CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
21-306

CHEMISTRY REVIEW(S)

BuTrans™ (Buprenorphine) Transdermal System

NDA 21-306

Summary of the Basis for the Recommended Action from Chemistry, Manufacturing, and Controls

Applicant: Purdue Pharma L.P.
One Stamford Forum
Standford, CT 06901-3431

Indication: BuTrans™ is indicated for the relief of moderate to severe pain in patients requiring continuous, around-the-clock opioid treatment for an extended period of time. BuTrans™ is intended to be used for the continual transdermal release of buprenorphine over a period of 7 days per system.

Presentation: BuTrans™ is supplied in cartons (secondary packaging) containing 4 individually-packaged patches and a pouch containing 4 patch-disposal systems. The primary packaging (pouch) adequately protects the Transdermal patch to assure compliance to specifications for the shelf-live of the product. A shelf-life of 21 months is granted. Recommended storage condition: Store at 25°C (77°F); excursions permitted between 15°C - 30°C (59°F - 86°F).

EER Status: Acceptable 22-FEB-2010.

Consults: **EA** – Categorical exclusion granted under 21 CFR §25.31(c)
Methods Validation – May be pursued as this is a complex dosage form.
Microbiology: N/A
Pharmacology/Toxicology –Acceptable

Original Submission : 3-Nov-2000,
Resubmission: 25-Sep-2009

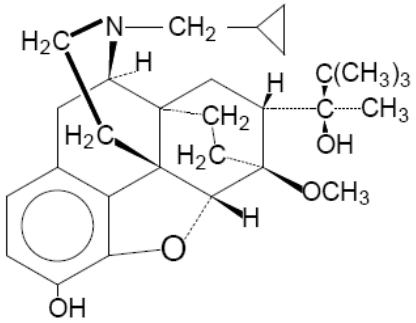
Post-Approval CMC Agreements:

1. The Applicant will update the specifications (validated test and acceptance criterion) for drug containing laminate to include testing for the adhesive strength as agreed to in the 16-Jun-2010 amendment. The proposed adhesion strength of the drug containing adhesive laminate specification will be submitted to the Agency before July 31, 2010, when data from an adequate number of BTDS batches will be available to establish a specification.

2. The Applicant proposed acceptance criteria for dissolution in amendment dated 16-Jun-2010 is accepted on an interim basis. The Applicant agrees to collect dissolution data from twelve patches for each lot manufactured within one year for each time

point on release and stability. The data with an analysis of its relation to the dissolution specification will be submitted to FDA before June 30, 2011.

Drug Substance:
Buprenorphine is a white or almost white, (b) (4) powder. It is very slightly soluble in water, freely soluble in acetone, soluble in methanol, slightly soluble in cyclohexane, and soluble in dilute solutions of acids. Its melting point is about 217 °C, and the pKa values are 8.5 and 10.0. (b) (4) The chemical name of buprenorphine is 6,14-ethenomorphinan-7-methanol, 17-(cyclopropylmethyl)- a-(1,1-dimethylethyl)-4, 5-epoxy-18,19-dihydro-3-hydroxy-6-methoxy-a-methyl-, [5a, 7a, (S)]. The molecular weight of buprenorphine base is 467.6; the empirical formula is $C_{29}H_{41}NO_4$. The structural formula is



Buprenorphine, a μ-opiod partial agonist, is a semi-synthetic opiate classified as a Schedule III controlled substance. Its analgesic effect is 25-40 times more potent than morphine.

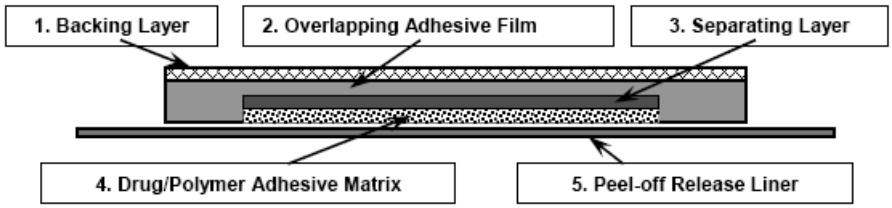
The synthesis and manufacture of buprenorphine base from (b) (4) is described in Type II DMF (b) (4) (b) (4) the holder of the DMF is the manufacturer and supplier of buprenorphine drug substance. The drug substance (b) (4) protected from moisture and light. A retest period of (b) (4) years is supported by data.

Buprenorphine is a well-known compound. Its hydrochloride salt is listed in the USP and both the base and the hydrochloride salt are subjects of the European Pharmacopoeia (Ph. Eur.) monographs. Buprenorphine base is analyzed according to the specifications of the Ph. Eur. In addition, Residual Solvents and Particle Size are part of the specifications. Testing for Residual Solvents is carried out according to USP <467>. Particle Size is accepted based on a Certificate of Analysis from (b) (4) The specifications for Buprenorphine base drug substance are stricter than those given in the Ph. Eur. monograph for buprenorphine and in USP monograph for buprenorphine HCl and include testing for Appearance, Identity (IR, HPLC), Appearance of Solution, Specific Optical Rotation, Assay, Related Substances, Organic Volatile Impurities, residual Solvents, Loss on Drying,

Conclusion: The drug substance is satisfactory.

Drug Product:

The buprenorphine transdermal delivery system (BTDS) is a rectangular or square beige-colored transdermal patch with rounded corners that is formulated to provide a controlled release of buprenorphine for a period of seven (7) days for the amelioration of chronic pain. The BTDS is a matrix system (b) (4). The rate of drug release is controlled by the diffusion of the buprenorphine in the adhesive matrix through the skin. The BTDS consists of a backing layer to prevent the buprenorphine-free adhesive matrix layer from sticking to clothing. The buprenorphine-free adhesive matrix allows the BTDS to adhere to the skin. A separating foil is present to prevent diffusion of the buprenorphine into the buprenorphine-free adhesive matrix during storage. The drug containing adhesive matrix contains the buprenorphine drug substance and is in direct contact with the skin. A (b) (4) release liner is used for easy removal prior to application. A cross section of the BTDS is shown below.



Selection and compatibility of excipients was carried out as part of pharmaceutical development. Levulinic acid was selected to (b) (4). Oleyl oleate is (b) (4), and povidone as (b) (4) are removed during manufacture, their presence in the drug product is limited to not more than (b) (4) %.

BTDS are manufactured in 3 different strengths, 5 µg/h, 10 µg/h, and 20 µg/h. The buprenorphine content of these strengths is 5 mg, 10 mg, and 20 mg, respectively. With the exception of the (b) (4) the amount of all other excipients, within strength formulations, are (b) (4). The amount of buprenorphine released from each system per hour is proportional to the drug containing surface area of the system. These delivery rates have been calculated and confirmed by in vivo and in vitro tests.

The manufacturing process consists of: (1) (b) (4) b) (4)

The specifications for the finished product include testing for Appearance (visual inspection and measurement of TDS areas, reservoir and skin colored web, with calibrated equipment), Identification (HPLC and Marquis' reagent), Content Uniformity (USP <905>), Purity (HPLC), In-vitro Release (USP <724>), Consistency and Legibility of Printing (visual), Tightness of pouches (vacuum), Adhesion Strength, Release Strength, and Residual Solvents (USP <467>).

There is a new ONDQA Transdermal Working group consisting of experts in transdermals, manufacturing, and biopharmaceutics disciplines within ONDQA. It is chaired by Dr. Terry Ocheltree. All CMC scientific and regulatory issues are discussed within the group. Several important issues were discussed pertaining to formulation development, residual drug, biopharm related in vitro release acceptance criteria, in vitro and in vivo data pertaining to patch age. They are summarized below.

- **It is unclear from a pharmaceutical development basis how much reformulating efforts will be required to minimize the residual buprenorphine in the drug product and still achieve similar efficacy characteristics. Therefore, in the absence of a specific guidance limiting the amount of residual drug in the transdermal patch a post approval commitment to reformulate the drug product is not currently being sought by the review team as an approvability issue.**

- **As indicated by the Biopharm review team, the in vitro drug release decreases with patch age by almost (b) (4) As this issue was being explored during the review team it was noted that the in vivo PK data (AUC and Cmax) for patches within the same lot aging within 6 months to 2.2 years, exhibited erratic variability of almost (b) (4). In fact patches that are aged tend to have an increased AUC and Cmax values. This issue of extreme variability was discussed with the clinical pharmacology team who also noted similar or even higher variability in the approved buprenorphine sublingual film. The clinical pharmacology team indicated to ONDQA biopharm team that the variability is not an issue from their perspective since several lots of patches of varying age used during clinical studies exhibited were deemed bioequivalent. As per the biopharm team the results of the in vitro variability with patch age is not an approvability issue (Review by Dr. Tapash Ghosh in DARRTS).**

- **Absence of quality issues found by Afrouz Nayernama of OSE, for patches marketed in Europe as reported in AERS reports of products failure associated with the use of transdermal buprenorphine products (3/10/2010).**

- **Although the draft guidance on residual drug content in transdermal products is ready for publication, it is not out for public comment. The principles of this new guidance will be applied to all forth coming applications.**

- **The clinical team along with the OSE agrees that the Risk Evaluation and Mitigation Strategy proposed by Purdue Pharma for managing excess residual buprenorphine is acceptable as indicated in the clinical and OSE reviews.**

The proposed commercial drug product is manufactured by Lohmann Therapie-Systemie, in Germany.

Based on the stability information provided by the applicant, which include stability data and their statistical analysis, a shelf-life of 21 months is granted. Recommended storage condition: Store at 25 °C (77 °F); excursions permitted between 15 °C-30 °C (59 °F-86 °F)

Outstanding issues:

- None from CMC

Conclusion: The drug product is recommended for approval.

Additional Items:
All associated Drug Master Files are acceptable or the pertinent information has been adequately provided in the application.

Method validation may be requested upon further internal discussion.

Overall Conclusion:
From a CMC perspective, the application is recommended for approval.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21306	ORIG-1	PURDUE PHARMA LP	Butrans (buprenorphine) Transdermal System

---

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

PRASAD PERI
06/21/2010
Approval from quality perspective.

NDA 21-306

BuTrans™
(Buprenorphine) Transdermal System

Purdue Pharma L.P.

Xavier Ysern, Ph.D.

Office of New Drug Quality Assessment

Division of Anesthesia, Analgesia and Rheumatoid Products

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-306

2. REVIEW #: # 3

3. REVIEW DATE: 16-JUN-2010

4. REVIEWER(S): Xavier Ysern, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents		Document Date
Original		03-NOV-2000
Amendment (N00 BC)		28-NOV-2000
Amendment (N00 BC)		15-DEC-2000
Amendment (N00 BCBM)		18-DEC-2000
Amendment (BC)		28-FEB-2001
Amendment (BC)		27-APR-2001
Amendment (BC)		11-JUL-2001
Complete Response Resubmission (Sequence *0000*)	*000*	25-SEP-2009
Amendment (Sequence 0004) Updated Form FDA 356h (establishment information)		08-OCT-2009
Amendment (sequence 0023) Removal of Microbial Testing		03-FEB-2010

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed		Document Date
Amendment (Dissolution, Phase IV Agreements)		16-Jun-2010
Amendment (Response to CMC Agency request dated 06-Apr-2010)	*032*	22-Apr-2010
Amendment (Request for information)	*031*	21-Apr-2010
Amendment (Response to CMC Agency requests dated 23-Feb-2010, item 11)	*029*	09-Mar-2010
Amendment (Response to CMC Agency requests dated 23-Feb-2010, items 1-10)	*028*	04-Mar-2010

7. NAME & ADDRESS OF APPLICANT:

Name:	Purdue Pharma L.P.
Address:	One Stamford Forum Standford, CT 06901-3431
Representative:	Richard J. Fanelli, PhD Executive Director, Regulatory Affairs
Telephone:	203-588-8365

8. DRUG PRODUCT NAME/CODE/TYPE:

- Proprietary Name: BuTrans™
- Non-Proprietary Name (USAN): Buprenorphine Transdermal System
- Code Name/# (ONDQA only):
- Chem. Type/Submission Priority (ONDQA only):
  - Chem. Type: 3
  - Submission Priority: S Resubmission

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: Opiod Analgesic

11. DOSAGE FORM: Transdermal System (Patch), controlled release

12. STRENGTH/POTENCY: 5 µg/h, 10 µg/h and 20 µg/h

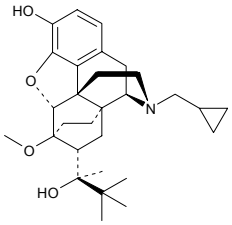
13. ROUTE OF ADMINISTRATION: Topical

14. Rx/OTC DISPENSED: Rx

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM): Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Buprenorphine (base)



$C_{29}H_{41}NO_4$
Molecular mass = 467.6 g/mole

CAS RN 52485-79-7

6,14-Ethenomorphinan-7-methanol,17-(cyclopropylmethyl)-α-(1,1-dimethylethyl)-4,5-epoxy-18,19-dihydro-3-hydroxy-6-methoxy-α-methyl-, [5α,7α,(*S*)]-,

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

Dmf #	Holder/ LOA Date	Item Referenced	Code[1]	Status[2]	Date Review Completed	LOA Date
Type II:						
(b) (4)		Buprenorphine	1	Adequate	10-Dec-2009	19-Feb-2009
Type III:						
(b) (4)			1	Adequate	21-Jan-2010	02-Feb-2008
			1	Adequate	25-Jan-2010	01-Apr-2009
			1	Adequate	21-Jan-2010	30-Jan-2009
				Adequate	21-Jan-2010	27-Jan-2009
			1	Adequate	26-Jan-2010	16-Feb-2009
			1	Adequate	25-Jul-2001	11-Feb-2009
			1	Adequate	25-Jul-2001	11-Feb-2009
			1	Adequate	15-Dec-2009	27-Jan-2009
			1	Adequate	22-Apr-2010	17-Jun-2009
			1	Adequate	28-Mar-2010	31-Mar-2009
			1	Adequate	28-Mar-2010	31-Mar-2009
Type IV:						
(b) (4)			1	Adequate	05-Feb-2010	10-Feb-2009

[1] Action codes for DMF Table: 1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

* Oral Solid Dosage Form

B. Other Documents:

Document	Application #	Description

--	--	--

18. STATUS:

This review, CMC review # 3, provides the CMC review documentation of the applicant responses (amendment 04-Mar-2010) to the CMC Agency request/comments given to the applicant on February 23, 2010.

Consults	Recommendation	Date	Reviewer
EES	Acceptable	22-Feb-2010	Office of Compliance
Biometrics	--		
Labeling	Acceptable (multidisciplinary review)		
Biopharmaceutics (ONDQA Team)	--		
Pharm/Tox	Acceptance criteria for the components of the (b) (4) from toxicological considerations were recommended by the Pharm-Tox review team.		
DAARP	No objection to the proposed proprietary name BuTrans™		
EA	Environment Assessment (EA) Categorical exclusion granted	20-Aug-2001	CMC Review # 1
Methods Validation	Revalidation by Agency Laboratories not recommended at this point because the analytical techniques involved in testing procedures are well established and widely used by the pharmaceutical industry.	N/A	Part of this review
Microbiology	N/A	N/A	

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the CMC point of view this application is recommended for approval. Based on the submitted stability data, an expiry of 21 months is granted under the recommended storage conditions: "Store at 25 °C (77 °F); excursions permitted between 15 °C - 30 °C (59 °F - 86 °F)".

B. Recommendation on Phase 4 (Post-Marketing), Agreements, and/or Risk Management Steps, if Approvable

Phase IV Agreements:

1. Adhesive strength specification for the drug containing laminate. The proposed adhesion strength of the drug containing adhesive laminate specification should be submitted to the Agency before July 31, 2010, when data from an adequate number of BTDS batches will be available to establish a specification.

2. Dissolution acceptance criteria. The Applicant proposed acceptance criteria in Amendment 16-Jun-2010 is accepted on an interim basis. The Applicant agrees to collect dissolution data from twelve patches for each lot manufactured within one year for each time point on release and stability. The data with an analysis of its relation to the dissolution specification will be submitted to FDA before July 1, 2011.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

- **Drug Substance**

The drug substance Buprenorphine is a white or almost white, (b) (4) powder. It is very slightly soluble in water, freely soluble in acetone, soluble in methanol, slightly soluble in cyclohexane, and soluble in dilute solutions of acids. Its melting point is about 217 °C, and the pKa values are 8.5 and 10.0. (b) (4)

Buprenorphine, a μ-opiod partial agonist, is a semi-synthetic opiate classified as a Schedule III controlled substance. Its analgesic effect is 25-40 times more potent than morphine. The synthesis and manufacture of buprenorphine base from (b) (4) is described in Type II DMF (b) (4) is the holder of the DMF, is the manufacturer and supplier of buprenorphine drug substance.

Buprenorphine is a well-known compound. Its hydrochloride salt is listed in the USP and both the base and the hydrochloride salt are subjects of the European Pharmacopoeia (Ph. Eur.) monographs. Buprenorphine base is analyzed according to the specifications of the Ph. Eur.. In addition, Residual Solvents and Particle Size are part of the specifications. Testing for Residual Solvents is carried out according to USP <467>. Particle Size is accepted based on a Certificate of Analysis from (b) (4) The specifications for Buprenorphine base drug substance are stricter than those given in the Ph. Eur. monograph for buprenorphine and in USP monograph for buprenorphine HCl.

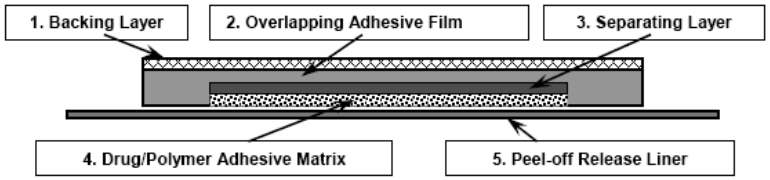
Lohmann Therapie-Systeme AG, Germany (LTS), the drug product manufacturer, receives buprenorphine base which is (b) (4) approved under Australian Standard AS2070 in (b) (4) containers that protect the drug substance from light and moisture (DMF (b) (4) assigns a retest date two years from the LTS Quality Control release testing date.

The stability data of buprenorphine drug substance is included in DMF (b) (4) The retest period of 2 years is fully supported by the stability data.

DMF (b) (4) has been reviewed and deemed acceptable for the use of buprenorphine base as drug substance in the manufacture of the drug product, Buprenorphine Transdermal System (BTDS), as described under NDA 21-306.

· **Drug Product**

The drug product, BuTrans™ (buprenorphine) transdermal delivery system (BTDS), is a rectangular or square beige-colored transdermal patch with rounded corners that is formulated to provide a controlled release of buprenorphine for a period of seven (7) days for the amelioration of chronic pain. The BTDS is a matrix system (b) (4) . The rate of drug release is controlled by the diffusion of the buprenorphine in the adhesive matrix through the stratum corneum of the epidermis. The BTDS consists of a backing layer to prevent the buprenorphine-free adhesive matrix layer from sticking to clothing. The buprenorphine-free adhesive matrix allows the BTDS to adhere to the skin. A separating foil is present to prevent diffusion of the buprenorphine into the buprenorphine-free adhesive matrix during storage. The drug containing adhesive matrix contains the buprenorphine drug substance and is in direct contact with the skin. A (b) (4) release liner is used for easy removal prior to application. A cross section of the BTDS is shown below.



Cross Section Diagram of BuTrans (not to scale).

In addition to the active component buprenorphine, the drug-containing adhesive matrix contains levulinic acid, povidone, oleyl oleate, and the polymer Duro-Tak® (b) (4)

Selection and compatibility of excipients was carried out as part of pharmaceutical development. Levulinic acid was selected to (b) (4) Oleyl oleate is (b) (4) and povidone as (b) (4) (b) (4) (b) (4) are removed during manufacture, and their presence in the drug product is limited to not more than (b) (4)

BTDS are manufactured in 3 different strengths, 5 µg/h, 10 µg/h, and 20 µg/h. The buprenorphine content of these strengths is 5 mg, 10 mg, and 20 mg, respectively. With the exception of the (b) (4) , the amount of all other excipients, within strength formulations, are (b) (4) The amount of buprenorphine released from each system per hour is proportional to the surface area of the drug-containing adhesive matrix. The skin is the limiting barrier to diffusion from the system.

The manufacturing process consists of: (1) (b) (4)

(b) (4)

Proposed specifications include Appearance (visual inspection and measurement of TDS areas, reservoir and skin colored web, with calibrated equipment), Identification (HPLC and Marquis' reagent), Content Average and Content Uniformity (USP <905>), Purity (HPLC), In-vitro Release (USP <724>), Consistency and Legibility of Printing (visual), Tightness of pouches (vacuum), Adhesion Strength, Release Strength, and Residual Solvents (USP <467>). Purity requires that the known related compounds (b) (4) to be not more than (b) (4) % and (b) (4) %, respectively. Each individual specified identified degradation product, or each individual unspecified degradation product, not to exceed (b) (4)%. The content of total degradation products cannot exceed (b) (4) %. The acceptance criterion of the dissolution test is still under discussion with the Applicant.

BTDS are designed for systemic delivery of buprenorphine for up to 7 days (usage time) with normal rates of 5 µg/h, 10 µg/h, and 20 µg/h, respectively. After usage more than (b) (4) of the buprenorphine remains in the patch. The patient is instructed to adequately dispose of the remaining patch. Clearly, deviations of the recommended usage and disposal are prone to misuse and/or abuse of this potential addictive drug.

LTS is the drug substance release tester, drug product manufacturer and the drug product packager.

BuTrans™ is supplied in cartons (secondary packaging) containing 4 individually-packaged patches and a pouch containing 4 patch-disposal systems. The primary packaging (pouch) adequately protects the Transdermal patch to assure compliance to specifications for the shelf-live of the product.

The requested shelf-life is (b) (4) months. However, based on the stability information provided by the applicant, which include stability data and their statistical analysis, a shelf-life of 21 months is granted. Recommended storage condition: Store at 25 °C (77 °F); excursions permitted between 15 °C - 30 °C (59 °F - 86 °F).

The lack of specification for the adhesion strength of the drug-containing laminate is now a Phase IV Agreement. All facilities involved in the manufacture of both drug substance and drug product have been found acceptable by the Office of Compliance. All pertinent DMFs are currently adequate to support this NDA.

B. Description of How the Drug Product is Intended to be Used

BuTrans™ is indicated for the relief of moderate to severe pain in patients requiring continuous, around-the-clock opioid treatment for an extended period of time.

BuTrans™ is intended to be used for the continual transdermal release of buprenorphine over a period of 7 days per system in patients with moderate to severe pain requiring continuous, around-the-clock opioid treatment for an extended period of time.

C. Basis for Approvability or Not-Approval Recommendation

Adequate CMC information has been submitted to allow a satisfactory evaluation of the quality of both drug substance ((b) (4) DMF (b) (4) Buprenorphine base) and drug product manufactured, BuTrans™ (buprenorphine) Transdermal System, tested and packaged in accordance with the procedures and recommendations given in the original submission, pertinent amendments and the complete response to the Agency's deficiency letter dated August 31, 2001. All pertinent related DMFs have been reviewed and deemed adequate to support NDA 21-306. From the standpoint of chemistry, manufacturing and controls (CMC) NDA 21-306 is **recommended for Approval**. This decision was taken after several internal discussions within the ONDQA and incorporating the recommendations of the Transdermal Working Group (chaired by Dr. Terry Ocheltree and other experts in transdermals and biopharmaceutics). Two Phase IV Agreements have been agreed by the Applicant.

The decision for approval of this application from a CMC basis took into account the following information and facts:

- The original application was submitted in 2000 when significant issues were identified and communicated to the sponsor. Responses to the identified issues were satisfactory from a quality issue except for the residual drug content.

- It is unclear from a pharmaceutical development basis how much reformulating efforts will be required to minimize the residual buprenorphine in the drug product and still achieve similar efficacy characteristics. Therefore, in the absence of a specific guidance limiting the amount of residual drug in the transdermal patch a post approval commitment to reformulate the drug product is not currently being sought by the review team as an approvability issue.

- An absence of quality issues for the patches marketed in Europe as reported in AERS reports of products failure associated with the use of transdermal buprenorphine products by Afrouz Nayernama of OSE.

- In general there is significant variability for the in vivo PK data for the approved sublingual film containing buprenorphine. This patch also shows similar trends.

- Although the draft guidance on residual drug content in transdermal products is ready for publication, it is not out for public comment. The principles of this new guidance will be applied to all forth coming applications.

- The clinical team along with the OSE agree that the Risk Evaluation and Mitigation Strategy proposed by Purdue Pharma for managing excess residual buprenorphine is acceptable as indicated in the clinical and OSE reviews.

III. Administrative

A.	**Reviewer's Signature**	Xavier Ysern, PhD	Review Chemist/ ONDQA/ DNDQA/ Branch VII
B.	**Endorsement Block**	Peri Prasad, PhD	Acting Branch Chief/ ONDQA/ DDNQA/ Branch VIII
C.	**CC Block**	Matthew Sullivan	Project Manager/ OND/ ODE II/ DAARP

35 Page(s) has been Withheld in Full as B4 (CCI/TS) immediately following this page

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21306	ORIG-1	PURDUE PHARMA LP	Butrans (buprenorphine) Transdermal System

---

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

XAVIER J YSERN
06/17/2010

PRASAD PERI
06/17/2010
I concur

NDA 21-306

BuTrans™
(Buprenorphine) Transdermal System

Purdue Pharma L.P.

Xavier Ysern, Ph.D.

Office of New Drug Quality Assessment

Division of Anesthesia, Analgesia and Rheumatoid Products

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-306

2. REVIEW #: # 2

3. REVIEW DATE: 23-Feb-2010

4. REVIEWER(S): Xavier Ysern, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original	03-NOV-2000
Amendment (N00 BC)	28-NOV-2000
Amendment (N00 BC)	15-DEC-2000
Amendment (N00 BCBM)	18-DEC-2000
Amendment (BC)	28-FEB-2001
Amendment (BC)	27-APR-2001
Amendment (BC)	11-JUL-2001

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Complete Response Resubmission (Sequence 0000)	25-SEP-2009
Amendment (Sequence 0004) Updated Form FDA 356h (establishment information)	08-OCT-2009
Amendment (sequence 0023) Removal of Microbial Testing	03-FEB-2010

7. NAME & ADDRESS OF APPLICANT:

Name:	Purdue Pharma L.P.
Address:	One Stamford Forum Standford, CT 06901-3431
Representative:	Richard J. Fanelli, PhD Executive Director, Regulatory Affairs
Telephone:	203-588-8365

8. DRUG PRODUCT NAME/CODE/TYPE:

- Proprietary Name: BuTrans™
- Non-Proprietary Name (USAN): Buprenorphine Transdermal System
- Code Name/# (ONDQA only):
- Chem. Type/Submission Priority (ONDQA only):
  - Chem. Type: 3
  - Submission Priority: S Resubmission

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: Opiod Analgesic

11. DOSAGE FORM: Patch, controlled release

12. STRENGTH/POTENCY: 5 µg/h, 10 µg/h and 20 µg/h

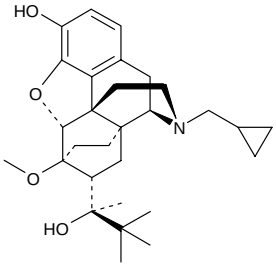
13. ROUTE OF ADMINISTRATION: Topical

14. Rx/OTC DISPENSED: Rx

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM): Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Buprenorphine (base)



$C_{29}H_{41}NO_4$

Molecular mass = 467.6 g/mole

CAS RN 52485-79-7

6,14-Ethenomorphinan-7-methanol,17-(cyclopropylmethyl)-α-(1,1-dimethylethyl)-4,5-epoxy-18,19-dihydro-3-hydroxy-6-methoxy-α-methyl-, [5α,7α,(*S*)]-,

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

Dmf #	Holder/ LOA Date	Item Referenced	Code[1]	Status[2]	Date Review Completed	LOA Date
Type II:						
(b) (4)		Buprenorphine	1	Adequate	10-Dec-2009	19-Feb-2009
Type III:						
(b) (4)			1	Adequate	21-Jan-2010	02-Feb-2008
			1	Adequate	25-Jan-2010	01-Apr-2009
			1	Adequate	21-Jan-2010	30-Jan-2009
				Adequate	21-Jan-2010	27-Jan-2009
			1	Adequate	26-Jan-2010	16-Feb-2009
			1	Adequate	25-Jul-2001	11-Feb-2009
			1	Adequate	25-Jul-2001	11-Feb-2009
			1	Adequate	15-Dec-2009	27-Jan-2009
			1	Inadequate	04-Feb-2010	17-Jun-2009
			1	Inadequate	14-Jan-2010	31-Mar-2009
			1	Inadequate	14-Jan-2010	31-Mar-2009
Type IV:						
(b) (4)			1	Adequate	05-Feb-2010	10-Feb-2009

[1] Action codes for DMF Table: 1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

* Oral Solid Dosage Form

B. Other Documents:

Document	Application #	Description
--	--	--

18. STATUS:

This review, CMC review # 2, provides the CMC review documentation to be entered into DARTS before the cycle review (17-Dec-2009).

Consults	Recommendation	Date	Reviewer
EES	Acceptable	22-Feb-2010	Office of Compliance
Biometrics	--		
Labeling	Pending (multidisciplinary review)		
Biopharmaceutics (ONDQA Team)	--		
Pharm/Tox	Pending		
DAARP	No objection to the proposed proprietary name BuTrans™™		
EA	Environment Assessment (EA) Categorical exclusion granted	20-Aug-2001	CMC Review # 1
Methods Validation	Revalidation by Agency Laboratories not recommended at this point because the analytical techniques involved in testing procedures are well established and widely used by the pharmaceutical industry.	N/A	Part of this review
Microbiology	N/A	N/A	

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the CMC point of view this application is approvable pending:

- Satisfactory response from the DMF holders to the deficiencies listed under DMFs (b) (4), and (b) (4)
- Satisfactory response to the deficiencies listed under "List of Deficiencies to be Communicated" (pages 97 and 98).

B. Recommendation on Phase 4 (Post-Marketing), Agreements, and/or Risk Management Steps, if Approvable

None

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

- **Drug Substance**

Buprenorphine is a white or almost white, (b) (4) powder. It is very slightly soluble in water, freely soluble in acetone, soluble in methanol, slightly soluble in cyclohexane, and soluble in dilute solutions of acids. Its melting point is about 217 °C, and the pKa values are 8.5 and 10.0. (b) (4)

Buprenorphine, a mu-opiod partial agonist and Schedule III controlled substance, is a semi-synthetic opiate. Its analgesic effect is 25-40 times more potent than morphine. The synthesis and manufacture of buprenorphine base from (b) (4) is described in Type II DMF (b) (4) is the holder and supplier of buprenorphine drug substance.

Buprenorphine is a well-known compound. Its hydrochloride salt is listed in the USP and both the base and the hydrochloride salt are subjects of the European Pharmacopoeia (Ph. Eur.) monographs. Buprenorphine base is analyzed according to the specifications (test and acceptance criteria) of the Ph. Eur.. In addition, Residual Solvents and Particle Size are part of the specifications. Testing for Residual Solvents is carried out according to USP <467>. Particle Size is accepted based on a Certificate of Analysis from (b) (4) The specifications for Buprenorphine base drug substance are stricter than those given in the Ph. Eur. monograph for buprenorphine and in USP monograph for buprenorphine HCl.

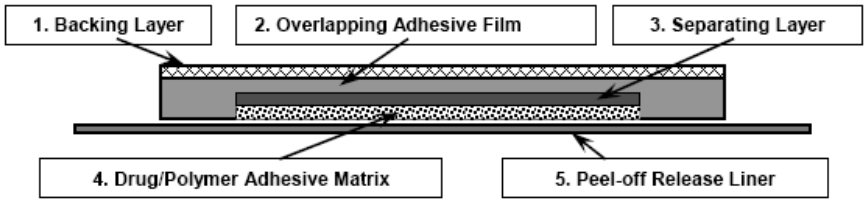
(b) (4) receives buprenorphine base (b) (4) approved under Australian Standard AS2070 in (b) (4) containers that protect the product from light and moisture (DMF (b) (4) assigns a retest date two years from the (b) (4) Quality Control release testing date.

The stability data is included in DMF (b) (4) The retest period of 2 years is fully supported by the stability data.

DMF (b) (4) has been reviewed and deemed acceptable for the use of buprenorphine base as drug substance in the manufacture of the drug product, Buprenorphine Transdermal System (BTDS), as described under NDA 21-306.

· **Drug Product**

The buprenorphine transdermal delivery system (BTDS) is a rectangular or square beige-colored transdermal patch with rounded corners that is formulated to provide a controlled release of buprenorphine for a period of seven (7) days for the amelioration of chronic pain. The BTDS is a matrix system (b) (4) The rate of drug release is controlled by the diffusion of the buprenorphine in the adhesive matrix through the stratum corneum of the epidermis. The BTDS consists of a backing layer to prevent the buprenorphine-free adhesive matrix layer from sticking to clothing. The buprenorphine-free adhesive matrix allows the BTDS to adhere to the skin. A separating foil is present to prevent diffusion of the buprenorphine into the buprenorphine-free adhesive matrix during storage. The drug containing adhesive matrix contains the buprenorphine drug substance and is in direct contact with the skin. A (b) (4) release liner is used for easy removal prior to application. A cross section of the BTDS is shown below.



Cross Section Diagram of BuTrans (not to scale).

In addition to the active component buprenorphine, the drug-containing adhesive matrix contains levulinic acid, povidone, oleyl oleate, and the polymer Duro-Tak® (b) (4)

Selection and compatibility of excipients was carried out as part of pharmaceutical development. Levulinic acid was selected to (b) (4) Oleyl oleate is (b) (4) and povidone as (b) (4). (b) (4) are removed during manufacture, their presence in the drug product is limited to not more than (b) (4)

BTDS are manufactured in 3 different strengths, 5 µg/h, 10 µg/h, and 20 µg/h. The buprenorphine content of these strengths is 5 mg, 10 mg, and 20 mg, respectively. With the exception of the (b) (4) the amount of all other excipients, within strength formulations, are (b) (4). The amount of buprenorphine released from each system per hour is proportional to the drug-containing surface area of the system. The skin is the limiting barrier to diffusion from the system to the skin.

The manufacturing process consists in: (b) (4)

Proposed specifications include Appearance (visual inspection and measurement of TDS areas, reservoir and skin colored web, with calibrated equipment), Identification (HPLC and Marquis' reagent), Content Average and Content Uniformity (USP <905>), Purity (HPLC), In-vitro Release (USP <724>), Consistency and Legibility of Printing (visual), Tightness of pouches (vacuum), Adhesion Strength, Release Strength, and Residual Solvents (USP <467>). Purity requires that the known related compounds (b) (4) to be not more than (b) (4) % and (b) (4) %, respectively. Each individual specified identified degradation product, or each individual unspecified degradation product, not to exceed (b) (4) %. The content of total degradation products cannot exceed (b) (4) %.

BTDS are designed for systemic delivery of buprenorphine for up to 7 days (usage time) with normal rates of 5 µg/h, 10 µg/h, and 20 µg/h, respectively. After usage more than (b) (4) of the buprenorphine remains in the patch. The patient is instructed to adequately dispose of the remaining patch. Clearly, deviations of the recommended usage and disposal are prone to misuse and/or abuse of this potential addictive drug.

BuTrans™ is supplied in cartons (secondary packaging) containing 4 individually-packaged patches and a pouch containing 4 patch-disposal systems. The primary packaging (pouch) adequately protects the Transdermal patch to assure compliance to specifications for the shelf-live of the product.

The requested shelf-life is (b) (4). However, based on the stability information provided by the applicant, which include stability data and their statistical analysis, a shelf-life of 21 months is granted. Recommended storage condition: Store at 25 °C (77 °F); excursions permitted between 15 °C-30 °C (59 °F-86 °F).

Deficiencies to the NDA submission, originated from the reviewer and from the Transdermal Working Group (TWG) within ONDQA, are listed on pages 97 and 98. These deficiencies include mainly a request for additional drug product specifications and for a scientific justification to support the amount of residual buprenorphine in the BTDS after usage. DMF s (b) (4) are still not adequate to support this NDA.

B. Description of How the Drug Product is Intended to be Used

BuTrans™ is indicated for the relief of moderate to severe pain in patients requiring continuous, around-the-clock opioid treatment for an extended period of time.

BuTrans™ is intended to be used for the continual transdermal release of buprenorphine over a period of 7 days per system in patients with moderate to severe pain requiring continuous, around-the-clock opioid treatment for an extended period of time.

C. Basis for Approvability or Not-Approval Recommendation

Adequate CMC information has been submitted to allow a satisfactory evaluation of the quality of both drug substance (b) (4) Buprenorphine base) and drug product manufactured, tested and packaged in accordance with the procedures and recommendations given in the original submission, pertinent amendments and the complete response to the Agency's deficiency letter dated August 31, 2001. NDA 21-306 is **recommended for Approval** from the standpoint of chemistry, manufacturing and controls (CMC) **pending**: (1) satisfactory response to the DMF deficiencies, and (2) satisfactory response to the deficiencies listed under "List of Deficiencies to be Communicated".

III. Administrative

A.	**Reviewer's Signature**	Xavier Ysern, PhD	Review Chemist/ ONDQA/ DPAI/ Branch II
B.	**Endorsement Block**	Peri Prasad, PhD	Acting Branch Chief/ ONDQA/ DPAI/ Branch II
C.	**CC Block**	Matthew Sullivan	Project Manager/ OND/ ODE II/ DAARP

93 Page(s) has been Withheld in Full as B4 (CCI/TS) immediately following this page

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21306	ORIG-1	PURDUE PHARMA LP	BuTrans (buprenorphine transdermal system)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

XAVIER J YSERN
02/26/2010

PRASAD PERI
02/26/2010
I concur

DIVISION OF ANESTHETICS, CRITICAL CARE AND ADDICTION DRUG PRODUCTS (DACCAD, HFD-170)

Review of Chemistry, Manufacturing, and Controls

NDA #: 21-306 **REVIEWED DATE:** 20-AUG-2001
CHEM.REVIEW #: 1 **REVIEWER:** Ravi S. Harapanhalli, Ph.D.

SUBMISSION/TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	03-NOV-00	03-NOV-00	15-JUN-01
Amendment (N00 BC)	28-NOV-00	29-NOV-00	15-JUN-01
Amendment (N00 BC)	15-DEC-00	18-DEC-00	15-JUN-01
Amendment (N00 BCBM)	18-DEC-00	19-DEC-00	15-JUN-01
Amendment (BC)	28-FEB-01	01-MAR-01	15-JUN-01
Amendment (BC)	27-APR-01	30-APR-01	15-JUN-01
Amendment (BC)	11-JUL-01	11-JUL-01	11-JUL-01

NAME & ADDRESS OF APPLICANT: PURDUE PHARMA L.P.
One Stamford Forum
Stamford, CT 06901-3431

DRUG PRODUCT NAME

Proprietary:	Norspan™
Nonproprietary/USAN:	Buprenorphine Transdermal System,
Code Names/#'s:	BTDS
Chemical Type/Therapeutic Class:	Opioid Analgesic

ANDA Suitability Petition/DESI/Patent Status: N/A
N/A [if applicable]

PHARMACOLOGICAL CATEGORY/INDICATION: Management of patients with pain requiring continuous Opioid Analgesia

DOSAGE FORM: Transdermal Patches
STRENGTHS: 5, 10, 20 mg
MAXIMUM DAILY DOSE: 0.71, 1.43, and 2.84 mg
ROUTE OF ADMINISTRATION: Topical
DISPENSED: _X_ **Rx** ___ **OTC**
SPECIAL PRODUCTS: Yes ___ **No** X
(If yes, fill out the form for special products and deliver to TIA through team leader for data entry)
CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:

6,14-Ethenomorphinan-7-methanol, 17-(cyclopropylmethyl)-a-(1,1-dimethylethyl)-4, 5-epoxy-18, 19-dihydro-3-hydroxy-6-methoxy-a-methyl-, [5a, 7a,(S)]-,
Molecular Formula: $C_{29}H_{41}NO_4$ Molecular Weight: 467.6
CAS Registry Number: 52485-79-7

SUPPORTING DOCUMENTS:

Type/ Number	Subject	Holder	Status	Review Date	Letter Date
DMF (b) (4)	Buprenorphine Base	(b) (4)	Adequate	30-APR-1996	N/A
	Buprenorphine Base	(b) (4)	Inadequate	12-JUN-2001	28-AUG-2001
		(b) (4)	Inadequate	03-AUG-2001	28-AUG-2001
			Inadequate	02-AUG-2001	28-AUG-2001
			Inadequate	15-JUL-2001	28-AUG-2001
			Inadequate	23-JUL-2001	28-AUG-2001
			Inadequate	18-JUL-2001	28-AUG-2001
			Inadequate	20-JUL-2001	28-AUG-2001
			Adequate	25-JUL-2001	N/A
			Inadequate	25-JUL-2001	28-AUG-2001
			Adequate	25-JUL-2001	N/A
			Inadequate	31-JUL-2001	28-AUG-2001
			Inadequate	26-JUL-2001	28-AUG-2001
			Adequate	Review not necessary	N/A

RELATED DOCUMENTS (if applicable): None

CONSULTS:

EER Consult: Acceptable

LNC/OPDRA Consult: Acceptable
Biometrics: Not consulted
Pharmtox: Recommended us to ask the applicant to provide supporting safety data

REMARKS/COMMENTS:
Analytical method validation should be requested after tests and specifications are agreed upon between the firm and the agency. The Office of Compliance recommended "acceptable" status to the firm during the PAIs. Several referenced DMFs were inadequate to support the NDA.

CONCLUSIONS & RECOMMENDATIONS: The NDA is not approvable from the standpoint of CMC owing to the magnitude of drug product quality issues listed at the end of the review.

Ravi S. Harapanhalli, Ph.D.
Review Chemist

cc: Orig. NDA 21-306
HFD-170/NDA Division File
HFD-170/harapanhalli/
HFD-170/MO/GDalPan
HFD-167/Pharmacologist/TPapion
HFD-170/PM/SShepherd
R/D Init by: Dale Koble, Ph.D.
filename: c:/mydocs/ndas/21306a

GENERAL CHECKLIST

REVIEW OF CONTENTS

		Adequate	Inadequate
A.	**DRUG SUBSTANCE**		
1.	Description and Characterization:	X	
	A. Description		
	B. Characterization/ Proof of structure	(See DMF review)	
2.	Manufacturer:	X	
3.	Synthesis/Method of manufacture:	(See DMF review)	
	A. Starting materials – Specs and Tests		
	B. Solvents, Reagents, etc.		
	C. Flow chart		
	D. Detailed description		
4.	Process Controls:	(See DMF review)	
	A. Reaction completion/ Other in-process tests		
	B. Intermediate Specs and Tests		
5.	Reference Standards (refer to 1.B also):		X
	A. Preparation		
	B. Specifications		
6.	Regulatory Specifications/Analytical Methods:		
	A. Drug Substance Specifications and Tests		X
	B. Purity Profile	X	
	C. Microbiology	X	
7.	Container/Closure System for Drug Substance Storage	(See DMF review)	
8.	Drug Substance Stability	(Seee DMF review)	
B.	**DRUG PRODUCT**		
1.	Components	X	
2.	Composition	X	
3.	Specifications & Methods for Drug Product Ingredients:		
	A. Active Ingredient(s)		X
	B. Inactive Ingredients		X
	1. Compendial Excipients		
	2. Non-compendial Excipients		
4.	Manufacturer	X	
5.	Methods of Manufacturing and Packing:		X
	A. Production Operations	X	
	B. In-Process Controls and Tests		X
	C. Reprocessing Operations	X	
6.	Regulatory Specifications and Methods for Drug Product:		X
	A. Sampling Procedures		X
	B. Regulatory Specifications and Methods		X
	C. Batch Analysis	X	
7.	Container /Closure System		X
8.	Microbiology	X	
9.	Drug Product Stability	X	
C.	**INVESTIGATIONAL FORMULATIONS**	X	

D.	**ENVIRONMENTAL ASSESSMENT**	**X**	
E.	**METHODS EVALUATION**		**X**
F.	**LABELING**		**X**
G.	**EATABLISHMENT INSPECTION**	**X**	
H.	**TRADENAME**	**X**	

I. DRAFT DEFICIENCY LETTER: Pages 113-117

J. PH. EUR. MONOGRAPH ON BUPRENORPHINE: PAGES 104-106

K. DRUG SUBSTANCE SPECIFICATIONS: PAGES 107-109

L. DRUG PRODUCT SPECIFICATIONS: PAGES 110-111

M. POST-APPROVAL STABILITY COMMITMENT: PAGE 112

CMC Summary of NDA 21306

The subject matter of the NDA is Norspan™, which is buprenorphine transdermal system (BTDS) available in 5, 10, and 20 mg dosage strengths. Norspan™ is intended to provide systemic delivery of buprenorphine continually for up to seven days with normal delivery rates of 5, 10, and 20 micrograms per hour respectively. Thus, Norspan™ is indicated for the management of patients with pain requiring continuous opioid analgesia.

The composition of all three strengths is identical except for size. The amount of the active in the adhesive matrix is the same in each strength, which is 10 % by weight. Norspan™ is a rectangular or square, beige colored system consisting of a protective liner and functional layers namely, web backing layer of polyester, an adhesive matrix rim without buprenorphine, a separating foil over the adhesive matrix, the buprenorphine-containing adhesive matrix, and a release liner.

The CMC section of the NDA is well organized and is replete with scientific data. However, there are several deficiencies and shortcomings that impede the approval of the NDA.

The information provided in the drug substance section does not ensure adequate control over impurities and their safety. It is not clear how the drug substance reference standard is qualified at the Purdue Pharma LLP and at (b) (4). The drug substance specifications need to be revised to conform to the ICHQ3A criteria. Buprenorphine base is described in the European Pharmacopoeia (EP) and the hydrochloride salt is described in United States Pharmacopoeia (USP), but the impurity profile is not clearly presented. Applicant's reference to EP is not sufficient justification for the safety of the impurities present in BTDS. The applicant referenced a Drug Master File (b) (4) from (b) (4) to support the drug substance synthesis and then amended the NDA to include another DMF (# (b) (4) from the same vendor. In the new DMF, the starting material (b) (4) without adequate justification. This and other issues resulted in the DMF being inadequate to support the NDA.

With regard to the non-compendial novel excipients (levulinic acid, oleyl oleate, DuroTak (b) (4)) and the impurities present in them, the applicant has not provided sufficient information on their dermal absorption and systemic toxicity. The acceptance specifications for these novel excipients should be revised to better control their quality, for use in the manufacture of BTDS.

The controls exerted over the manufacturing process are not adequate to ensure proper and consistent production of the drug product. Several in-process tests need to be established and the sampling plan should be provided for the drug product release. The impurities present in the drug product need to be treated according to the ICH Q3B

guidelines. Two degradants present in the drug product need to be specified and identified. The in vitro drug release specification should be tightened to ensure proper release of the drug and the USP<724> acceptance criteria should be included.

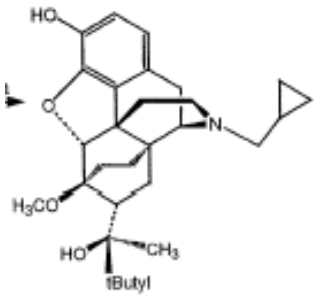
There are several stability issues that need to be resolved. Stability trends were noted in the assay, degradants, in vitro drug release, adhesion and release strength. The drug release and adhesion and release strength are critical to the functioning of the patches since the patches should adhere to the patients for seven days and the drug should consistently diffuse out of the matrix into the skin during this period. The issue of mass imbalance in the stability data was not adequately addressed. The applicant should provide revised regression analysis of the stability data including the 95 % confidence intervals for the stability-indicating attributes.

Several DMFs were deemed inadequate to support the NDA. The deficiency letters were sent to the following DMFs on August 31, 2001: DMF (b) (4)

Thus, owing to the magnitude of issues pertaining to the drug product quality that impact on the safety and efficacy, the application is not recommended for “approval”. The applicant should satisfactorily resolve all the listed deficiencies before the approval of this NDA.

A. DRUG SUBSTANCE

The drug substance, buprenorphine hydrochloride is described in Type II DMF [redacted] originally submitted by [redacted] Subsequently, the applicant referenced another Type II DMF from the same vendor, DMF [redacted] and requested that this DMF be reviewed in place of the earlier DMF in support of the drug substance. The difference between the two DMFs is with regard to the identity of the starting material. The original DMF defined [redacted] as the starting material whereas the new DMF [redacted] Although the applicant requested us to consider the [redacted] as the starting material, we deferred the decision and did not respond to the applicant's request. Our position is that in a semi-synthesis involving synthetic transformation of a natural product such as [redacted], the naturally isolated chemical should be considered a starting material. Therefore, DMF No. [redacted] was reviewed with reference to this NDA and was deemed inadequate partly because of the definition of the starting material. However, the NDA review contains only the information actually in the NDA. The letter of authorization from [redacted] to reference DMF [redacted] is provided in the submission dated November 28, 2000 and is copied here.



Buprenorphine base

110 Page(s) has been Withheld in Full as B4 (CCI/TS) immediately following this page

---

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Ravi Harapanhalli
8/30/01 04:48:16 PM
CHEMIST

Dale Koble
8/30/01 05:00:44 PM
CHEMIST

45 DAY MEETING CHECKLIST
(Answer Yes or No to the questions below)

FILEABILITY:

On initial overview of the NDA application: 21-306

CHEMISTRY, MANUFACTURING AND CONTROLS:

(1) On its face, is the M&C section of the NDA organized in a manner to allow substantive review to begin?

Yes.

(2) Is the M&C section of the NDA indexed and paginated in a manner to allow substantive review to begin?

Yes.

(3) On its face, is the M&C section of the NDA legible so that substantive review can being?

Yes.

(4) Are all of the facilities (manufacturing, packaging, testing, sterilization, etc.) appropriately delineated with full addresses?

Yes.

(5) Has the applicant submitted a complete environmental impact assessment?

Yes.

(6) Has the applicant developed appropriate controls assessment procedures that are presently ready for FDA verification?

Yes.

(7) For an antibiotic, has the applicant submitted an appropriate validation package and committed to the readiness of exhibit samples?

Yes.

(8) Has the applicant submitted all special studies studies/data requested by the Division during pre-submission discussions with the sponsor?

Yes.

(9) Has the applicant submitted draft labeling consistent with 201.56 and 201.57, current divisional labeling policies, and the design of the development package?

Yes.

(10) Has the applicant submitted stability data to support and justify the proposed expiry?

Yes.

(11) Has the applicant stated that they are ready now (Priority Drugs) for inspections of the facilities or that they will be ready within the next 6 months (Standard Drugs)?

Yes.

(12) From a manufacturing and controls perspective, is the NDA fileable? If "no", please state below why it is not.

Yes.

/s/

Naiqi Ya
12/19/00 02:22:53 PM
CHEMIST

Dale Koble
12/20/00 11:49:46 AM
CHEMIST