	58	31.4 (3.6)	48	50.9 (3.4)	162	37.4 (2.2)
Female	Baseline	41	66.6 (4.4)	35	69.4 (4.5)	38	70.6 (4.0)	114	68.8 (2.5)
	1	40	46.3 (3.1)	35	49.2 (4.2)	37	63.5 (3.9)	112	52.9 (2.2)
	2	37	31.0 (3.6)	31	35.0 (4.8)	37	60.5 (4.0)	105	42.6 (2.7)
	3	35	25.8 (4.1)	30	38.2 (4.9)	34	60.0 (4.5)	99	41.3 (2.9)
	4	30	25.4 (4.1)	28	36.4 (5.5)	31	61.8 (4.7)	89	41.5 (3.2)
All Subjects	Baseline	109	62.4 (2.6)	104	63.3 (2.7)	109	65.6 (2.4)	322	63.8 (1.5)
	1	108	44.4 (2.2)	104	45.7 (2.3)	107	60.5 (2.2)	319	50.2 (1.4)
	2	98	33.8 (2.4)	93	33.2 (2.6)	100	57.0 (2.3)	291	41.6 (1.6)
	3	95	30.2 (2.6)	89	35.6 (2.8)	90	54.4 (2.6)	274	39.9 (1.7)
	4	86	29.8 (2.8)	86	33.0 (3.0)	79	55.1 (2.8)	251	38.9 (1.8)

Table 11. Summary statistics of mean adjusted opiate craving scores, by ethnicity

Ethnicity	Week	Combination Therapy		Monotherapy		Placebo		All Subjects	
		N	Mean (SE)	N	Mean (SE)	N	Mean (SE)	N	Mean (SE)
White	Baseline	65	61.1 (3.4)	61	63.5 (3.5)	70	67.0 (2.8)	196	63.9 (1.9)
	1	64	46.3 (3.0)	61	47.5 (2.8)	68	63.8 (2.5)	193	52.8 (1.7)
	2	58	35.0 (3.2)	52	34.0 (3.3)	63	60.5 (2.7)	173	44.0 (2.0)
	3	56	32.4 (3.6)	50	38.1 (3.7)	56	56.4 (3.1)	162	42.5 (2.2)
	4	52	31.4 (3.8)	48	34.7 (3.9)	50	56.4 (3.3)	150	40.8 (2.3)
Black	Baseline	32	60.3 (4.8)	35	63.1 (4.8)	25	62.4 (5.4)	92	62.0 (2.8)
	1	32	39.9 (3.7)	35	40.7 (4.6)	25	54.0 (5.0)	92	44.0 (2.6)
	2	30	30.7 (3.9)	34	31.3 (4.5)	24	50.5 (4.8)	88	36.3 (2.7)
	3	29	27.9 (3.9)	32	31.2 (4.8)	23	51.1 (5.7)	84	35.5 (2.9)
	4	27	28.2 (4.5)	31	28.3 (5.0)	21	53.9 (5.9)	79	35.1 (3.2)
Other	Baseline	12	75.3 (5.8)	8	61.8 (10.9)	14	64.5 (8.2)	34	67.7 (4.7)
	1	12	46.3 (7.2)	8	53.1 (6.5)	14	56.3 (7.6)	34	52.0 (4.3)
	2	10	35.9 (9.7)	7	36.2 (12.3)	13	51.9 (7.7)	30	42.9 (5.5)
	3	10	24.7 (10.1)	7	37.1 (11.1)	11	51.2 (9.1)	28	38.2 (6.0)
	4	7	23.9 (10.2)	7	42.1 (11.9)	8	50.7 (10.6)	22	39.4 (6.5)
All Subjects	Baseline	109	62.4 (2.6)	104	63.3 (2.7)	109	65.6 (2.4)	322	63.8 (1.5)
	1	108	44.4 (2.2)	104	45.7 (2.3)	107	60.5 (2.2)	319	50.2 (1.4)
	2	98	33.8 (2.4)	93	33.2 (2.6)	100	57.0 (2.3)	291	41.6 (1.6)
	3	95	30.2 (2.6)	89	35.6 (2.8)	90	54.4 (2.6)	274	39.9 (1.7)
	4	86	29.8 (2.8)	86	33.0 (3.0)	79	55.1 (2.8)	251	38.9 (1.8)

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Gender, and Ethnicity Conclusions from Study CR96/013

Results from the 4-week, double blind, placebo controlled efficacy study demonstrate that sublingual administration of 16mg Suboxone and 16mg Subutex was effective in the outpatient management of opiate abuse and dependence. Compared with placebo treated patients, those treated with Suboxone and Subutex had statistically significantly higher percentages of urine samples negative for opiates, and significantly lower opiate craving scores. They also showed statistically significantly greater improvement based on subjects' and clinicians' global impression scores since the last assessment and since the start of study than the placebo subjects.

Results were consistent across centers and there were no center-by-treatment interactions. There was no effect of age on the efficacy results and there were no meaningful differences between the genders or the different ethnic groups.

There were no obvious differences in effectiveness between Suboxone and Subutex; both products produced similar increases in the number of opioid negative urine samples and reduced opioid craving by similar amounts. Post-hoc statistical analysis detected no significant differences in effectiveness between the two products.

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**ATTACHMENT 4:
Exposure of Suboxone by Dose and Duration**

1. All subjects in Study CR96/013 + CR96/014

Table 29 of the #1008 study report (NDA Volume 93, page 65)

Summary of Person-Days Exposure to Combination Therapy by Dose in the Safety Study (All Subjects)

Dose	N	Prescribed		Actual	
		Person-Days	Average Person-Days	Person-Days	Average Person-Days
Other [†]	34	597	17.6	556	16.4
4	131	2698	20.6	2506	19.1
8	181	7097	39.2	6742	37.2
12	323	19872	61.5	18601	57.6
16	394	35713	90.6	32443	82.4
20	198	27733	140.1	25832	130.5
24	48	6580	137.1	6245	130.1
All	472	100290	212.5	92930	196.9

[†] "Other" doses (buprenorphine 2 mg/naloxone 0.5 mg and buprenorphine 6 mg/naloxone 1.5 mg) were only used when subjects were being tapered off the study medication.

2. Subjects Exposed ≥ 6 Months in Study CR96/013 + CR96/014

Table 13.2.4 of the #1008 study report (NDA Volume 93, page 172)
Appendix 1.3.2 of the ISS (NDA Volume 154, page 10).

Summary of Person-Days Exposure to Combination Therapy by Dose in the Safety Study (Subjects Exposed to Combination Therapy ≥ 6 Months)

Dose (mg)	Number of Subjects Exposed ≥ 6 Months	Prescribed		Actual	
		Person-Days	Average Person-Days	Person-Days	Average Person-Days
Other	31	567	18.3	542	17.5
4	118	2573	21.8	2393	20.3
8	152	6285	41.3	6032	39.7
12	199	15836	79.6	15032	75.5
16	230	29081	126.4	27176	118.2
20	138	24317	176.2	22885	165.8
24	34	5659	166.4	5414	159.2
All	261	84318	323.1	79474	304.5

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ON ORIGINAL

NDA 20-733

JUN 28 1999

Reckitt & Colman Pharmaceuticals
1909 Huguenot Road (Suite 300)
Richmond, Virginia 23235

Attention: Alan N. Young
Director, Regulatory Affairs

Dear Mr. Young:

Please refer to the teleconference between representatives of your firm and FDA on June 25, 1999. The purpose of the teleconference was to identify the deficiencies in the Suboxone application that we have identified thus far that are potential filing issues.

As promised, a copy of our minutes of that teleconference is enclosed. Please notify us of any significant differences in understanding you may have regarding the meeting outcomes.

If you have any questions, please contact Tony Chite, P.D., Regulatory Project Manager, at (301) 827-7410.

Sincerely,

[|S|]

Corinne P. Moody
Chief, Project Management Staff
Division of Anesthetic, Critical Care and
Addiction Drug Products, HFD-170
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

**APPEARS THIS WAY
ON ORIGINAL**

Memorandum of Telecon Meeting Minutes



Meeting Date: June 25, 1999

Time: 11:30 a.m.

Location: Parklawn Building – 9B 45

Type of Meeting: TELECON

NDA # / Drug Name: 20-733/ Suboxone

Sponsor: Reckitt & Colman Pharmaceuticals

Meeting Chair: Cynthia McCormick, M.D.

FDA Attendees:	Titles:
Cynthia G. McCormick, M.D.	Division Director
Celia J. Winchell, M.D.	Medical Team Leader/ Drug Abuse
Chang-Qing Li, M.D.	Medical Reviewer/Drug Abuse
Corinne P. Moody	Chief, Project Management Staff
Tony Chite, P.D.	Consumer Safety Officer

Sponsor Attendees:	Titles:
Charles O'Keefe	President, Reckitt & Colman
Don Walter, Ph.D.	
Dr. Chris Chapleo	
Dr. Nicholas Varey	

Purpose of the Telecon

The purpose of the teleconference was to identify the deficiencies in the Suboxone application that have been identified thus far that may prevent it from being filed.

Discussion Items:

1. Unless Reckitt and Colman owns or has right of reference to all data and findings cited in the submission, NDA 20-733 should be filed under 505(b)(2) rather than 505(b)(1). It will also be necessary to identify those parts of the application in which data are relied upon which Reckitt and Colman does not own or does not have right of reference. This includes data relied upon to support all claims throughout the labeling.

2. It will not be possible to waive the requirement for case report tabulations. These are essential to the review and must be submitted in order for the NDA to be filable. There was some discussion of how these should be formatted, and the agency agreed to fax Reckitt and Colman the guidance on Electronic Submission that explains how to prepare the tabulations.
3. The interim study report for Study CR96/005 (Australia) is from August 1997. The agency requires the full study report, including efficacy data and CRFs. Dr. Walter explained that the safety data is not ready to submit because the contractor had mixed withdrawal symptoms into the adverse events, and other personnel are presently attempting to sort out the adverse event section. This will take several months. Reckitt and Colman had not anticipated the need to submit this study, as it did not use the Suboxone tablet, but the Agency explained that this data is needed to support the Suboxone NDA. The Agency agreed to accept the efficacy data now, for filing, with the understanding that the safety data must be included in the 4 month safety update.
4. The requirement for a safety update was discussed. Reckitt and Colman indicated this would be available in late September 1999. The safety update should be cumulative and should lay out the data in three columns, indicating the data submitted in the NDA, the additional data included in the update, and a cumulative analysis.
5. Reckitt and Colman agreed to provide the volume and page number where the following items could be located in the NDA:
 - Analysis of efficacy by demographic subgroups such as sex and race (in ISE).
 - Table of exposure, dose by duration, for study 1008, especially for 1008b (in ISS).
 - Protocols for Study 1008a and 1008b.
6. Reckitt and Colman agreed to clarify numerical discrepancies in Table 23, 27 and Table 24, 25 in ISS, where total patient numbers of the combination tablet vary between 472 in Table 23 and 27 vs N = 497 in Table 24 and 25.
7. Reckitt and Colman agreed to clarify the exact method of tablet administration (how many tablets at a time, held for how long, etc.) used in Study 1008a/b.

The agency explained that all requested information above must be submitted before July 25, 1999 in order to permit filing of this NDA.

The agency alerted Reckitt and Colman to the likelihood that the Biopharmaceutics reviewer would have additional questions in the next week. The agency requested, and Reckitt and Colman agreed to submit, 1 desk copy of NDA 20-733 Volume 1.4, 1.5 and 1.168.

Certification: Financial Interests & Arrangements of Clinical Investigators

Attached is a list of the clinical investigators of Suboxone, their study numbers, and the sponsors of their studies. Two studies were sponsored by Reckitt & Colman, U.K.; the remainder by NIDA and health authorities of foreign countries or Schering Plough, France. There is a certification for the studies sponsored by Reckitt & Colman and a separate certification for the studies sponsored by government authorities.

**APPEARS THIS WAY
ON ORIGINAL**

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

- (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators	
------------------------	--

- (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

- (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME Alan N. Young	TITLE Director, Regulatory Affairs
FIRM/ORGANIZATION Reckitt & Colman Pharmaceuticals, Inc.	
SIGNATURE <i>Alan N. Young</i>	DATE June 3, 1999

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

- (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators		

- (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

- (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME Alan N. Young	TITLE Director, Regulatory Affairs
FIRM/ORGANIZATION Reckitt & Colman Pharmaceuticals, Inc.	
SIGNATURE <i>alan N. Young</i>	DATE June 3, 1999

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C
Rockville, MD 20857

5 Page(s) Withheld

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on page 2.

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC,
OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

FOR FDA USE ONLY

APPLICATION NUMBER

20-733

APPLICANT INFORMATION

NAME OF APPLICANT Reckitt & Colman Pharmaceuticals	DATE OF SUBMISSION June 3, 1999
TELEPHONE NO. (Include Area Code) (804) 379-1090	FACSIMILE (FAX) Number (Include Area Code) (804) 379-1215
APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued): 1909 Huguenot Road (Suite 300) Richmond, VA 23235	AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone number) IF APPLICABLE  

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (if previously issued)	20-733	
ESTABLISHED NAME (e.g., Proper name, USP/USAN name) Buprenorphine HCl/Naloxone HCl	PROPRIETARY NAME (trade name) IF ANY Suboxone	
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (if any)	CODE NAME (if any)	
DOSAGE FORM: tablet	STRENGTHS: 2mg/0.5mg 8mg/2mg	ROUTE OF ADMINISTRATION: Sublingual
(PROPOSED) INDICATION(S) FOR USE: Treatment of		

APPLICATION INFORMATION

APPLICATION TYPE (check one) <input checked="" type="checkbox"/> NEW DRUG APPLICATION (21 CFR 314.50) <input type="checkbox"/> ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94) <input type="checkbox"/> BIOLOGICS LICENSE APPLICATION (21 CFR part 601)
IF AN NDA, IDENTIFY THE APPROPRIATE TYPE <input checked="" type="checkbox"/> 505 (b) (1) <input type="checkbox"/> 505 (b) (2) <input type="checkbox"/> 507
IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION Name of Drug: _____ Holder of Approved Application: _____
TYPE OF SUBMISSION (check one) <input checked="" type="checkbox"/> ORIGINAL APPLICATION <input type="checkbox"/> AMENDMENT TO A PENDING APPLICATION <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> PRESUBMISSION <input type="checkbox"/> ANNUAL REPORT <input type="checkbox"/> ESTABLISHMENT DESCRIPTION SUPPLEMENT <input type="checkbox"/> SUPAC SUPPLEMENT <input type="checkbox"/> EFFICACY SUPPLEMENT <input type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT <input type="checkbox"/> OTHER
REASON FOR SUBMISSION Marketing application
PROPOSED MARKETING STATUS (check one) <input checked="" type="checkbox"/> PRESCRIPTION PRODUCT (Rx) <input type="checkbox"/> OVER THE COUNTER PRODUCT (OTC)
NUMBER OF VOLUMES SUBMITTED <u>3</u> 333 THIS APPLICATION IS <input type="checkbox"/> PAPER <input checked="" type="checkbox"/> PAPER AND ELECTRONIC <input type="checkbox"/> ELECTRONIC

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

See attached

References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

DMFs _____

This application contains the following items: (Check all that apply)	
X	1. Index
X	2. Labeling (check one) <input checked="" type="checkbox"/> Draft Labeling <input type="checkbox"/> Final Printed Labeling
X	3. Summary (21 CFR 314.50 (c))
X	4. Chemistry section
X	A. Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50 (d) (1), 21 CFR 601.2)
	B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)
X	C. Methods validation package (e.g. 21 CFR 314.50 (e) (2) (i), 21 CFR 601.2)
X	5. Nonclinical pharmacology and toxicology section (e.g. 21 CFR 314.50 (d) (2), 21 CFR 601.2)
X	6. Human pharmacokinetics and bioavailability section (e.g. 21 CFR 314.50 (d) (3), 21 CFR 601.2)
	7. Clinical Microbiology (e.g. 21 CFR 314.50 (d) (4))
X	8. Clinical data section (e.g. 21 CFR 314.50 (d) (5), 21 CFR 601.2)
	9. Safety update report (e.g. 21 CFR 314.50 (d) (5) (vi) (b), 21 CFR 601.2)
X	10. Statistical section (e.g. 21 CFR 314.50 (d) (6), 21 CFR 601.2)
X	11. Case report tabulations (e.g. 21 CFR 314.50 (f) (1), 21 CFR 601.2)
X	12. Case report forms (e.g. 21 CFR 314.50 (f) (2), 21 CFR 601.2)
X	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
	14. A patent certification with respect to any patent which claims the drug (21 U.S.C 355 (b) (2) or (j) (2) (A))
	15. Establishment description (21 CFR Part 600, if applicable)
X	16. Debarment certification (FD&C Act 306 (k)(1))
X	17. Field copy certification (21 CFR 314.50 (k) (3))
X	18. User Fee Cover Sheet (Form FDA 3397)
X	19. OTHER (Specify) Prescription Drug User Fee waiver; orphan designation

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211, 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been review and, to the best of my knowledge are certified to be true and accurate.

Warning: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT <i>Alan N. Young</i>	TYPED NAME AND TITLE Alan N. Young, Director Regulatory Affairs	DATE June 3, 1999
ADDRESS (Street, City, State, and ZIP Code) 1909 Huguenot Road, Suite 300; Richmond, VA 23235		Telephone Number (804) 379-1090

Public reporting burden for this collection of information is estimated to average 40 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

DHHS, Reports Clearance Officer
Paperwork Reduction Project (0910-0338)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, DC 20201

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0297
Expiration Date: 2/28/97

USER FEE COVER SHEET

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Paperwork Reduction Project (0910-0297)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, DC 20201

"An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number."

Please DO NOT RETURN this application to this address.

See Instructions on Reverse Before Completing This Form

1. APPLICANT'S NAME ADDRESS

Reckitt & Colman Pharmaceuticals, Inc.
1909 Huguenot Road, Suite 300
Richmond, Virginia 23235

2. USER FEE BILLING NAME, ADDRESS, AND CONTACT

Reckitt & Colman Pharmaceuticals, Inc.
1909 Huguenot Road, Suite 300
Richmond, Virginia 23235

Charles O'Keefe, President

3. TELEPHONE NUMBER (Include Area Code)

(804) 379-1090

4. PRODUCT NAME

Suboxone (formerly

5. DOES THIS APPLICATION CONTAIN CLINICAL DATA?

YES

NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

USER FEE I.D. NUMBER

3012

7. LICENSE NUMBER/ANDA NUMBER

20-733

8. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED BEFORE 9/1/92

THE APPLICATION IS SUBMITTED UNDER 505(b)(2)
(See reverse before checking box.)

AN INSULIN PRODUCT SUBMITTED UNDER 506

FOR BIOLOGICAL PRODUCTS ONLY

WHOLE BLOOD OR BLOOD COMPONENT FOR TRANSFUSION

A CRUDE ALLERGENIC EXTRACT PRODUCT

BOVINE BLOOD PRODUCT FOR TOPICAL APPLICATION LICENSED BEFORE 9/1/92

AN "IN VITRO" DIAGNOSTIC BIOLOGIC PRODUCT LICENSED UNDER 351 OF THE PHS ACT

9. a. HAS THIS APPLICATION QUALIFIED FOR A SMALL BUSINESS EXCEPTION?

YES

NO

(See reverse if answered YES)

b. HAS A WAIVER OF APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION?

YES

NO

(See reverse if answered YES)

This completed form must be signed and accompany each new drug or biologic product, original or supplemental.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE

TITLE

DATE

Charles O'Keefe

President

June 3, 1999

FORM FDA 3397 (11/96)

13

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Suboxone

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information

NDA 20-733	Efficacy Supplement Type SE-	Supplement Number
Drug: buprenorphine HCl/naloxone dihydrate HCl		Applicant: Reckitt Benckiser
RPM: Sara E. Stradley		HFD-170 Phone # 77430
Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)		Reference Listed Drug (NDA #, Drug name): na
❖ Application Classifications:		
• Review priority		<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority
• Chem class (NDAs only)		4PV
• Other (e.g., orphan, OTC)		Orphan drug
❖ User Fee Goal Dates		
❖ Special programs (indicate all that apply)		<input checked="" type="checkbox"/> None Subpart H <input type="checkbox"/> 21 CFR 314.510 (accelerated approval) <input type="checkbox"/> 21 CFR 314.520 (restricted distribution) <input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review
❖ User Fee Information		
• User Fee		<input type="checkbox"/> Paid
• User Fee waiver		<input type="checkbox"/> Small business <input type="checkbox"/> Public health <input type="checkbox"/> Barrier-to-Innovation <input type="checkbox"/> Other
• User Fee exception		<input checked="" type="checkbox"/> Orphan designation <input type="checkbox"/> No-fee 505(b)(2) <input type="checkbox"/> Other
❖ Application Integrity Policy (AIP)		
• Applicant is on the AIP		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• This application is on the AIP		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• Exception for review (Center Director's memo)		---
• OC clearance for approval		---
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification and certifications from foreign applicants are co-signed by U.S. agent.		<input checked="" type="checkbox"/> Verified
❖ Patent		
• Information: Verify that patent information was submitted		<input type="checkbox"/> Verified
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted		21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> I <input type="checkbox"/> II <input type="checkbox"/> III <input type="checkbox"/> IV 21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).		<input type="checkbox"/> Verified
Exclusivity Summary (approvals only)		X
❖ Administrative Reviews (Project Manager, ADRA) (indicate date of each review)		na

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General Information

❖ Actions	
• Proposed action 10/8/02	(x) AP () TA () AE () NA
• Previous actions (specify type and date for each action taken)	1/26/02 (AE), 12/7/99 (AE)
• Status of advertising (approvals only)	(x) Materials requested in AP letter () Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	(x) Yes () Not applicable
• Indicate what types (if any) of information dissemination are anticipated	() None () Press Release (X) Talk Paper () Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	See AP letter for final label
• Most recent applicant-proposed labeling	X
• Original applicant-proposed labeling	X
• Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews) and minutes of labeling meetings (indicate dates of reviews and meetings)	X
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	
Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	X
• Applicant proposed	X
• Reviews	
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	X
• Documentation of discussions and/or agreements relating to post-marketing commitments	X
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	X
❖ Memoranda and Telecons	X (see outgoing correspond)
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	---
• Pre-NDA meeting (indicate date)	---
• Pre-Approval Safety Conference (indicate date; approvals only)	---
• Other	See section and see memo/TC
❖ Advisory Committee Meeting	
• Date of Meeting	2/10/97, 4/6/95
• 48-hour alert	--
❖ Federal Register Notices, DESI documents, NAS, NRC (if any are applicable)	x

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Clinical and Summary Information

❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) (indicate date for each review)	10/8/02, 9/27/02, 1/24/01, 12/7/99
❖ Clinical review(s) (indicate date for each review)	1/10/01, 11/22/99, 10/29/99
❖ Microbiology (efficacy) review(s) (indicate date for each review)	NA
❖ Safety Update review(s) (indicate date or location if incorporated in another review)	5/17/02
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	X
❖ Statistical review(s) (indicate date for each review)	7/1/02, 10/6/99
❖ Biopharmaceutical review(s) (indicate date for each review)	9/20/02, 6/5/02, 3/12/02, 11/30/00, 4/12/99,
❖ Controlled Substance Staff review(s) and recommendation for scheduling (indicate date for each review)	1/25/01
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	---
• Bioequivalence studies	----

CMC Information

❖ CMC review(s) (indicate date for each review)	10/8/02, 1/26/01, 12/2/99, 11/4/99, 11/7/99
❖ Environmental Assessment	
• Categorical Exclusion (indicate review date)	
• Review & FONSI (indicate date of review)	
• Review & Environmental Impact Statement (indicate date of each review)	
❖ Micro (validation of sterilization & product sterility) review(s) (indicate date for each review)	
❖ Facilities inspection (provide EER report)	Date completed: (x) Acceptable () Withhold recommendation
❖ Methods validation	() Completed (x) Requested () Not yet requested

Nonclinical Pharm/Tox Information

❖ Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	10/7/02, 12/11/01, 10/26/99
❖ Nonclinical inspection review summary	---
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	4/11/00
❖ CAC/ECAC report	X

APPEARS THIS WAY
ON ORIGINAL

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Partial copy
of 1-1

June 3, 1999

Cynthia McCormick, MD
Division Director,
Division of Anesthetic, Critical Care and Addiction Research Products
HFD-170
Office of Drug Evaluation III
Center for Drug Evaluation and Research
5600, Fishers Lane
Rockville, Maryland 20857



NDA 20-733

Dear Dr McCormick,

Enclosed is a New Drug Application for sublingual tablets containing a combination of buprenorphine hydrochloride and naloxone hydrochloride dihydrate. The above New Drug Application number was assigned previously to facilitate identification of the application.

This combination product, Suboxone, is a companion to Subutex (buprenorphine hydrochloride) to which naloxone has been added to deter misuse by injection. Naloxone is poorly absorbed sublingually, but it acts as an opiate antagonist when injected.

The present application is a complete compilation of data and available information about buprenorphine for the treatment of narcotic addiction. Hence, it includes data from Subutex NDA 20-732, which is now pending in the Division of Anesthetic, Critical Care and Addiction Drug Products, HFD-170. We are preparing a separate response to your letter dated June 30, 1998 regarding that application. Both submissions contain many identical elements such as the ISS, the report of study #1008 (CR96/013 and CR96/014) and the Drug Abuse Liability Assessment package.

The present application, NDA 20-733, for Suboxone tablets has been prepared in accordance with the Guidelines for Industry, and taking note of the recommendations provided by your Division at a pre-NDA meeting held March 27, 1998, as indicated below.

Medical

1. The pivotal trial for this NDA is study #1008, the one in which buprenorphine/naloxone sublingual tablets were studied. The presentation of these data should be prominent and clearly set apart in the clinical section.

Study #1008 [CR96/013 (double blind efficacy) and CR96/014 (open safety)] has been completed and the full study results are presented in Report RC990123 that comprises Volumes 93 through 112 of the application (Section 8.D.2.1.1). The study results are

summarized in the Summary of Effectiveness (Volume 152) in Section 8.G.2 and in the Integrated Summary of Safety (Volumes 153 through 166) in Section 8.H. An abbreviated summary is also provided in Section 8.D: Controlled Clinical Trials.

2. Because the data from the studies involving the sublingual solution (CR88/130 and CR92/099) are considered as background data for review of the combination tablet, (as they were for the mono tablet), these study reports should be submitted to the NDA 20-733, with a statement certifying that they are identical to the reports submitted to the NDA 20-732 or with documentation highlighting changes that have been made.

The reports of studies CR88/130, CR92/099, CR92/100 (original submission) and CR92/102 (Amendment of September 5 1997), including data listings and appropriate CRFs, were submitted to the Subutex NDA 20-732 and are also submitted in the present NDA 20-733 for Suboxone tablets in the following locations.

Study	Section	Volumes	CRF Volumes
CR88/130	8.D.3.3.1	117-119	327-331
CR92/099	8.D.4.4.1	121-128	317-325
CR92/100	8.D.4.4.2	129-135	317-325
CR92/102	8.D.2.2.1	113-114	332-335

These study reports and the data have not changed from those presented in the Subutex application. However missing or mixed up data listings identified during the review of Subutex have been corrected in the present application.

Adverse Event data, Biochemistry, Hematology and Urinalysis data and Vital Sign data from studies CR88/130, CR92/099, CR92/100 and CR92/102 have been pooled for use in the Integrated Summary of Safety (see below). Vital Sign data from studies CR92/099 and CR92/100 were not presented in the report submitted in the Subutex NDA and are therefore new data. Listings of these data are given in Appendix 2.2.6.1 of the ISS (Volume 166, page 1650).

Concomitant medications from studies CR88/130, CR92/099 and CR92/100 were presented in the Subutex NDA as an Amendment on December 19, 1997, in 7 volumes (Reports RC97361 through RC97367) entitled "An assessment of drug interactions with buprenorphine in the treatment of opioid dependence (Concomitant Medications Report). This report is also submitted in the present NDA 20-733 in Volumes 136-142 (Section 8.D.4.4.3).

3. Analysis of primary safety data by demographic subsets (race, sex, age, drug use history and baseline liver function) is required

Descriptive analysis of adverse events by gender, ethnicity, duration of heroin abuse, and baseline liver function are reported in Section 9.1.1.3 of the study report of CR96/013 and CR96/014 (NDA Volume 93, page 83). These data are also discussed in Section 11 of the ISS (Drug Demographic and Drug-Disease Interactions). Analysis by age has not been undertaken because of the narrow age range of the patients.

4. *In addition, long term study (CR96/014) should be available for review and the data format will be discussed at the Pre-NDA meeting.*

The full report for study #1008 (CR96/013 and CR96/014) is presented in Volumes 93-112 of the NDA.

Based on some of the deficiencies noted with NDA 20-732 (mono tablet), we would offer the following advice regarding the NDA for the combo tablet.

1. *The safety database in the mono NDA appears to be in part good clinical practice (GCP) based studies (with prospective protocol, CRFs) of the sublingual solution (SLS); non GCP-based studies of the SLS (many individual investigator studies, case series, reports) for which there are no protocols, no primary data and no CRFs; postmarketing passive reports of adverse events with the sublingual tablet (SLT) in France and (yet to be submitted) prospective GCP-based studies of the SLT. Assuming similar sources for you combo NDA, the safety data in tables should be displayed to reflect these various sources. The primary data for this NDA would be prospective GCP-based studies of the SLT and supportive GCP based studies (with prospective protocol, CRFs) of the sublingual solution.*

— The ISS (Volumes 153-166 of the NDA 20-733) has been written with this in mind. The primary database is study CR96/013 and CR96/014. Other tablet studies that provide safety data are reviewed. A secondary database is pooled data from SLS studies CR88/130, CR92/099, CR92/100 and CR92/102.

2. *In NDA 20-732, there are no exposure tables (numbers of patients exposed by dose and duration of treatment). In your integrated summary and safety update for NDA 20-733, it will be necessary to detail the number of subjects who received buprenorphine sublingual tablets in prospective clinical trials, their duration of exposure, and the number of patients who were treated at each dose (exposure by dose, duration and dose by duration). These could be tabulated to reflect the primary safety database first and the secondary database (SLS) second.*

The arrangement of subject samples and the extent of exposure is presented in Section 6 of the ISS (NDA Volume 153 page 49)

3. *The integrated summary of safety (ISS) for NDA 20-732 is largely a compilation of adverse events from three NDA studies done with the SLS. The tables are in some cases arranged with adverse events in alphabetical order, not sorted by dose. Terminations due to adverse events are listed for three studies. The tables for these studies are sorted by AE in alphabetical order. Instead they should be displayed by dose so that comparisons of the incidences of the various AEs can be made between doses as indicated below.*

<i>Adverse Event</i>	<i>Bup 1mg (N=)</i>	<i>Bup 4mg (N=)</i>	<i>Bup 8mg (N=)</i>	<i>Bup 16mg (N=)</i>	<i>Methadone 20mg (N=)</i>	<i>Methadone 60mg (N=)</i>
	<i>N(%)</i>	<i>N(%)</i>	<i>N(%)</i>	<i>N(%)</i>	<i>N(%)</i>	<i>N(%)</i>

All tables in the ISS should reflect these principals and should be pooled as primary data, secondary database making the appropriate dose or placebo or active control comparisons where applicable and should be compiled for adverse events, laboratory studies, vital signs

Adverse events, laboratory studies, and vital signs data are presented in Sections 7, 8 and 9 of the ISS (NDA Volume 153), and by dose where available. Discontinuations from treatment are discussed in Section 6 of the ISS.

- Please refer to the Guidance of Industry-Content and Format of Clinical and Statistical Sections of the NDA for further details about presenting these data.*

This Guidance note has been used in the preparation of the ISS and other parts of the NDA

- Information on Pregnancy and outcomes should be collected over the entire database, primary, secondary and tertiary (postmarketing, literature reports, etc)*

Information on pregnancy, and neonates has been collected and the reports are presented in Section 8.F: Other Studies and Information (NDA Volume 147). The pregnancy / neonate data are also reviewed in the ISS Section 11.4.1 (NDA Volume 153).

- All foreign labeling should be provided with English translation*

Foreign Labeling of Subutex, approved in France, Luxembourg, UK, Argentina and Switzerland, with English translations, is provided in Section 8.F.6.1.1 (NDA Volume 147, pages 248).

Statistics

- Analysis of primary efficacy variables by demographic subsets (race and gender) is required for filing. Analysis by age may not be necessary because of the target population, but the application should state this.*

Analysis of primary efficacy variables: urine samples negative for opiates, and mean adjusted opiate cravings scores, are summarized by study center, gender, and ethnicity in the report of study CR96/013 and CR96/014 (NDA Volume 93, page 69)

- The exact statistical procedure used by the Data Monitoring Board to recommend termination of recruitment should be documented. This documentation should include a statement as to whether interim looks were taken, as well as an explanation of the calculated probability of finding no difference if recruitment had continued.*

Under the VA Cooperative Studies Program guidelines, and as stated in the protocol for the #1008A study (CR96/013), an independent Data Monitoring Board (DMB) was convened. Members were selected by the VA Cooperative Studies Program Coordinating Center (CSPCC), and were independent of both NIDA and Reckitt & Colman. Members were drawn from academia and the VA and included physicians and other professionals experienced in the treatment of drug abuse, and statisticians (a list of the members is given in the minutes of the DMB in NDA Volume 112, page 358). As described in the protocol, the board was scheduled to meet at least once yearly for the purpose of reviewing the safety and efficacy data from the double blind efficacy phase.

The first meeting of the DMB was held June 24th 1997 at which a report prepared by the CSPCC (Perry Point VA) was reviewed. This was a blinded analysis of 45% of the efficacy data and the meeting concluded that this was insufficient (see minutes of this meeting in NDA Volume 112, page 358). A further meeting of the DMB was convened for July 17th. A new report of a blinded analysis was prepared by the CSPCC of the available data (this report is given in NDA Volume 112, page 298). The DMB concluded that the data were now satisfactory for them to conclude that recruitment into the efficacy phase should stop. However the DMB asked that a "worse case" calculation be undertaken to confirm that the highly significant effect would not be compromised. The minutes of this meeting are given in NDA Volume 112, page 296, and the worse case calculations are given on page 362. The blind was then broken and recruitment to the efficacy phase was stopped. All remaining patients could elect to be transferred to the open safety phase of the study

Abuse Liability

21 CFR 314.50(5)(vii) states that if the drug has a potential for abuse, a description and analysis of studies or information related to abuse of the drug, including a proposal for "scheduling" under the Controlled Substances Act, be included in the NDA. This information was not included in the NDA when originally submitted. Specifically, the following should be submitted:

- 1. A separate abuse liability assessment package must be submitted. This package should contain in detail the following data:*
 - a) Specialized preclinical and clinical behavioral studies.*
 - b) Chemistry, pharmacology, pharmacokinetics/metabolism and epidemiology data relevant to the drug product.*
 - c) Integrated Summary of Safety and Safety Update.*
 - d) All available information/data on abuse of currently marketed sublingual buprenorphine products must be include in the NDA package*
- 2. Also, per CFR 314.50(5)(vii), a description and analysis of data based on medical, scientific, and public health considerations that relate to the potential abuse must be included in the NDA.*

3. *Per CFR 314.50(5)(vii), a description of any studies related to overdose including information on antidotes or other treatments, if known.*
4. *You must clearly identify which clinical studies conducted support the claim that the combo product has lower abuse potential than the mono product*
5. *A statement on how you intend to market the drug, and supporting literature must be submitted.*

The Drug Abuse Liability Assessment package (NDA Volumes 167-168) has been prepared as requested and in accordance with CFR 314.50(5)(vii). A copy of the Integrated Summary of Safety (NDA Volumes 153-166) is also provided in the Abuse Liability Assessment package.

Introductory promotional material in the U.S. will be based on approved labeling and cannot be prepared until the labeling has been finalized. At that time, all proposed materials will be submitted in draft form to your Division and to the Division of Drug Marketing, Advertising and Communications (HFD-40).

Pharmacology / Toxicology

Data should be submitted in accordance with the ICH guidelines entitled "Study for Effects on Prenatal and Postnatal Development, including Maternal Function" (previously known as the Segment III reproductive toxicology study) with naloxone, or preferably, with the buprenorphine-naloxone 4:1 combination. Also, according to ICH guidelines, a complete battery of genotoxicity tests, including an in-vivo test, should be done before filing, since we have only three in-vitro tests for naloxone. We will need 2-year carcinogenicity studies for the combination tablet. The latter could be a phase 4 commitment and is not required for filing.

1. Segment III studies have been conducted with buprenorphine and are presented in Section 5.G.4 of the Suboxone NDA. The proposed labeling for Suboxone recommend that patients who become pregnant during treatment with Suboxone should be transferred to Subutex (when approved) or to methadone. Therefore it is considered that an additional Segment III study conducted with 4:1 buprenorphine : naloxone is not required. This was stated in our letter sent to the FDA on May 11, 1998, following the pre-NDA meeting of March 27, 1998.
2. Three standard mutagenicity studies (one *in-vivo* and two *in-vitro*) with a 4:1 combination of buprenorphine HCl : naloxone HCl dihydrate have been undertaken and are presented in Section 5.F.5, as follows:
 - a) Report RC980112, Study of buprenorphine / naloxone (4:1 mixture) in bacterial mutation assays using *Salmonella typhimurium* and *Escherichia coli*. (Study YV425; Report P/6017)
 - b) RC980113, Study of buprenorphine / naloxone (4:1 mixture) using an *in vitro* cytogenetic assay in human lymphocytes (Study SV0959; Report P/6052)

- c) Report RC980114, Study of buprenorphine / naloxone (4:1 mixture) using a rat bone marrow micronucleus test — Study SR0958; — Report — /P/6063)

3. Preparatory work leading to a life-time dietary carcinogenicity study is in progress. Toxicokinetic method development and validation, and dose-finding studies are underway.

As requested at the March 1998 pre-NDA meeting, the Suboxone NDA contains all mono buprenorphine toxicology data from the Subutex NDA 20-732, to avoid the problem of cross-referral to an unapproved application. Therefore, it should not be necessary to re-evaluate these data. However, the following new items relating to the mouse carcinogenicity data were not submitted in the Subutex NDA. These are presented in Suboxone NDA Volume 45 in Section 5.G.6.23, as shown below.

Section	Title	Report	Volume
5.G.6.23	Mouse Toxicity and Toxicokinetics Following Dietary Administration of Buprenorphine.	Report RC980117	45
	Contains:		
5.G.6.23.1	M 60029 Toxicity to Mice in Continuous Dietary Administration over 4 Weeks	RPEX 30000/071	45
5.G.6.23.2	Analysis of Buprenorphine Hydrochloride in Diet and in Blood Plasma Samples	SORA 30000/072	45
5.G.6.23.3	M 60029 Preliminary Assessment of Toxicity to Mice by Continuous Dietary Administration for 13 weeks	RPEX 30001/072	45
5.G.6.23.4	Plasma Concentrations of Buprenorphine in Mice Following Continuous Dietary Administration (weeks 1-84. — Study RKT221)	RPSL 30001/084	45
5.G.6.23.5	Potential tumorigenic Effects of Buprenorphine on Prolonged Dietary Administration to Mice (RKT221) Buprenorphine Content of the Feed throughout the Study	RPSL 30001/085	45
5.G.6.23.6	Potential tumorigenic Effects of Buprenorphine on Prolonged Dietary Administration to Mice (— 12). Buprenorphine Content of the Feed (weeks 1, 6 and 13	RPSL 30008/001	45
5.G.6.23.7	Plasma Concentrations of Buprenorphine in Mice Following Continuous Dietary Administration (weeks 1-100. — Study — /12)	RPSL 30008/005	45
5.G.6.23.8	Potential tumorigenic Effects of Buprenorphine on Prolonged Dietary Administration to Mice (— /12). A Radioimmunoassay Validation Report	RPSL 30008/003	45
5.G.6.23.9	Potential tumorigenic Effects of Buprenorphine on Prolonged Dietary Administration to Mice (/ 12). A High Performance Liquid Chromatography Validation Report	RPSL 30008/002	45

Clinical Pharmacology

1. *Since it was stated in the preliminary report (study CR96/012) that it is not practical to administer three 8mg tablets to achieve the 24mg dose, if alternate dosing strategy is to be used for doses higher than 16mg, then pharmacokinetic data to support the alternate dosing scheme(s) is needed.*

The labeling proposes that up to 2 tablets can be taken at any one time.

2. *Since sublingual tablets are formulated to disintegrate rapidly, the use of a basket rotation speed of 75 rpm for the proposed dissolution method seems to be relatively high and the ability of it to predict the in vivo dissolution is a concern. Please provide in vitro dissolution data at lower basket rotation speeds in media reflecting normal saliva (i.e., buffer at the appropriate saliva pH) ideally using batches (within expiration dates) of the 2mg and 8 mg dosage strength that was studied in the pharmacokinetic and/or clinical studies (i.e., n=12 dosage units per tablet batch).*

Dissolution studies have been undertaken as requested and presented and reviewed in Section 6.E in NDA Volume 53, page 130. A basket rotation speed of 75 rpm is now proposed.

3. *Upon drinking acidic or alkaline beverages immediately preceding the administration of buprenorphine sublingual tablets, the pH in the patient's mouth could be significantly altered. Please explain how this might affect the absorption of buprenorphine from the sublingual tablet and its clinical implications. Please provide in vitro dissolution profile of the sublingual tablets as a function of pH.*

This has been reviewed in Section 6.E: Dissolution, in NDA Volume 53, page 130.

4. *Although the sublingual tablet is meant to be placed underneath the tongue and disintegrate by itself, there is concern that there might be instances when the patient might (i) swallow whole tablets (ii) chew and retain in the mouth or (iii) chew and swallow the tablet. Under IND 35,877 (serial 078) submitted on January 16, 1998, a protocol is proposed to assess the oral bioavailability (ie, swallowing the whole tablet) of the 8mg buprenorphine/2mg naloxone combination tablet. Consideration should be given to modifying this protocol to address the above concerns of both mono and combo tablets.*

The clinical part of the above study has been completed and currently the data are being assessed. It was considered impractical to change the protocol. However, it is thought that chewing will produce intermediate results between sublingual and oral administration.

5. *A search of the scientific literature relative to the cytochrome P450 enzyme(s) relationship to buprenorphine metabolism and drugs which are likely to be coadministered with buprenorphine should be performed. Also, in vitro studies should be conducted as appropriate as covered in FDA's guidance "Guidance for*

Industry: Drug Metabolism/Drug Interaction studies in the Drug Development Process: Studies in Vitro” (<http://www.fda.gov/cder/guidance.htm>).

A review of the literature relating to the metabolism of buprenorphine by cytochrome P450 enzymes is presented in Section 6.B.2 (NDA Volume 53, page 45). The published reports are presented in Section 6.F.3.6 (NDA Volume 68, page 168 *et seq*). An *in vitro* study of the interaction of flunitrazepam and buprenorphine is given in Section 6.F.3.6.8 (NDA Volume 68, page 234).

6. *From completed or to be completed pharmacokinetic studies, analyses assessing the effect of age, weight and gender on the pharmacokinetics of buprenorphine sublingual tablets should be carried out.*

A population PK analysis of data from the #1008 study (CR96/013 and CR96/014) and other tablet pharmacokinetic studies has been undertaken to determine the important covariates that affect the pharmacokinetics of buprenorphine. This is presented in Section 6.F.2.1.4 (NDA Volume 57) and in Section 8.C.2.2.4 (NDA Volume 75)

7. *In the proposed Package Insert (Clinical Pharmacology Section) submitted with NDA 20-733 please provide: data restricted to that from tablets, inter-patient and intra-patient variability data, experimental details on tables, dose proportionality data, basic PK and P450 information, gender, weight and age relationships, and details of the method of administration.*

The package insert has been written with these points in mind.

8. *Final study reports with pharmacokinetic data for studies CR97/007, CR96/013 and CR96/014 must be submitted with the combo NDA. The NDA will not be regarded as complete for filing without this information.*

The final report for CR97/007 is submitted in Section 6.F.2.1.2 (NDA Volumes 55-56) and Section 8.C.2.2.2 (NDA Volumes 72-73). A population PK report of PK data from the #1008 study (CR96/013 and CR96/014) and other tablet pharmacokinetic studies is presented in Section 6.F.2.1.4 (NDA Volume 57) and in Section 8.C.2.2.4 (NDA Volume 75).

9. *Please note item #2 under Chemistry*

Chemistry

1. *If the estimated concentration of buprenorphine at the point of entry into the aquatic environment is less than one (1) part per billion, you may be eligible for a categorical exclusion from the requirement to provide an environmental assessment. The regulations covering an exclusion can be found in the Federal Register notice dated July 29, 1997 and entitled “National Environment Policy Act; Revision of Policies and Procedures; Final Rule”. The certification that you prepare should*

refer to 21 CFR 25.31(b). Information regarding the format of the categorical exclusion claim can be found in 21 CFR 25.15(d).

A categorical exclusion from the requirement to provide an environmental assessment is claimed on the basis that the estimated concentration of buprenorphine and naloxone at the point of entry into the aquatic environment are less than 1 ppb, respectively. A certification with documentation is provided in Section 4.B.9 (NDA Volume 3, page 397)

- 2. The dissolution method needs to be performed on equipment that can be easily obtained commercially. The proposed regulatory method does not meet this standard and therefore needs to be revised and a new specification needs to be set. Please refer to the USP Monograph for Isosorbide Dinitrate Sublingual tablets (Page 859 in USP XXIII)*

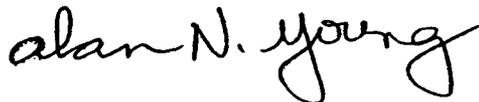
Dissolution testing of Suboxone tablets is conducted on standard equipment described in the USP. A number of studies have been conducted at various conditions and these are summarized in Sections 4.B.10.15 through 4.B.10.19 (NDA Volume 5, pages 1-192). A revised method (USP basket assembly at \sim rpm) is proposed in Section 4.B.6.

- 3. Please provide a linkage table to show correspondence between the clinical study number and the clinical study lot number.*

Linkage of clinical study number and the clinical study lot number is presented in Section 4.B.10.20 (NDA Volume 5, page 193).

Thank you for the review of these products.

Yours sincerely,



Alan N. Young
Director, Regulatory Affairs

**APPEARS THIS WAY
ON ORIGINAL**

2 Page(s) Withheld



Office of the Commissioner
Food and Drug Administration
5600 Fishers Lane
Room 14-105, HF-7
Rockville, MD 20857
301-827-3390

Food and Drug Administration
Rockville MD 20857

August 22, 1996

Mr. Charles O'Keeffe
President
Reckitt & Colman Pharmaceuticals, Inc.
1901 Huguenot Road
Richmond, VA 23235

Re: Prescription Drug User Fee Act of 1992
Waiver Request
Our file: _____

Dear Mr. O'Keeffe:

This letter responds to your letter on behalf of Reckitt & Colman, Inc., dated April 16, 1996, requesting a waiver of the application fees assessable upon submission of the marketing applications covering _____ (NDA 20-733, buprenorphine/naloxone) and Subutex® (NDA 20-732, buprenorphine) pursuant to the Prescription Drug User Fee Act of 1992, 21 U.S.C. § 379h(a)(1). For the reasons described below, the Food and Drug Administration (FDA) grants the waivers requested.

Reckitt and Colman stated in its letter requesting a waiver that it plans to submit marketing applications covering _____ and Subutex®, both indicated for the treatment of narcotic addiction, in the near future. During fiscal year (FY) 1996, an application fee in the amount of \$204,000 is assessable upon submission of a marketing application. Reckitt and Colman requested a waiver of assessable fees under two statutory waiver provisions: first, that a waiver is necessary to protect the public health, 21 U.S.C. § 379h(d)(1); and second, that the fee is a significant barrier to innovation, 21 U.S.C. § 379h(d)(2).

In support of its waiver request, Reckitt and Colman stated that there are currently only two medications approved for the treatment of opioid addiction, methadone and naltrexone. According to Reckitt and Colman,

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methadone is a full agonist, and patients have difficulty withstanding its protracted withdrawal symptoms. Furthermore, according to Reckitt and Colman, fatal accidental overdoses in unintended methadone users have been reported. Reckitt and Colman stated further that naltrexone, an agonist, is used to maintain abstinence in detoxified opioid addicts, but has found limited acceptance as it generally requires highly motivated patients to be successful.

Reckitt and Colman stated that buprenorphine is a semi-synthetic, highly lipophilic opioid derived from thebaine. It is a partial agonist, and as such, according to Reckitt and Colman, can act as either an agonist or an antagonist, depending on the circumstances of its use. Reckitt and Colman stated that in abstinent, morphine-dependent dogs, buprenorphine suppresses signs of withdrawal, while in stabilized opioid-dependent dogs, buprenorphine precipitates withdrawal. Reckitt and Colman stated further that the effects of buprenorphine in non-tolerant individuals is dose dependent within a limited range, beyond which increasing doses do not produce corresponding increases in effect. According to Reckitt and Colman, it is this ceiling that accounts for buprenorphine's safety and lack of toxicity. Reckitt and Colman explained that naloxone is included in _____ to prevent misuse; the single entity product will be reserved for pregnant addicts or others whose medical condition precludes the combination product.

FDA's Office of Orphan Product Development (OPD) has designated _____ and Subutex® as orphan products, on the ground that there is no reasonable expectation that the costs of developing and making the products available will be recovered from sales during the period of orphan exclusivity. OPD rejected Reckitt and Colman's argument that for purposes of orphan product designation, the patient population is the number of treatment slots available under state and federal antiaddiction programs (approximately 115,000, according to Reckitt and Colman), concluding instead that the patient population is the number of opioid addicts, estimated to be between 1,000,000 and 1,500,000. However, Reckitt and Colman stated, and OPD agreed, that the projected revenue from sales of _____ and Subutex® during their first year of marketing is _____, On this basis, OPD designated _____ and Subutex® as orphan products.

Reckitt and Colman stated further that the total annual revenue for the entity as whole was _____ in 1995.¹ The total revenue for Reckitt and Colman Pharmaceuticals for the same year was _____

Ordinarily, FDA will find that a fee is a significant barrier to innovation on the basis of two showings: first, that the entity is engaged in the research or development of an innovative product; and second, that the fee is a significant barrier to the entity's continued research, development or marketing of the innovative product due to limited resources or other circumstances.

In applying the first criterion, in order to determine whether a product is innovative, FDA looks to the nature of the product and to whether one or more of its characteristics (including, but not limited to, its dosage form, route of administration, indication, safety or effectiveness data) are new in relation to currently marketed products. FDA also looks at whether the applicant's claims regarding the product are supported by a reasonable, scientific rationale; however, a product need not necessarily be approved or approvable in order to be found innovative.

With respect to the first criterion, notwithstanding FDA's inability to predict at this time whether Reckitt and Colman will be able to carry the burden of demonstrating the safety and efficacy of _____ and Subutex®, FDA concludes that _____ and Subutex®, products intended to treat opiate addiction that may be better tolerated and less toxic than currently available products, are innovative products within the meaning of the term in the context of the User Fee Act. This conclusion is based, in part, on OPD's conclusion that there is adequate clinical evidence to establish a medically plausible basis for expecting the buprenorphine to be effective. See 21 CFR § 316.25.

In applying the second criterion, FDA balances a variety of factors, including, but not limited to, the estimated patient population and the revenue to be derived from sales of the drug product, and the total annual revenue of the entity. In addition, FDA may also consider other circumstances that would significantly impede the development of innovative drug products. Ordinarily, a fee is not a significant barrier to innovation because the revenue to be derived

¹ Reckitt and Colman's headquarters are located in London. According to the 1995 annual report, as a whole, the company generated _____ in turnover. Based on an exchange rate of _____ FDA understands that this is roughly equivalent to a total annual revenue of _____

from sales of the drug product, the entity's gross annual revenue, or other factors, provide a sufficient basis for payment of the fee.

With respect to the second criterion, FDA concludes that Reckitt and Colman has shown that assessment of the fee is a significant barrier to the continuation of researching, developing, or marketing innovative products. In this case, because Reckitt and Colman's total annual revenue is _____, it should have sufficient resources to pay the assessable application fees. However, FDA recognizes that, in some cases, a fee may present a significant barrier to innovation based on circumstances other than a company's current resources. FDA notes that in cases where the projected revenue of a product is limited, a fee may create a substantial chilling effect, discouraging the future research, development and marketing of the product on which the fee is assessed and on similarly situated products. FDA recognizes that orphan products, as a class, are particularly susceptible to this chilling effect because orphan products generally do not produce revenue to the extent of non-orphan products. The extent of this chilling effect is proportional to the size of the fee and is inversely proportional to the size of projected sales revenue. A relatively large fee will have minimal chilling effect on the development of products with large estimated sales revenue by companies with large current resources. However, the chilling effect increases as the projected revenue for the drug product decreases, even with regard to companies with large current resources. Therefore, a fee could have a substantial chilling effect on and consequently pose a significant barrier to the development of orphan products that are expected to generate low revenue.

Reckitt and Colman estimates that if approved, _____ and Subutex® would generate limited sales revenue of _____ during the first year of marketing. FDA concludes that due to the limited commercial potential of _____ and Subutex®, assessment of the application fees would create a substantial chilling effect on future research, development and marketing of these products and other similarly situated orphan products. Therefore, in balancing Reckitt and Colman's total annual revenue, the commercial potential of the products, and the potential for a fee to substantially chill or deter the development of these products and similar future orphan products, FDA concludes that assessment of application fees in this case would present a significant barrier to the researching, developing, and marketing of an innovative product.

Reckitt and Colman
August 22, 1996
Page 5

Accordingly, based on this particular combination of factors, FDA grants Reckitt and Colman a waiver of the application fees assessable upon submission of the marketing applications of _____ (NDA 20-733) and Subutex® (NDA 20-732) on the ground that the fees are a significant barrier to innovation, 21 U.S.C. § 379h(d)(2).² Reckitt and Colman should include a copy of this letter in its marketing applications.

Please note that as announced in User Fee Correspondence 3, dated August 5, 1993, FDA plans to disclose information about its actions granting or denying waivers consistent with the laws and regulations governing the disclosure of confidential commercial or financial information.

If you have any questions about this matter, please call Suzanne O'Shea, of this office, at 301-827-3390.

Sincerely yours,

[/S/]

Amanda Bryce Norton
Chief Mediator and Ombudsman

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² Because FDA is granting Reckitt and Colman's request for a waiver on the ground that the fee is a significant barrier to innovation, FDA need not consider whether a waiver is also justified on the ground that a waiver is necessary to protect the public health, 21 U.S.C. § 379h(d)(1).

**NATIONAL INSTITUTES OF HEALTH
ALCOHOL, DRUG ABUSE AND MENTAL HEALTH ADMINISTRATION
COOPERATIVE RESEARCH AND DEVELOPMENT AGREEMENT***

This Cooperative Research and Development Agreement, hereinafter referred to as the "CRADA," consists of this Cover Page, an attached Agreement, a Signature Page and various Appendices referenced in the Agreement. This Cover Page serves to identify the Parties to this CRADA:

(1) the following Bureau(s), Institute(s) or Division(s) of the National Institutes of Health: National Institute on Drug Abuse, hereinafter singly or collectively referred to as the "NIH/ADAMHA;" and

(2) Reckitt & Colman Pharmaceuticals, Inc., which has offices at 1901 Huguenot Road, Richmond, Virginia, 23235, hereinafter referred to as the "Collaborator."

Although drafted for two Parties, the attached CRADA may also be used for any number. This Cover Page, however, should be modified by repeating block (2) to identify other Parties to the CRADA. All non-NIH/ADAMHA Parties are hereinafter collectively referred to as the "Collaborator." Use of the terms "Collaborator," "Party" and "Parties" should be construed as appropriate for the actual number of CRADA participants.

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*This Cooperative Research and Development Agreement form is effective on an interim basis, and will be revised after October 1, 1989 for use in CRADAs entered into by NIH/ADAMHA after that date. Questions or comments about this CRADA and requests for updated versions should be directed to the NIH Office of Technology Transfer at (301) 496-0750.

CRADA SIGNATURE PAGE

FOR NIH

ISI

APR 26 1994

Date

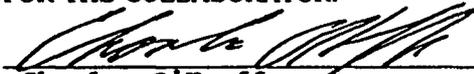
Alan I. Leshner, Ph.D.
Director, NIDA

Mailing Address for Notices:

Alan I. Leshner, Ph.D.
Director
National Institute on Drug Abuse
Parklawn Building, Room 11A55
5600 Fishers Lane
Rockville, Maryland 20857

ATTENTION: Mr. Lee Cummings
(301) 443-1428
(301) 443-2599 FAX

FOR THE COLLABORATOR:



Charles O'Keefe
Executive Vice President

4/29/94
Date

Mailing Address for Notices:

Reckitt & Colman Pharmaceuticals, Inc.
1901 Huguenot Road
Richmond, VA 23235

**APPEARS THIS WAY
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[Include additional signature and address blocks as necessary for all Parties to this CRADA.]

Office of Orphan Products Development(HF-35)
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

June 15, 1994

Reckitt & Colman Pharmaceuticals, Inc.
Attention: Mr. Charles O'Keeffe
Executive Vice President
1901 Huguenot Road
Richmond, VA 23235

Dear Mr. O'Keeffe:

Reference is made to your orphan drug application of May 5, 1993 submitted pursuant to Section 526 of the Federal Food, Drug, and Cosmetic Act (FFDCA) for the designation of buprenorphine hydrochloride as an orphan drug (application # ———). We also refer to your amendment dated November 15, 1993.

We have completed the review of this application, as amended, and have determined that buprenorphine qualifies for orphan designation for the treatment of opiate addiction in opiate users under Section 526(a)(2)(B) of the FFDCA. Please note that it is buprenorphine and not its formulation that has received orphan designation.

Prior to marketing approval, sponsors of designated orphan products are requested to submit written notification to this Office of their intention to exercise orphan drug exclusivity if they are the first sponsor to obtain such approval for the drug. This notification will assist FDA in assuring that approval for the marketing of the same drug is not granted to another firm for the statutory period of exclusivity. Also please be advised that if buprenorphine were approved for an indication broader than the orphan designation, your product might not be entitled to exclusive marketing rights pursuant to Section 527 of the FFDCA. Therefore, prior to final marketing approval, sponsors of designated orphan products are requested to compare the designated orphan indication with the proposed marketing indication and to submit additional data to amend their orphan designation prior to marketing approval if warranted.

In addition, please inform this office annually as to the status of the development program, and at such time as a marketing application is submitted to the FDA for the use of buprenorphine as designated. If you need further assistance in the development of your product for marketing, please feel free to contact Dr. John McCormick at (301) 443-471.

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Please refer to this letter as official notification of designation and congratulations on obtaining your orphan drug designation.

Sincerely yours,

[/S/]
Marlene E. Haffner, M.D., M.P.H.
Director

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94 **Draft Labeling Page(s) Withheld**