

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

20-732

20-733

CHEMISTRY REVIEW(S)

**DIVISION OF ANESTHETIC, CRITICAL CARE, AND ADDICTION
DRUG PRODUCTS (HFD-170)**

Review of Chemistry, Manufacturing, and Controls

SUBOXONE SUBLINGUAL TABLETS

NDA #: 20-733

DATE REVIEWED: 10/08/02

REVIEW #: 3

REVIEWER: Ali Al-Hakim

<u>SUBMISSION TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
Original NDA	06/03/1999	06/07/1999	
Amendment	07/28/2000	07/28/2000	
Amendment	11/29/2000	12/18/2000	
Amendment	02/27/2001		
Amendment	06/07/2001		
Amendment	08/21/2001		
Amendment	11/20/2001	11/26/2001	
Amendment	01/14/2002	01/14/2002	
Amendment	02/01/2002	02/04/2002	
Amendment	02/14/2002	02/19/2002	
Amendment	03/13/2002	03/14/2002	
Amendment	04/26/2002	05/03/2002	
Amendment	05/02/2002	05/03/2002	
Amendment	05/07/2002	05/08/2002	
Amendment	05/13/2002	05/13/2002	
Amendment	05/17/2002	05/17/2002	
Amendment	05/21/2002	05/21/2002	
Amendment	06/07/2002	06/10/2002	
Amendment	06/17/2002	06/17/2002	
Amendment	06/25/2002	06/26/2002	
Amendment	08/07/2002	08/07/2002	
Amendment	08/23/2002	08/17/2002	
Amendment	09/03/2002	09/04/2002	
Amendment	09/24/2002	09/26/2002	
Amendment	09/27/2002	09/30/2002	
Amendment	09/30/2002	10/01/2002	
Amendment	10/02/2002	10/07/2002	
Amendment	10/03/2002	10/04/2002	
Amendment	10/04/2002	10/04/2002	
Amendment	10/07/2002	10/07/2002	

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NAME & ADDRESS OF APPLICANT: Reckitt Benckiser Pharmaceuticals Inc.
1909 Huguenot Road
Richmond, VA 23235

DRUG PRODUCT NAME:

<u>Proprietary:</u>	Suboxone
<u>Nonproprietary/USAN:</u>	Buprenorphine/Naloxone
<u>Code Name/#:</u>	None
<u>Chem.Type/Ther.Class:</u>	4/PV

PHARMACOLOGICAL CATEGORY:	Opioid Agonist/Antagonist
INDICATION:	Treatment of narcotic addiction
DOSAGE FORM:	Sublingual Tablet
STRENGTH:	2mg/0.5mg and 8mg/2mg
ROUTE OF ADMINISTRATION:	Oral
HOW DISPENSED:	Rx <input checked="" type="checkbox"/> OTC <input type="checkbox"/>
SPECIAL PRODUCT:	Yes <input type="checkbox"/> No <input checked="" type="checkbox"/>

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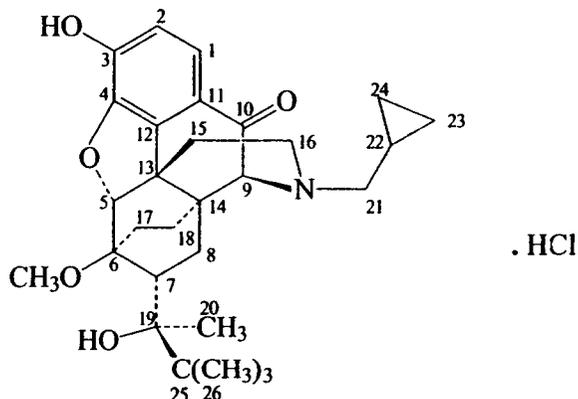
CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:
Suboxone consists of two active ingredients, Buprenorphine and Naloxone. Chemical name, structural formula, molecular weight and molecular formula for those components are shown below.

Buprenorphine

Chemical Name:

21 -Cyclopropyl -7 α -[(S)-1-hydroxy-1,2,2-trimethylpropyl]-6,14-endo-ethano-6,7,8,14-tetrahydrooropavine hydrochloride

Structural Formula:



Molecular Formula: $C_{29}H_{41}NO_4 \text{ HCl}$

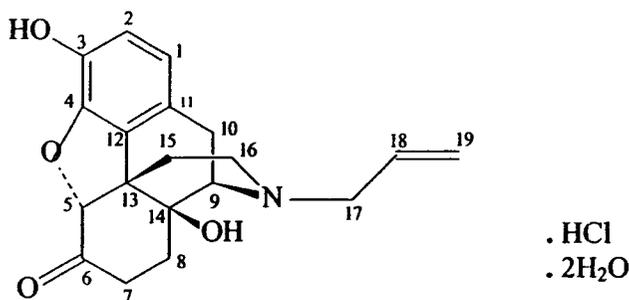
Molecular Weight: 504.09

Naloxone

Chemical Name:

17-Allyl-4,5 α -epoxy-3,14-dihydroxymorphinan-6-one hydrochloride dihydrate

Structural Formula



Molecular Formula: $C_{19}H_{21}NO_4 \text{ HCl} \cdot 2H_2O$

Molecular Weight: 399.87

SUPPORTING DOCUMENTS:

DMF Number and Type	Item referenced	Holder	Status	Review Date and Reviewer's Name	Autho. Letter Date
II	Buprenorphine HCl	Reckitt and Benckiser	Adequate	P. Maturu, HFD-170 May 08, 2002	N/A
II			Adequate	P. Maturu, HFD-170 October 7, 2002	03/31/93
			Withdrawn		12/12/01
III			Not Reviewed*		12/14/01
III			Adequate	P. Maturu, HFD-170 June 21, 2002	01/11/02
III			Adequate	P. Maturu, HFD-170 June 26, 2002	12/19/01
III			Adequate	P. Parsad, HFD-570 08/06/01	12/10/01
III			Withdrawn		12/16/01
III			Withdrawn		01/09/02

*DMF is not reviewed; however, adequate information to the NDA (amendment dated May 17, 2002)

RELATED DOCUMENTS (if applicable):

NDA 20-732 Subutex (Buprenorphine Sublingual Tablets).

CONSULTS:

- Biopharmaceutics: Acceptable
- Nomenclature (OPDRA): Acceptable
- Statistics: Completed (see recommended expiration dating)
- Microbiology: Satisfactory
- Establishment Evaluation Report Acceptable

REMARKS/COMMENTS:

- This review deals mainly with the major chemistry, manufacturing and control amendment, dated March 13, 2002, for the above NDA. The applicant reported that this amendment contains a complete description of the Chemistry, Manufacturing and Control procedures for the proposed commercial product. However, the review contains additional supporting information/data from amendments submitted before and after March 13, 2002.
- The _____ was withdrawn from the NDA.
- The firm has agreed to submit formal validation of the HPLC method for the _____ impurity when the reference standard becomes available.
- The firm has agreed that in the event that it is determined that _____ is genotoxic, that they will investigate the presence of this potential degradation product in the drug product, and work with the agency as necessary to limit it's level.
- See phase IV commitment concerning the _____ impurity in the drug substance.

CONCLUSIONS & RECOMMENDATIONS:

The application may be approved from the Chemistry, Manufacturing and Controls point of view.
See CMC related phase IV commitment.



Ali Al-Hakim, Ph.D.
Review Chemist, HFD-180



Dale Koble, Ph.D.
Chemistry Team Leader, HFD-170

cc:

NDA # 20-733

HFD-170/S.McCormick

HFD-170/Div File/NDA # 20-733

HFD-180/A.Al-Hakim

HFD-170/D.Koble

HFD-170/S.Shepherd

HFD-820/E. Duffy

10/07/02/C:\Wordfiles\New Drug Applications\Suboxone 20-733.3

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this page is the manifestation of the electronic signature.**

/s/

Ali Al-Hakim
10/8/02 03:20:36 PM
CHEMIST

Dale Koble
10/8/02 03:31:13 PM
CHEMIST

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**DIVISION OF ANESTHETIC, CRITICAL CARE, AND ADDICTION
DRUG PRODUCTS (HFD-170)**

Review of Chemistry, Manufacturing, and Controls

NDA #: 20-733 **DATE REVIEWED:** 01/11/2001

REVIEW #: 2 **REVIEWER:** Ali Al-Hakim

<u>SUBMISSION TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
Amendment (BC)	11/29/2000	12/01/2000	12/04/2000

NAME & ADDRESS OF APPLICANT: Reckitt & Colman Pharmaceuticals, Inc.
1909 Huguenot Road
Richmond, VA 23235

DRUG PRODUCT NAME:

<u>Proprietary:</u>	Suboxone
<u>Nonproprietary/USAN:</u>	Buprenorphine/Naloxone
<u>Code Name/#:</u>	None
<u>Chem.Type/Ther.Class:</u>	4/PV

PHARMACOLOGICAL CATEGORY:	Opioid Agonist/Antagonist
INDICATION:	Treatment of Drug addiction
DOSAGE FORM:	Sublingual Tablet
STRENGTH:	8mg/2mg, 2mg/0.5mg
ROUTE OF ADMINISTRATION:	Oral
HOW DISPENSED:	Rx <input checked="" type="checkbox"/> OTC <input type="checkbox"/>
SPECIAL PRODUCT:	Yes <input type="checkbox"/> No <input checked="" type="checkbox"/>

**CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA,
MOL.WT:**

See next page

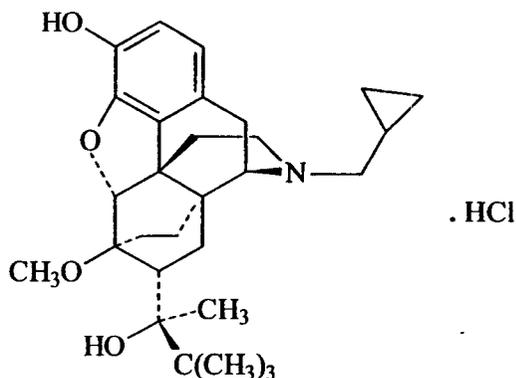
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**CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA,
MOL.WT:****Buprenorphine**

Chemical Name:

17-(cyclopropylmethyl)-a-(1,1-dimethylethyl)-4,5-epoxy-18,19-dihydro-3-hydroxy-6-methoxy-a-methyl-16,14-ethenomorphinan-7-methanol, hydrochloride.

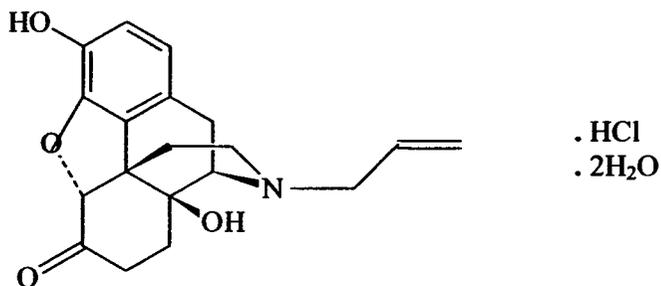
Structural Formula:

Molecular Formula: $C_{29}H_{41}NO_4 \text{ HCl}$

Molecular Weight: 504.09

NaloxoneChemical Name: (-)-17-Allyl-4,5 α -epoxy-3, 14-dihydroxymorphinan-6-one hydrochloride

Chemical Structure:

Molecular Formula: $C_{19}H_{21}NO_4 \text{ HCl} \cdot 2H_2O$

Molecular Weight: 399.87

**APPEARS THIS WAY
ON ORIGINAL**

SUPPORTING DOCUMENTS:

DMF Number and Type	Item referenced	Holder	Status	Review Date and Reviewer's Name	Letter Date
Type II	Buprenorphine HCl	Reckitt and Colman	Adequate	Pat Maturu, HFD-170 01/21/1998	N/A
Type II			Adequate	LL Huang, HFD-627 12/17/1996	N/A
Type III			Adequate	Sung Kim, HFD-150 10/29/1997	N/A
Type III			Adequate	R. Frankewich, HFD-180 02/23/1999	
DMF Type III			Adequate	Kenneth J. Furnkranz, HFD-525 February 13, 1995	N/A
DMF Type III			Adequate	Rober: Trimmer, HFD-625 November 29, 1995	N/A

RELATED DOCUMENTS (if applicable):

NDA 20-732 Subutex (Buprenorphine Sublingual Tablets).

Information request letter dated October 30, 2000

CONSULTS:**Biopharmaceutics Comments**

- Oval tablets were used in clinical pharmacokinetic/clinical studies, however, bioavailability and clinical data have been provided to support the efficacy and safety of both tablets.
- Dissolution testing was performed using $\frac{1}{2}$ and $\frac{1}{4}$ rpm; specification are $Q = \frac{1}{2}$ and $\frac{1}{4}$ after 5 minutes for buprenorphine and naloxone respectively.

Nomenclature: Office of Postmarketing Drug Risk Assessment (pending)**Statistics:** Not applicable due to short length of stability data

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REMARKS/COMMENTS:

The amendment contains responses to the information request letter (faxed to the firm on October 30, 2000 based on the Teleconference held on October 25, 2000). The main issue, which remains unresolved, is stability testing and related data of drug product.

CONCLUSIONS & RECOMMENDATIONS:

This NDA remains Unapprovable from Chemistry, Manufacturing and Control point of view. The NDA applicant should provide additional and satisfactory information delineated in the draft deficiency letter at the end of this review.

/S/

Ali Al-Hakim, Ph.D.
Review Chemist, HFD-18C

/S/

Dale Koble, Ph.D.
Chemistry Team Leader, HFD-170

cc:
NDA # 20-733
HFD-170/S.McCormick
HFD-170/Div File/NDA # 20-733
HFD-180/A.Al-Hakim
HFD-170/D.Koble
HFD-170/S.Shepherd
HFD-820/S.Koepke
R/D Init by:
AA: 01/10/01//MSWord/NDA/20-733.2AA

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/s/

Ali Al-Hakim
1/26/01 01:08:46 PM
CHEMIST

Dale Koble
1/26/01 01:56:24 PM
CHEMIST

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NDA# 20733

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**DIVISION OF ANESTHETIC, CRITICAL CARE AND ADDICTION
DRUG PRODUCTS, HFD-170**

Review of Chemistry, Manufacturing, and Controls

NDA#: 20-733

REVIEW# 3

DATE REVIEWED: 12.2.1999

<u>SUBMISSION TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
SUBMISSION	11.10.99		

NAME & ADDRESS OF APPLICANT:

Reckitt & Colman Pharmaceuticals Inc
1909 Huguenot Rd
Richmond, VA 23235
Alan Young, Director RA

DRUG PRODUCT NAME

Proprietary: SUBOXONE
Established: Buprenorphine HCl and Naloxone HCl dihydrate
sublingual tablets
Code Name/#:
Chem.Type/Ther.Class: 3S

PHARMACOL. CATEGORY: Orphan drug for the treatment of opioid
addiction

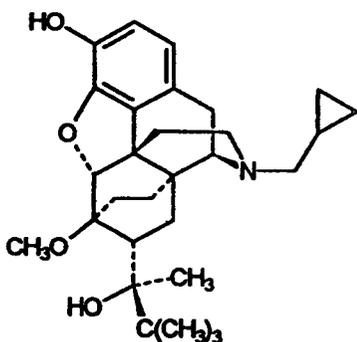
DOSAGE FORM: Replaced color tablets with tablets
STRENGTHS: 2mg/0.5mg and 8mg/2mg

ROUTE OF ADMINISTRATION: Oral
DISPENSED: X Rx OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA AND WEIGHT:

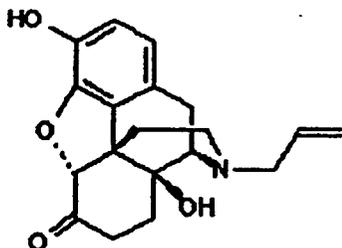
Chemically Buprenorphine HCl is 17-cyclopropylmethyl-alpha-1,1-
dimethylethyl-4,5-epoxy-18,19-dihydro-3-hydroxy-6-methoxy-alpha
methyl-6,14-ethanomorphinan-7-methanol, hydrochloride. C29 H41 N
O4. HCl and the Mw is 504.1. pKas =

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Chemically Naloxone HCl dihydrate is (-)-17-allyl-4,5-epoxy-3,14-dihydroxymorphinan-6-one, hydrochloride. C₁₉ H₂₁ N O₄ HCl 2(H₂O) and the MW is 399.9.



RELATED DOCUMENTS:

- 1) NDA 20732 is for Subutex, Buprenorphine HCl sublingual tablets. CMC information for Buprenorphine HCl drug substance is adequate by reference to NDA 20732.
- 2) NDA 18401 is for Buprenorphine HCl injection. CMC information for Buprenorphine HCl drug substance is adequate by reference to NDA 18401.
- 3) DMF _____ is for Buprenorphine HCl drug substance. CMC information for Buprenorphine HCl in DMF _____ is adequate by reference to NDA 18401.
- 4) DMF _____ is for _____ . CMC information in DMF _____ is adequate by reference to NDA 18733 for Talwin NX and NDA 16636 for Narcan. However, some deficiencies relating to SOPs were issued by Edwin Ramos, OGD, on 22 July 99. _____ has responded to these issues on 7th Sept 99, and Edwin Ramos has agreed to review ASAP. In my view, _____ responses are adequate for NDA. 20733. A review

document is being generated for DMF _____ to expedite a regulatory action for this high priority NDA.

- 5) IND 45220 is for Buprenorphine and Naloxone sublingual tablets.
- 6) DMF _____ for _____ supplied by _____ LOA to DMF was submitted in vol.1 p.36. This DMF is adequate by reference to reviews dated 29 Oct 97 by Drs. Sung Kim and Rebecca Wood, HFD-150.
- 7) DMF _____ for _____ supplied by _____ LOA to DMF was submitted in vol.1 p.38. This DMF is adequate by reference to reviews dated 23 Feb 99 by Drs. Raymond Frankowich and Eric Duffy, HFD-180.
- 8) DMF _____ for _____ supplied by _____ for the _____ supplied to VA Medical Center. This DMF is adequate by reference to review dated 25 Nov 95 by Drs. R.Trimmer and M.Smela, HFD-625.

REMARKS:

The applicant has provided a complete response to information request (IR) dated 2 Nov 99 addressed to NIH/NIDA to support stability of packaged white Suboxone lots in _____ for the clinical study duration. Responded items include the following

- 1) Stability data on Suboxone tablets in _____ compiled by NIDA using 'non-NDA' assay methods. _____ are not child resistant, which is a new requirement per 16 CFR 1700.14a4.
- 2) _____ chromatograms for _____ Suboxone clinical lots at zero time point and _____ retest point using 2 different LC methods of NIH/NIDA. Chromatograms at _____ test point has

_____ However, Naloxone potency is in the range _____ of claim. NIDA's test methods for assay are different from NDA test methods, and

- 3) Revised sampling plan for _____ testing of each lot transmitted by Rickett & Colman.
- 4) Tentative release specifications for _____ and _____ are set at _____ with rest to Naloxone for each individual decomposition products. No data is provided to support these specs.
- 5) _____ results in _____ from supplier's data.
- 6) A statement that _____ of Naloxone was converted to _____

by _____ at _____ for

Once again, no details are provided on the study to support these statements. More analytical work needs to be done on this issue.

- 7) A letter of authorization (LOA) to DMF# _____ for _____ component of _____ The applicant has committed to provide a LOA to _____ part supplied by _____.

The following items will also be provided at a later date to re-review the current approvable recommendation. These items are expected within 9 months.

(1) Retest results for Suboxone clinical lots packaged in child resistant closures in _____ with stability indicating methods for Naloxone.

(2) Identification of all decomposition products at or above _____ of the active ingredient to set specifications for decomposition products.

(3) Accelerated _____ studies per ICH Q1A.

(4) _____ to show compliance with USP 671 standards.

(5) Analytical reports to examine that a _____ did result in _____.

(6) Testing protocol for child resistance feature of the _____.

(7) _____ tests for _____ clinical lots to show compliance with USP 61 and USP 1111 standards.

Questions 1 to 5: (1) Certificate of analysis (COA) for packaged _____ Suboxone lots in _____ supplied as NIH/NIDA clinical test materials at _____.

(2) The retest results for these lots to support stability for the clinical study duration. (3) Test methods used for stability. (4) CFN#, if any, for the packaging site, _____.

(5) Name of suppliers for _____ with the corresponding DMFs and LOA to DMFs.

Response: To support market authorization request for _____ Suboxone tablets in _____ stored at CRT protected from excessive humidity, satisfactory stability at ambient RT storage, 17-20C and 30-60%RH, for up to _____ was submitted for _____ Suboxone tablets packaged in _____ using NIH/NIDA _____ assay methods. This stability data generated at _____ site was for Buprenorphine and Naloxone only, without any dissolution data

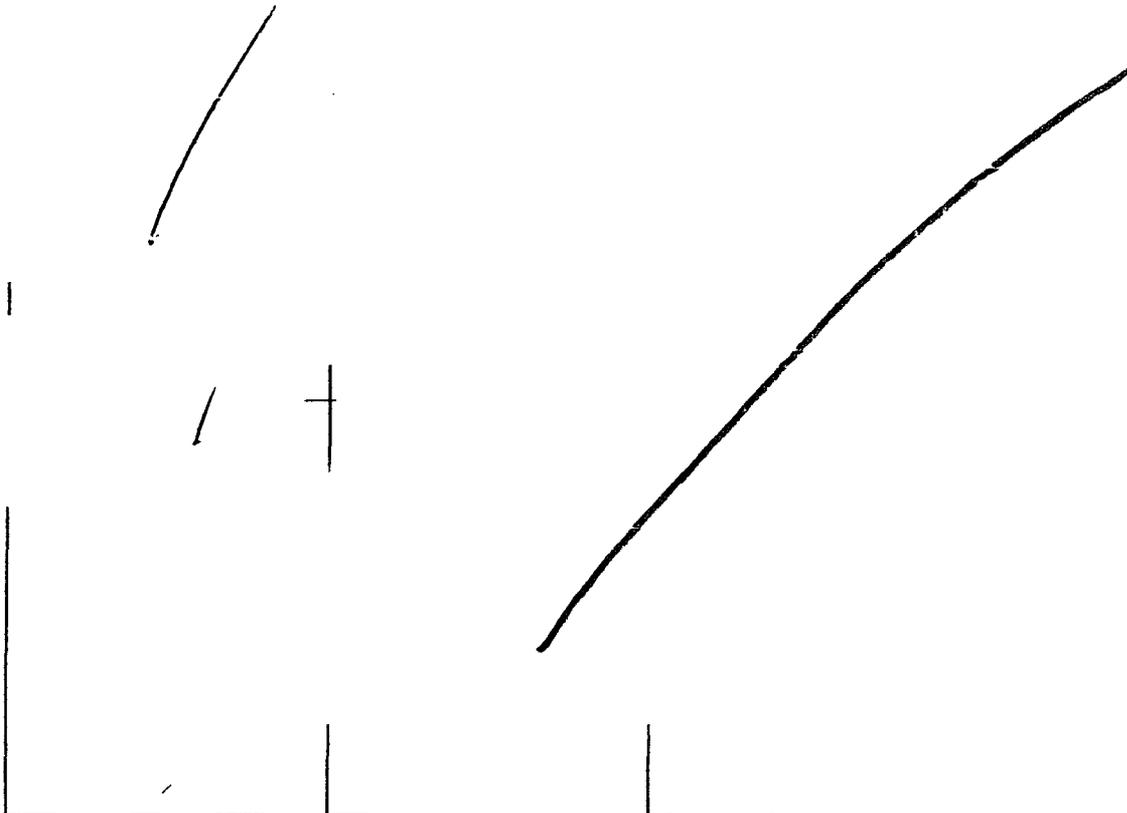
for Buprenorphine and Naloxone. Analytical results for _____ Suboxone lots per potency, was compiled and presented in subsequent pages, as tables 1, 3 and 4. These analytical results are not considered adequate. Dissolution data for Suboxone tablets was not monitored, as per attached tables, to show conformity with dissolution Q at 5 min of _____ for Buprenorphine and _____ for Naloxone

The November 10th, 1999, response has included _____ chromatograms for _____ Suboxone lots at zero release time point and _____ re-test point using two different LC methods employed by NIH/NIDA. Chromatograms at _____

_____ as per enclosed chromatograms. However, Naloxone potency is in the range _____ of claim. NIH/NIDA assay methods are different from NDA test methods, and _____

NIH/NIDA stability protocol for clinical materials is for assay only.

LC conditions	NIH/NIDA LC method at zero release time	NIH/NIDA LC method at _____ re-test	NDA 20733 LC method
---------------	---	-------------------------------------	---------------------



[REDACTED]

[REDACTED] packaging site for NIH/NIDA
Suboxone tablets has used ; [REDACTED]
[REDACTED] for this [REDACTED] is [REDACTED] at [REDACTED]
[REDACTED] for [REDACTED] (DIN [REDACTED] This
package is not a child resistant [REDACTED] DMF [REDACTED] for [REDACTED]
[REDACTED] part of [REDACTED] is adequate by review dated 29 Nov
99 by Drs. R.Trimmer and M.Smela, HFD-625.

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As per stability protocol of NIH/NIDA for Suboxone tablets, only assay was performed, and not tested for dissolution and decomposition products. The applicant was asked to develop test methods for Naloxone decomposition products and generate stability data to set specifications for Naloxone decomposition products.

A review of assay results for _____ Suboxone tablets packaged in _____ and stored at ambient RT storage, 17-20C and 30-60%RH, for up to _____ has shown acceptable stability by using NIH/NIDA assay methods. Naloxone potency at _____ was within the range _____ of claim, and without any decomposition product peaks. Analytical methods research is in progress at Rickett & Colman to identify assay methods that _____

Rickett & Colman has proposed for Suboxone tablets release a wider band of _____ for Naloxone content for 2mg/0.5mg tablets in comparison to _____ Naloxone content for 8mg/2mg tablets. Naloxone potencies were expressed in terms of free base equivalent. This is an exceptional request, because usually the release specs are closer to _____ of label claim.

Rickett & Colman has agreed to test _____ of each lot of Suboxone for release

The applicant has provided temperature and humidity readings for the _____ storage area for Suboxone tablets, _____ test results for _____ is about _____ for _____ (DIN _____). This package is not child resistant.

In summary, my recommendation is approvable (AE) action for _____ Suboxone tablets in _____. The applicant has made a verbal commitment to retest NIH/NIDA clinical supplies packaged in _____ and stored at ICH accelerated conditions for _____ using stability indicating methods. These results are due within 9 months.

List of deficiencies:

[]



[/S/]
P.Maturu, PhD, Review Chemist

[/S/] 12/2/99
A.D'Sa, Team Leader

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APPROVABLE

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NDA# 20733
Page -1

**DIVISION OF ANESTHETIC, CRITICAL CARE AND ADDICTION
DRUG PRODUCTS, HFD-170**

Review of Chemistry, Manufacturing, and Controls

NDA#: 20-733

REVIEW# 2

DATE REVIEWED: Rev 11.4.99

<u>SUBMISSION TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
FAX SUBMISSION	29 Oct 99		
FAX SUBMISSION	27 Oct 99		
SUBMISSION	5 Oct 99		
SUBMISSION	27 Aug 99		

NAME & ADDRESS OF APPLICANT:

Reckitt & Colman Pharmaceuticals Inc
1909 Huguenot Rd
Richmond, VA 23235
Alan Young, Director RA

DRUG PRODUCT NAME

Proprietary: SUBOXONE
Established: Buprenorphine HCl and Naloxone HCl dihydrate
sublingual tablets
Code Name/#:
Chem.Type/Ther.Class: 3S

PHARMACOL. CATEGORY: Orphan drug for the treatment of opioid
addiction

DOSAGE FORM: Replaced — color tablets with — tablets
STRENGTHS: 2mg/0.5mg and 8mg/2mg

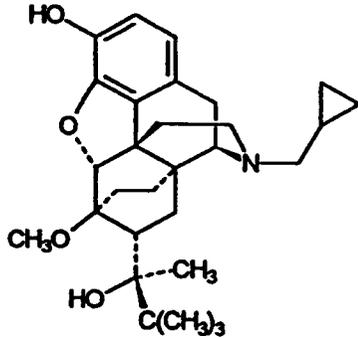
ROUTE OF ADMINISTRATION: Oral

DISPENSED: X Rx OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA AND WEIGHT:

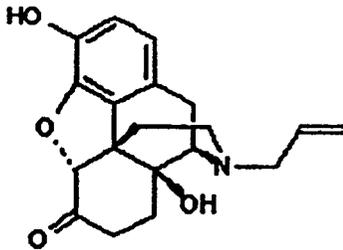
Chemically Buprenorphine HCl is 17-cyclopropylmethyl-alpha-1,1-
dimethylethyl-4,5-epoxy-18,19-dihydro-3-hydroxy-6-methoxy-alpha
methyl-6,14-ethanomorphinan-7-methanol, hydrochloride. C29 H41 N
O4. HCl and the Mw is 504.1. pKas = —

**APPEARS THIS WAY
ON ORIGINAL**



**APPEARS THIS WAY
ON ORIGINAL**

Chemically Naloxone HCl dihydrate is (-)-17-allyl-4,5-epoxy-3,14-dihydroxymorphinan-6-one, hydrochloride. C₁₉ H₂₁ N O₄ HCl 2(H₂O) and the MW is 399.9.



RELATED DOCUMENTS:

- 1) NDA 20732 is for Subutex, Buprenorphine HCl sublingual tablets. CMC information for Buprenorphine HCl drug substance is adequate by reference to NDA 20732.
- 2) NDA 18401 is for Buprenorphine HCl injection. CMC information for Buprenorphine HCl drug substance is adequate by reference to NDA 18401.
- 3) DMF _____ is for Buprenorphine HCl drug substance. CMC information for Buprenorphine HCl in DMF _____ is adequate by reference to NDA 18401.
- 4) DMF _____ is for _____. CMC information in DMF _____ is adequate by reference to NDA 18733 for Talwin NX and NDA 16636 for Narcan. However, some deficiencies relating to SOPs were issued by Edwin Ramos, OGD, on 22 July 99 _____ has responded to these issues on 7th Sept 99, and Edwin Ramos has agreed to review ASAP. In my view,

_____ responses are adequate for NDA. 20733. A review document is being generated for DMF _____ to expedite a regulatory action for this high priority NDA.

- 5) IND 45220 is for Buprenorphine and Naloxone sublingual tablets.
- 6) DMF _____ for _____ supplied by _____ to DMF was submitted in vol.1 p.36. This DMF is adequate by reference to reviews dated 29 Oct 97 by Drs. Sung Kim and Rebecca Wood, HFD-150.
- 7) DMF _____ for _____ supplied by _____ to DMF was submitted in vol.1 p.38. This DMF is adequate by reference to reviews dated 23 Feb 99 by Drs. Raymond Frankowich and Eric Duffy, HFD-180.

REMARKS:

The applicant has provided a partial response to information request (IR) dated 19 Aug 99 and 27 Oct 99. Responded items include additional stability data on Suboxone tablets, removal of _____ mfg site for Buprenorphine HCl drug substance, _____ and content uniformity data, a counter proposal for : _____ sampling plan for _____ testing, and on going test methods for Naloxone decomposition products. Pending items are retest results for packaged Suboxone clinical lots in _____, identification of the suppliers for _____, and _____ test results.

Question 1(Q.1): Provide all available stability data on Suboxone tablets.

Response 1(R.1): As per IR dated 19 Aug 99, Reckitt and Colman (RC) has responded on 5th Oct 99 with stability data for _____ 2mg and 8mg Suboxone tablets stored as bulk tablets in _____ containers with a _____, and stability figures for repackaged bulk in _____ are used for packaging NIH/NIDA clinical supplies.

**APPEARS THIS WAY
ON ORIGINAL**

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NIH/NIDA Clinical materials are 8mg/2mg tablet lots 6001/071/1995, 6001/086/1997 and 6001/137/1997, and 2mg/0.5mg tablet lot # as 6001/070/1995, 6001/085/1997 and 6001/136/1997. Tablet batch sizes were in the range _____ tablets to _____ tablets. These _____ Suboxone tablets, were mfg at Rickitt & Colman, Hull, UK, and stored in _____ containers with a _____ performed packaging in _____

Comment: A review of stability studies undertaken on Suboxone tablets suggest that _____ package will allow _____ shelf-life and it is a first viable option. _____ package was used by NIDA.

_____ option pursued by applicant will shorten allowable expiry date to _____ for 8mg _____ Suboxone tablets and _____ for 2mg _____ Suboxone tablets.

As per stability protocol, decomposition products of Naloxone are not tested. In my view, the applicant has to develop test methods for Naloxone decomposition products and revise stability protocol with the inclusion of a test for Naloxone decomposition products.

An information request was made to NIDA on 27 Oct 99 which includes COA and retest results for packaged Suboxone lots in _____ identification of the suppliers for _____ with the corresponding DMFs and LOA to DMFs.

Satisfactory stability under _____ storage condition for up to _____ was submitted for orange Suboxone tablets packaged in _____ in a fax submission dated 27 October 1999. This data was for Buprenorphine and Naloxone only, without any dissolution data for Buprenorphine and Naloxone. The applicant needs to provide dissolution data for Suboxone tablets packaged in _____ and stored under _____ storage condition to show conformity with dissolution Q at 5min of _____ for Buprenorphine and _____ for Naloxone

Q.2: Provide all available reports to examine _____

R.2. Review of analytical research relating to stability studies has shown detrimental effect of _____ on

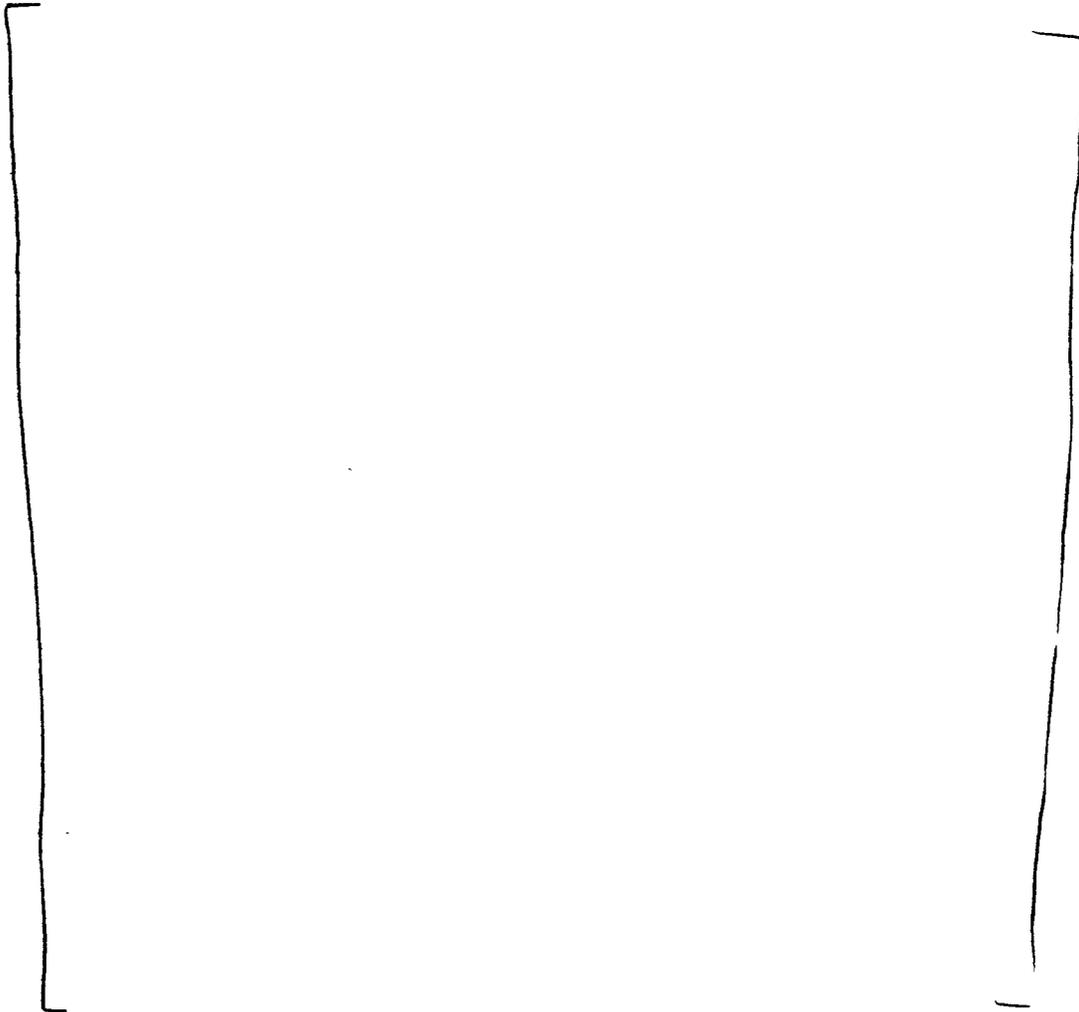
Naloxone in presence of Buprenorphine. [redacted] chromatograms were not submitted but a statement was made that observed peaks [redacted] (5th Oct 99 submission, attachment 6, p.2)

[redacted] are not submitted but a statement was made that observed [redacted] at base line for orange Suboxone tablets gave a positive response to [redacted]. This [redacted] at [redacted] base line was further analyzed by [redacted] but the presence of Naloxone could not be confirmed (5th Oct 99 submission, attachment 6, p.2-4).

Naloxone [redacted] decomposition products were reported on 27 Oct 99 for LC-MS study of Suboxone stored at [redacted] for [redacted] was proposed based on [redacted]

**APPEARS THIS WAY
ON ORIGINAL**

1 Page(s) Withheld



Conclusion: In my view, the response is inadequate, and the applicant has to develop test methods for Naloxone decomposition products. This issue was further discussed in telecon dated 27 Oct 99: a commitment was asked to develop test methods for Naloxone decomposition products and to set tentative specs for Naloxone decomposition products.

Q. 3: Submit uniformity of drug substance in —
pharmaceuticals and process development reports.

R.3 Up to 3% coefficient of variation (CV) for Buprenorphine and Naloxone assays were reported for — as a part of

— uniformity studies for — Suboxone — batches 34 and 36, in fax submission dated 29 October 99. Up to 5% CV for Buprenorphine and Naloxone assays were submitted for tablets drawn through out the tableting process as a part of content uniformity studies for — Suboxone tablets batches from — different lots, in fax submission dated 29 Oct 99.

Batch No	Sample Position	Buprenorphine Content	Naloxone Content
		Buprenorphine	Naloxone
06001/034			
Mean (mg)		2.05	0.51
% CV		1.19	1.71
Range (mg)			
06001/036			
Mean (mg)		2.05	0.51
% CV		1.80	3.64
Range (mg)			
Acceptance (Mean)	Ph.Eur (±5%)		
Acceptance (Range)	Ph.Eur (±15%)		

APPEARS THIS WAY
ON ORIGINAL

2mg Suboxone tablets

Table C.19: Naloxone content uniformity, mg per nominal tablet weight

Sample Time (Mins)	Batch Number - 06001/141		
	Mean	Range	%CV
0-30	0.490	[]	1.75
30-60	0.469		1.70
60-90	0.472		1.83
90-110	0.477		1.35
110-150	0.482		1.70
Acceptance Range Relative S.D. (%CV)	(———) (±15% USP/Ph.Eur) 6% maximum (USP)		

Table C.20: Naloxone content uniformity, mg per nominal tablet weight

Sample Time (Mins)	Batch Number - 06001/142		
	Mean	Range	%CV
0-30	0.490	[]	1.32
30-60	0.484		1.61
60-90	0.487		1.53
90-110	0.487		1.71
110-150	0.491		1.67
Acceptance Range Relative S.D. (%CV)	(———) (±15% USP/Ph.Eur) 6% maximum (USP)		

Table C.21: Naloxone content uniformity, mg per nominal tablet weight

Sample Time (Mins)	Batch Number - 06001/143		
	Mean	Range	%CV
0-30	0.485	[]	1.30
30-60	0.478		1.50
60-90	0.488		1.75
90-110	0.489		0.99
110-150	0.490		1.78

Batch	Buprenorphine mg per tablet			Naloxone mg per tablet		
	Mean	Range	%Cv	Mean	Range	%Cv
06001/070	2.03	[]	1.87	0.51	[]	1.95
06001/085	2.00		2.82	0.53		2.07
06001/136	1.99		1.24	0.47		0.82

Buprenorphine Acceptance:

Range: _____ (+/- 15% USP/PhEur)
Relative SD (%CV): 6% maximum

Naloxone Acceptance:

Range: _____ (+/- 15% USP/PhEur)
Relative SD (%CV): 6% maximum

Comment: The response is adequate. The uniformity and content uniformity data presented post release supplements weight uniformity test done to release clinical lots and reported in a fax dated 5 November 1997 to IND 45220.

Q.4: Delete _____ as mfg site for Buprenorphine HCl drug substance.

R.4 Agreed to delete _____ Site for Buprenorphine, as per submission dated 27 Aug 99.

Comment: The response is adequate. In view of applicants request in Oct 99, EES request to delete this site was initiated on 4 Nov 99. An e-mail request was made to _____ for overall compliance recommendation.

Q.5: Add tests for _____ and _____ to release Suboxone tablets. You have proposed testing for _____ batch

R.5. The applicant has made a counter proposal to test _____ batches for _____ and then a _____ sampling plan from _____ in fax submission dated 29 October 99.

Comment: The response is inadequate. It is premature to discuss _____ sampling plan for _____ given Suboxone has about _____ which

Q.6: Provide linkage between clinical protocol no and Suboxone

lots, and COA for Suboxone lots and drug substance lots.

R.6. The applicant has provided a linkage table between Suboxone lots and drug substance lots in submission dated 5th Oct 99.

Comment: NIH/NIDA clinical supplies of _____ Suboxone tablets were formulated from Buprenorphine HCl lots R01041, S12111 and T12101, and Naloxone HCl lots _____1526 and _____95/02. It may be possible to link Naloxone lots to _____ mfg site upon receipt of NIDA data, as promised in telecon dated 27 Oct 99.

Q.7: Provide analytical test results, _____ test results and acceptance criteria for the release of _____ used for packaging primary stability lots and clinical test lots of Suboxone

R.7. Not responded yet

Comment: This information is critical, and re-requested in telecon dated 27 Oct 99. A response is expected soon, as promised in telecon dated 27 Oct 99. This information is critical because _____ the decomposition of Naloxone HCl and Naloxone content is critical to prevent substance abuse of Buprenorphine HCl.

Overall summary comments: Instability of Naloxone in presence of Buprenorphine was reported for _____ orange colored Suboxone tablets packaged in _____ Instability of Naloxone was defined as _____ (Failure). The applicant was asked to develop test methods to determine Naloxone decomposition products in presence of Buprenorphine in a telecon dated 27 Oct 99.

In my view, _____ used for NIDA clinical materials, is the preferred container/closure system, as per figures 19 and 20 contained in 5th October 99 submission. However, to recommend a _____ expiry data, I would like to see test results and chromatograms for the data contained in figures 19 and 20. This data was requested from NIDA and promised delivery in telecon dated 27 Oct 99.

_____ the instability of Naloxone in the presence of Buprenorphine. _____ stability of Suboxone was not monitored and no data exists as of October 1999 as per telecon dated 27 Oct 99. In _____ packages, _____ shelf life is feasible for 2mg _____ tablets

and _____ shelf life for 8mg tablets.

CONCLUSIONS & RECOMMENDATIONS:

Instability of Naloxone in presence of Buprenorphine was reported for Suboxone tablets based on analytical research with LC _____ and _____ methods. Further work is warranted to explain _____

As per stability protocol, decomposition products of Naloxone are not tested. The applicant was asked to develop test methods for Naloxone decomposition products and to set tentative specifications for Naloxone decomposition products, in telecon dated 27 Oct 99.

A review of stability studies undertaken on Suboxone tablets suggest that _____ package is a first viable option to salvage this high priority file, NDA 20733/IND 45220, a joint venture of NIH/NIDA under CRDA.

The applicant has proposed for Suboxone tablets release a wider band of _____ for Naloxone content for 2mg/0.5mg tablets in comparison to _____ Naloxone content for 8mg/2mg tablets. Naloxone potencies were expressed in terms of free base equivalent. This is an exceptional request, because usually the release specs are closer to _____ of label claim.

Methods validation (MV) for _____ colored Suboxone tablets was initiated on 22 July 99 and EER was initiated on 19 July 99.

The applicant is willing to tests _____ of _____ production batches and then _____ sampling plan _____
_____ The response is inadequate given that Suboxone has about _____

The applicant has verbally agreed to provide analytical test results, _____ test results and acceptance criteria for the release of _____
_____ used for packaging primary stability lots and clinical test lots of Suboxone

**APPEARS THIS WAY
ON ORIGINAL**

In summary, my recommendation is to approve Suboxone tablets with _____ shelf life in _____ Another option is to store under _____ conditions for a shelf life of _____ The third option is to package Suboxone in _____ for a longer shelf life at CRT under ambient humidity conditions. The applicant has to make a phase IV commitment to develop test methods for Naloxone decomposition products, include a test for Naloxone decomposition products _____ as a part of the revised stability protocol for commercial batches of Suboxone tablets.

[/S/] / 11-5-99
P.Maturu, PhD, Review Chemist

[/S/] 11/3/99
A.D'Sa, Team Leader

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NDA# 20733

Page -1

**DIVISION OF ANESTHETIC, CRITICAL CARE AND ADDICTION
DRUG PRODUCTS, HFD-170**

Review of Chemistry, Manufacturing, and Controls

NDA#: 20-733

REVIEW# 1

DATE REVIEWED: 8.27.99

<u>SUBMISSION TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
SUBMISSION	3 June 99		

NAME & ADDRESS OF APPLICANT:

Reckitt & Colman Pharmaceuticals Inc
1909 Huguenot Rd
Richmond, VA 23235
Charles O'Keefe, President, tel.804-379-1090.

DRUG PRODUCT NAME

Proprietary: SUBOXONE
Established: Buprenorphine HCl and Naloxone HCl dihydrate
sublingual tablets
Code Name/#:
Chem.Type/Ther.Class: 3S

PHARMACOL. CATEGORY: Orphan drug for the treatment of opioid addiction

DOSAGE FORM: ——— color ——— tablets

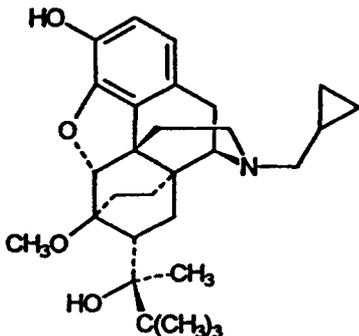
STRENGTHS: 2mg/0.5mg and 8mg/2mg

ROUTE OF ADMINISTRATION: Oral

DISPENSED: X Rx OTC

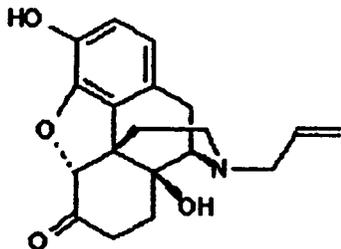
CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA AND WEIGHT:

Chemically Buprenorphine HCl is 17-cyclopropylmethyl- α -1,1-dimethylethyl-4,5-epoxy-18,19-dihydro-3-hydroxy-6-methoxy- α -methyl-6,14-ethanomorphinan-7-methanol, hydrochloride. C₂₉ H₄₁ N O₄. HCl and the Mw is 504.1. pK_as = ———



**APPEARS THIS WAY
ON ORIGINAL**

Chemically Naloxone HCl dihydrate is (-)-17-allyl-4,5-epoxy-3,14-dihydroxymorphinan-6-one, hydrochloride. C19 H21 N O4 HCl 2(H2 O) and the MW is 399.9.



RELATED DOCUMENTS:

- 1) NDA 20732 is for Subutex, Buprenorphine HCl sublingual tablets. CMC information for Buprenorphine HCl drug substance is adequate by reference to NDA 20732.
- 2) NDA 18401 is for Buprenorphine HCl injection. CMC information for Buprenorphine HCl drug substance is adequate by reference to NDA 18401.
- 3) DMF _____ is for Buprenorphine HCl drug substance. CMC information for Buprenorphine HCl in DMF _____ is adequate by reference to NDA 18401.
- 4) DMF _____ is for Naloxone HCl drug substance. CMC information in DMF _____ is adequate by reference to NDA 18733 for Talwin NX and NDA 16636 for Narcan.
- 5) IND 45220 is for Buprenorphine and Naloxone sublingual tablets.
- 6) DMF _____ for _____ supplied by _____ LOA to DMF was submitted in vol.1 p.36. This DMF is adequate by reference to reviews dated 29 Oct 97 by Drs. Sung Kim and Rebecca Wood, HFD-150.
- 7) DMF _____ for _____ supplied by _____ LOA to DMF was submitted in vol.1 p.38. This DMF is adequate by reference to reviews dated 23 Feb 99 by Drs. Raymond Frankowich and Eric Duffy, HFD-180.

REMARKS:

Clinical effectiveness studies for Suboxone were sponsored by NIH/NIDA under Cooperative Research and Development Agreement (CRDA) dated 29 April 94. Pre NDA meeting was held on 3 Nov 97 with the following information request: (a) certification for estimated environmental concentration (EEC) in aquatic compartment as less than 1ppb, (b) identification of clinical

materials, and (c) test for dissolution with USP apparatus. Except for the linkage between clinical protocol no and clinical test material, an adequate response was made to IND 45220 on 3 Dec 97, and to NDA 20733 on 3 June 99 in vol.1 p.10 and vol.5 p.193.

- (a)EEC is LT 1ppb.
- (b)Clinical materials have used Buprenorphine drug substance lots RP07251, R01041 and S12111 and Naloxone drug substance lots DS9140 and DS9235.
- (c)Clinical materials are 8mg/2mg tablet lots 6001/037, 6001/071 and 6001/086, and 2mg/0.5mg tablet lot # as 6001/040, 6001/070 and 6001/085.
- (d)Revised dissolution test has used USP basket apparatus at RPM.

Review of executed batch records for clinical materials submitted to NDA 20733 has shown Reckett & Colman as mfg. site for [redacted] and [redacted] as mfg. site for [redacted]. See executed batch records dated April/May 95 in vol. 1.5 p.194-258 and records dated June 95 and March 97 in vol. 1.5 p.259-305, 306-340, 341-373.

Clinical testing was with [redacted] tablets, and later on an orange color tablets with FDC Yellow no 6 dye was considered for US marketing. MV for [redacted] colored Suboxone tablets and EER were initiated to comply with priority review designation with 6 months review time from June 99 (Dec 99).

Instability of Naloxone was reported for Suboxone tablets, colored tablets and [redacted] tablets in NDA 20733 vol.4 p.185-220 and 283-294. [redacted] stability data was submitted for the colored tablets [redacted] test lots per potency in [redacted] [redacted] stability data was submitted for [redacted] tablets [redacted] test lots per potency in [redacted] Sponsor has requested only [redacted] shelf life for Suboxone tablets.

Instability of Naloxone was defined as [redacted] (Failure). In Oct 99, [redacted] test results will be available for colored Suboxone tablets to reexamine.

**APPEARS THIS WAY
ON ORIGINAL**

CONCLUSIONS & RECOMMENDATIONS:

Clinical testing was done with _____ Suboxone (Buprenorphine/Naloxone) sublingual tablets, and later on an orange color tablets with FDC Yellow no 6 dye was considered for US marketing. The reason for the addition of yellow color at _____ w/w is to allow discrimination between Suboxone tablets (Buprenorphine/Naloxone combination product) from Subutex tablets (Buprenorphine only). DMFs for actives and _____ containers are adequate.

Instability of Naloxone was reported for Suboxone tablets by a LC _____ method. The applicant has proposed a wider band for Naloxone content in 2mg/0.5mg Suboxone tablets. Same _____

were used to prepare 2mg/0.5mg and 8mg/2mg Suboxone tablets. Potencies for Buprenorphine/Naloxone were expressed in terms of free base equivalent. Sponsor has requested only _____ shelf life for Suboxone tablets.

Methods validation (MV) for _____ colored Suboxone tablets was initiated on 22 July 99 and EER was initiated on 19 July 99, to comply with priority review designation with 6 months review time from June 99 (Dec 99).

Naloxone is poorly absorbed sublingually but it acts as an opiate antagonist when injected. Clinical effectiveness studies for Suboxone tablets were sponsored by NIH/NIDA under CRDA dated 29 April 94. As a part of the CMC review the following information request (IR) was made to the sponsor in a telecon dated Aug 19, 1999

Chemists portion of IR to applicant

- 1 Provide all available stability data on Suboxone tablets.
- 2 Provide all available reports to examine why _____
- 3 Submit uniformity of drug substance in _____ development pharmaceuticals and process development reports.
- 4 Delete _____ as mfg site for Buprenorphine HCl drug substance.
- 5 Add tests for _____ quality and _____ to release Suboxone tablets. You have proposed testing for _____ every _____
- 6 Provide linkage between clinical protocol no and Suboxone lots, and COA for Suboxone lots and drug substance lots.

- 7 Provide analytical test results, test results and acceptance criteria for the release of primary stability lots and clinical test lots of Suboxone tablets.

The applicant has indicated that IR will be provided. The recommendation therefore is that this product is APPROVABLE BUT WITH ONLY A SHELF LIFE.

[/S/]

P.Maturu, PhD, Review Chemist

[/S/] 10/15/99

A.D'Sa, Team Leader

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ON ORIGINAL**

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ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Application: NDA 20733/000 Priority: 4P Org Code: 170
Stamp: 07-JUN-1999 Regulatory Due: 08-OCT-2002 Action Goal: District Goal: 09-AUG-2002
Applicant: RECKITT BENCKISER Brand Name: SUBOXONE(BUPRENORPHINE HCL/NALOXONE HCL)
1909 HUGUENOT RD STE 300
RICHMOND, VA 232354314
Established Name:
Generic Name: BUPRENORPHINE HCL/NALOXONE HCL)
Dosage Form: TAB (TABLET)
Strength: 2MG/0.5MG, 8MG/2MG
FDA Contacts: S. SHEPHERD (HFD-170) 301-827-7430 , Project Manager
A. AL HAKIM (HFD-820) 301-827-7467 , Review Chemist
D. KOBLE (HFD-170) 301-827-7428 , Team Leader

Overall Recommendation:

ACCEPTABLE on 17-JUL-2002 by J. D AMBROGIO (HFD-324) 301-827-0062
ACCEPTABLE on 01-MAY-2002 by J. D AMBROGIO (HFD-324) 301-827-0062
ACCEPTABLE on 19-FEB-2002 by J. D AMBROGIO (HFD-324) 301-827-0062
ACCEPTABLE on 07-DEC-2000 by J. D AMBROGIO (HFD-324) 301-827-0062
ACCEPTABLE on 04-NOV-1999 by S. FERGUSON (HFD-324) 301-827-0062

Establishment:

DMF No:
AADA No:

Profile: TCM OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 17-JUL-2002
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

Responsibilities:

Establishment:

DMF No:
AADA No:

Profile: CSN OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 17-JUL-2002
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

Responsibilities:

Establishment:

DMF No:
AADA No:

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Milestone Date: 17-JUL-2002
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Application: NDA 20733/000 Action Goal:
Stamp: 07-JUN-1999 District Goal: 09-AUG-2002
Regulatory Due: 08-OCT-2002 Brand Name: SUBOXONE (BUPRENORPHINE
Applicant: RECKITT BENCKISER HCL/NALOXONE HCL)
1909 HUGUENOT RD STE 300 Estab. Name:
RICHMOND, VA 232354314 Generic Name: BUPRENORPHINE HCL/NALOXONE
Priority: 4P HCL)
Org Code: 170 Dosage Form: (TABLET)
Strength: 2MG/0.5MG, 8MG/2MG

Application Comment: WE ARE REQUESTING THAT THE MANUFACTURING SITE (CFN 9610643, HULL ENGLAND) FOR THE SUBUTEX AND SUBOXONE DRUG PRODUCTS (NDA 20-732 AND NDA 20-733) BE REINSPECTED. THE ORIGINAL INSPECTION WAS PERFORMED IN 1999. SUBSEQUENTLY, SIGNIFICANT CHANGES HAVE BEEN MADE IN THE DRUG PRODUCT AND IN THE ANALYTICAL METHODOLOGY:

1. THE SUBOXONE TABLETS HAVE (REPORTED TO US THIS YEAR). THIS PROBLEM MAY HAVE BEEN EVIDENT TO THE FIRM SIGNIFICANTLY PRIOR TO THEIR REPORTING IT TO US TO SOLVE THIS PROBLEM, THE TABLET SHAPE FOR SUBOXONE WAS CHANGED FROM TO HEXAGONAL.
WE WOULD LIKE THE INSPECTION TO INCLUDE AN INVESTIGATION TO ENSURE THAT THE PROBLEM HAS BEEN RESOLVED.
2. THE ANALYTICAL METHOD AND SPECIFICATIONS FOR IMPURITIES HAVE CHANGED: E.G., FOR BUPRENORPHINE DRUG SUBSTANCE AND SUBOXONE DRUG PRODUCT.
3. THE DISSOLUTION METHOD (MIXING SPEED) AND ACCEPTANCE CRITERIA WERE CHANGED.
4. DUE TO STABILITY PROBLEMS FOR THE DRUG PRODUCT PACKAGED IN A NEW PACKAGING CONFIGURATION (HDPE BOTTLES) WAS INTRODUCED. NOTE THAT THE PACKAGING WILL BE WITHDRAWN.
5. THE ORIGINAL STABILITY DATA IN SUPPORT OF THE APPLICATION WAS CONDUCTED UNDER NON-ICH CONDITIONS. SUBSEQUENTLY, NEW STABILITY DATA HAS BEEN GENERATED USING ICH CONDITIONS, INCLUDING MOST RECENTLY OF STABILITY DATA FOR THE NEW HEXAGONAL SUBOXONE TABLET.
VERIFY THAT INDEED THERE ARE NO FORMULATION OR PROCESS CHANGES FOR THE HAXAGONAL TABLETS. (on 26-SEP-2002 by A. AL HAKIM (HFD-820) 301-827-7467)

FDA Contacts: S. SHEPHERD (HFD-170) 301-827-7430 , Project Manager
A. AL HAKIM (HFD-820) 301-827-7467 , Review Chemist
D. KOBLE (HFD-170) 301-827-7428 , Team Leader

Overall Recommendation: ACCEPTABLE on 19-FEB-2002 by J. D AMBROGIO (HFD-324) 301-827-0062
ACCEPTABLE on 17-JUL-2002 by J. D AMBROGIO (HFD-324) 301-827-0062
ACCEPTABLE on 07-DEC-2000 by J. D AMBROGIO (HFD-324) 301-827-0062
ACCEPTABLE on 04-NOV-1999 by S. FERGUSON (HFD-324) 301-827-0062
ACCEPTABLE on 01-MAY-2002 by J. D AMBROGIO (HFD-324) 301-827-0062

Establishment:

DMF No: /
 Responsibilities: /
 Profile: TCM OAI Status: NONE
 Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	19-FEB-2002				ALHAKIMA
OC RECOMMENDATION	20-FEB-2002			ACCEPTABLE BASED ON PROFILE	DAMBROGIOJ
SUBMITTED TO OC	17-JUL-2002				ALHAKIMA
OC RECOMMENDATION	17-JUL-2002			ACCEPTABLE BASED ON PROFILE	DAMBROGIOJ

Establishment.

DMF No: — AADA:
 Responsibilities: /
 Profile: CSN OAI Status: NONE
 Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	15-JUL-1999				MATURU
SUBMITTED TO DO	16-JUL-1999	GMP			EGASM
SUBMITTED TO OC	19-JUL-1999				MATURU
SUBMITTED TO DO	22-JUL-1999	10D			EGASM
DO RECOMMENDATION	23-JUL-1999			ACCEPTABLE BASED ON FILE REVIEW	KRODEN

A PRE-APPROVAL INSPECTION OF (CFN — WAS
 CONDUCTED ON 2/26-3/20/98 COVERING PROFILE CLASS CSN. MINOR DEFICIENCIES
 WERE NOTED BUT LARGELY CORRECTED PRIOR TO THE CLOSE OF THE INSPECTION.
 BASED ON THE INSPECTIONAL FINDINGS, — BRANCH RECOMMENDS
 APPROVAL OF THIS APPLICATION.

OC RECOMMENDATION	23-JUL-1999			ACCEPTABLE DISTRICT RECOMMENDATION	FERGUSONS
SUBMITTED TO OC	19-FEB-2002				ALHAKIMA
OC RECOMMENDATION	19-FEB-2002			ACCEPTABLE BASED ON PROFILE	DAMBROGIOJ
SUBMITTED TO OC	19-FEB-2002				ALHAKIMA
OC RECOMMENDATION	20-FEB-2002			ACCEPTABLE BASED ON PROFILE	DAMBROGIOJ
SUBMITTED TO OC	17-JUL-2002				ALHAKIMA
OC RECOMMENDATION	17-JUL-2002			ACCEPTABLE BASED ON PROFILE	DAMBROGIOJ

Establishment:

DMF No: — AADA:
 Responsibilities: —
 Profile: TCM OAI Status: NONE
 Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	27-FEB-2002				ALHAKIMA
OC RECOMMENDATION	27-FEB-2002			ACCEPTABLE BASED ON PROFILE	FERGUSONS
SUBMITTED TO OC	17-JUL-2002				ALHAKIMA
OC RECOMMENDATION	17-JUL-2002			ACCEPTABLE BASED ON PROFILE	DAMBROGIOJ

Establishment: /

DMF No:

AADA:

Responsibilities: /

Profile: TCM

OAI Status: NONE

Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	07-DEC-2000				ALHAKIMA
OC RECOMMENDATION	07-DEC-2000			ACCEPTABLE BASED ON PROFILE	DAMBROGIOJ
SUBMITTED TO OC	17-JUL-2002				ALHAKIMA
OC RECOMMENDATION	17-JUL-2002			ACCEPTABLE BASED ON FILE REVIEW	DAMBROGIOJ

Establishment: 9610643

RECKITT BENCKISER INC
CHAPMAN STREET & DANSON LANE
HULL, EAST YORKSHIRE, UK HU8 7DS

DMF No: /

AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER
FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE PACKAGER

Profile: CSN

OAI Status: NONE

Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	15-JUL-1999				MATURU
OC RECOMMENDATION	16-JUL-1999			ACCEPTABLE BASED ON PROFILE	EGASM
SUBMITTED TO OC	19-FEB-2002				ALHAKIMA
OC RECOMMENDATION	19-FEB-2002			ACCEPTABLE BASED ON PROFILE	GARCIA M
SUBMITTED TO OC	17-JUL-2002				ALHAKIMA
OC RECOMMENDATION	17-JUL-2002			ACCEPTABLE BASED ON PROFILE	DAMBROGIOJ

Profile: TCM

OAI Status: NONE

Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	15-JUL-1999				MATURU
SUBMITTED TO DO	16-JUL-1999	10D			EGASM
DO RECOMMENDATION	16-JUL-1999			ACCEPTABLE BASED ON FILE REVIEW	EGASM
OC RECOMMENDATION	16-JUL-1999			ACCEPTABLE	EGASM

BASED ON EI OF 11/17-21/97

SUBMITTED TO OC	19-JUL-1999		DISTRICT RECOMMENDATION	
SUBMITTED TO DO	20-JUL-1999	10D		MATURU
DO RECOMMENDATION	23-JUL-1999		ACCEPTABLE	EGASM
				ADAMSS
OC RECOMMENDATION	23-JUL-1999		BASED ON FILE REVIEW	
			ACCEPTABLE	ADAMSS
SUBMITTED TO OC	19-FEB-2002		DISTRICT RECOMMENDATION	
OC RECOMMENDATION	19-FEB-2002			ALHAKIMA
			ACCEPTABLE	GARCIA
SUBMITTED TO OC	17-JUL-2002		BASED ON FILE REVIEW	
OC RECOMMENDATION	17-JUL-2002			ALHAKIMA
			ACCEPTABLE	DAMBROGIOJ
			BASED ON PROFILE	

Establishment:

DMF No:

AADA:

Responsibilities:

Profile: TCM

OAI Status: NONE

Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	19-FEB-2002				ALHAKIMA
SUBMITTED TO DO	19-FEB-2002	GMP			GARCIA
ASSIGNED INSPECTION	22-FEB-2002	GMP			GARCIA
DO RECOMMENDATION	01-MAY-2002			ACCEPTABLE	DAMBROGIOJ
				BASED ON FILE REVIEW	

ACCEPTABLE PER JOHN DIETRICK.

OC RECOMMENDATION	01-MAY-2002			ACCEPTABLE	DAMBROGIOJ
				DISTRICT RECOMMENDATION	
SUBMITTED TO OC	17-JUL-2002				ALHAKIMA
OC RECOMMENDATION	17-JUL-2002			ACCEPTABLE	DAMBROGIOJ
				BASED ON PROFILE	

ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application: NDA 20733/000	Priority: 4P	Org Code: 170
Stamp: 07-JUN-1999 Regulatory Due: 28-JAN-2001	Action Goal:	District Goal: 29-NOV-2000
Applicant: RECKITT AND COLMAN 1909 HUGUENOT RD RICHMOND, VA 23235	Brand Name: SUBOXONE(BUPRENORPHINE HCL/NALOXONE HCL)	
	Established Name:	
	Generic Name: BUPRENORPHINE HCL/NALOXONE HCL)	
	Dosage Form: TAB (TABLET)	
	Strength: 2.MG/0.5MG, 8MG/2MG	
FDA Contacts: S. SHEPHERD		, Project Manager
A. AL HAKIM (HFD-820)	301-827-7310	, Review Chemist
D. KOBLE (HFD-170)	301-827-7428	, Team Leader

Overall Recommendation:

ACCEPTABLE on 07-DEC-2000 by J. D AMBROGIO(HFD-324)301-827-0062
ACCEPTABLE on 04-NOV-1999 by S. FERGUSON(HFD-324)301-827-0062

Establishment: /	DMF No: /
	AADA No

Profile: CSN	OAI Status: NONE	Responsibilities: /
Last Milestone: OC RECOMMENDATION		
Milestone Date 23-JUL-1999		
Decision: ACCEPTABLE		
Reason: DISTRICT RECOMMENDATION		

Establishment: /	DMF No:
	AADA No:

Profile: TCM	OAI Status: NONE	Responsibilities: -
Last Milestone: OC RECOMMENDATION		
Milestone Date 07-DEC-2000		
Decision: ACCEPTABLE		
Reason: BASED ON PROFILE		

Establishment: 9610643	DMF No: -
RECKITT AND COLMAN PRODUCTS	AADA No:

HULL, EAST YORKSHIRE, UK

Profile: CSN OAI Status: NONE

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Responsibilities: **DRUG SUBSTANCE
MANUFACTURER
FINISHED DOSAGE
MANUFACTURER**

Last Milestone: **OC RECOMMENDATION**
Milestone Date **16-JUL-1999**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Profile: **TCM** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date **23-JUL-1999**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

**APPEARS THIS WAY
ON ORIGINAL**

**APPEARS THIS WAY
ON ORIGINAL**

Application: NDA 20733/000
Stamp: 07-JUN-1999
Regulatory Due: 28-JAN-2001
Applicant: RECKITT AND COLMAN
1909 HUGUENOT RD
RICHMOND, VA 23235
Priority: 4P
Org Code: 170

Action Goal:
District Goal: 29-NOV-2000
Brand Name: SUBOXONE (BUPRENORPHINE
HCL/NALOXONE HCL)
Estab. Name:
Generic Name: BUPRENORPHINE HCL/NALOXONE
HCL)
Dosage Form: (TABLET)
Strength: 2MG/0.5MG, 8MG/2MG

Application Comment: THIS SITE PACKAGES THE FINISHED DRUG PRODUCT, SUBOXONE. (on 07-DEC-2000 by A. AL HAKIM (HFD-820) 301-827-7310)

FDA Contacts: S. SHEPHERD , Project Manager
A. AL HAKIM (HFD-820) 301-827-7310 , Review Chemist
D. KOBLE (HFD-170) 301-827-7428 , Team Leader

Overall Recommendation: ACCEPTABLE on 07-DEC-2000 by J. D AMBROGIO (HFD-324) 301-827-0062
ACCEPTABLE on 04-NOV-1999 by S. FERGUSON (HFD-324) 301-827-0062

Establishment:

DMF No: — AADA:
Responsibilities: —
Profile: CSN OAI Status: NONE
Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	15-JUL-1999				MATURU
SUBMITTED TO DO	16-JUL-1999	GMP			EGASM
SUBMITTED TO OC	19-JUL-1999				MATURU
SUBMITTED TO DO	22-JUL-1999	10D			EGASM
DO RECOMMENDATION	23-JUL-1999			ACCEPTABLE	KRODEN

BASED ON FILE REVIEW
A PRE-APPROVAL INSPECTION OF — CFN WAS
CONDUCTED ON 2/26-3/20/98 COVERING PROFILE CLASS CSN. MINOR DEFICIENCIES
WERE NOTED BUT LARGELY CORRECTED PRIOR TO THE CLOSE OF THE INSPECTION.
BASED ON THE INSPECTIONAL FINDINGS, — BRANCH RECOMMENDS
APPROVAL OF THIS APPLICATION.

→ OC RECOMMENDATION 23-JUL-1999 ACCEPTABLE FERGUSONS
DISTRICT RECOMMENDATION

Establishment:

DMF No: — AADA:
Responsibilities: —
Profile: TCM OAI Status: NONE
Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	07-DEC-2000				ALHAKIMA
→ OC RECOMMENDATION	07-DEC-2000			ACCEPTABLE	DAMBROGIOJ

BASED ON PROFILE

Establishment: 9610643

RECKITT AND COLMAN PRODUCTS LTD PHARMACEUTICAL D
HULL, EAST YORKSHIRE, UK

DMF No: — AADA:
Responsibilities: DRUG SUBSTANCE MANUFACTURER
FINISHED DOSAGE MANUFACTURER
Profile: CSN OAI Status: NONE
Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	15-JUL-1999				MATURU
OC RECOMMENDATION	16-JUL-1999			ACCEPTABLE BASED ON PROFILE	EGASM

Profile: TCM OAI Status: NONE
Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	15-JUL-1999				MATURU
SUBMITTED TO DO	16-JUL-1999	10D			EGASM
DO RECOMMENDATION	16-JUL-1999			ACCEPTABLE BASED ON FILE REVIEW	EGASM
OC RECOMMENDATION	16-JUL-1999			ACCEPTABLE DISTRICT RECOMMENDATION	EGASM
SUBMITTED TO OC	19-JUL-1999				MATURU
SUBMITTED TO DO	20-JUL-1999	10D			EGASM
DO RECOMMENDATION	23-JUL-1999			ACCEPTABLE BASED ON FILE REVIEW	ADAMSS
→ OC RECOMMENDATION	23-JUL-1999			ACCEPTABLE DISTRICT RECOMMENDATION	ADAMSS

**APPEARS THIS WAY
ON ORIGINAL**

**ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT**

Application: NDA 20733/000	Priority: 4P	Org Code: 170
Stamp: 07-JUN-1999 Regulatory Due: 07-DEC-1999	Action Goal:	District Goal: 08-OCT-1999
Applicant: RECKITT AND COLMAN 1909 HUGUENOT RD RICHMOND, VA 23235	Brand Name: SUBOXONE(BUPRENORPHINE HCL/NALOXONE HCL)	
	Established Name:	
	Generic Name: BUPRENORPHINE HCL/NALOXONE HCL)	
	Dosage Form: TAB (TABLET)	
	Strength: 2MG/0.5MG, 8MG/2MG	
FDA Contacts: A. CHITE (HFD-170)	301-827-7410	, Project Manager
P. MATURU (HFD-170)	301-827-7434	, Review Chemist
A. D SA (HFD-170)	301-827-7443	, Team Leader

Overall Recommendation:

ACCEPTABLE on 04-NOV-1999 by S. FERGUSON (HFD-324) 301-827-0062

Establishment:

DMF No:

AADA No:

Profile: **CSN** OAI Status: **NONE**
 Last Milestone: **OC RECOMMENDATION**
 Milestone Date: **23-JUL-1999**
 Decision: **ACCEPTABLE**
 Reason: **DISTRICT RECOMMENDATION**

Responsibilities:

Establishment: **9610643**
RECKITT AND COLMAN PRODUCTS
CHAPMAN STREET & DANSON LAN
HULL, EAST YORKSHIRE, UK

DMF No: —

AADA No:

Profile: **CSN** OAI Status: **NONE**
 Last Milestone: **OC RECOMMENDATION**
 Milestone Date: **16-JUL-1999**
 Decision: **ACCEPTABLE**
 Reason: **BASED ON PROFILE**

Responsibilities: **DRUG SUBSTANCE
MANUFACTURER
FINISHED DOSAGE
MANUFACTURER**

Profile: **TCM** OAI Status: **NONE**
 Last Milestone: **OC RECOMMENDATION**
 Milestone Date: **23-JUL-1999**
 Decision: **ACCEPTABLE**
 Reason: **DISTRICT RECOMMENDATION**

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application: NDA 20732/000
Stamp: 31-MAR-1997 Regulatory Due: 08-OCT-2002
Applicant: RECKITT BENCKISER
1909 HUGUENOT RD STE 300
RICHMOND, VA 232354314

Priority: 3S
Action Goal:
Brand Name: SUBUTEX (BUPRENORPHINE
HCL)0.4MG/2MG/8MG
Established Name:
Generic Name: BUPRENORPHINE HCL
Dosage Form: TAB (TABLET)
Strength: 0.4, 2 & 8 MG

FDA Contacts: S. SHEPHERD (HFD-170) 301-827-7430 , Project Manager
P. MATURU (HFD-170) 301-827-7434 , Review Chemist
D. KOBLE (HFD-170) 301-827-7428 , Team Leader

Overall Recommendation:

ACCEPTABLE on 17-JUL-2002 by J. D AMBROGIO (HFD-324) 301-827-0062
ACCEPTABLE on 27-FEB-2002 by S. FERGUSON (HFD-324) 301-827-0062
ACCEPTABLE on 20-FEB-2002 by J. D AMBROGIO (HFD-324) 301-827-0062
ACCEPTABLE on 25-JAN-2001 by EGASM
ACCEPTABLE on 20-FEB-1998 by EGASM

Establishment:

/
/

DMF No:
AADA No:

Profile: TCM OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 17-JUL-2002
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

Responsibilities:

/

Establishment:

/
/

DMF No:
AADA No:

Profile: TCM OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 17-JUL-2002
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

Responsibilities:

—

Establishment:

/
/

DMF No:
AADA No:

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Profile: **TCM** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **17-JUL-2002**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities: /

Establishment: **9610643**
RECKITT BENCKISER INC
CHAPMAN STREET & DANSON LANI
HULL, EAST YORKSHIRE, UK HU8 7

DMF No: —
AADA No:

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **17-JUL-2002**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities: **DRUG SUBSTANCE**
MANUFACTURER
FINISHED DOSAGE
MANUFACTURER
FINISHED DOSAGE PACKAGER

Profile: **TCM** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **17-JUL-2002**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Establishment: /

DMF No:
AADA No:

Profile: **TCM** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **17-JUL-2002**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities: /

Application: NDA 20732/000 Action Goal:
Stamp: 31-MAR-1997 District Goal: 29-NOV-1997
Regulatory Due: 08-OCT-2002 Brand Name: SUBUTEX (BUPRENORPHINE
HCL) 0.4MG/2MG/8MG
Applicant: RECKITT BENCKISER Estab. Name:
1909 HUGUENOT RD STE 300
RICHMOND, VA 232354314 Generic Name: BUPRENORPHINE HCL
Priority: 3S Dosage Form: (TABLET)
Org Code: 170 Strength: 0.4, 2 & 8 MG
Application Comment: FUR 7/17/2002 (on 17-JUL-2002 by J. D AMBROGIO (HFD-324) 301-827-0062)
FDA Contacts: S. SHEPHERD (HFD-170) 301-827-7430 . Project Manager
P. MATURU (HFD-170) 301-827-7434 . Review Chemist
D. KOBLE (HFD-170) 301-827-7428 . Team Leader

Overall Recommendation: ACCEPTABLE on 27-FEB-2002 by S. FERGUSON (HFD-324) 301-827-0062
ACCEPTABLE on 25-JAN-2001 by EGASM
ACCEPTABLE on 20-FEB-2002 by J. D AMBROGIO (HFD-324) 301-827-0062
ACCEPTABLE on 20-FEB-1998 by EGASM
ACCEPTABLE on 17-JUL-2002 by J. D AMBROGIO (HFD-324) 301-827-0062

Establishment.

DMF No: AADA:
Responsibilities:
Profile: TCM OAI Status: NONE
Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	19-FEB-2002				ALHAKIMA
OC RECOMMENDATION	20-FEB-2002			ACCEPTABLE BASED ON PROFILE	DAMBROGIOJ
SUBMITTED TO OC	17-JUL-2002				ALHAKIMA
OC RECOMMENDATION	17-JUL-2002			ACCEPTABLE BASED ON PROFILE	DAMBROGIOJ

Establishment:

DMF No: AADA:
Responsibilities:
Profile: TCM OAI Status: NONE
Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	27-FEB-2002				ALHAKIMA
OC RECOMMENDATION	27-FEB-2002			ACCEPTABLE BASED ON PROFILE	FERGUSONS
SUBMITTED TO OC	17-JUL-2002				ALHAKIMA
OC RECOMMENDATION	17-JUL-2002			ACCEPTABLE BASED ON PROFILE	DAMBROGIOJ

Establishment: 1118920

DMF No: AADA:
 Responsibilities:
 Profile: TCM OAI Status: NONE
 Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	28-SEP-2000				MATURU
OC RECOMMENDATION	29-SEP-2000			ACCEPTABLE BASED ON PROFILE	FERGUSONS
SUBMITTED TO OC	17-JUL-2002				ALHAKIMA
OC RECOMMENDATION	17-JUL-2002			ACCEPTABLE BASED ON PROFILE	DAMBROGIOJ

4/11/2000

Establishment: 9610643

RECKITT BENCKISER INC
 CHAPMAN STREET & DANSON LANE
 HULL, EAST YORKSHIRE, UK HU8 7DS

DMF No: AADA:
 Responsibilities: DRUG SUBSTANCE MANUFACTURER
 FINISHED DOSAGE MANUFACTURER
 FINISHED DOSAGE PACKAGER
 Profile: CSN OAI Status: NONE

Estab. Comment: WE ARE REQUESTING THAT THE MANUFACTURING SITE (CFN 9610643, HULL ENGLAND) FOR THE SUBUTEX AND SUBOXONE DRUG PRODUCTS (NDA 20-732 AND NDA 20-733) BE REINSPECTED. THE ORIGINAL INSPECTION WAS PERFORMED IN 1999. SUBSEQUENTLY, SIGNIFICANT CHANGES HAVE BEEN MADE IN THE DRUG PRODUCT AND IN THE ANALYTICAL METHODOLOGY:

1. THE SUBOXONE TABLETS HAVE BEEN REPORTED TO US THIS YEAR). THIS PROBLEM MAY HAVE BEEN EVIDENT TO THE FIRM SIGNIFICANTLY PRIOR TO THEIR REPORTING IT TO US. TO SOLVE THIS PROBLEM, THE TABLET SHAPE FOR SUBOXONE WAS CHANGED FROM TO HEXAGONAL. WE WOULD LIKE THE INSPECTION TO INCLUDE AN INVESTIGATION TO ENSURE THAT THE PROBLEM HAS BEEN RESOLVED.

2. THE ANALYTICAL METHOD AND SPECIFICATIONS FOR IMPURITIES HAVE CHANGED: E.G., FOR BUPRENORPHINE DRUG SUBSTANCE AND SUBOXONE DRUG PRODUCT.

3. THE DISSOLUTION METHOD (MIXING SPEED) AND ACCEPTANCE CRITERIA WERE CHANGED.

4. DUE TO STABILITY PROBLEMS FOR THE DRUG PRODUCT PACKAGED IN A NEW PACKAGING CONFIGURATION (HDPE BOTTLES) WAS INTRODUCED. NOTE THAT THE PACKAGING WILL BE WITHDRAWN.

5. THE ORIGINAL STABILITY DATA IN SUPPORT OF THE APPLICATION WAS CONDUCTED UNDER NON-ICH CONDITIONS. SUBSEQUENTLY, NEW STABILITY DATA HAS BEEN GENERATED USING ICH CONDITIONS, INCLUDING MOST RECENTLY OF STABILITY DATA FOR THE NEW HEXAGONAL SUBOXONE TABLET. (on 26-SEP-2002 by A. AL HAKIM (HFD-820) 301-827-7467)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
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FDA CDR 223
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

SUBMITTED TO OC	15-MAY-1997		EGASM
SUBMITTED TO DO	15-MAY-1997	GMP	EGASM
ASSIGNED INSPECTION	'16-MAY-1997	GMP	EGASM
INSPECTION PERFORMED	30-JAN-1998	21-NOV-1997	EGASM
DO RECOMMENDATION	20-FEB-1998		ACCEPTABLE EGASM
OC RECOMMENDATION	20-FEB-1998		INSPECTION ACCEPTABLE EGASM DISTRICT RECOMMENDATION
SUBMITTED TO OC	28-SEP-2000		MATURU
SUBMITTED TO OC	28-SEP-2000		MATURU
SUBMITTED TO DO	02-OCT-2000	GMP	DAMBROGIOJ
ASSIGNED INSPECTION	'03-OCT-2000	GMP	ADAMSS
INSPECTION SCHEDULED	18-DEC-2000	19-JAN-2001	IRIVERA
INSPECTION PERFORMED	23-JAN-2001	19-JAN-2001	EGASM
DO RECOMMENDATION	25-JAN-2001		ACCEPTABLE EGASM INSPECTION
PER 483 AND PRELIMINARY RESPONSE RECEIVED			
OC RECOMMENDATION	25-JAN-2001		ACCEPTABLE EGASM DISTRICT RECOMMENDATION
SUBMITTED TO OC	17-JUL-2002		ALHAKIMA
OC RECOMMENDATION	17-JUL-2002		ACCEPTABLE DAMBROGIOJ BASED ON PROFILE

Profile: TCM OAI Status: NONE
 Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	15-MAY-1997				EGASM
SUBMITTED TO DO	15-MAY-1997	GMP			EGASM
ASSIGNED INSPECTION	'16-MAY-1997	GMP			EGASM
INSPECTION PERFORMED	30-JAN-1998		21-NOV-1997		EGASM
DO RECOMMENDATION	20-FEB-1998			ACCEPTABLE	EGASM
OC RECOMMENDATION	20-FEB-1998			INSPECTION ACCEPTABLE EGASM DISTRICT RECOMMENDATION	
SUBMITTED TO OC	28-SEP-2000				MATURU
SUBMITTED TO DO	02-OCT-2000	GMP			DAMBROGIOJ
ASSIGNED INSPECTION	'03-OCT-2000	GMP			ADAMSS
INSPECTION SCHEDULED	18-DEC-2000		19-JAN-2001		IRIVERA
INSPECTION PERFORMED	23-JAN-2001		19-JAN-2001		EGASM
DO RECOMMENDATION	25-JAN-2001			ACCEPTABLE EGASM INSPECTION	
PER 483 AND PRELIMINARY RESPONSE RECEIVED					
OC RECOMMENDATION	25-JAN-2001			ACCEPTABLE EGASM DISTRICT RECOMMENDATION	
SUBMITTED TO OC	17-JUL-2002				ALHAKIMA
OC RECOMMENDATION	17-JUL-2002			ACCEPTABLE DAMBROGIOJ BASED ON PROFILE	

FUR

Establishment:

DMF No:

AADA:

Responsibilities:

Profile: TCM

OAI Status: NONE

Etab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	19-FEB-2002				ALHAKIMA
OC RECOMMENDATION	20-FEB-2002			ACCEPTABLE BASED ON FILE REVIEW	GARCIA M
FUR					
SUBMITTED TO OC	17-JUL-2002				ALHAKIMA
OC RECOMMENDATION	17-JUL-2002			ACCEPTABLE BASED ON PROFILE	DAMBROGIO J
FUR					

APPEARS THIS WAY
ON ORIGINAL