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

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

**DRUG PRODUCT NAME:**
- **Proprietary:**
- **Nonproprietary/USAN:**
  - Suboxone
  - Buprenorphine/Naloxone
- **Code Name/#:**
  - None
- **Chem.Type/Ther.Class:**
  - 4/PV

**PHARMACOLOGICAL CATEGORY:**
- Opioid Agonist/Antagonist
- Treatment of narcotic addiction

**INDICATION:**
- Sublingual Tablet
- 2mg/0.5mg and 8mg/2mg

**STRENGTH:**
- Oral

**ROUTE OF ADMINISTRATION:**
- Rx __
- OTC __

**HOW DISPENSED:**
- Yes __
- No __

**SPECIAL PRODUCT:**

*Appears this way on original*
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-7α-[(S)-1-hydroxy-1,2,2-trimethylpropyl]-6,14-endo-ethano-6,7,8,14-tetrahydrooropavine hydrochloride

Structural Formula:

![Buprenorphine structural formula](image)

Molecular Formula: \( \text{C}_{29}\text{H}_{41}\text{NO}_{4} \cdot \text{HCl} \)
Molecular Weight: 504.09

**Naloxone**

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

Structural Formula:

![Naloxone structural formula](image)

Molecular Formula: \( \text{C}_{19}\text{H}_{21}\text{NO}_{4} \cdot \text{HCl} \cdot 2\text{H}_{2}\text{O} \)
Molecular Weight: 399.87
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* 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 its 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
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/s/
Ali Al-Hakim
10/8/02 03:20:36 PM
CHEMIST

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

APPEARS THIS WAY ON ORIGINAL
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

SUBMISSION TYPE  DOCUMENT DATE  CDER DATE  ASSIGNED DATE

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

DRUG PRODUCT NAME:
Proprietary: Suboxone
Nonproprietary/USAN: Buprenorphine/Naloxone
Code Name/#: None
Chem.Type/Ther.Class: 4/PV

PHARMACOLOGICAL CATEGORY: Opioid Agonist/Antagonist
INDICATION: Treatment of Drug addiction
DOSED FORM: Sublingual Tablet
STRENGTH: 8mg/2mg, 2mg/0.5mg
ROUTE OF ADMINISTRATION: Oral
HOW DISPENSED: Rx  OTC
SPECIAL PRODUCT: Yes  No

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

See next page

APPEARS THIS WAY ON ORIGINAL
**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-6methoxy-a-methyl-16,14-ethenomorphinan-7-methanol, hydrochloride.

Structural Formula:

![Buprenorphine Structural Formula](image)

Molecular Formula: $C_{29}H_{41}NO_4\cdot HCl$
Molecular Weight: 504.09

**Naloxone**

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

Chemical Structure:

![Naloxone Structural Formula](image)

Molecular Formula: $C_{19}H_{21}NO_4\cdot HCl\cdot 2H_2O$
Molecular Weight: 399.87
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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 and at rpm; specification are and 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

APPEARS THIS WAY ON ORIGINAL

• 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
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

SUBMISSION TYPE DOCUMENT DATE CDER DATE ASSIGNED DATE
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 = " "

APPEARS THIS WAY ON ORIGINAL
Chemically Naloxone HCl dihydrate is (-)-17-allyl-4,5-epoxy-3,14-dihydroxymorphinan-6-one, hydrochloride. C19 H21 N 04 HCl 2(H2 0) 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 Frankwich 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. NIDAs 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 _______
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 _______ 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, 17-20°C 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.

<table>
<thead>
<tr>
<th>LC conditions</th>
<th>NIH/NIDA LC method at zero release time</th>
<th>NIH/NIDA LC method at — re-test</th>
<th>NDA 20733 LC method</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Suboxone tablets has used for this is at packaging site for NIH/NIDA for this (DIN This package is not a child resistant DMF for part of is adequate by review dated 29 Nov. 99 by Drs. R. Trimmer and M. Smela, HFD-625.
15 Page(s) Withheld
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:
NDA# 20733
Page 24

[\(\text{S}\)]
P.Maturu, PhD, Review Chemist

[\(\text{S}\)] 12/2/99
A.D'Sa, Team Leader

File:n20733r3.99.doc
APPROVABLE

APPEARS THIS WAY
ON ORIGINAL
DIVISION OF ANESTHETIC, CRITICAL CARE AND ADDICTION
DRUG PRODUCTS, HFD-170

Review of Chemistry, Manufacturing, and Controls

NDA#: 20-733

DATE REVIEWED: Rev 11.4.99

<table>
<thead>
<tr>
<th>SUBMISSION TYPE</th>
<th>DOCUMENT DATE</th>
<th>CDER DATE</th>
<th>ASSIGNED DATE</th>
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</thead>
<tbody>
<tr>
<td>FAX SUBMISSION</td>
<td>29 Oct 99</td>
<td></td>
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<td>FAX SUBMISSION</td>
<td>27 Oct 99</td>
<td></td>
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<td>SUBMISSION</td>
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</tr>
<tr>
<td>SUBMISSION</td>
<td>27 Aug 99</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

Naloxone decomposition products were reported on 27 Oct 99 for LC-MS study of Suboxone stored at based on

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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 pharmaceutics 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.

<table>
<thead>
<tr>
<th>Batch No</th>
<th>Sample Position</th>
<th>Buprenorphine Content</th>
<th>Naloxone Content</th>
</tr>
</thead>
<tbody>
<tr>
<td>06001/034</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (mg)</td>
<td></td>
<td>2.05</td>
<td>0.51</td>
</tr>
<tr>
<td>% CV</td>
<td></td>
<td>1.19</td>
<td>1.71</td>
</tr>
<tr>
<td>Range (mg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>06001/036</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (mg)</td>
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<td>2.05</td>
<td>0.51</td>
</tr>
<tr>
<td>% CV</td>
<td></td>
<td>1.80</td>
<td>3.64</td>
</tr>
<tr>
<td>Range (mg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acceptance (Mean)</td>
<td></td>
<td>Ph Eur (+5%)</td>
<td>Ph Eur (+15%)</td>
</tr>
</tbody>
</table>
### 2mg Suboxone tablets

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

<table>
<thead>
<tr>
<th>Sample Time (Mins)</th>
<th>Batch Number - 06001/141</th>
<th>Mean</th>
<th>Range</th>
<th>%CV</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-30</td>
<td></td>
<td>0.490</td>
<td></td>
<td>1.75</td>
</tr>
<tr>
<td>30-60</td>
<td></td>
<td>0.469</td>
<td></td>
<td>1.70</td>
</tr>
<tr>
<td>60-90</td>
<td></td>
<td>0.472</td>
<td></td>
<td>1.83</td>
</tr>
<tr>
<td>90-110</td>
<td></td>
<td>0.477</td>
<td></td>
<td>1.35</td>
</tr>
<tr>
<td>110-150</td>
<td></td>
<td>0.482</td>
<td></td>
<td>1.70</td>
</tr>
</tbody>
</table>

Acceptance Range: (±15% USP/Ph.Eur)  
Relative S.D. (%CV): 6% maximum (USP)

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

<table>
<thead>
<tr>
<th>Sample Time (Mins)</th>
<th>Batch Number - 06001/142</th>
<th>Mean</th>
<th>Range</th>
<th>%CV</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-30</td>
<td></td>
<td>0.490</td>
<td></td>
<td>1.32</td>
</tr>
<tr>
<td>30-60</td>
<td></td>
<td>0.484</td>
<td></td>
<td>1.61</td>
</tr>
<tr>
<td>60-90</td>
<td></td>
<td>0.487</td>
<td></td>
<td>1.53</td>
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<td>90-110</td>
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<td>0.487</td>
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<td>1.71</td>
</tr>
<tr>
<td>110-150</td>
<td></td>
<td>0.491</td>
<td></td>
<td>1.67</td>
</tr>
</tbody>
</table>

Acceptance Range: (±15% USP/Ph.Eur)  
Relative S.D. (%CV): 6% maximum (USP)

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

<table>
<thead>
<tr>
<th>Sample Time (Mins)</th>
<th>Batch Number - 06001/143</th>
<th>Mean</th>
<th>Range</th>
<th>%CV</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-30</td>
<td></td>
<td>0.485</td>
<td></td>
<td>1.30</td>
</tr>
<tr>
<td>30-60</td>
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<td>1.50</td>
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<td>60-90</td>
<td></td>
<td>0.488</td>
<td></td>
<td>1.75</td>
</tr>
<tr>
<td>90-110</td>
<td></td>
<td>0.489</td>
<td></td>
<td>0.99</td>
</tr>
<tr>
<td>110-150</td>
<td></td>
<td>0.490</td>
<td></td>
<td>1.78</td>
</tr>
</tbody>
</table>
### Table

<table>
<thead>
<tr>
<th>Batch</th>
<th>Buprenorphine mg per tablet</th>
<th>Naloxone mg per tablet</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>Range</td>
</tr>
<tr>
<td>06001/070</td>
<td>2.00</td>
<td>1.99</td>
</tr>
<tr>
<td>06001/085</td>
<td>2.00</td>
<td>1.99</td>
</tr>
<tr>
<td>06001/136</td>
<td>1.99</td>
<td>1.99</td>
</tr>
</tbody>
</table>

**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 _________

### 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 telecom dated 27 Oct 99. In packages, shelf life is feasible for 2mg 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.

\[\text{[S]}\] 11-5-99
P. Maturu, PhD, Review Chemist

\[\text{[S]}\] 11-3-99
A. D'Sa, Team Leader

APPEARS THIS WAY ON ORIGINAL

BEST POSSIBLE COPY
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

SUBMISSION TYPE
DOCUMENT DATE
CDER DATE
ASSIGNED DATE
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-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 = ---
Chemically Naloxone HCl dihydrate is (-)-17-allyl-4,5-epoxy-3,14-dihydroxymorphinan-6-one, hydrochloride. C19 H21 N 04 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 and as mfg. site for 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 tablets, and later on an orange color tablets with FDC Yellow no 6 dye was considered for US marketing. MV for 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 tablets in NDA 20733 vol.4 p.185-220 and 283-294. stability data was submitted for the colored tablets test lots per potency in stability data was submitted for tablets test lots per potency in Sponsor has requested only shelf life for Suboxone tablets.

Instability of Naloxone was defined as (Failure). In Oct 99, test results will be available for colored Suboxone tablets to reexamine.
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 pharmaceutics and process development reports.
4. Delete as mfg site for Buprenorphine HCl drug substance.
5. Add tests for in 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.
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 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.

P. Maturu, PhD, Review Chemist

A. D'Sa, Team Leader

APPROVABLE

APPEARS THIS WAY ON ORIGINAL
Application: FDA

 Establishment: NDA 20733/000

Priority: 4P

Org Code: 170

Action Goal:

District Goal: 09-AUG-2002

Applicant: RECKITT BENCKISER

1909 HUGUENOT RD STE 300

RICHMOND, VA 232354314

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: 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

Profile: TCM

OAI Status: NONE

Responsibilities:

Last Milestone: OC RECOMMENDATION

Milestone Date: 17-JUL-2002

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

Profile: CSN

OAI Status: NONE

Responsibilities:

Last Milestone: OC RECOMMENDATION

Milestone Date: 17-JUL-2002

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

Establishment:

DMF No: AADA No:

Establishment:

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Establishment:

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Milestone Date: 17-JUL-2002
Decision: ACCEPTABLE
Reason: BASED ON PROFILE
Application: NDA 20733/000
Stamp: 07-JUN-1999
Regulatory Due: 08-OCT-2002
Applicant: RECKITT BENCKISER
1909 HUGUENOT RD STE 300
RICHMOND, VA 232354314
Priority: 4P
Org Code: 170

Action Goal:
District Goal: 09-AUG-2002
Brand Name: SUBOXONE (BUPRENORPHINE HCL/NALOXONE HCL)
Estab. Name: SUBOXONE (HCL/NALOXONE HCL)
Generic Name: BUPRENORPHINE HCL/NALOXONE HCL
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 RECTANGULAR 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 HEXAGONAL 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

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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.

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Establishment: [Signature]

DMF No: AADA:
Responsibilities: TCM
Profile: TCM
OAI Status: NONE
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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:

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Application: NDA 20733/000
Applicant: RECKITT AND COLMAN
1909 HUGUENOT RD
RICHMOND, VA 23235

Priority: 4P
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: S. SHEPHERD
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

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

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

Establishment: 9610643
DMF No: AADA No:
RECKITT AND COLMAN PRODUCTS
HULL, EAST YORKSHIRE, UK

Profile: CSN
OAI Status: NONE
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Responsibilities:
- DRUG SUBSTANCE MANUFACTURER
- FINISHED DOSAGE MANUFACTURER
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/C.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. ROBLE (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:

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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: — OAI Status: NONE
Profile: TCM
Estab. Comment:

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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

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OAI Status: NONE

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APPEARS THIS WAY ON ORIGINAL
FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application: NDA 20733/000
Priority: 4P
Org Code: 170
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

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

Establishment: 9610643
DMF No: —
AADA No: —
RECKITT AND COLMAN PRODUCTS
CHAPMAN STREET & DANSON LAN
HULL, EAST YORKSHIRE, UK

Profile: CSN OAI Status: NONE 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
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
Org Code: 170
Action Goal:
District Goal: 29-NOV-1997

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

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

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Application: NDA 20732/000
Action Goal:
Stamp: 31-MAR-1997
District Goal: 29-NOV-1997
Regulatory Due: 08-OCT-2002
Brand Name: SUBUTEX (BUPRENOINE HCL) 0.4MG/2MG/8MG
Applicant: RECKITT BENCKISER
1909 HUGUENOT RD STE 300
RICHMOND, VA 232354314
Estab. Name: Generic Name: SUPRENOINE HCL
Priority: 3S
Org Code: 170
Dosage Form: (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 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: TCM
Profile: OAI Status: NONE
Estab. Comment:

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Establishment: 1118920
Responsibilities: DRUG SUBSTANCE MANUFACTURER
FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE PACKAGER

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

Establishment: 9610643

DMF No: AADA:

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 BUPRENOPIPHONE 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)

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**PER 483 AND PRELIMINARY RESPONSE RECEIVED**

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| SUBMITTED TO OC          | 17-JUL-2002|           |            |                   | ALHAKIMA |
| OC RECOMMENDATION        | 17-JUL-2002|           |            | ACCEPTABLE        | DAMBROGIOJ |
|                         |            |           |            |                   | BASED ON PROFILE |

Profile: TCM  
OAI Status: NONE

Establishment:
/  

DMF No: AADA:  
Responsibilities: /  
Profile: TCM  
OAI Status: NONE
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