

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

204442Orig1s000

PRODUCT QUALITY REVIEW(S)



NDA 204-442

Probuphine[®]

(Buprenorphine Implant)

For Sub-Dermal Use

Titan Pharmaceuticals, Inc.

Chemistry Review #3

29-Jan-2016

Recommendation: Approval

Xiaobin Shen, Ph.D.

ONDP/Division II/Branch IV

for

Division of Anesthesia, Analgesia, and Addiction Products Product

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Chemistry Review Data Sheet

1. NDA: 204-442
2. REVIEW #: 3
3. REVIEW DATE: 29-Jan-2016
4. REVIEWER: Xiaobin Shen, Ph.D.
5. Related DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Original NDA	31-Oct-2012
Amendment 0008	30-Jan-2013
Amendment 0009	15-Feb-2013
Amendment 0012	18-Mar-2013
Amendment 0016	05-Apr-2013

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Amendment 0030	27-Aug-2015
Amendment 0033	17-Sep-2015
Amendment 0056	06-Jan-2016

Other amendments not listed as of data of review completion do not contain CMC information.

7. NAME & ADDRESS OF APPLICANT:

Name:	Titan Pharmaceuticals, Inc.
Address:	400 Oyster Point Blvd., Suite 505 South San Francisco, CA 94080
Telephone:	650-989-2260
Agent:	Braeburn Pharmaceuticals Attn: Frank E. Young, MD, PhD 47 Hulfish Street, Suite 441 Princeton, NJ 08542 Tel: 301-908-3182

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Probuphine® (buprenorphine Hydrochloride Implant)
b) Non-Proprietary Name (USAN): Buprenorphine Hydrochloride
c) Code Name:
d) Chem. Type/Submission Priority:
• Chem. Type: 3 (new formulation)
• Submission Priority: P

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

10. PHARMACOL. CATEGORY: Opioid agonist

11. DOSAGE FORM: Implants (subdermal)

12. STRENGTH/POTENCY: 80 mg of buprenorphine HCl/rod

13. ROUTE OF ADMINISTRATION: subdermal implants

14. Rx/OTC DISPENSED: Rx OTC

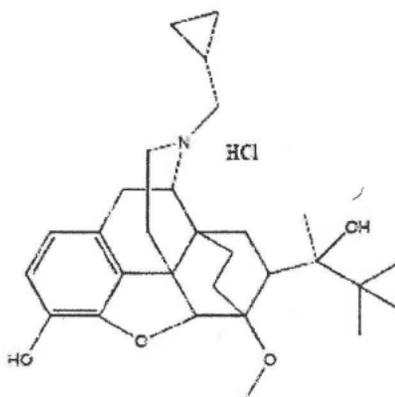
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product

Not a SPOTS product

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

Buprenorphine Hydrochloride



Empirical Formula: $C_{29}H_{41}NO_4 \cdot HCl$

Molecular Weight: 504.1

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
16419	II	Teva	Buprenorphine Hydrochloride	1	Adequate	16-Dec-2015	
(b) (4)	III	(b) (4)	(b) (4)	4			

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)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NA		

18. STATUS:

ONDP:CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	approval	4/5/2013	Dr. David Petullo
Biopharm	approval	3/31/2013	Dr. Elsebeth Chikhale
EES	acceptable	1/28/2016	Dr. Ebern Dobbin
Pharm/Tox	approval	4/5/2013	Dr. Gary Bond
Methods Validation	Not necessary		
EA	acceptable	3/11/2013	Dr. Raanan A Bloom



Executive Summary Section

The Chemistry Review for NDA 204-442

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The NDA is recommended for approval per 21 CFR 314.105 from the CMC perspective.

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

None.

II. Summary of Chemistry Assessments

The evaluations of dissolution and microbiology are deferred to the corresponding reviews in DARRTS.

The review of the applicator was consulted to CDRH. The applicator performance aspects reviewed by Mr. John McMichael is recommended for approval. The review of the compliance aspects of the applicator is pending.

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

The drug substance is Buprenorphine Hydrochloride (BPN). It is not a NME. The characterization of this compound has been well documented in the literature, and the applicant has adequately confirmed the structure of the drug substance they produced. The drug substance does not contain structural alert moieties. Only one crystal form of BPN was observed. Neither polymorphism nor (b) (4) was observed.

BPN is manufactured through multiple steps of synthesis. The detailed CMC information is incorporated by reference to DMF 16419. This DMF is considered adequate to support this NDA. The proposed drug substance specification meets and exceeds that required by the USP monograph for BPN. The quality and stability of the registration batches of the drug substance BPN are adequately demonstrated by release and stability data. The drug substance is packaged (b) (4). There are no safety concerns for the container/closure system. The proposed retest period of (b) (4) months is supported by real time stability data.

The current supplier of BPN is Teva. While some clinical and registration batches were manufactured using BPN from (b) (4) batches of BPN manufactured by the two suppliers and drug product batches using these drug substance batches are comparable.

Executive Summary Section

The establishment Teva received "Acceptable" recommendation from the Office of Compliance for this NDA.

The drug product Probuphine[®] (buprenorphine HCl implant) is a subdermal implant containing 80 mg buprenorphine hydrochloride USP (BPN) coextruded with (b) (4) mg of ethylene vinyl acetate copolymer (EVA, the only excipient) as a matrix (b) (4). Each implant measures 26 mm in length and 2.5 mm in diameter. The implants are individually packaged into laminated foil pouches. The pouches are terminally sterilized using gamma irradiation. (b) (4)

(b) (4)
The release profile consists of an initial burst followed by a slow steady state drug release over a period of 6 months.

Ethylene vinyl acetate is listed in the inactive ingredient database for several approved applications with similar dosage forms. The quantity of (b) (4) mg used in this formulation is well below the largest amount used in the listed applications. The EVA used in this drug product contains (b) (4) % of vinyl acetate. It is biocompatible, but not biodegradable.

The commercial batch size for the drug product will be (b) (4) kg. The drug product is manufactured by DPT in Texas. The recommendation from the Office of Compliance for this establishment is approve. The manufacturing process of the drug product involves (b) (4)

(b) (4)
packaging, and terminal sterilization.

Various experiments were conducted during pharmaceutical development stage to better understand and optimize the manufacturing process. Adequate in-process and material controls are in place. One batch of EVA (from (b) (4)) is used in the manufacturing of the development, clinical, registration, and immediate commercial batches. This batch is well characterized and controlled, including extractables.

The proposed drug product specification is acceptable from safety perspective and supported by release and stability data. The sterilization process and sterility controls have been evaluated by the microbiology team and are considered acceptable. Release data from eight batches (four commercial scale of (b) (4) kg, and four (b) (4) g to (b) (4) g scale) are provided. Release batch data are acceptable per specification. Up to 48 months of stability data are provided from the four (b) (4) g to (b) (4) g scale batches. No significant trend is observed for assay and impurity levels. The requested shelf life of 36 months is supported by stability data and therefore granted.

The Probuphine implants are packaged in a laminated foil pouch (b) (4). No safety issues associated with the container/closure system are identified. Extractable study was conducted, and no evidence of leachables in the drug product is observed.

Executive Summary Section

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

Four PROBUPHINE implants are inserted sub-dermally in the upper arm using the included applicator. PROBUPHINE must be removed by the end of the sixth month and may be replaced by new implants (in the opposite arm, if possible) at the time of removal, if continued treatment is desired.

The implant is only in brief contact with the applicator during the implanting process. No specific drug and device chemical compatibility study has been identified. However, there is no perceived risk considering that the applicator cannula needle is made of medical grade 304 stainless steel and the rather stable (and inert) nature of the implant rod.

C. Basis for Approvability or Not-Approval Recommendation

- 1. The applicant of the NDA has provided sufficient information to assure the identity, strength, purity, and quality of the drug product. The referenced DMF 16419 and (b) (4) are found adequate to support this NDA.*
- 2. The application received "acceptable" recommendation from the Office of Compliance on 1/28/2016.*

III. Administrative**A. Reviewer's Signature**

Xiaobin Shen -S	Digitally signed by Xiaobin Shen -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Xiaobin Shen -S, 0.9.2342.19200300.100.1.1=2000423313 Date: 2016.01.29 14:57:13 -05'00'
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Xiaobin Shen, Ph. D., CMC Reviewer, Division II, Branch IV, ONDP

B. Endorsement Block

Julia C. Pinto -S	Digitally signed by Julia C. Pinto -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Julia C. Pinto -S, 0.9.2342.19200300.100.1.1=1300366849 Date: 2016.01.29 15:00:35 -05'00'
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Julia Pinto, Ph. D., Branch Chief, Division II, Branch IV, ONDP.



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Executive Summary Section

EES Report from Office of Compliance

The screenshot displays a web application interface for CDER. The main heading is "Overall Manufacturing Inspection Recommendation". Below this, there are navigation tabs for "Task Summary", "Task Details", "Tasks", "Task List Table", "Updates", "Application History", and "Inspection Management Tools". The "Task Details" tab is active, showing a breadcrumb trail: "Overall Application Recommendations". A "Form Link" is provided at the bottom of the main content area. On the right side, a "Task Assign" panel is open, listing assigned users: "OPF Reviewer", "Ebern Dobbin", and "IM - OPI Reviewer". The panel also shows the date "This was done on Jan 28, 2016" and the status "Status: Complete".

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NDA 204,442

Probuphine® (Buprenorphine Hydrochloride Implant)

For Subdermal Use

Titan Pharmaceuticals, Inc.

Chemistry Review #2

April 30, 2013

Recommendation: Approval

Edwin Jao, Ph.D.

ONDQA/Division III/Branch VIII

for

Division of Anesthesia, Analgesia, and Addiction Products Product

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Chemistry Review Data Sheet

1. NDA 20442
2. REVIEW #:1
3. REVIEW DATE: April 7, 2013
4. REVIEWER: Edwin Jao, Ph.D.
5. Related DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
IND 070852	12-20-2004
Pre-NDA meeting minutes	11-22-2011

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	
Original NDA	10-31-2012
Amendment	1-31-2013
Amendment	2-15-2013
Amendment	3-18-2013
Amendment	4-5-2013

7. NAME & ADDRESS OF APPLICANT:

Name:	Titan Pharmaceuticals, Inc.
Address:	400 Oyster Point Blvd., Suite 505 South San Francisco, CA 94080
Representative:	
Telephone:	650-989-2260

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8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Probuphine® (buprenorphine Hydrochloride Implant)
- b) Non-Proprietary Name (USAN): Buprenorphine Hydrochloride
- c) Code Name:
- d) Chem. Type/Submission Priority:
 - Chem. Type: 3 (new formulation)

- Submission Priority: P

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

10. PHARMACOL. CATEGORY:

opioid agonists

11. DOSAGE FORM: implants (subdermal)

12. STRENGTH/POTENCY:

80 mg of buprenorphine HCl/rod

13. ROUTE OF ADMINISTRATION: subdermal implants

14. Rx/OTC DISPENSED: Rx OTC

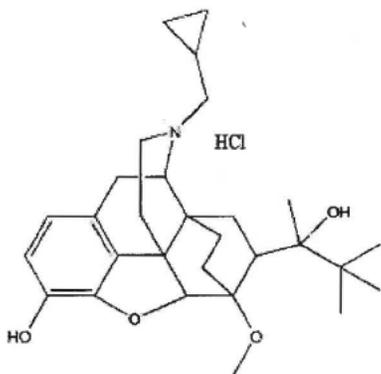
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product

Not a SPOTS product

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

Buprenorphine Hydrochloride



Empirical Formula: $C_{29}H_{41}NO_4 HCl$

Molecular Weight: 504.1

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
16419	II	Teva	Buprenorphine Hydrochloride	3	adequate	11/5/2012	
(b) (4)	III		(b) (4)	4			

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)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
na		

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	approval	4/5/2013	Dr. David Petullo
Biopharm	approval	3/31/2013	Dr. Elsebeth Chikhale
EES	acceptable	4/29/2013	
Pharm/Tox	approval	4/5/2013	Dr. Gary Bond
Clinpharm	approval	4/1/2013	Dr. David Lee



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Chemistry Review Data Sheet

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LNC	N.A.		
Methods Validation	Not necessary		
EA	acceptable	3/11/2013	Dr. Raanan A Bloom
Microbiology	acceptable	3/26/2013	Dr. Vinayak Pawar
CDRH	approval	4/5/2013	Dr. Jacqueline Ryan

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Executive Summary Section

The Chemistry Review for NDA 22-472

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the ONDQA perspective, this NDA is recommended for approval per 21 CFR 314.105.

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

None

II. Summary of Chemistry Assessments

The evaluations of dissolution and microbiology are deferred to the corresponding reviews in DARRTS. The applicator was consulted to CDRH and the review of the applicator was consulted to CDRH.

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

The drug substance is Buprenorphine Hydrochloride (BPN). It is not a NME. The characterization of this compound has been well documented in the literature, and the applicant has adequately confirmed the structure of the drug substance they produced. The drug substance does not contain structural alert moieties. Only one crystal form of BPN was observed. Neither polymorphism (b) (4) was observed. The current supplier of BPN is Teva. While some clinical and registration batches were manufactured using BPN from (b) (4), batches of BPN manufactured by the two suppliers and drug product batches using these drug substance batches are comparable. The establishment Teva received "Acceptable" recommendation from the Office of Compliance for this NDA. BPN is manufactured through multiple steps of synthesis. The detailed CMC information is incorporated by reference to DMF 16419. This DMF is considered adequate to support this NDA. The proposed drug substance specification meets and exceeds that required by the USP monograph for BPN. The quality and stability of the registration batches of the drug substance BPN are adequately demonstrated by release and stability data. The drug substance is packaged (b) (4). There are no safety concerns for the container/closure system. The proposed retest period of (b) (4) months is supported by real time stability data. The drug product Probuphine® (buprenorphine HCl implant) is a subdermal implant containing 80 mg buprenorphine hydrochloride USP (BPN) in a (b) (4) mg of ethylene vinyl acetate copolymer (EVA, the only excipient) matrix. Each implant measures 26 mm in length and 2.5 mm in diameter. Implants are individually packaged

Executive Summary Section

into laminated foil pouches. The pouches are terminally sterilized using gamma irradiation. (b) (4)

(b) (4)

The release profile consists of initial burst followed by a slow steady state drug release over a period of 6 months. Ethylene vinyl acetate is listed in the inactive ingredient database for several approved applications with similar dosage forms. The quantity of (b) (4) mg used in this formulation is well below the largest amount used in the listed applications. The EVA used in this drug product contains (b) (4) % of vinyl acetate. It is biocompatible, but not biodegradable. The commercial batch size for the drug product will be (b) (4) kg. The drug product is manufactured by DPT of Texas. The recommendation from the Office of Compliance for this establishment is pending. The manufacturing process of the drug product involves (b) (4)

(b) (4) packaging, and terminal sterilization. Various experiments were conducted during pharmaceutical development stage to better understand and optimize the manufacturing process. Adequate in-process and material controls are in place. One batch of EVA (from (b) (4)) is used in for the manufacturing of the development, clinical, registration, and immediate commercial batches. This batch is well characterized and controlled, including extractables. The proposed drug product specification is acceptable from safety perspective and supported by release and stability data. The sterilization process and sterility controls have been evaluated by the microbiology team and are considered acceptable. Release data from five batches (one commercial scale of (b) (4) kg, and four (b) (4) g to (b) (4) g scale) are provided. Release batch data are acceptable per specification. Up to 48 months of stability data are provided from the four (b) (4) g to (b) (4) g scale batches. No significant trend is observed for assay and impurity levels. The requested shelf life of 36 months is supported by stability data and therefore granted. Probuphine implants are packaged in a laminated foil pouch (b) (4) (b) (4) No safety issues associated with the container/closure system are identified. Extractable study was conducted, and no evidence of leachables in the drug product is observed.

All comments pertinent to labeling and container labels have been conveyed to the team.

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

Four to five PROBUPHINE implants are inserted subdermally in the upper arm using the included applicator. PROBUPHINE must be removed by the end of the sixth month and may be replaced by new implants (in the opposite arm, if possible) at the time of removal, if continued treatment is desired.

Executive Summary Section

C. Basis for Approvability or Not-Approval Recommendation

1. *The applicant of the NDA has provided sufficient information to assure the identity, strength, purity, and quality of the drug product. The referenced DMF 16419 and (b)(4) are found adequate to support this NDA.*
2. *The application received "acceptable" recommendation from the Office of Compliance on 4/29/2013.*

III. Administrative**A. Reviewer's Signature**

(See appended electronic signature page)

Edwin Jao, Ph. D., CMC Reviewer, Division III, Branch VIII, ONDQA

B. Endorsement Block

Prasad Peri, Ph. D., Branch Chief, Division III, Branch VIII, ONDQA.

C. CC Block

Olen Stephens, Ph. D., CMC Lead, Division III, ONDQA

A copy of summary report from the Office of Compliance is duplicated below:



CHEMISTRY REVIEW



Executive Summary Section

FDA CDER EES ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Application:	NDA 204442/000	Sponsor:	TITAN PHARMS
Org. Code:	170		711
Priority:	3		FOX ISLAND, WA 98333
Stamp Date:	31-OCT-2012	Brand Name:	BUPRENORPHINE HCL/ETHYLENE VINYL ACETATE
PDUFA Date:	30-APR-2013	Estab. Name:	
Action Goal:		Generic Name:	BUPRENORPHINE HCL/ETHYLENE VINYL ACETATE
District Goal:	01-MAR-2013	Product Number; Dosage Form; Ingredient; Strengths	001; IMPLANT; BUPRENORPHINE HYDROCHLORIDE, 80MG

FDA Contacts:	E. JAO	Prod Qual Reviewer		3017961684
	L. RIVERA	Product Quality PM		3017964013
	L. BASHAM	Regulatory Project Mgr	(HFD-170)	3017961175
	D. CHRISTODOULOU	Team Leader		3017961342

Overall Recommendation:	ACCEPTABLE	on 29-APR-2013	by R. SAFAAI-JAZI	()	3017964463
	PENDING	on 27-DEC-2012	by EES_PROD		
	PENDING	on 27-DEC-2012	by EES_PROD		
	PENDING	on 12-DEC-2012	by EES_PROD		
	PENDING	on 06-DEC-2012	by EES_PROD		
	PENDING	on 06-DEC-2012	by EES_PROD		
	PENDING	on 06-DEC-2012	by EES_PROD		

Establishment:	CFN:	FEI:	(b) (4)
			(b) (4)
DMF No:		AADA:	
Responsibilities:	FINISHED DOSAGE MANUFACTURER		
Profile:	NOT ELSEWHERE CLASSIFIED	OAI Status:	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	08-FEB-2013		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		

Review of the amendment dated 4/5/2013

In this amendment the applicant submitted officially to the NDA all previous email correspondences in response to various Agency's IR comments. The responses and evaluations were documented in the review 1 of this NDA. Any new information submitted in this amendment is evaluated below.

6 Page(s) have 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/

EDWIN JAO
04/30/2013

PRASAD PERI
04/30/2013
I Concur

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Application: NDA 204442/000
np Date: 31-OCT-2012
Regulatory: 30-APR-2013

Action Goal:
District Goal: 01-MAR-2013

Applicant: TITAN PHARMS
 711
 FOX ISLAND, WA 98333

Brand Name: BUPRENORPHINE HCL/ETHYLENE VINYL ACETATE
Estab. Name:
Generic Name: BUPRENORPHINE HCL/ETHYLENE VINYL ACETATE

Priority: 3
Org. Code: 170

Product Number; Dosage Form; Ingredient; Strengths
 001; IMPLANT; BUPRENORPHINE HYDROCHLORIDE; 80MG

Application Comment: STERILE IMPLANT- PRIORITY REVIEW (on 05-DEC-2012 by R. RAGHAVACHARI () 3017961738)

FDA Contacts:	E. JAO	Prod Qual Reviewer	3017961684
	L. RIVERA	Product Quality PM	3017964013
	L. BASHAM	Regulatory Project Mgr (HFD-170)	3017961175
	D. CHRISTODOULOU	Team Leader	3017961342

Overall Recommendation:	ACCEPTABLE	on 29-APR-2013	by R. SAFAAI-JAZI	()	3017964463
	PENDING	on 27-DEC-2012	by EES_PROD		
	PENDING	on 27-DEC-2012	by EES_PROD		
	PENDING	on 12-DEC-2012	by EES_PROD		
	PENDING	on 06-DEC-2012	by EES_PROD		
	PENDING	on 06-DEC-2012	by EES_PROD		
	PENDING	on 06-DEC-2012	by EES_PROD		

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Establishment: CFN: [REDACTED] FEI: (b) (4)
 [REDACTED] (b) (4)
 [REDACTED] (b) (4)
DMF No: [REDACTED] **AADA:**

Responsibilities: FINISHED DOSAGE MANUFACTURER

Establishment Comment: THIS FACILITY PERFORMS MANUFACTURE AND ASSEMBLY OF APPLICATOR (on 12-DEC-2012 by D. CHRISTODOULOU
 () 3017961342)
Profile: NOT ELSEWHERE CLASSIFIED **OAI Status:** NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	12-DEC-2012				CHRISTODOULO
SUBMITTED TO DO	17-DEC-2012	10-Day Letter			SMITHDE
PLEASE SEE COMMENTS FROM REVIEW - SITE MANUFACTURES AND ASSEMBLES THE APPLICATOR FOR THE IMPLANT					
SUBMITTED TO OC	27-DEC-2012				RIVERAL
SUBMITTED TO DO	28-DEC-2012	10-Day Letter			SHARPT
FD MFR: (MIS)--STERILE IMPLANT- PRIORITY REVIEW					
DO RECOMMENDATION	05-FEB-2013			ACCEPTABLE INSPECTION	NLYONS
REVIEW OF PREVIOUS EIR 1/8/12 WAS VAI FOR PROFILE CLASS MIS. DISTRICT RECOMMENDS APPROVAL					
OC RECOMMENDATION	08-FEB-2013			ACCEPTABLE DISTRICT RECOMMENDATION	SAFAAIJAZIR

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Establishment: CFN: 1628114 FEI: 1000117684
DPT LABORATORIES INC
200/307 E JOSEPHINE STREET
SAN ANTONIO, TX 78215

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE OTHER TESTER
FINISHED DOSAGE RELEASE TESTER
FINISHED DOSAGE STABILITY TESTER

Establishment Comment: RELEASE AND STABILITY TESTING OF DRUG PRODUCT. DRUG PRODUCT STABILITY SAMPLE STORAGE (b) (4),
TESTING (on 08-NOV-2012 by L. RIVERA () 3017964013)
Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	06-DEC-2012				CHRISTODOULO
SUBMITTED TO DO	06-DEC-2012	Product Specific			SHARPT
SITE APPEARS TO HAVE NO HISTORY OF CONTRACT TESTING/TESTING OF IMPLANT PRODUCTS.					
SUBMITTED TO OC	27-DEC-2012				RIVERAL
SUBMITTED TO DO	05-JAN-2013	10-Day Letter			SMITHDE
IS SITE AC FOR FD STABILITY AND RELEASE TESTING?					
RECOMMENDATION	10-JAN-2013			ACCEPTABLE	JMARTIN1
BASED ON JULY 2012 INSPECTION. FIRM IS A DRUG PRODUCT MFR WITH AN IN-HOUSE LABORATORY. PROFILE CLASS - "CTL" IS NOT APPLICABLE.				BASED ON FILE REVIEW	
OC RECOMMENDATION	17-JAN-2013			ACCEPTABLE	SHARPT
DISTRICT RECOMMENDATION					

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Establishment: CFN: (b) (4) FEI: (b) (4)

(b) (4)

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE STERILITY TESTER

Establishment Comment: STERILITY AND ENDOTOXIN RELEASE TESTING OF DRUG PRODUCT. STERILITY, ENDOTOXIN AND PACKAGING INTEGRITY TESTING FOR STABILITY TESTING OF DRUG PRODUCT. ENDOTOXIN AND MICROBIAL TESTING FOR EVA (on 08-NOV-2012 by L. RIVERA () 3017964013)
 STERILITY AND ENTOTOXIN RELEASE TESTING OF DRUG PRODUCT. STERILITY, ENDOTOXIN AND PACKAGING INTEGRITY TESTING FOR STABILITY TESTING OF DRUG PRODUCT. ENDOTOXIN AND MICROBIAL TESTING FOR EVA (on 08-NOV-2012 by L. RIVERA () 3017964013)
 ENDOTOXIN TESTING FOR DRUG SUBSTANCE AND THE APPLICATOR (DEVICE)
 CONTACT FOR THE DEVICE TESTING IS: (b) (4)
 (on 06-DEC-2012 by D. CHRISTODOULOU () 3017961342)

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	06-DEC-2012				CHRISTODOULO
OC RECOMMENDATION	06-DEC-2012			ACCEPTABLE BASED ON PROFILE	SHARPT
SUBMITTED TO OC	27-DEC-2012				RIVALAL
OC RECOMMENDATION	28-DEC-2012			ACCEPTABLE BASED ON PROFILE	SHARPT

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Establishment: CFN: (b) (4) FEI: (b) (4)
(b) (4)

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE OTHER TESTER

Establishment Comment: ALTERNATE DRUG SUBSTANCE ENDOTOXIN TESTING (on 08-NOV-2012 by L. RIVERA () 3017964013)

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	06-DEC-2012				CHRISTODOULO
OC RECOMMENDATION	06-DEC-2012			ACCEPTABLE BASED ON PROFILE	SHARPT
SUBMITTED TO OC	27-DEC-2012				RIVERAL
OC RECOMMENDATION	28-DEC-2012			ACCEPTABLE BASED ON PROFILE	SHARPT

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Establishment: CFN: SHARP CORPORATION
7451 KEEBLER WAY
ALLENTOWN, PA 18106
FEI: 3004161147

DMF No: AADA:

Responsibilities: FINISHED DOSAGE PACKAGER

Establishment Comment: SECONDARY PACKAGING OF DRUG PRODUCT (on 08-NOV-2012 by L. RIVERA () 3017964013)

THIS FACILITY PERFORMS CO-PACKAGING THE APPLICATOR AND THE DRUG PRODUCT (KITTING) (on 12-DEC-2012 by D. CHRISTODOULOU () 3017961342)

Profile: NOT ELSEWHERE CLASSIFIED **OAI Status:** NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	06-DEC-2012				CHRISTODOULO
SUBMITTED TO DO	17-DEC-2012	10-Day Letter			SMITHDE
PLEASE SEE REVIEW COMMENTS - SITE PACKAGES THE KIT FOR THIS IMPLANT.					
DO RECOMMENDATION	21-DEC-2012			ACCEPTABLE	VMATUSOV
PREVIOUS GMP EI DATED (b) (4) IS CLASSIFIED NAI. THERE ARE NO PENDING ENFORCEMENT ACTIONS THAT WOULD IMPACT THIS RECOMMENDATION.				BASED ON FILE REVIEW	
OC RECOMMENDATION	26-DEC-2012			ACCEPTABLE	SAFAAIJAZIR
				DISTRICT RECOMMENDATION	
SUBMITTED TO OC	27-DEC-2012				RIVERAL
OC RECOMMENDATION	09-JAN-2013			ACCEPTABLE	STOCKM
PREVIOUS DO AND OC RECOMMENDATIONS STILL STAND				DISTRICT RECOMMENDATION	

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Establishment: CFN: [REDACTED] (b) (4) FEI: [REDACTED] (b) (4)

DMF No: [REDACTED] **AADA:**

Responsibilities: DRUG SUBSTANCE [REDACTED] (b) (4)
DRUG SUBSTANCE RELEASE TESTER

Establishment Comment: NOTE THAT EVA IS A FUNCTIONAL EXCIPIENT CRITICAL TO DRUG PRODUCT FORMULATION (on 05-DEC-2012 by D. CHRISTODOULOU () 3017961342) TESTING [REDACTED] (b) (4) OF EVA, RELEASE TESTING OF [REDACTED] (b) (4) EVA (on 12-NOV-2012 by L. RIVERA () 3017964013)

Profile: API [REDACTED] (b) (4) NEC [REDACTED] (b) (4) **OAI Status:** NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	06-DEC-2012				CHRISTODOULO
SUBMITTED TO DO	06-DEC-2012	Product Specific			SHARPT
SUBMITTED TO OC	27-DEC-2012				RIVERAL
SUBMITTED TO DO	31-DEC-2012	Product Specific			SAFAAIJAZIR
ASSIGNED INSPECTION TO IB	10-JAN-2013	Product Specific			JMARTIN1
INSPECTION PERFORMED	[REDACTED] (b) (4)		[REDACTED] (b) (4)		JMARTIN1
DO RECOMMENDATION	29-APR-2013			ACCEPTABLE INSPECTION	TMARTINEZ
DO RECOMMENDATION	29-APR-2013			ACCEPTABLE INSPECTION	TMARTINEZ
OC RECOMMENDATION	29-APR-2013			ACCEPTABLE DISTRICT RECOMMENDATION	SAFAAIJAZIR

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Establishment: CFN: (b) (4) FEI: (b) (4)

(b) (4)

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE STERILIZER

Establishment Comment: GAMMA IRRADIATION OF DRUG PRODUCT (on 08-NOV-2012 by L. RIVERA () 3017964013)

Profile: RADIATION STERILIZATION PROCESS **OAI Status:** NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
Comment				Reason	
INSPECTION PERFORMED	(b) (4)		(b) (4)		LDESOUZA
A 2 ITEM 483 WAS ISSUED AT CLOSE OF INSPECTION ON (b) (4). SUBSEQUENT FDA INSPECTION ON (b) (4) VERIFIED ADEQUACY OF PREVIOUS CORRECTIVE ACTIONS.					
SUBMITTED TO OC	06-DEC-2012				CHRISTODOULO
SUBMITTED TO DO	06-DEC-2012	10-Day Letter			SHARPT
SUBMITTED TO OC	27-DEC-2012				RIVERAL
SUBMITTED TO DO	28-DEC-2012	10-Day Letter			SHARPT
FD STERILIZER (RSP): STERILE IMPLANT- PRIORITY REVIEW					
DO RECOMMENDATION	04-JAN-2013			ACCEPTABLE	LDESOUZA
BASED ON FIRM'S RESPONSE RECEIVED ON 6/20/12 AND DISCUSSION OF EIR AND 483 OBSERVATIONS, (b) (4)-DO RECOMMENDS "ACCEPTABLE".					
OC RECOMMENDATION	08-JAN-2013			ACCEPTABLE	SHARPT
PRIORITY REVIEW					
				DISTRICT RECOMMENDATION	

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Establishment: CFN: (b) (4) FEI: (b) (4)

(b) (4)

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE STERILIZER

Establishment Comment: THIS FACILITY PERFORMS STERILIZATION OF THE DEVICE (APPLICATOR) (b) (4). (on 06-DEC-2012 by D. CHRISTODOULOU () 3017961342)

Profile: (b) (4) **OAI Status:** NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	06-DEC-2012				CHRISTODOULO
OC RECOMMENDATION	07-DEC-2012			ACCEPTABLE BASED ON PROFILE	SHARPT
SUBMITTED TO OC	27-DEC-2012				RIVERAL
SUBMITTED TO DO FD STERILIZER (b) (4) STERILE IMPLANT- PRIORITY REVIEW	28-DEC-2012	10-Day Letter			SHARPT
DO RECOMMENDATION INSPECTION OF FACILITY IN (b) (4) FOR PROFILE (b) (4) WAS NAI. DISTRICT RECOMMENDS APPROVAL.	05-FEB-2013			ACCEPTABLE INSPECTION	NLYONS
OC RECOMMENDATION	08-FEB-2013			ACCEPTABLE DISTRICT RECOMMENDATION	SAFAAIJAZIR

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Establishment: CFN: 9610088 FEI: 1000282452

TEVA CZECH INDUSTRIES S.R.O. (FRMLY IVAX)

OSTRAVSKA 29
OPAVA-KOMAROV, , CZECH REPUBLIC

DMF No: 16149 **AADA:**

Responsibilities: DRUG SUBSTANCE MANUFACTURER

Establishment Comment: CLARIFICATION: THE DMF HOLDER IS TEVA PHARMACEUTICALS IN ISRAEL; THE DRUG SUBSTANCE MANUFACTURER IS TEVA CHECH INDUSTRIES. (on 05-DEC-2012 by D. CHRISTODOULOU () 3017961342)
MANUFACTURE OF THE DRUG SUBSTANCE. DMF 16419 IS TEVA PHARMACEUTICALS INDUSTRIES LOCATED IN 5 BASEL ST. P O B 3190 PETAH TIQVA ISRAEL (on 08-NOV-2012 by L. RIVERA () 3017964013)
Profile: NON-STERILE API BY CHEMICAL SYNTHESIS **OAI Status:** NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	06-DEC-2012				CHRISTODOULO
OC RECOMMENDATION	06-DEC-2012			ACCEPTABLE BASED ON PROFILE	SHARPT
SUBMITTED TO OC	27-DEC-2012				RIVERAL
OC RECOMMENDATION	28-DEC-2012			ACCEPTABLE BASED ON PROFILE	SHARPT

Basham, Lisa

From: ees_admin@fda.gov
Sent: Monday, April 08, 2013 9:44 AM
To: Olagbaju, Bose*; Godwin, Francis; Basham, Lisa; Rivera, Luz E (CDER); Salganik, Maria*; Spain, Nancy*; Raghavachari, Ramesh; Kyada, Yogesh*
Subject: Overall OC Recommendation NDA 201655/006 Decision: ACCEPTABLE, Decision Date: 04/08/2013, Re-evaluation Date: 01/17/2015

This is a system generated email message to notify you that the Overall Compliance Recommendation has been made for the above Application.

For general questions about how to use EES in your work, send an email to EESQUESTIONS (EESQUESTIONS@cderr.fda.gov). To contact the EES technical staff, send an email to CDER EES Help (EESHHELP@fda.hhs.gov). Thank you.

CMC
Edwin Jao
4/5/2013

NDA 204,442

Probuphine® (Buprenorphine Hydrochloride) Implant

For Subdermal Use

Titan Pharmaceuticals, Inc.

Chemistry Review #1

April 7, 2013

Recommendation: Approval

Edwin Jao, Ph.D.

ONDQA/Division III/Branch VIII

for

Division of Anesthesia, Analgesia, and Addiction Products Product

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Field Code Changed

Formatted: Swedish (Sweden)

Chemistry Review Data Sheet

1. NDA 20442
2. REVIEW #:1
3. REVIEW DATE: April 7, 2013
4. REVIEWER: Edwin Jao, Ph.D.
5. Related DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
IND 070852	12-20-2004
Pre-NDA meeting minutes	11-22-2011

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	
Original NDA	10-31-2012
Amendment	1-31-2013
Amendment	2-15-2013
Amendment	3-18-2013

7. NAME & ADDRESS OF APPLICANT:

Name:	Titan Pharmaceuticals, Inc.
Address:	400 Oyster Point Blvd., Suite 505 South San Francisco, CA 94080
Representative:	
Telephone:	650-989-2260

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8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Probuphine® (buprenorphine hCL) Implant
- b) Non-Proprietary Name (USAN): Buprenorphine Hydrochloride
- c) Code Name:
- d) Chem. Type/Submission Priority:
 - Chem. Type: 3 (new formulation)

- Submission Priority: P

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

10. PHARMACOL. CATEGORY:

opioid agonists

11. DOSAGE FORM: implants (subdermal)

12. STRENGTH/POTENCY:

80 mg of buprenorphine HCl/rod

13. ROUTE OF ADMINISTRATION: subdermal implants

14. Rx/OTC DISPENSED: Rx OTC

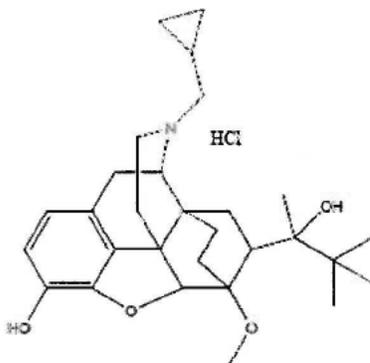
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product

Not a SPOTS product

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

Buprenorphine Hydrochloride



Empirical Formula: $C_{29}H_{41}NO_4 \cdot HCl$

Molecular Weight: 504.1

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
16419	II	Teva	Buprenorphine Hydrochloride	3	adequate	11/5/2012	
(b) (4)	III			(b) (4) 4	adequate		

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)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
na		

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics			Dr. David Petullo
Biopharm	approval	3/31/2013	Dr. Elsebeth Chikhale
EES	pending	4/7/2013	Facilities not been inspected yet
Pharm/Tox	approval	4/5/2013	Dr. Gary Bond
Clinpharm	approval	4/1/2013	Dr. David Lee



CHEMISTRY REVIEW



Chemistry Review Data Sheet

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LNC	N.A.		
Methods Validation	Not necessary		
EA	acceptable	3/11/2013	Dr. Raanan A Bloom
Microbiology	acceptable	3/26/2013	Dr. Vinayak Pawar
CDRH	Acceptable from CDRH OC perspective		

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Executive Summary Section

The Chemistry Review for NDA 22-472

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the ONDQA perspective, this NDA is recommended for approval per 21 CFR 314.105, pending on the final acceptable recommendation from the Office of Compliance.

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

None

II. Summary of Chemistry Assessments

The evaluations of dissolution and microbiology are deferred to the corresponding reviews in DARRTS. The applicator was consulted to CDRH and the review of the applicator was consulted to CDRH.

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

The drug substance is Buprenorphine Hydrochloride (BPN). It is not a NME. The characterization of this compound has been well documented in the literature, and the applicant has adequately confirmed the structure of the drug substance they produced. The drug substance does not contain structural alert moieties. Only one crystal form of BPN was observed. Neither polymorphism (b) (4) was observed. The current supplier of BPN is Teva. While some clinical and registration batches were manufactured using BPN from (b) (4), batches of BPN manufactured by the two suppliers and drug product batches using these drug substance batches are comparable. The establishment Teva received "Acceptable" recommendation from the Office of Compliance for this NDA. BPN is manufactured through multiple steps of synthesis. The detailed CMC information is incorporated by reference to DMF 16419. This DMF is considered adequate to support this NDA. The proposed drug substance specification meets and exceeds that required by the USP monograph for BPN. The quality and stability of the registration batches of the drug substance BPN are adequately demonstrated by release and stability data. The drug substance is packaged (b) (4). There are no safety concerns for the container/closure system. The proposed retest period of (b) (4) months is supported by real time stability data. The drug product Probuphine® (buprenorphine HCl implant) is a subdermal implant containing 80 mg buprenorphine hydrochloride USP (BPN) in a (b) (4) mg of ethylene vinyl acetate copolymer (EVA, the only excipient) matrix. Each implant

Executive Summary Section

measures 26 mm in length and 2.5 mm in diameter. Implants are individually packaged into laminated foil pouches. The pouches are terminally sterilized using gamma irradiation. (b) (4)

The release profile consists of initial burst followed by a slow steady state drug release over a period of 6 months. Ethylene vinyl acetate is listed in the inactive ingredient database for several approved applications with similar dosage forms. The quantity of (b) (4) mg used in this formulation is well below the largest amount used in the listed applications. The EVA used in this drug product contains (b) (4) % of vinyl acetate. It is biocompatible, but not biodegradable. The commercial batch size for the drug product will be (b) (4) kg. The drug product is manufactured by DPT of Texas. The recommendation from the Office of Compliance for this establishment is pending. The manufacturing process of the drug product involves (b) (4)

packaging, and terminal sterilization. Various experiments were conducted during pharmaceutical development stage to better understand and optimize the manufacturing process. Adequate in-process and material controls are in place. One batch of EVA (from (b) (4)) is used in for the manufacturing of the development, clinical, registration, and immediate commercial batches. This batch is well characterized and controlled, including extractables. The proposed drug product specification is acceptable from safety perspective and supported by release and stability data. The sterilization process and sterility controls have been evaluated by the microbiology team and are considered acceptable. Release data from five batches (one commercial scale of (b) (4) kg, and four (b) (4) g to (b) (4) g scale) are provided. Release batch data are acceptable per specification. Up to 48 months of stability data are provided from the four (b) (4) g to (b) (4) g scale batches. No significant trend is observed for assay and impurity levels. The requested shelf life of 36 months is supported by stability data and therefore granted. Probuphine implants are packaged in a laminated foil pouch (b) (4) (b) (4) No safety issues associated with the container/closure system are identified. Extractable study was conducted, and no evidence of leachables in the drug product is observed.

All comments pertinent to labeling and container labels have been conveyed to the team.

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

Four to five PROBUPHINE implants are inserted subdermally in the upper arm using the included applicator. PROBUPHINE must be removed by the end of the sixth month and may be replaced by new implants (in the opposite arm, if possible) at the time of removal, if continued treatment is desired.

Executive Summary Section

C. Basis for Approvability or Not-Approval Recommendation

1. *The applicant of the NDA has provided sufficient information to assure the identity, strength, purity, and quality of the drug product. The referenced DMF 16419 and (b) (4) are found adequate to support this NDA.*
2. *The recommendation from the Office of Compliance for this NDA is pending upon completion of inspection of the drug product manufacturing site (DPT) and the (b) (4) release testing site of the critical excipient ethylene vinyl acetate copolymer (b) (4)*

III. Administrative**A. Reviewer's Signature**

(See appended electronic signature page)

Edwin Jao, Ph. D., CMC Reviewer, Division III, Branch VIII, ONDQA

B. Endorsement Block

Prasad Peri, Ph. D., Branch Chief, Division III, Branch VIII, ONDQA.

C. CC Block

Olen Stephens, Ph. D., CMC Lead, Division III, ONDQA

121 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/

PRASAD PERI

12/21/2012

Filable from CMC perspective

BIOPHARMACEUTICS REVIEW Office of New Drug Quality Assessment			
Application No.:	NDA 204442	Biopharmaceutics Reviewer: Elsbeth Chikhale, PhD	
Submission Date:	October 31, 2012		
Division:	Division of Anesthesia, Analgesia and Addiction Products	Biopharmaceutics Team Leader: Angelica Dorantes, PhD	
Applicant:	Titan Pharmaceuticals Inc.	Acting Supervisor: Richard Lostritto, PhD	
Trade Name:	Probuphine (buprenorphine) Implant	Date Assigned:	October 31, 2012
Generic Name:	Buprenorphine HCl	Date of Review:	March 30, 2013
Indication:	Treatment of opioid dependence	Type of Submission: 505(b)(2) Priority Original New Drug Application	
Dosage form/ strengths	Implant/ 80 mg/implant		
Route of Administration	Subdermal		

SUMMARY:

Submission: This 505(b)(2) New Drug Application is for an extended release implantable drug product containing 80 mg buprenorphine HCl (BPN; active ingredient) and (b)(4) mg ethylene vinyl acetate (polymer) per implant for subcutaneous insertion under the arm using an applicator. The implants will stay implanted for a period of 6 months.

Review: The Biopharmaceutics review for this NDA will be focused on the evaluation and acceptability of 1) the proposed dissolution methodology, and 2) the dissolution acceptance criteria.

RECOMMENDATION:

The dissolution method and acceptance criteria as summarized below are acceptable.

➤ Dissolution method:

USP Apparatus II (paddle)
Temperature: 37 °C
Rotation speed: 50 rpm
Medium: 900 mL water

➤ Dissolution acceptance criteria (% drug released):

24 hrs: (b)(4) %
48 hrs: (b)(4) %
144 hrs: NLT (b)(4) %

From the Biopharmaceutics perspective, NDA 204442 for Probuphine Implants containing 80 mg bupronorphine HCl per implant is recommended for **APPROVAL**.

Elsbeth Chikhale, Ph.D.

Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Angelica Dorantes, Ph.D.

Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

BIOPHARMACEUTICS ASSESSMENT –REVIEWER NOTES

SUBMISSION:

This 505(b)(2) New Drug Application is for an extended release implantable drug product containing 80 mg buprenorphine HCl (BPN; active ingredient) and (b)(4) mg ethylene vinyl acetate (polymer) per implant for subcutaneous insertion under the arm using an applicator device. The proposed drug product is indicated for the maintenance treatment of opioid dependence. This application is an electronic NDA that provides for a new dosage form (implant instead of the already approved sublingual tablet). The NDA is filed as a 505(b)(2) application, with Subutex (NDA 20732) and Suboxone (NDA 20733) as the reference drugs. The Applicant has identified the following Quality Target Product Profile and the Critical Quality Attributes:

Quality Target Product Profile	Critical Quality Attributes
Ease of Product Identification: Drug Product Dosage Strength	Appearance Identity
Efficacy and In-vivo Performance: Target Probuphine® formulation will exhibit a sustained therapeutic Buprenorphine plasma profile with low fluctuation when dosed six months.	Assay Content Uniformity Dissolution
Safety	(b)(4) (b)(4) Sterility Endotoxin level

Probuphine implants were designed to be administered subdermally and to deliver a desired sustained release profile for a period of 6 months. (b)(4)

The in vitro and in vivo drug substance release profile of the probuphine implant consists of initial rapid release of BPN followed by steady-state release of BPN at low levels for an extended period of time. (b)(4)

Bioavailability data from Study PRO-810 and data from Study TTP-400-02-01 demonstrate that the mean plasma buprenorphine concentrations are overall markedly lower after Probuphine insertion than after dosing with sublingual (SL) buprenorphine. The relative bioavailability of 4 Probuphine implants (80 mg buprenorphine per implant) based on the mean AUC₀₋₂₄ at steady state was 70% less than that observed after SL buprenorphine (16 mg once daily). Similarly, the mean plasma concentrations at steady state for Probuphine were 38% to 48% less than trough concentrations for SL buprenorphine dosing at steady state. The Applicant has conducted several clinical efficacy studies. These studies will be reviewed by the Clinical Pharmacology and Clinical reviewers.

REVIEW:

The Biopharmaceutics review for this NDA will be focused on the evaluation and acceptability of
1) the proposed dissolution methodology, and
2) the dissolution acceptance criteria.

BIOPHARMACEUTICS INFORMATION:

Composition of the proposed subdermal implantable drug product:

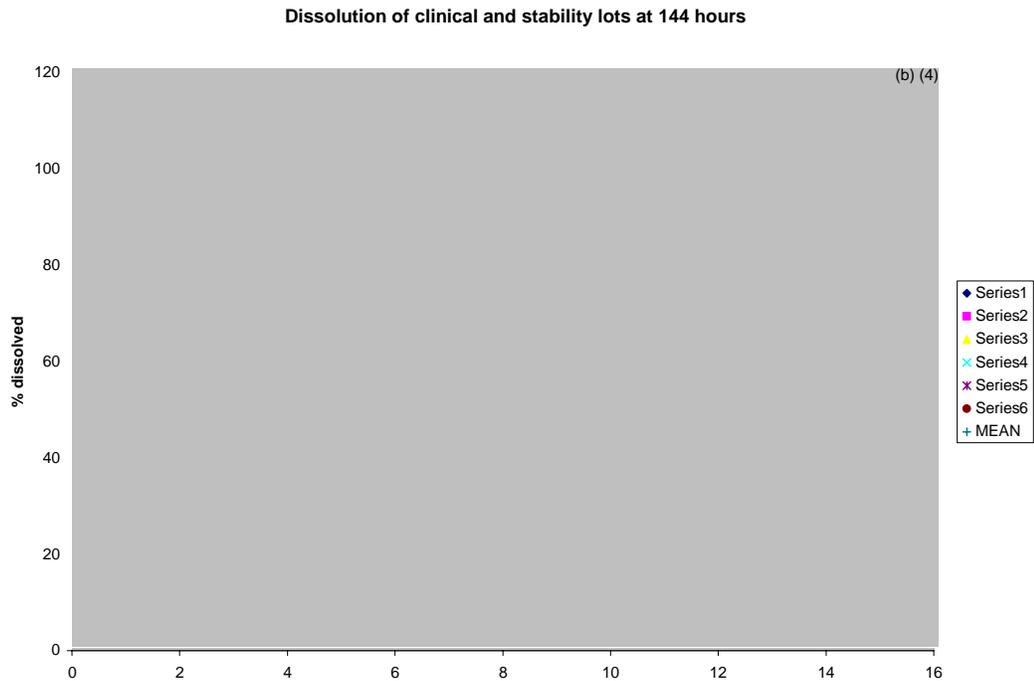
Component	Quality Standard	Function	mg/implant
Buprenorphine hydrochloride	USP	Active pharmaceutical ingredient	80
Ethylene vinyl Acetate	In house specification	Excipient / Polymeric matrix	(b) (4)

DISSOLUTION METHOD:

The proposed drug release/dissolution method is:

- Apparatus 2 (paddle)
- 900 mL water
- 50 rpm
- HPLC analysis
- Sampling times: (b) (4) 24, 48, (b) (4) 144, (b) (4) hours

For the 144 hr time point:



The following requests were sent to the Applicant on 3/21/13:

1. *Revise your dissolution acceptance criteria as follows:*

- $(b) (4)$ % at 24 hours
- $(b) (4)$ % at 48 hours
- Not less than $(b) (4)$ % at 144 hours

2. *Provide a revised drug product specification table*

3. *Submit all correspondences dated 3/15/2013 officially to the NDA*

On 3/25/13, the Applicant provided the following responses:

1. *The dissolution acceptance criteria will be revised as requested.*

2. *A copy of the revised Titan specification for the drug product is presented in Attachment 1. This revised specification includes both requested revisions by the Agency.*

- *Inclusion of package appearance and acceptance criteria (Titan response to question 4 from Information Request dated March 4, 2013)*
- *Revised dissolution acceptance criteria (Response to FDA Question #1 above).*

3. *All correspondence dated 3/15/2013 will be submitted officially to the NDA by 05 April 2013. Titan also plans to include the information provided in this response as part of that submission.*

Reviewer's Final Assessment on the revised dissolution acceptance criteria: Acceptable

All clinical batches passed the revised dissolution acceptance criteria at release (stability time point of zero months). Therefore, the revised dissolution criteria reflect the dissolution properties of the clinical batches, assuming that the batches were used in the clinical trials shortly after release. Evaluation of the dissolution data obtained during the drug product stability do not indicate a trend, upwards or downwards, when the drug product is stored at room temperature for up to 48 months. It should be noted that the dissolution-stability data showed a few points outside the dissolution acceptance criteria limits. However, since upward or downward trends were not observed, Biopharmaceutics does not recommend a change in the requested 36 months shelf-life.

RECOMMENDATION:

- The applicant's dissolution methodology, as summarized below is acceptable by the Agency:

USP Apparatus II (paddle)
Temperature: 37 °C
Rotation speed: 50 rpm
Medium: 900 mL water

- Dissolution acceptance criteria:

Based on the dissolution data provided, the following dissolution acceptance criteria are acceptable:

24 hrs: (b) (4) %
48 hrs: (b) (4) %
144 hrs: NLT (b) (4) %

From the Biopharmaceutics perspective, NDA 204442 for Probuphine Implants containing 80 mg bupronorphine HCl per implant is recommended for **APPROVAL**.

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/s/

ELSBETH G CHIKHALE
03/30/2013

ANGELICA DORANTES
03/31/2013

Product Quality Microbiology Review

March 21, 2013

NDA: 204442

Drug Product Name

Proprietary: Probuphine®

Non-proprietary: buprenorphine hydrochloride/ethylene vinyl acetate.

Review Number: 1

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
October 27, 2012	October 31, 2012	November 05, 2012	November 08, 2012

Submission History (for 2nd Reviews or higher) – N/A

Applicant/Sponsor

Name: Titan Pharmaceuticals Inc.

Address: 400 Oyster Point Blvd, S San Francisco, CA 94080

Representative: Sunil Bhonsle, President

Telephone: Allene Dodge, Reg. Affairs Consultant
253-549-0751

Name of Reviewer: Vinayak B. Pawar, Ph.D.

Conclusion: Recommend approval.

Product Quality Microbiology Data Sheet

- A. 1. **TYPE OF SUBMISSION:** Original NDA
2. **SUBMISSION PROVIDES FOR:** A sub-dermal implant for continuous delivery of buprenorphine for six months.
3. **MANUFACTURING SITE:**
Probuphine Implant: DPT Laboratories, San Antonio, Texas
4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:** Sub-dermal implant, 80 mg
5. **METHOD(S) OF STERILIZATION:**
Applicator: (b) (4)
Drug product: Terminal Gamma Radiation sterilization.
6. **PHARMACOLOGICAL CATEGORY:** Probuphine is indicated for the maintenance treatment of opioid dependence.
- B. **SUPPORTING/RELATED DOCUMENTS:** None applicable to drug product microbiology.
- C. **REMARKS:** The original NDA 204442 provides for a sub-dermal implant for continuous delivery of the drug product, buprenorphine. IQA was filed by CMC's Peri Prasad on December 12, 2012. This is an electronic submission. (b) (4) which performs microbiological testing was last inspected by FDA in (b) (4). This was a product directed inspection for NDA approval. No inspection report is available for DPT laboratories to date. The drug product kit contains an applicator with a stylet, cannula and a swivel nut and is sterilized by (b) (4). The applicator will be reviewed for product quality by CDRH according to ONDQA.

filename: N204442R1

Executive Summary

I. Recommendations

- A. Recommendation on Approvability** – Recommend approval
- B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable** – N/A

II. Summary of Microbiology Assessments

- A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology** – The drug product implant is manufactured by a process which includes [REDACTED] (b) (4) [REDACTED] primary packaging and terminal sterilization by gamma radiation.
- B. Brief Description of Microbiology Deficiencies** – N/A
- C. Assessment of Risk Due to Microbiology Deficiencies** – N/A
- D. Contains Potential Precedent Decision(s)- Yes [-] No [X]**

III. Administrative

- A. Reviewer's Signature** _____
Vinayak B. Pawar, Ph.D., Sr. Microbiology Reviewer, OPS/CDER
- B. Endorsement Block** _____
Bryan S. Riley, Ph.D., Acting Team Leader, OPS, CDER
- C. CC Block**
N/A

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/s/

VINAYAK B PAWAR
03/25/2013

BRYAN S RILEY
03/26/2013
I concur.

From: Bloom, Raanan
Sent: Monday, March 11, 2013 1:57 PM
To: Rivera, Luz E (CDER); Jao, Edwin
Subject: FW: Finalized - NDA 204442 Environmental Assessment Consult Request (FRM-CONSULT-30)

Luz, Edwin;

This is my evaluation of the provided information.

Titan Pharmaceuticals, Inc. has submitted a Claim of Categorical Exclusion under 21 CFR §25.31(b); Expected Environmental Concentration (EIC) < 1 µg/L (ppb). Supporting information (2017 production estimates and environmental exposure data) was provided by the applicant in a document titled 'Environmental Assessment' (Note: an EA is not required for a claim of categorical exclusion). The EIC is estimated at (b) (4) µg/L. The provided information supports the claim for categorical exclusion. Based on a search of the literature including the PPCP database (<http://www.epa.gov/ppcp/lit.html>) we find no indication of 'extraordinary circumstances' for this application.

The action qualifies for categorical exclusion under §25.31(b).

Raanan Bloom
Senior Environmental Officer
OPS/IO

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/s/

RAANAN A BLOOM
03/11/2013