

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

204442Orig1s000

OTHER REVIEW(S)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration

Center for Devices and Radiological Health


Office of Compliance, Division of Enforcement A

General Hospital Devices Branch

DATE: January 22, 2013

TO: Lisa Basham, Division of Anesthesia, Analgesia, and
Addiction Products, Office of Drug Evaluation II, Office of
New Drugs, Center for Drug Evaluation and Research
WO22, Room 3156

Cc: Office of Combination Products at combination@fda.gov

THRU: Carl Fischer, Ph.D., Chief, General Hospital Devices Branch,
Division of Enforcement A, Office of Compliance, CDRH,
WO-66, Room 3526  1/22/13

FROM: Latoya Oliver-Powell, General Hospital Devices Branch,
Division of Enforcement A, Office of Compliance, CDRH,
WO-66, Room 3552

SUBJECT: Inter-Center consult requested by CDER/OND for NDA
204442

CONSULT DAAP requests CDRH/OC assistance with facility
INSTRUCTIONS: inspections for the device component of this application.

Objective

The Office of Compliance at CDRH received a consult request from CDER/DAAP requesting CDRH/OC assistance with facility inspections for the device component associated with this application.

Product Description

The product is: Probuphine Applicator (buprenorphine subdermal implant)

The intended use is:

1. Intended to place Probuphine in the subdermal space of the body, by trained healthcare providers.
2. Implantable formulation developed for maintenance for opioid dependence.

Titan Pharmaceuticals provided their NDA submission, the sponsor indicates that it has produced a device that is substantially equivalent to predicate devices marketed and or/ cleared.

Consult Evaluation

CDRH Office of Compliance has reviewed the list of manufacturing and testing sites.

Manufacturing and assembly of the Applicator will take place at (b) (4) (FEI: (b) (4)). This facility had a medical device inspection (b) (4) and was classified Voluntary Action Indicated (VAI). Based on the classification and the date of the inspection, CDRH does not believe that an additional inspection is needed.

Sterility and Endotoxin release testing will be contracted out and take place at (b) (4) (FEI: (b) (4)). CDRH does not believe that other inspections are needed related to the applicable device manufacturing regulations.

(b) (4) will be contracted out and take place at (b) (4) (FEI: (b) (4)). CDRH does not believe that other inspections are needed related to the applicable device manufacturing regulations.

Secondary Packaging of Probuphine Kits and Warehousing will be contracted out and will take place at Sharp Corporation (FEI: 3004161147). CDRH does not believe that other inspections are needed related to the applicable device manufacturing regulations.

CDRH Recommendation

Upon review of the available documentation, CDRH is not recommending additional inspections related to compliance with medical device manufacturing regulations.



Latoya Oliver-Powell

Prepared/typed: LOliver-Powell: 01/18/2013, 1/22/2013
Reviewed: CFischer:
Revised:

cc:
WO66-3515 (DOE-A Firm File)
WO66-3515 (Division Chron File)
WO66-3552 (LOliver-Powell, Reviewer)

CTS No.: ICC1200262

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/s/

SWATI A PATWARDHAN
05/31/2016

MEMORANDUM
REVIEW OF REVISED LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	May 23, 2016
Requesting Office or Division:	Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Application Type and Number:	NDA 204442
Product Name and Strength:	Probuphine (buprenorphine) implant, 74.2 mg
Submission Date:	May 19, 2016 (via email)
Applicant/Sponsor Name:	Titan Pharmaceuticals, Inc.
OSE RCM #:	2015-2114
DMEPA Primary Reviewer:	Millie Shah, PharmD, BCPS
DMEPA Team Leader:	Vicky Borders-Hemphill, PharmD

1 PURPOSE OF MEMO

The Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) requested that we review the revised training slides, insertion/removal instructions for use (IFU) booklet, procedural competency checklist, and training video script for Probuphine to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous labeling review.¹

2 CONCLUSION

The revised training slides, insertion/removal instructions for use (IFU) booklet, procedural competency checklist, and training video script for Probuphine are acceptable from a medication error perspective. We have no further recommendations at this time.

¹ Shah M. Human Factors, Label and Labeling Review for Probuphine (buprenorphine) implant (NDA 204442). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2016 MAY 06. 4 p. OSE RCM No.: 2015-2114.

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/s/

MILLIE C BRAHMBHATT
05/23/2016

BRENDA V BORDERS-HEMPHILL
05/23/2016

Date: February 16, 2016

To: Xiaobin Shen, Ph.D., CMC Reviewer, Branch IV, Division II, Office of
New Drug Product, Office of Product Quality

CDER, FDA Xiaobin.Shen@fda.hhs.gov

Office of combination products at combination@fda.gov

Through: Francisco Vicenty, Chief, REGO, DMQ, OC, CDRH

From: LT Viky Verna, Branch Lead, REGO, DMQ, OC, CDRH

Applicant: Titan Pharmaceuticals Inc.
400 Oyster Point Blvd, Suite 505
South San Francisco, CA 94080

FEI: 3003415553

Application # NDA 204442

Consult # ICC1500422

Product Name: Probuphine Implant

Inspection Needed: No - Date: 1/15/2016

Desk Review: No Additional Information Required

Final Recommendation: **APPROVAL**

The Office of Compliance at CDRH received a consult request from CDER to evaluate the applicant's compliance with applicable Quality System Requirements for the approvability of the submission NDA 204442 for the Probuphine Implant.

PRODUCT DESCRIPTION

Probuphine is a subdermally implantable formulation of the active ingredient buprenorphine hydrochloride (buprenorphine) in a solid matrix of ethylene vinyl acetate polymer (EVA) that is intended to provide sustained delivery of buprenorphine for 6 months for maintenance treatment of opioid dependence.

The recommended clinical dosage of Probuphine is 4 implants (80 mg buprenorphine per implant) inserted for 6 months. Patients should be clinically stable on 8 mg or less of sublingual buprenorphine prior to transitioning to Probuphine. Individuals may be treated for additional 6-month treatment periods, using a site on the opposite arm from that used for the prior Probuphine treatment.

The Probuphine Applicator device description and its intended use are similar to that of other hypodermic single lumen needles or trocars as they are more commonly referred to. The Probuphine Applicator is a device intended to place Probuphine Implants in the subdermal space of the upper arm.

The Probuphine Applicator being supplied for Probuphine delivery is a sterile, single patient use device, composed of a cannula and blunt ended stylet with a handle that is intended to place Probuphine in the subdermal space of the body, by trained health care providers.

REGULATORY HISTORY

The following facility was identified as being subject to applicable Quality System Requirements under 21 CFR part 820:

1. Titan Pharmaceuticals Inc.
400 Oyster Point Blvd, Suite 505
South San Francisco, CA 94080
FEI: 3003415553

Responsibility: The firm is the sponsor for the application.

Inspection History: An analysis of the firm's inspection history over the past 2 years showed that an inspection has not been performed recently.

A pre-approval inspection is not recommended for this firm because:

- The firm's compliance with applicable 21 CFR 820 requirements will be reviewed through the documentation review.
2. Sharp Corporation
7451 Keebler Way
Allentown, PA 18106
FEI: 3004161147

Responsibility: Secondary packaging, labeling and kitting with Probuphine and Warehousing of the Probuphine "Kit" (Drug Product)

Inspection History: An analysis of the firm's inspection history over the past 2 years showed that an inspection was performed on 06/18/2014 - 06/19/2014, and was classified NAI.

A pre-approval inspection is not recommended for this firm because:

- The firm's recent inspection was acceptable.

DESK REVIEW

(b) (4)



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Desk Review Recommendation

This application was deficient overall. Additional information is required for an adequate desk review.

UPDATE 2/16/16

The firm's response dated February 10, 2016, was reviewed and deemed to be adequate.

RECOMMENDATION

The Office of Compliance at CDRH recommends **APPROVAL** of application NDA 204442 for the Probuphine Implant

Viky Verna -S

Digitally signed by Viky Verna -S
DN: c=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People, cn=Viky Verna -S,
0.9.2342.19200300.100.1.1=2000495623
Date: 2016.02.16 17:23:09 -05'00'

LT Viky Verna, MS BME, MS Pharm, RAC

Prepared: VVerna: 1/14/2015 ; 1/15/16; 2/16/16

Reviewed: FMLast name: Month/Day/Year

CTS No.: ICC1200262

NDA 204442

Review Cycle Meeting Attendance:

Month/Day/Year

Month/Day/Year

Month/Day/Year

To: ORA

Inspectional Guidance

1. Titan Pharmaceuticals Inc.
400 Oyster Point Blvd, Suite 505
South San Francisco, CA 94080
FEI: 3003415553

CDRH recommends that the follow-up routine inspection at the firm listed above to covers compliance with 21 CFR part 4, applicable Quality System (21CFR 820) requirements – Management Controls (21 CFR 820.20), Design Controls (21 CFR 820.30), Purchasing Controls (21 CFR 820.50), and CAPA (21 CFR 820.100).

REGULATORY STRATEGY

The establishment inspection report (EIR) for the firm should be shared with CDRH (The EIR should be assigned to CDER and then sent to CDRH as a consult for review). If the inspection is being classified Official Action Indicated (OAI), the District should consider recommending appropriate regulatory action with consultation from CDER and CDRH and whether the violation is drug or device related.

Questions regarding this consult should be referred to one of the following individuals:

Primary Contact

LT Viky Verna
Combination Product Branch Lead
REGO, DMQ
Office of Compliance, WO66 -3435
Phone: 301-796-2909

Secondary Contacts (if Primary is unavailable and a timely answer is required)

Francisco Vicenty
Branch Chief
REGO, DMQ
Office of Compliance

THIS ATTACHMENT IS NOT TO BE PROVIDED TO THE FIRM OR SHOWN TO THEM DURING THE INSPECTION. THIS ATTACHMENT CONTAINS PREDECISIONAL INFORMATION

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/s/

SWATI A PATWARDHAN

05/20/2016

on behalf of CDRH-OC Reviewer Viky Verna

MEMORANDUM

REVIEW OF REVISED LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	May 11, 2016
Requesting Office or Division:	Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Application Type and Number:	NDA 204442
Product Name and Strength:	Probuphine (buprenorphine) implant, 74.2 mg
Product Type:	Single ingredient
Rx or OTC:	Rx
Applicant/Applicant Name:	Titan Pharmaceuticals, Inc.
Submission Date:	May 3, 2016
OSE RCM #:	2015-2114
DMEPA Primary Reviewer:	Millie Shah, PharmD, BCPS
DMEPA Team Leader:	Vicky Borders-Hemphill, PharmD

1 REASON FOR REVIEW

Titan Pharmaceuticals, Inc. submitted revised carton labeling for Probuphine (buprenorphine) implant. The revised carton labeling includes a serial number that the healthcare professional (HCP) who inserts Probuphine will record on the Probuphine REMS Insertion and Removal Log on the day Probuphine is inserted. The Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) and the Division of Risk Management (DRISK) requested we evaluate the revised carton labeling from a medication error perspective. We provided recommendations to the Applicant in OSE #2015-2114¹² dated April 22, 2016 and April 28, 2016 (See Appendix A for DMEPA's previous comments). The Applicant responded to our recommendations on May 3, 2016 (See Appendix B for Applicant's response). Thus, this memo provides comments to the Applicant's response.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review.

Table 1. Materials Considered for this Review
Material Reviewed
DMEPA Recommendations to Applicant: Appendix A
Applicant's Response to DMEPA Comments: Appendix B
Carton Labeling: Appendix C

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We evaluated the Applicant's response to our recommendations from a medication error perspective.

- The Applicant revised the carton labeling to include the serial number on the back panel under the lot number and expiration date.
- The Applicant decreased the number of digits in the serial number (b) (4) to 7 digits.
- The Applicant accepted our recommendation and replaced the abbreviation "SN" with the full intended meaning "Serial Number."
- The Applicant did not accept our recommendation to print the serial number under the lot number and expiration date on the individual container labels. Instead, the

¹ Shah M. Memorandum Review of Revised Labeling for Probuphine (NDA 204442). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2016 APR 22. 5 p. OSE RCM No.: 2015-2114.

² Shah M. Memorandum Review of Revised Labeling for Probuphine (NDA 204442). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2016 APR 28. 5 p. OSE RCM No.: 2015-2114.

Applicant proposes to include the following statement that will be located on the area where the container pouches with the implants are located:

**ATTENTION
HEALTHCARE PROVIDER
Who Inserts Probuphine:**

*Record Serial Number on
the REMS Insertion and
Removal Log on the day
Probuphine is inserted!
The Serial Number appears
on the back panel
of this carton.*

We accept the Applicant's proposal to include the statement to Healthcare Providers Who Insert Probuphine on the carton labeling. We previously agreed with their rationale for the location of the serial number to be on the back panel under the lot number and expiration date (see Appendix A).

4 CONCLUSION & RECOMMENDATIONS

The revised serial number and carton labeling are acceptable from a medication error perspective. We have no further recommendations at this time.

APPENDIX A. DMEPA RECOMMENDATIONS TO APPLICANT

Recommendations dated April 28, 2016

1. We agree with your rationale for the location of the serial number to be on the back panel under the lot number and expiration date.
2. We agree with your rationale to decrease the number of digits in the serial number (b) (4) to 7 digits.
3. You did not respond to our recommendation to include an explanation of the purpose of the serial number for the HCP Who Inserts Probuphine. We are concerned that not all healthcare professionals will know that the abbreviation “SN” refers to Serial Number, which may lead to confusion and recording of the wrong number on the Probuphine REMS Insertion and Removal Log. Therefore, we recommend that you replace the abbreviation “SN” with the full, intended meaning “Serial Number” for clarity and to mitigate confusion with other numbers that will appear near the serial number.
4. We do not agree with your rationale that including the serial number on the individual container labels would add significant time and cost to the packaging process. Including the serial number on the container label may provide an additional measure for accurate documentation in the REMS documents. We are concerned that the carton labeling may be discarded before the HCP Who Inserts Probuphine records the serial number on the Probuphine REMS Insertion and Removal Log. Thus, we recommend that you print the serial number under the lot number and expiration date on the individual container labels (paper label) to minimize the risk for these errors.

Recommendations dated April 22, 2016

1. Relocate the serial number to the top right corner of the principal display panel. As currently presented, the serial number is located on the back panel, under the lot number and expiration date, which may lead to confusion with the lot number or expiration date. Additionally, the current location of the serial number on the back panel may not be readily located by HCPs Who Insert Probuphine. Ensure that the font for the serial number is large enough for easy readability.
2. Provide your rationale for the selection of a (b) (4) digit serial number versus a serial number with fewer digits. We are concerned that the (b) (4) digit serial number may lead to errors in transcribing when the HCP Who Inserts Probuphine records the serial number on the Probuphine REMS Insertion and Removal Log. We recommend you decrease the number of digits in the serial number to minimize transcription errors. Ensure that the number of digits for the serial number differs significantly in length and format (b) (4) (b) (4) to minimize the risk for confusion (b) (4).
3. Include an explanation for the purpose of the serial number for the HCP Who Inserts Probuphine to improve clarity. For example, consider the following:

SN: ###

Attention HCP Who Inserts Probuphine:
Record the Serial Number (SN) on the
Probuphine REMS Insertion and Removal
Log on the day Probuphine is inserted.

4. Add the corresponding serial number to the Probuphine container labels for the implants in the same format and location as on the carton labeling. We recommend that the serial number also be added to the Probuphine implant individual container labels so that the serial number can be located in instances where the carton labeling is thrown away before the HCP Who Inserts Probuphine records the serial number on the Probuphine REMS Insertion and Removal Log.

APPENDIX B: APPLICANT'S RESPONSE TO DMEPA COMMENTS

Response dated May 3, 2016

1. FDA Comment: We agree with your rationale for the location of the serial number to be on the back panel under the lot number and expiration date.
Sponsor Response 1: Changes have been made to the kit.
2. FDA Comment: We agree with your rationale to decrease the number of digits in the serial number (b) (4) to 7 digits.
Sponsor Response 2: Changes have been made to the kit.
3. FDA Comment: You did not respond to our recommendation to include an explanation of the purpose of the serial number for the HCP Who Inserts Probuphine. We are concerned that not all healthcare professionals will know that the abbreviation "SN" refers to Serial Number, which may lead to confusion and recording of the wrong number on the Probuphine REMS Insertion and Removal Log. Therefore, we recommend that you replace the abbreviation "SN" with the full, intended meaning "Serial Number" for clarity and to mitigate confusion with other numbers that will appear near the serial number.
Sponsor Response 3: During the REMS training, using slide #26, the sponsor will stress the importance of HCP Who Inserts Probuphine recording the serial number on the Probuphine REMS Program Insertion/Removal Log Form for tracking and accountability purposes of this controlled substance. We have also added the location to the Insertion/Removal Log Form. As requested, we have added the full text "Serial Number" to the package for clarity.
4. FDA Comment 4: We do not agree with your rationale that including the serial number on the individual container labels would add significant time and cost to the packaging process. Including the serial number on the container label may provide an additional measure for accurate documentation in the REMS documents. We are concerned that the carton labeling may be discarded before the HCP Who Inserts Probuphine records the serial number on the Probuphine REMS Insertion and Removal Log. Thus, we recommend that you print the serial number under the lot number and expiration date on the individual container labels (paper label) to minimize the risk for these errors.
Sponsor Response 4: Braeburn has conducted further due diligence with third party

packagers who provide serialization services to evaluate the feasibility of adding the serial number on the individual container (pouch) labels. According to the third party packagers we consulted, use of repeat serialization on multiple units is not industry standard and therefore these third party packagers do not currently have the quality controls in place to allow for this approach. Braeburn understands the risk that you have described and would propose to include the following prominent notice that will be located on the area where the container pouches with the implants is located to further mitigate against this potential risk.

“ATTENTION HEALTHCARE PROVIDER Who Inserts Probuphine:

Record Serial Number on the REMS Insertion and Removal Log on the day Probuphine is inserted. The Serial Number appears on the back panel of this carton.”

This approach would meet industry standard and also meet the requirements of the Drug Supply Chain Act (DSCA) that goes in to effect November 27, 2017. The DSCA will require the manufacturer to serialize down to the smallest unit sold, which in this case would be the full kit containing all four implants.

Response dated April 25, 2016

Printing the Serial Number at a different location than the current position (under Lot number and exp. date) poses a problem in that the carton would have to go through a separate secondary printing process. This adds additional time and cost. Printing the serial number on each implant pouch is not required by regulation and had not been planned for at all. This change would add significant time and cost to the packaging process. We would propose that the traditional location for the serial number be retained and that clinician training can be expected to ensure they are able to locate the serial number for inclusion on the Probuphine REMS Program Insertion/Removal Log. As for the number of digits, (b) (4) digits was chosen (b) (4) (b) (4) We can, however; reduce the total number of digits to 7 to meet the request of the agency. The Sponsor seeks your concurrence with our proposal.

APPENDIX C: REVISED CARTON LABELING

(b) (4)



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/s/

MILLIE C BRAHMBHATT

05/11/2016

BRENDA V BORDERS-HEMPHILL

05/11/2016

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology Review (OSE)
Office of Pharmacovigilance and Epidemiology (OPE)**

Epidemiology: Memorandum on Post-Marketing Requirement

Date:	May 10, 2016
Reviewer:	James Phillip Trinidad, M.P.H., M.S. Division of Epidemiology II
Team Leader	Tamra E. Meyer, Ph.D., M.P.H. Division of Epidemiology II
Acting Division Director	David Moeny, R.Ph., M.P.H. Division of Epidemiology II
Drug Name(s):	Buprenorphine (PROBUPHINE)
Subject	Memorandum on post-marketing requirement for epidemiological study of insertion-, localization-, and removal-related events associated with Probuphine, a buprenorphine implant
Application Type/Number:	NDA 204442
Submission Number:	ORIG-1 of NDA 204442 (SDN 31 / eCTD 0030, submitted Aug 27, 2015)
Applicant/sponsor:	Titan Pharmaceuticals, Inc.
OSE RCM #:	2016-683

MEMORANDUM

1 EXECUTIVE SUMMARY

The Division of Anesthesia, Analgesia, and Addiction Products consulted the Division of Epidemiology II on the development of language for a post-marketing requirement (PMR) to assess the safety of Probuphine, an implantable formulation of buprenorphine. The Division of Epidemiology II (DEPI II) recommends that the sponsor of NDA 204442, Probuphine (Titan Pharmaceuticals), conduct a prospective descriptive observational cohort study to describe insertion-, localization-, and removal-related events and their sequelae associated with Probuphine use. The data should arise from a U.S. registry of Probuphine prescribers and health care providers who performed the insertion and removal procedures and necessary post-operative check-ups. Clinically significant implant migrations – a composite outcome that includes implant migrations greater than 2 cm, implant migration less than 2 cm but of clinical consequence (e.g., nerve damage), and protrusions and expulsions within 6 months of insertion – are of particular interest because they may indicate a potential need to re-assess the tools, technique, and training related to Probuphine and its safety profile.

DEPI II recommends the following PMR language for NDA 204442:

A prospective descriptive observational cohort study of insertion-, localization-, and removal-related events and their sequelae associated with PROBUPHINE use. The data for this study shall be collected from a prospective U.S. registry of PROBUPHINE prescribers and health care providers who performed the insertion and removal procedures and necessary follow-up (e.g., post-operative check-up). Sufficient information shall be collected to enable follow-up of patients and providers through deterministic (e.g., unique identification number on the PROBUPHINE kit) and probabilistic linkage (e.g., patient year of birth, sex, and date of insertion). The insertions that could not be linked to removals shall be reported as loss to follow-up events. The study shall accrue a sufficient sample size to rule out an excess risk of 1.5% or more of clinically significant implant migrations that occur within 6 months of insertion, as determined on removal forms. Clinically significant implant migrations shall include implant migrations greater than 2 cm, implant migration less than 2 cm but of clinical consequence (e.g., associated with nerve damage), and protrusions and expulsions. Annual interim status reports and the final report shall describe the following:

- Numbers of: providers in the study, linked insertion-removal pairs, patients lost to follow-up
- Patient characteristics: for example, age, sex, race/ethnicity, BMI, prior opioid maintenance therapy
- Health care provider characteristics: for example, type of provider (e.g., surgeon), extent of prior experience with PROBUPHINE insertion/removal procedures (e.g., number performed), type of institution (e.g., outpatient)
- Insertion characteristics: for example, site of PROBUPHINE insertion, insertion attempts, number of treatment cycles
- Insertion/removal tools and techniques that differ from marketed tools and techniques
- Insertion-related events, such as:
 - o Pain, bruising, scarring, bleeding, infection, nerve damage, altered strength/range of motion, disability
- Localization- and removal-related events, such as:

- Pain, bruising, scarring, bleeding, infection, nerve damage, altered strength/range of motion, disability
- Reason for removal (other than completing full treatment cycle)
- Implant protrusion, expulsion, palpability, damage or tampering (by patient)
- Implant migration; if migration to distant site is identified, document location, sequelae, time since insertion when migration was identified (e.g., within 6 months vs. after 6 months), and intervention (e.g., surgical procedures to remove implants)
 - enumerate implant migrations greater than 2 cm
 - enumerate implant migrations less than 2 cm but of clinical consequence
- Implant fragmentation and documentation of removal of all fragments
- Imaging modalities, if any, used to locate implants (e.g., ultrasound, MRI) prior to removal
- Referral to surgical specialties to complete removal
- Non-localized implants/implants never removed

2 INTRODUCTION

The Division of Anesthesia, Analgesia, and Addiction Products consulted the Division of Epidemiology II on the development of language for post-marketing requirement (PMR) to assess the safety of Probuphine, an implantable formulation of buprenorphine. Titan Pharmaceuticals, Inc. is the sponsor for the Probuphine (NDA 204442).

Probuphine is designed to provide sustained delivery of buprenorphine for six months (Skeete 2016). The intended Probuphine patient population has opioid dependence (opioid addiction), has achieved and sustained clinical stability, and has been maintained long-term on a buprenorphine-containing transmucosal product at a dose of no more than 8 mg/day (as a Subutex tablet or Suboxone tablet equivalent). For each six-month treatment cycle, four Probuphine implants, or rods, are inserted into the inner surface of the upper arm in an outpatient surgical procedure, and later removed in another in-office procedure at the end of six months.

The real and potential benefits of implantable drug products, such as Probuphine, may be outweighed by the potential risks posed by the implant itself and the procedures for insertion/removal. Potential benefits specific to implantable buprenorphine include less potential for accidental (pediatric) exposure and less vulnerability for overdose, abuse, or diversion. Potential risks include insertion-, localization-, and removal-related events (e.g., pain, bruising, infection, nerve damage, implant migration, implant protrusion, and damaged to the implant).

Data from the Sentinel System was deemed insufficient to help assess the safety of Probuphine --- the data would not be able to capture some important events, such as implant migration (Trinidad 2016).

This memorandum describes the study design considerations of an observational study that the Division of Epidemiology II (DEPI II) recommends that Titan Pharmaceuticals conduct to describe insertion-, localization-, and removal-related events and their sequelae associated with Probuphine use. This memorandum provides recommended PMR language in Section 4.

3 STUDY DESIGN CONSIDERATIONS

3.1 STUDY OBJECTIVE

The study objective should be to describe insertion-, localization-, and removal-related events and their sequelae associated with Probuphine use. The merits of a comparative safety study or a study of risk factors for the adverse events were also considered. A comparative safety study was deemed not feasible because there are no implantable drug products currently approved for opioid maintenance therapy. In addition, it would be difficult to determine the appropriate sample size for a study of risk factors without better knowledge of the potential risk factors and their prevalence.

3.2 STUDY TYPE

Consistent with the study objective, the study type should be a prospective descriptive observational cohort study. The strength of the prospective design lies in the accuracy in data collection, especially with regards to identification of events that are observable at insertion or removal (e.g., difficulty with implantation). A cohort study design allows for the estimation of event risk.

3.3 DATA SOURCE

The data source should be a U.S. registry of Probuphine prescribers and health care providers who performed the insertion and removal procedures and necessary follow-up (particularly, post-operative check-up). A provider registry would enable collection of all the necessary exposure, outcome, and covariate information necessary to fulfill the study objective, without requiring patient enrollment. Patient enrollment may deter patients from necessary treatment, and patient enrollment and/or follow-up could be poor.

However, patient follow-up is still necessary for the investigation of the association between provider, procedural, and patient characteristics at insertion and events observed after insertion. In the absence of patient enrollment, deterministic and probabilistic linkage of patients and providers has the potential for ensuring patient follow-up. For example, patients could be linked by way of unique identification numbers on Probuphine kits, or by patient year of birth, sex, and date of insertion. It is anticipated that some patients will be lost to follow-up (e.g., they may not have follow-up visits or removal of their Probuphine implant). Insertions not linked to removals should be reported as loss to follow-up.

3.4 EXPOSURE

The exposure should be Probuphine. There are no appropriate comparator groups.

3.5 OUTCOME

The outcome should include insertion-, localization-, and removal-related events and their sequelae. Events include actual harm to the patient (e.g., pain, bruising, and nerve damage) and events that could lead to patient harm (e.g., implant migration, implant fragmentation, lack of implant palpability, and no implant removal).

In the clinical trials PRO-806 and PRO-814, the proportion of Probuphine-exposed subjects experiencing any implant site treatment emergent adverse events (TEAEs) was 27% and 18%,

respectively. No Probuphine-exposed subjects experienced serious implant-related adverse events in PRO-806 or PRO-814.

The outcomes of interest range in severity and include:

- Insertion-related events: Pain, bruising, scarring, bleeding, infection, nerve damage, altered strength/movement, and disability
- Localization-related events: Implant migration, protrusion, expulsion, and lack of palpability
- Removal-related events: Pain, bruising, scarring, bleeding, infection, nerve damage, altered strength/movement, disability
- Implant damage: fragmentation and damage or tampering (by patient)

The outcome considered for power/sample size calculations should be clinically significant implant migrations, a composite outcome that includes implant migrations greater than 2 cm, implant migration less than 2 cm but of clinical consequence (e.g., nerve damage), and protrusions and expulsions that occur within 6 months of insertion, as determined by removal forms. Several factors were considered in determining which event to consider for power/sample size calculations:

- Event severity and clinical significance. Migration of implantable drug products can pose various degrees of harm to the patient. One case report described migration of Implanon – a formulation of etonogestrel which is inserted in the upper arm – into the pulmonary artery and subsequent removal (Heudes, Querat et al. 2015). Unlike migration to the pulmonary vasculature, most migrations of Implanon were of relatively short distances and are of little clinical consequence; indeed, migrations greater than 2 cm are unlikely to occur if the implant is inserted properly (Ismail, Mansour et al. 2006). Therefore, migrations greater than 2 cm may indicate potential problems with insertion tools or techniques. By definition, implant expulsion is a migratory event greater than 2 cm.
- Event identification. Migrations can be identified at follow-up visits, including post-operative check-ups and removal procedures. Lack of implant palpability can indicate implant migration, but should be verified through diagnostic techniques (e.g., ultrasound). Event identification may be hindered by patient loss to follow-up.
- Event rate. In clinical studies PRO-806 and PRO-814 and extension trial PRO-811, Probuphine migrations were not reported. However, although uncommon, expulsion or protrusion of the Probuphine implant occurred among 3 patients out of 429 patients with at least one insertion procedure (0.7%). In a study with active identification of Implanon migrations, migration greater than 2 cm occurred once among 95 insertions (1.1%) after three months of follow-up (Ismail, Mansour et al. 2006). No expulsions were reported.

3.6 COVARIATES AND OTHER MEASURES

This study provides the opportunity to describe the events by selected patient, health care provider, and insertion characteristics. Although there may be patient-, provider-, and insertion-related characteristics that increase the risk of any of the measured adverse events, there are no *a priori* risk factors of interest for this study. Therefore, the post-marketing requirement should require that the study capture easily measureable covariates of interest that may be risk factors for insertion-, localization-, and removal-related events: e.g., patient age, sex, race/ethnicity, and body mass index; provider type (for example, surgeon), prior experience with insertions and

removals, type of institution; and insertion site, number of insertions, and number of treatment cycles; and whether the insertion/removal tools and techniques differed from marketed tools and labeled directions for insertion/removal.

3.7 STUDY POWER/SAMPLE SIZE

The study should have a sufficient sample size to rule out a risk of 1.5% or more of clinically significant implant migrations (i.e., implant migrations greater than 2 cm, implant migration less than 2 cm but of clinical consequence, and protrusions and expulsions) that occur within six months of insertion. In the context of implantable drug products, a risk of 1.5% could represent a clinically meaningful, elevated risk of clinically significant implant migrations, and could indicate a potential need to re-assess the tools, technique, and training related to Probuphine and its safety profile. In a study with active identification of Implanon migrations, one migration greater than 2 cm was observed among 95 insertions at 3 months post-insertion and among 87 insertions at 12 months post-insertion. No protrusions and expulsions were reported in this study, so the overall risk clinically significant implant migrations was roughly 1.1% at both 3 and 12 months post-insertion. A risk of 1.5% represents an excess risk of 0.4% and a relative risk of 36% over the clinical experience of Implanon.

3.8 ANALYSIS

The proposed study should be descriptive in nature and provide confidence intervals around event rate estimates. The unit of analysis should be each treatment cycle (i.e., insertion with or without removal), not patient or rod. Patients can have multiple cycles of treatment. Each rod should not be considered the unit of analysis since 1) it may be difficult to ascertain the offending rod (e.g., insertion site pain may involve more than one rod) and 2) risk factors generally affect all rods implanted (e.g., the health care provider uses same tools and techniques to insert each rod).

4 RECOMMENDATION

Given the study design considerations in Section 3, DEPI II recommends the following PMR language for NDA 204442:

A prospective descriptive observational cohort study of insertion-, localization-, and removal-related events and their sequelae associated with PROBUPHINE use. The data for this study shall be collected from a prospective U.S. registry of PROBUPHINE prescribers and health care providers who performed the insertion and removal procedures and necessary follow-up (e.g., post-operative check-up). Sufficient information shall be collected to enable follow-up of patients and providers through deterministic (e.g., unique identification number on the PROBUPHINE kit) and probabilistic linkage (e.g., patient year of birth, sex, and date of insertion). The insertions that could not be linked to removals shall be reported as loss to follow-up events. The study shall accrue a sufficient sample size to rule out an excess risk of 1.5% or more of clinically significant implant migrations that occur within 6 months of insertion, as determined on removal forms. Clinically significant implant migrations shall include implant migrations greater than 2 cm, implant migration less than 2 cm but of clinical consequence (e.g., associated with nerve damage), and protrusions and expulsions. Annual interim status reports and the final report shall describe the following:

- Numbers of: providers in the study, linked insertion-removal pairs, patients lost to follow-up

- Patient characteristics: for example, age, sex, race/ethnicity, BMI, prior opioid maintenance therapy
- Health care provider characteristics: for example, type of provider (e.g., surgeon), extent of prior experience with PROBUPHINE insertion/removal procedures (e.g., number performed), type of institution (e.g., outpatient)
- Insertion characteristics: for example, site of PROBUPHINE insertion, insertion attempts, number of treatment cycles
- Insertion/removal tools and techniques that differ from marketed tools and techniques
- Insertion-related events, such as:
 - o Pain, bruising, scarring, bleeding, infection, nerve damage, altered strength/range of motion, disability
- Localization- and removal-related events, such as:
 - o Pain, bruising, scarring, bleeding, infection, nerve damage, altered strength/range of motion, disability
 - o Reason for removal (other than completing full treatment cycle)
 - o Implant protrusion, expulsion, palpability, damage or tampering (by patient)
 - o Implant migration; if migration to distant site is identified, document location, sequelae, time since insertion when migration was identified (e.g., within 6 months vs. after 6 months), and intervention (e.g., surgical procedures to remove implants)
 - enumerate implant migrations greater than 2 cm
 - enumerate implant migrations less than 2 cm but of clinical consequence
 - o Implant fragmentation and documentation of removal of all fragments
 - o Imaging modalities, if any, used to locate implants (e.g., ultrasound, MRI) prior to removal
 - o Referral to surgical specialties to complete removal
 - o Non-localized implants/implants never removed

5 REFERENCES

Heudes, P. M., V. L. Querat, E. Darnis, C. Defrance, F. Douane and E. Frampas (2015). "Migration of a contraceptive subcutaneous device into the pulmonary artery. Report of a case." Case Reports in Women's Health(8): 6-8.

Ismail, H., D. Mansour and M. Singh (2006). "Migration of Implanon." J Fam Plann Reprod Health Care **32**(3): 157-159.

Skeete, R. (2016). Clinical Review: NDA 204442 (Class 2 Resubmission) - Probuphine (Buprenorphine) Implant. FDA/CDER/OND. Submitted to DARRTS on Feb 8, 2016, for NDA #204442

Trinidad, J. (2016). ARIA Sufficiency Memo: Probuphine and insertion-, localization-, and removal-related events. FDA/CDER/OSE. Submitted to DARRTS on May 05, 2016, for NDA #204442

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/s/

JAMES TRINIDAD
05/10/2016

TAMRA E MEYER
05/10/2016

DAVID G MOENY
05/10/2016

REVISED REMS MATERIALS REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	May 6, 2016
Requesting Office or Division:	Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Application Type and Number:	NDA 204442
Product Name and Strength:	Probuphine (buprenorphine) implant, 74.2 mg
Product Type:	Single ingredient
Rx or OTC:	Rx
Applicant/Applicant Name:	Titan Pharmaceuticals, Inc.
Submission Date:	May 4, 2016
OSE RCM #:	2015-2114
DMEPA Primary Reviewer:	Millie Shah, PharmD, BCPS
DMEPA Team Leader:	Vicky Borders-Hemphill, PharmD

1 REASON FOR REVIEW

Titan Pharmaceuticals, Inc. submitted revised Risk Evaluation and Mitigation Strategy (REMS) materials for Probuphine (buprenorphine) implant. The Division of Risk Management (DRISK) requested we evaluate the following materials from a medication error perspective:

- training slides,
- insertion/removal instructions for use (IFU) booklet,
- procedural competency checklist,
- knowledge assessment questions,
- training video script

DMEPA previously conducted a review of the revised REMS materials submitted on February 11, 2016 in OSE #2015-2115¹ dated March 22, 2016. Additionally, DMEPA previously evaluated the Human Factors validation study (HFS) results and labels and labeling for Probuphine.² In our previous reviews, DMEPA provided recommendations for DRISK to consider for the REMS materials based on the findings of the HFS.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review.

Table 1. Materials Considered for this Review
Material Reviewed
Training Slides
Instructions for Use (IFU) Insertion/Removal Instruction Booklet
Procedural Competency Checklist
Knowledge Assessment Questions
Training Video Script

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We performed a risk assessment of the proposed training slides, insertion/removal IFU booklet, procedural competency checklist, knowledge assessment questions, and training video script to

¹ Fitzgerald D and Blair JE. REMS Review Interim Comments #3 for Probuphine (buprenorphine) implant (NDA 204442). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Risk Management (US); 2016 MAR 22. 83 p. OSE RCM No.: 2015-2115.

² Shah M. Human Factors, Label and Labeling Review for Probuphine (buprenorphine) implant (NDA 204442). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2016 JAN 22. 49 p. OSE RCM No.: 2015-2114.

identify deficiencies that may lead to medication errors and areas for improvement to support the safe and effective use of the product.

General Comments for Training Slides, Insertion/Removal IFU Booklet, and Training Video Script

We identified areas for improvement to increase clarity of important information including use of consistent language across all documents and correction of spelling and grammatical errors throughout the materials and provide recommendations in Section 4.1 below.

There is inconsistency with language in section 2.9 (Continuation of Therapy) in the Full Prescribing Information (FPI), which has been revised since our previous review. Thus, we recommend the following materials be updated to be consistent with the language in the FPI and provide this recommendation in Section 4.1 below:

1. Training slides 65 and 66
2. Insertion/Removal IFU booklet page 11
3. Training Video Script

We determined that additional information regarding the purpose of recording the serial number is lacking (e.g., on training slides 26 and 46 and on the training video script in #43). Therefore, we recommend adding this information so that healthcare providers understand the purpose and importance of recording the serial number, thus minimizing the risk that the serial number will not be recorded and provide this recommendation in Section 4.1 below.

Procedural Competency Checklist

Our review of the procedural competency checklist determined that our previous recommendations were implemented. However, we identified trailing zeros, which could lead to a ten-fold misinterpretation. Thus, we provide recommendations to minimize the risk for error in Section 4.1 below.

Knowledge Assessment Questions

Our review of the knowledge assessment questions did not identify any deficiencies. Thus, we do not have any recommendations at this time.

4 CONCLUSION & RECOMMENDATIONS

We identified areas for improvement in the training slides, insertion/removal IFU booklet, procedural competency checklist, and training video script to increase clarity and to ensure consistency between the labeling components and to promote safe use of this product.

4.1 RECOMMENDATIONS FOR TITAN PHARMACEUTICALS, INC

We recommend Titan Pharmaceuticals, Inc. implement the following recommendations prior to approval of this NDA:

A. General Comments

1. Ensure spelling and grammatical errors are corrected including use of consistent language throughout all materials (e.g., replace (b) (4) with “serial number” in Step 11 on slide 73 of the training slides, page 7 of IFU, #85 of training video script) to ensure consistent terminology between all documents and to minimize confusion.
2. Consider expanding on the purpose of recording the serial number (e.g., on training slides 26 and 46 and on the training video script in #43). Expanding on the purpose of recording the serial number may help healthcare providers understand the importance of the serial number, thus minimizing the risk that it would not be recorded.
3. Ensure the following materials are consistent with the language in Section 2.9 (Continuation of Therapy) of the Full Prescribing Information that was communicated to you on May 5, 2016 to minimize the risk for confusion.
 - i. Training slides 65 and 66
 - ii. Insertion/Removal booklet page 11
 - iii. Training Video Script

B. Procedural Competency Checklist

1. Remove the trailing zero in Steps 3 and 10 of the Insertion Procedural Competency checklist to avoid a ten-fold misinterpretation.³

³ Food and Drug Administration. *Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors*, April 2013. Available at:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>.

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/s/

MILLIE C BRAHMBHATT
05/06/2016

BRENDA V BORDERS-HEMPHILL
05/06/2016

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research| Office of Surveillance and Epidemiology (OSE)

Epidemiology: ARIA Sufficiency

Date:	May 4, 2016
Reviewer:	James Phillip Trinidad, M.P.H., M.S. Division of Epidemiology II
Team Leader	Tamra E. Meyer, Ph.D., M.P.H. Division of Epidemiology II
Acting Division Director	David Moeny, R.Ph., M.P.H. Division of Epidemiology II
Subject:	ARIA Sufficiency Memo: Probuphine and insertion-, localization-, and removal-related events
Drug Name(s):	Buprenorphine (PROBUPHINE)
Application Type/Number:	NDA 204442
Submission Number:	ORIG-1 of NDA 204442 (SDN 31 / eCTD 0030, submitted Aug 27, 2015)
Applicant/sponsor:	Titan Pharmaceuticals, Inc.
OSE RCM #:	2016-0683

EXECUTIVE SUMMARY *(place "X" in appropriate boxes)*

Memo type	
-Initial	X
-Interim	
-Final	X
Source of safety concern	
-Peri-approval	X
-Post-approval	
Is ARIA sufficient to help characterize the safety concern?	
-Yes	
-No	X
If "No", please identify the area(s) of concern.	
-Surveillance or Study Population	X
-Exposure	X
-Outcome(s) of Interest	X
-Covariate(s) of Interest	
-Surveillance Design/Analytic Tools	

1. BACKGROUND INFORMATION

1.1. Medical Product

Probuphine (buprenorphine) is an implantable formulation of buprenorphine designed to provide sustained delivery of buprenorphine for six months (Skeete 2016). The intended Probuphine patient population has opioid dependence (opioid addiction), has achieved and sustained clinical stability, and has been maintained long-term on a buprenorphine-containing transmucosal product at a dose of no more than 8 mg/day (as a Subutex tablet or Suboxone tablet equivalent). For each six-month treatment cycle, four Probuphine implants, or rods, are inserted into the inner surface of the upper arm in an outpatient surgical procedure, and later removed in another in-office procedure at the end of six months.

1.2. Describe the Safety Concern

The real and potential benefits of implantable drug products, such as Probuphine, may be outweighed by the potential risks posed by the implant itself. Potential benefits specific to implantable buprenorphine include less potential for accidental (pediatric) exposure and less vulnerability for overdose, abuse, or diversion. Potential risks include insertion-, localization-, and removal-related events (e.g., pain, bruising, infection, nerve damage, implant migration, implant protrusion, and damage to the implant). In the clinical trials PRO-806 and PRO-814, the proportion of Probuphine-exposed subjects experiencing any implant site treatment emergent adverse events (TEAEs) was 27% and 18%, respectively. No Probuphine-exposed subjects experienced serious implant-related adverse events in PRO-806 or PRO-814.

An observational study describing the incidence of insertion-, localization-, and removal-related events and their sequelae is warranted to better understand the benefit-risk profile of Probuphine in a real-world setting. These adverse events could be described as a composite outcome. A description of these events by patient characteristics (e.g., age and sex) as well as health care provider characteristics (e.g., prior experience with insertion/removal procedures) could provide insight into potential risk factors for implant-related adverse events.

1.3. FDAAA Purpose (per Section 505(o)(3)(B))

Purpose (place an "X" in the appropriate boxes; more than one may be chosen)

Assess a known serious risk	
Assess signals of serious risk	
Identify unexpected serious risk when available data indicate potential for serious risk	X

1.4. Statement of Purpose

The observational study should describe insertion-, localization-, and removal-related events and their sequelae in patients using Probuphine. The information gleaned from this analysis may be used to inform labeling and risk mitigation efforts.

1.5. Effect Size of Interest or Estimated Sample Size Desired

The study should have a sufficient sample size to rule out a risk of 1.5% or more of clinically significant migrations (i.e. implant migrations greater than 2 cm, implant migration less than 2 cm but of clinical consequence, and protrusions and expulsions) that occur within six months of insertion.

2. SURVEILLANCE OR DESIRED STUDY POPULATION

2.1 Population

The study population shall include patients who receive Probuphine.

2.2 Is ARIA sufficient to assess the intended population?

Until procedural codes are available to help identify Probuphine-related procedures, ARIA will not be sufficient to assess the intended population (see Section 3).

3 EXPOSURES

3.1 Treatment Exposure(s)

The exposure of interest is Probuphine, which is surgically implanted and removed (likely in outpatient surgery settings). Probuphine is not intended to be dispensed in pharmacy settings.

3.2 Comparator Exposure(s)

There is no appropriate comparator exposure.

3.3 Is ARIA sufficient to identify the exposure of interest?

Because Probuphine is surgically implanted and removed, ARIA will not be sufficient to identify the exposure of interest, at least until procedural codes are available to help identify Probuphine-related procedures. Probuphine will not be dispensed from pharmacies, so medication dispensing data cannot be used to identify Probuphine.

4 OUTCOME(S)

4.1 Outcomes of Interest

The outcomes of interest include insertion-, localization-, and removal-related events and their sequelae. The outcomes of interest range in severity and include:

- Insertion-related events: Pain, bruising, scarring, bleeding, infection, nerve damage, altered strength/movement, and disability
- Localization-related events: Implant migration, protrusion, expulsion, and lack of palpability
- Removal-related events: Pain, bruising, scarring, bleeding, infection, nerve damage, altered strength/movement, disability

- Implant damage: fragmentation and damage or tampering (by patient)

The outcome considered for power/sample size calculations should be clinically significant implant migrations, a composite outcome that includes implant migrations greater than 2 cm, implant migration less than 2 cm but of clinical consequence (e.g., nerve damage), and protrusions and expulsions within 6 months of insertion, as determined by removal forms. Migration of implantable drug products can pose various degrees of harm to the patient. One case report described migration of Implanon – a formation of etonogestrel which is inserted in the upper arm – into the pulmonary artery and subsequent removal (Heudes, Querat et al. 2015). Unlike migration to the pulmonary vasculature, most migrations of Implanon were of relatively short distances and are of little clinical consequence; indeed, migrations greater than 2 cm are unlikely to occur if the implant is inserted properly (Ismail, Mansour et al. 2006). Therefore, migrations greater than 2 cm may indicate potential problems with insertion tools or techniques. By definition, implant expulsion is a migratory event greater than 2 cm.

4.2 Is ARIA sufficient to assess the outcome of interest?

ARIA is not sufficient to assess these outcomes of interest because they include events that are not generally coded in claims (e.g., implant migration, implant expulsion/protrusion, site pain, bruising, altered strength/movement, palpability, extent of scarring, difficulties with implant and removal, and implant damage/tampering).

5 COVARIATES

Skipped given responses in Sections 2, 3, and 4.

6 SURVEILLANCE DESIGN / ANALYTIC TOOLS

Skipped given responses in Sections 2, 3, and 4.

7 NEXT STEPS

ARIA is deemed insufficient for describing Probuphine insertion-, localization-, and removal-related events and their sequelae. With guidance provided by the Division of Epidemiology II and the Division of Biostatistics VII, the Division of Anesthesia, Analgesia, and Addiction Products will issue a post-marketing requirement to Titan Pharmaceuticals, Inc. to conduct a prospective descriptive observational cohort study of insertion-, localization-, and removal-related events and their sequelae associated with PROBUPHINE use.

8 REFERENCES

Heudes, P. M., V. L. Querat, E. Darnis, C. Defrance, F. Douane and E. Frampas (2015). "Migration of a contraceptive subcutaneous device into the pulmonary artery. Report of a case." Case Reports in Women's Health(8): 6-8.

Ismail, H., D. Mansour and M. Singh (2006). "Migration of Implanon." J Fam Plann Reprod Health Care **32**(3): 157-159.

Skeete, R. (2016). Clinical Review: NDA 204442 (Class 2 Resubmission) - Probuphine (Buprenorphine) Implant. Submitted to DARRTS on Feb 8, 2016, for NDA #204442

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/s/

JAMES TRINIDAD
05/04/2016

TAMRA E MEYER
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05/05/2016

ROBERT BALL
05/05/2016

MEMORANDUM

REVIEW OF REVISED LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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Date of This Review:	April 28, 2016
Requesting Office or Division:	Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Application Type and Number:	NDA 204442
Product Name and Strength:	Probuphine (buprenorphine) implant, 74.2 mg
Product Type:	Single ingredient
Rx or OTC:	Rx
Applicant/Applicant Name:	Titan Pharmaceuticals, Inc.
Submission Date:	April 25, 2016
OSE RCM #:	2015-2114
DMEPA Primary Reviewer:	Millie Shah, PharmD, BCPS
DMEPA Team Leader:	Vicky Borders-Hemphill, PharmD

1 REASON FOR REVIEW

Titan Pharmaceuticals, Inc. submitted revised carton labeling for Probuphine (buprenorphine) implant. The revised carton labeling includes a serial number that the healthcare professional (HCP) who inserts Probuphine will record on the Probuphine REMS Insertion and Removal Log on the day Probuphine is inserted. The Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) and the Division of Risk Management (DRISK) requested we evaluate the revised carton labeling from a medication error perspective. We provided recommendations to the Applicant in OSE #2015-2114¹ dated April 22, 2016 (See Appendix A for DMEPA's previous comments). The Applicant responded to our recommendations on April 25, 2016 (See Appendix B for Applicant's response). Thus, this memo provides comments to the Applicant's response.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review.

Table 1. Materials Considered for this Review
Material Reviewed
DMEPA Recommendations to Applicant: Appendix A
Applicant's Response to DMEPA Comments: Appendix B
Carton Labeling: Appendix C

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We evaluated the Applicant's response to our recommendations from a medication error perspective.

- We find the Applicant's rationale for the location of the serial number on the back panel under the lot number and expiration date acceptable.
- The Applicant accepted our recommendation to decrease the number of digits in the serial number. The Applicant proposes to decrease the serial number to 7 digits, which we find acceptable.
- The Applicant did not respond to our recommendation to include an explanation for the purpose of the serial number for the HCP Who Inserts Probuphine.

We continue to recommend that the abbreviation "SN" be replaced with the full intended meaning "Serial Number" since not all healthcare professionals may know that the abbreviation "SN" refers to serial number for clarity and to mitigate confusion with other numbers that will appear near the serial number.

¹ Shah M. Memorandum Review of Revised Labeling for Probuphine (NDA 204442). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2016 APR 22. 5 p. OSE RCM No.: 2015-2114.

- The Applicant did not accept our recommendation to include the serial number on the individual container labels. The Applicant stated that including the serial number on the individual container labels would add significant time and cost to the packaging process.

We do not agree with the Applicant's rationale and continue to recommend that the serial number be included on the individual container labels. Including the serial number on the container label may provide an additional measure for accurate documentation in the REMS documents. We are concerned that the carton labeling may be discarded before the HCP Who Inserts Probuphine records the serial number on the Probuphine REMS Insertion and Removal Log.

4 CONCLUSION & RECOMMENDATIONS

We identified areas for improvement for the container label, carton labeling, and serial number to increase clarity and to promote safe use of this product.

4.1 RECOMMENDATIONS FOR TITAN PHARMACEUTICALS, INC

We recommend Titan Pharmaceuticals, Inc. implement the following recommendations prior to approval of this NDA:

- A. Serial Number on Container label and Carton Labeling
 1. We agree with your rationale for the location of the serial number to be on the back panel under the lot number and expiration date.
 2. We agree with your rationale to decrease the number of digits in the serial number (b) (4) to 7 digits.
 3. You did not respond to our recommendation to include an explanation of the purpose of the serial number for the HCP Who Inserts Probuphine. We are concerned that not all healthcare professionals will know that the abbreviation "SN" refers to Serial Number, which may lead to confusion and recording of the wrong number on the Probuphine REMS Insertion and Removal Log. Therefore, we recommend that you replace the abbreviation "SN" with the full, intended meaning "Serial Number" for clarity and to mitigate confusion with other numbers that will appear near the serial number.
 4. We do not agree with your rationale that including the serial number on the individual container labels would add significant time and cost to the packaging process. Including the serial number on the container label may provide an additional measure for accurate documentation in the REMS documents. We are concerned that the carton labeling may be discarded before the HCP Who Inserts Probuphine records the serial number on the Probuphine REMS Insertion and Removal Log. Thus, we recommend that you print the serial number under the lot number and expiration date on the individual container labels (paper label) to minimize the risk for these errors.

APPENDIX A. DMEPA RECOMMENDATIONS TO APPLICANT (dated April 22, 2016)

1. Relocate the serial number to the top right corner of the principal display panel. As currently presented, the serial number is located on the back panel, under the lot number and expiration date, which may lead to confusion with the lot number or expiration date. Additionally, the current location of the serial number on the back panel may not be readily located by HCPs Who Insert Probuphine. Ensure that the font for the serial number is large enough for easy readability.
2. Provide your rationale for the selection of a (b) (4) digit serial number versus a serial number with fewer digits. We are concerned that the (b) (4) digit serial number may lead to errors in transcribing when the HCP Who Inserts Probuphine records the serial number on the Probuphine REMS Insertion and Removal Log. We recommend you decrease the number of digits in the serial number to minimize transcription errors. Ensure that the number of digits for the serial number differs significantly in length and format (b) (4) (b) (4) to minimize the risk for confusion (b) (4)
3. Include an explanation for the purpose of the serial number for the HCP Who Inserts Probuphine to improve clarity. For example, consider the following:

SN: ###

Attention HCP Who Inserts Probuphine:
Record the Serial Number (SN) on the
Probuphine REMS Insertion and Removal
Log on the day Probuphine is inserted.

4. Add the corresponding serial number to the Probuphine container labels for the implants in the same format and location as on the carton labeling. We recommend that the serial number also be added to the Probuphine implant individual container labels so that the serial number can be located in instances where the carton labeling is thrown away before the HCP Who Inserts Probuphine records the serial number on the Probuphine REMS Insertion and Removal Log.

APPENDIX B: APPLICANT'S RESPONSE TO DMEPA COMMENTS (dated April 25, 2016)

Printing the Serial Number at a different location than the current position (under Lot number and exp. date) poses a problem in that the carton would have to go through a separate secondary printing process. This adds additional time and cost. Printing the serial number on each implant pouch is not required by regulation and had not been planned for at all. This change would add significant time and cost to the packaging process. We would propose that the traditional location for the serial number be retained and that clinician training can be expected to ensure they are able to locate the serial number for inclusion on the Probuphine REMS Program Insertion/Removal Log. As for the number of digits, (b) (4) digits was chosen (b) (4) (b) (4) We can, however; reduce the total number of digits to 7 to meet the request of the agency. The Sponsor seeks your concurrence with our proposal.

APPENDIX C: REVISED CARTON LABELING

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/s/

MILLIE C BRAHMBHATT
04/28/2016

BRENDA V BORDERS-HEMPHILL
04/28/2016

MEMORANDUM

REVIEW OF REVISED LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	April 22, 2016
Requesting Office or Division:	Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Application Type and Number:	NDA 204442
Product Name and Strength:	Probuphine (buprenorphine) implant, 74.2 mg
Product Type:	Single ingredient
Rx or OTC:	Rx
Applicant/Applicant Name:	Titan Pharmaceuticals, Inc.
Submission Date:	April 19, 2016
OSE RCM #:	2015-2114
DMEPA Primary Reviewer:	Millie Shah, PharmD, BCPS
DMEPA Team Leader:	Vicky Borders-Hemphill, PharmD

1 REASON FOR REVIEW

Titan Pharmaceuticals, Inc. submitted revised carton labeling for Probuphine (buprenorphine) implant. The revised carton labeling includes a serial number that the healthcare professional (HCP) who inserts Probuphine will record on the Probuphine REMS Insertion and Removal Log on the day Probuphine is inserted. The Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) and the Division of Risk Management (DRISK) requested we evaluate the revised carton labeling from a medication error perspective.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review.

Table 1. Materials Considered for this Review
Material Reviewed
Carton Labeling: Appendix A

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We performed a risk assessment of the proposed carton labeling, which has been revised to include a serial number, to identify deficiencies that may lead to medication errors and areas for improvement to support the safe and effective use of the product.

Carton Labeling

Our review of the carton labeling determined that the serial number is a (b) (4) digit number that is located on the back panel, under the lot number and expiration date. The Sponsor uses “SN” as an abbreviation for serial number.

As currently presented, the location of the serial number may be difficult for the HCP who inserts Probuphine to readily locate. Additionally, the location of the serial number under the lot number and expiration date may increase the risk for confusion with the lot number and expiration date. Thus, we recommend the Sponsor relocate the serial number to the top right corner of the principal display panel.

The Sponsor proposes a (b) (4) digit number for the serial number. Since the HCP Who Inserts Probuphine will need to record the serial number on the Probuphine REMS Insertion and Removal Log on the day Probuphine is inserted, a long number may lead to errors during transcribing. To minimize the risk for confusion (b) (4) we recommend that the serial number have less digits (b) (4). Thus, we recommend the Sponsor shorten the number of digits for the serial number.

As currently presented, the serial number does not include its purpose to the HCP who inserts Probuphine to record the serial number on the Probuphine REMS Insertion and Removal Log on the day Probuphine is inserted. Thus, we recommend adding this information to improve

clarity. Additionally, the Sponsor uses the abbreviation “SN” for serial number. The abbreviation “SN” may not be known to all HCPs Who Insert Probuphine, thus potentially leading to confusion. Therefore, we recommend the Sponsor define the abbreviation “SN”.

The Sponsor did not submit revised container labels with the serial number. We recommend that the serial number also be added to the Probuphine implant individual container labels so that the serial number can be located in instances where the carton labeling is thrown away before the HCP who inserts Probuphine records the serial number on the Probuphine REMS Insertion and Removal Log.

4 CONCLUSION & RECOMMENDATIONS

We identified areas for improvement for the carton labeling and serial number to increase clarity and to promote safe use of this product.

4.1 RECOMMENDATIONS FOR TITAN PHARMACEUTICALS, INC

We recommend Titan Pharmaceuticals, Inc. implement the following recommendations prior to approval of this NDA:

A. Serial Number on Carton Labeling

1. Relocate the serial number to the top right corner of the principal display panel. As currently presented, the serial number is located on the back panel, under the lot number and expiration date, which may lead to confusion with the lot number or expiration date. Additionally, the current location of the serial number on the back panel may not be readily located by HCPs Who Insert Probuphine. Ensure that the font for the serial number is large enough for easy readability.
2. Provide your rationale for the selection of a (b) (4) digit serial number versus a serial number with fewer digits. We are concerned that the (b) (4) -digit serial number may lead to errors in transcribing when the HCP Who Inserts Probuphine records the serial number on the Probuphine REMS Insertion and Removal Log. We recommend you decrease the number of digits in the serial number to minimize transcription errors. Ensure that the number of digits for the serial number differs significantly in length and format (b) (4) to minimize the risk for confusion (b) (4)
3. Include an explanation for the purpose of the serial number for the HCP Who Inserts Probuphine to improve clarity. For example, consider the following:

SN: ###

Attention HCP Who Inserts Probuphine:
Record the Serial Number (SN) on the
Probuphine REMS Insertion and Removal
Log on the day Probuphine is inserted.

4. Add the corresponding serial number to the Probuphine container labels for the implants in the same format and location as on the carton labeling. We recommend that the serial number also be added to the Probuphine implant individual container labels so that the serial number can be located in instances where the carton labeling is thrown away before the HCP Who Inserts Probuphine records the serial number on the Probuphine REMS Insertion and Removal Log.

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/s/

MILLIE C BRAHMBHATT
04/22/2016

BRENDA V BORDERS-HEMPHILL
04/22/2016

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: April 13, 2016

To: Sharon Hertz, MD
Director
Division of Anesthesia Analgesia, and Addiction Products (DAAAP)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Barbara Fuller, RN, MSN, CWOCN
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Morgan Walker, PharmD, MBA, CPH
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

L. Shenee' Toombs, Pharm.D.
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Medication Guide (MG)

Drug Name (established name) PROBUPHINE (buprenorphine) implant for subdermal administration, CIII

Dosage Form and Route:

Application Type/Number: NDA 204442

Applicant: Titan Pharmaceuticals, Inc. c/o Braeburn Pharmaceuticals

1 INTRODUCTION

On August 27, 2015, Titan Pharmaceuticals, Inc. c/o Braeburn Pharmaceuticals submitted for the Agency's review a resubmission for New Drug Application (NDA) 204442 for PROBUPHINE (buprenorphine) implant for subdermal administration in response to a Complete Response (CR) letter dated April 30, 2013. On February 11, 2016 the Agency received a major amendment to this application from the Applicant. The Agency extended the goal date by three months to provide time for a full review of the submission.

The proposed indication for PROBUPHINE (buprenorphine) is for the maintenance treatment of opioid dependence in patients who have achieved and sustained prolonged clinical stability on low-to-moderate doses of a transmucosal buprenorphine-containing product (i.e., doses of no more than 8 mg per day of Subutex or Suboxone sublingual tablet or generic equivalent).

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Anesthesia Analgesia, and Addiction Products (DAAAP) on September 21, 2015, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for PROBUPHINE (buprenorphine) implant for subdermal administration.

The Risk Evaluation and Mitigation Strategy (REMS) is being reviewed by the Division of Risk Management (DRISK) and will be provided to DAAAP under separate cover.

2 MATERIAL REVIEWED

- Draft PROBUPHINE (buprenorphine) MG received on August 27, 2015, and received by DMPP and OPDP on March 25, 2016.
- Draft PROBUPHINE (buprenorphine) Prescribing Information (PI) received on August 27, 2015, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on March 25, 2016.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the MG the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APFont to make medical information more accessible for patients with vision loss. We have reformatted the MG using the Arial font, size 10.

In our collaborative review of the MG we have:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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/s/

MORGAN A WALKER
04/13/2016

LATOYA S TOOMBS
04/13/2016

BARBARA A FULLER
04/13/2016

LASHAWN M GRIFFITHS
04/13/2016

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

******Pre-decisional Agency Information******

Memorandum

Date: April 12, 2016

To: Swati Patwardhan, Regulatory Project Manager
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)

From: L. Shenee Toombs, Regulatory Review Officer (OPDP)

CC: Olga Salis, Senior Regulatory Health Project Manager (OPDP)
Michael Wade, Regulatory Health Project Manager (OPDP)

Subject: NDA 204442
OPDP labeling comments for PROBUPHINE (buprenorphine) implant for
subdermal administration, CIII
Labeling Review

OPDP has reviewed the proposed package insert (PI) for PROBUPHINE (buprenorphine) implant for subdermal administration, CIII (Probuphine) that was submitted for consult on September 21, 2015. Comments on the proposed PI are based on the version sent via email from Swati Patwardhan (RPM) on March 25, 2016 entitled "NDA 204442 Draft Label Comments to Sponsor March 25-2016.docx".

Comments regarding the PI are provided on the marked version below.

Please note that comments on the Medication Guide will be provided under separate cover as a collaborative review between OPDP and the Division of Medical Policy Program (DMPP).

Thank you for the opportunity to comment.

If you have any questions, please contact Shenee' Toombs at (301) 796-4174 or latoya.toombs@fda.hhs.gov.

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/s/

LATOYA S TOOMBS
04/12/2016

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	February 12, 2016
Requesting Office or Division:	Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Application Type and Number:	NDA 204442
Product Name and Strength:	Probuphine (buprenorphine) implant, 74.2 mg per implant
Submission Date:	February 5, 2016
Applicant/Sponsor Name:	Titan Pharmaceuticals, Inc.
OSE RCM #:	2015-2114
DMEPA Primary Reviewer:	Millie Shah, PharmD, BCPS
DMEPA Team Leader:	Vicky Borders-Hemphill, PharmD

1 PURPOSE OF MEMO

The Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) requested that we review the revised labels and labeling for Probuphine (buprenorphine) implant (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.¹

2 CONCLUSION

The revised container label, carton labeling, patient chart label, patient identification card, and Instructions for Use (IFU) for Probuphine (buprenorphine) implant are acceptable from a medication error perspective. Additionally, the Applicant implemented our recommendations for the Training Slides. However, the revised Quick Reference Guide is unacceptable from a medication error perspective because the Applicant did not implement our previous

¹ Shah M. Label and Labeling Review for Probuphine (buprenorphine) implant (NDA 204442). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2016 JAN 22. 49 p. OSE RCM No.: 2015-2114.

recommendations and did not provide rationale for not implementing our recommendations. Therefore, we provide recommendations below.

3 RECOMMENDATIONS FOR TITAN PHARMACEUTICALS, INC.

We recommend the Applicant implement the following prior to approval of this NDA:

A. Quick Reference Guide

1. Revise Step 5 under Insertion [REDACTED] (b) (4)
[REDACTED] to, "Check applicator function by removing the obturator from the cannula and relocking it." We previously communicated this recommendation to you as recommendation B.1 on January 26, 2016.
2. Revise Step 1 under Insertion [REDACTED] (b) (4)
[REDACTED] As currently presented, Step 1 needs improvement for clarity.

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/s/

MILLIE C BRAHMBHATT
02/12/2016

BRENDA V BORDERS-HEMPHILL
02/12/2016

MEMORANDUM

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

CLINICAL INSPECTION SUMMARY

DATE: February 3, 2016

TO: Swati Patwardhan, Regulatory Project Manager
Rachel Skeete, M.D., Medical Officer
Celia Winchell, M.D., Clinical Team Leader
Sharon Hertz, M.D., Division Director
Division of Anesthesia, Analgesia, and Addiction Products (**DAAAP**)

FROM: John Lee, M.D., Medical Officer
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations (**OSI**)

THROUGH: Janice Pohlman, M.D., M.P.H., Team Leader
Kassa Ayalew, M.D., M.P.H., Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation, OSI

SUBJECT: Evaluation of Clinical Inspections

APPLICATION: NDA 204442

APPLICANT: Titan Pharmaceuticals, Inc.
US Agent: Frank Young, Braeburn Pharmaceuticals, Inc.

DRUG: Buprenorphine Hydrochloride Implant (Probuphine®)

NME: No

INDICATION: Maintenance treatment of opioid dependence

REVIEW CLASSIFICATION:	Class 2 Resubmission
APPLICATION SUBMISSION DATE:	August 27, 2015
DARRTS CONSULTATION DATE:	October 2, 2015
INSPECTION SUMMARY GOAL DATE:	January 27, 2016
REGULATORY ACTION GOAL DATE:	February 26, 2016
PDUFA DUE DATE:	February 27, 2016

I. BACKGROUND

Titan Pharmaceuticals, Inc. (**Titan**) submitted this original NDA 204442 for Probuphine[®], a subdermal implant formulation of buprenorphine (**BPN**) for long-term (six month) maintenance treatment of opioid addiction. Two Phase 3 pivotal studies supported the original submission, and a third study (PRO-814) supports this Class 2 resubmission.

As an integral part of a broader management program, pharmacotherapy has been critical in achieving durable recovery from opioid dependence. BPN (partial opioid mu-receptor agonist) has been used more widely than other agents (methadone or naltrexone), particularly since 2002 with the availability of the sublingual (**SL**) formulation. SL BPN is currently marketed worldwide (34 countries) and its use continues to increase, despite the need for daily dosing and the potential for accidental misuse or abuse (including diversion for illicit use). Probuphine[®] is a long-acting (six-month), abuse-deterrent subdermal implant formulation of BPN inherently less susceptible to the major disadvantages of SL dosing. Probuphine[®] may be readily implanted and removed (at therapy completion) in a brief in-office procedure.

For this Class 2 resubmission NDA, Study PRO-814 was identified for on-site audit at good clinical practice (**GCP**) inspections of four (of 21) clinical investigator (**CI**) sites, based on site-specific efficacy results (enrollment and effect size) and protocol deviations (rescue medication use and urine sample collection). Study PRO-814 is briefly described below.

Study PRO-814

A Randomized, Double-Blind, Double-Dummy, Active-Controlled Multicenter Study of Adult Outpatients with Opioid Dependence Transitioned from a Daily Maintenance Dose of 8 mg or Less of Sublingual Buprenorphine or Buprenorphine/Naloxone to Four Probuphine[®] Subdermal Implants

This double-blind, active-controlled study (originally sponsored by Braeburn Pharmaceuticals, Inc.) was conducted between June 2014 and May 2015 (under IND 70852) in 177 subjects randomized at 21 CI sites in the United States. The primary study objective was to demonstrate the efficacy of Probuphine[®] (four subdermal implants) in maintaining opioid-independence after switching from SL BPN (≤ 8 mg). The study consisted of three periods (up to 29 weeks): (1) screening, up to three weeks; (2) maintenance therapy of opioid dependence, 24 weeks; and (3) follow up, two weeks.

Subject Selection

- Adults (age 18-65 years) with a primary diagnosis of opioid dependence according to the criteria specified in *Diagnostic and Statistical Manual of Psychiatric Disorders, Edition IV Text Revised (DSM-IV-TR)* and deemed to be clinically stable (treating clinician judgment), as confirmed by:
 - Treatment with SL BPN for at least 24 weeks,
 - SL BPN dose of ≤ 8 mg daily for at least the last 90 days, and
 - No positive urine toxicology results (for illicit opioids) in the last 90 days
- Free from significant opioid withdrawal symptoms, as demonstrated at screening by Clinical Opiate Withdrawal Scale (**COWS**) score ≤ 5

Exclusion Criteria

- Any pain condition requiring chronic opioid use, including for acute pain flares
- DSM-IV-TR diagnosis of drug dependence (including alcohol, other than on opioids or nicotine)
- Acquired immune deficiency syndrome (**AIDS**)
- Need for use of agents metabolized through CYP3A4
- Coagulopathy diagnosed within last 90 days or current anticoagulation therapy
- Significant abnormalities in (screening) laboratory indicators of liver/renal function or coagulation
- Hypersensitivity to ethylene vinyl acetate (**EVA**) or naloxone (components of study medication)

- Exposure to any investigational drug within eight weeks
- Per CI discretion, any condition that increases subject risk and/or complicates study conduct

Treatment Groups and Regimens

- Subjects were randomized in equal ratio to either of the following two treatment groups. Implants were placed on Day 1 (baseline Visit 2) and removed at end-of-treatment (EOT) Visit 9.
 - Group A: SL BPN/naloxone tablets (≤ 8 mg BPN per day), AND four placebo implants
 - Group B: four 80 mg Probuphine® implants, AND daily SL placebo tablets
- BPN and placebo tablets were administered as 2 or 8 mg tablets (same as pre-study). The placebo implants contained only EVA.
- All treatments (either group) were expected to yield BPN plasma concentrations of 0.5-1.0 ng/mL. At implant removal, subjects were transitioned back as needed to the pre-study treatment.

Major Study Evaluations

- Primary endpoint: urine toxicology test results indicative of opioid use OR self-report of opioid use
 - After baseline Visit 2, subjects returned to the CI site at Week 1 for post-implant follow up.
 - Subjects then returned every four weeks (Weeks 4, 8, 12, 16, 20, and 24) for study evaluations.
 - Ten urine samples were collected for toxicology, six scheduled (monthly) and four random (anytime).
- Primary analysis: non-inferiority (NI) responder rate comparison of Probuphine® implant (test article) versus SL BPN (active control) maintenance therapies, using the following definitions:
 - Responder: subject with no more than two (of six) months with any evidence of illicit opioid use
 - Illicit opioid use: positive opioid urine toxicology result or self-report of illicit opioid use
 - Non-inferiority: 20% margin (if met, followed by chi square testing for superiority)
- Major secondary efficacy endpoints: time to first evidence of (illicit) opioid use, desire/need to use opioids, and opioid withdrawal:
 - Visual analog scale (VAS) questionnaires: *Desire to Use Opioid* and *Need to Use Opioid*
 - COWS and Subjective Opioid Withdrawal Scale (SOWS)
- Safety: Adverse events (AEs), clinical laboratory tests, electrocardiogram (ECG), physical examination, vital signs, implant site examination, and concomitant medications use

Major Sponsor-Reported Outcomes

- Treatment efficacy was maintained for six months after opioid-dependent subjects (clinically stable on ≤ 8 mg SL BPN) were switched to four Probuphine® implants.
 - Responder rates of 96% for Probuphine® and 88% for SL-BPN were consistent with the pre-defined 20% NI margin (two-sided 95% confidence interval 0.009 - 0.167).
 - By chi square testing, the observed responder rate after switching to Probuphine® was significantly higher than that for continued SL BPN ($p = 0.034$).
- With the exception of mild/moderate transient AEs after subdermal implantation, Probuphine® safety profile was consistent with that known for BPN. New (unexpected) AEs were not observed.
 - Overall, 57% of the subjects experienced at least one treatment-emergent AE (TEAE), including 18% with at least one implant site TEAE.
 - The most common TEAEs were: nasopharyngitis (6%), headache (5%), implant site pain (5%), and depression (5%).

II. INSPECTIONS

In auditing Study PRO-814, four CI sites were identified for GCP inspection based on their (large) contributions to the overall efficacy outcome and (many) protocol deviations for rescue medication use and/or urine sample collection, with special attention to the following concerns:

- All four sites: Urine samples may not have been collected with due diligence. Up to 10 samples were to be collected for toxicology testing (six scheduled and four random).
- Sites 007 and 011: Unexpected (for stable subjects) frequent and considerable use of rescue medication use suggests that unstable, study-ineligible subjects may have been enrolled.

At preliminary NDA review, no special concerns were otherwise identified regarding biased study conduct, including CI conflict of interest, safety monitoring, and AE/protocol deviations reporting.

	Clinical Investigator Site	Site Enrollment	Inspection Dates Outcome
1	Paul W. Schkolnik, M.D. Maryhaven Institute 1791 Alum Creek Drive Columbus, OH	Site 002 6 randomized	Nov 17 – 25, 2015 NAI*
2	John V. Bernard, M.D. Wellness and Research Center 526 Water Street Belvidere, NJ	Site 005 29 randomized	Jan 19 – 22, 2016 NAI*
3	Amit K. Vijapura, M.D. 9141 Cypress Green Drive, Suite 1 Jacksonville, FL	Site 007 26 randomized	Nov 17 – 23, 2015 VAI
4	James G. Sullivan, M.D. Parkway Medical Center 1160 Huffman Road Birmingham, AL	Site 011 20 subjects	Nov 30 – Dec 3, 2015 NAI

NAI = no action indicated (no significant violations); VAI = voluntary action indicated (minor violations)

*For Sites 002 and 005, the final Establishment Inspection Report (**EIR**) has not been received from the field office. The inspection outcome shown is based on preliminary communication with the field investigator, pending verification at EIR receipt and review. See *Note* below, Section III.

1. Paul W. Schkolnik, M.D.**a. What was inspected:**

General records: study conduct including institutional review board (**IRB**) and sponsor oversight of study conduct, CI financial disclosure, drug accountability and disposition, and subject records

Subject case records: subject screening and eligibility evaluation, informed consent, treatment compliance, AEs and safety monitoring, and data verification

Data verification: subject randomization, primary efficacy endpoint, safety (clinical AEs), protocol deviations, and subject discontinuations

b. General observations and comments:

Study PRO-814, Site 002: eight subjects were screened, six were enrolled (randomized), and five completed the study. Case records were completely reviewed for all subjects.

No significant deficiencies were observed and a Form FDA 483 was not issued. Study conduct at this CI site appeared adequate, including IRB/sponsor oversight of study conduct. All audited data were verifiable among source records, case report forms (**CRFs**), and NDA data listings.

c. Assessment of data integrity: The data from this study site appear reliable.**2. John V. Bernard, M.D****a. What was inspected:**

General records: study conduct including IRB and sponsor oversight of study conduct, CI financial disclosure, drug accountability and disposition, and subject records

Subject case records: subject screening and eligibility evaluation, informed consent, treatment compliance, AEs and safety monitoring, and data verification

Data verification: subject randomization, primary efficacy endpoint, safety (clinical AEs), protocol deviations, and subject discontinuations

b. General observations and comments:

Study PRO-814, Site 005: 33 subjects were screened, 29 were enrolled (randomized), and 29 completed the study. Case records were reviewed for all subjects, including detailed (or complete) review for 12 enrolled subjects.

No significant deficiencies were observed and a Form FDA 483 was not issued. Study conduct at this CI site appeared adequate, including IRB/sponsor oversight of study conduct. All audited data were verifiable among source records, CRFs, and NDA data listings.

c. Assessment of data integrity: The data from this study site appear reliable.**3. Amit K. Vijapura, M.D.****a. What was inspected:**

General records: study conduct including IRB and sponsor oversight of study conduct, CI financial disclosure, drug accountability and disposition, and subject records

Subject case records: subject screening and eligibility evaluation, informed consent, treatment compliance, AEs and safety monitoring, and data verification

Data verification: subject randomization, primary efficacy endpoint, safety (clinical AEs), protocol deviations, and subject discontinuations

b. General observations and comments:

Study PRO-814, Site 007: 28 subjects were screened, 26 were enrolled (randomized), and 26 completed the study. Case records were reviewed in detail for all enrolled subjects, including complete review for nine subjects. A Form FDA 483 was issued for minor GCP deficiencies, including the following:

- Subject (b) (6): The study protocol specifies medical monitor consultation and subject exclusion for drug dependence (per DSM-IV-TR). This subject on benzodiazepines (assessed at subject screening to be not dependent on benzodiazepines) was enrolled without consulting the medical monitor.
- Subjects (b) (6): For these 10 subjects, the investigational product was implanted by staff (adequately skilled but apparently) lacking documentation of protocol-specific training and/or implantation training.
- Protocol-specified requirements for maintaining the study blind may not have been followed: blinded staff were not rigorously excluded from the following study procedures assigned to unblinded staff:
 - Subjects (b) (6) and (b) (6): The investigational product was implanted possibly in the presence of a blinded study coordinator, without documentation of rigorous exclusion from observing the implantation procedure.
 - Blinded study coordinators participated in recording the receipt of the investigational product, as indicated on the drug accountability log (18 implant and 48 bottle kits).

OSI Comments:

According to the study protocol: (1) "All subjects will be blinded to treatment assignment, as will all study staff with the exception of the clinician(s) performing the implant procedure and designated personnel who will be responsible for drug accountability (i.e. counting the active and placebo SL BPN returned tablets)," (2) "Designated site personnel will remain unblinded to maintain drug accountability records for all dispensed and returned SL BPN or SL placebo tablets," and (3) "This unblinded site personnel must not participate in efficacy evaluations nor discuss with other study staff any information regarding the SL tablets in reference to the subjects." The protocol does not prohibit blinded study personnel from recording the receipt of placebo or test kits (implant and bottle), which were not readily distinguishable. In documenting the receipt of the kits on the drug accountability log (separate log for implants and tablets), only the kit numbers and tablet doses were recorded.

- For 12 of the 26 subjects enrolled at this study site, the initials of the blinded study coordinators were present at the top of the investigational medication dispensing records.

OSI Comments:

At an interim study monitoring visit (1/21/2015), the study monitor raised the concern about the initials of the blinded study personnel at the top of the dispensing record page. The monitor was informed that the blinded study personnel initialed the dispensing record (and all other source study records) at the top of the page to indicate having performed a routine compliance check (protocol adherence). The blinded staff did not evaluate treatment compliance (BPN versus placebo) nor actually saw the tablets/implants, for any subject. The unblinded study staff initialed and dated the bottom of this page, under the statement about only the unblinded personnel being authorized to dispense the study medication. Upon the study monitor's request: (1) this explanation was documented as a Note to File (1/22/2015), and (2) at the top of this page, for 12 of the 26 subjects enrolled at this CI site (24 of 29 drug dispensing sheets), the unblinded staff crossed out the initials of the blinded study personnel and added their own initials and dates. This explanation provided by the study staff to the study monitor was consistent with the CI's statement in his December 29, 2015 letter in response to the Form FDA 483 issued at the close of the inspection. This deficiency observation appears to be consistent with poor documentation rather than unblinding.

The observed deficiencies appear unlikely to be significant. Study conduct at this CI site appeared adequate, including IRB/sponsor oversight of study conduct. All audited data were verifiable among source records, CRFs, and NDA data listings.

- c. Assessment of data integrity: The data from this study site appear reliable.

4. James G. Sullivan, M.D.

- a. What was inspected:

General records: study conduct including IRB and sponsor oversight of study conduct, CI financial disclosure, drug accountability and disposition, and subject records

Subject case records: subject screening and eligibility evaluation, informed consent, treatment compliance, AEs and safety monitoring, and data verification

Data verification: subject randomization, primary efficacy endpoint, safety (clinical AEs), protocol deviations, and subject discontinuations

- b. General observations and comments:

Study PRO-814, Site 011: 25 subjects were screened, 20 were enrolled (randomized), and 19 completed the study. Case records were reviewed in detail for all enrolled subjects.

No significant deficiencies were observed and a Form FDA 483 was not issued. Study conduct at this CI site appeared adequate, including IRB/sponsor oversight of study conduct. All audited data were verifiable among source records, CRFs, and NDA data listings.

- c. Assessment of data integrity: The data from this study site appear reliable.

III. OVERALL ASSESSMENT AND RECOMMENDATIONS

In support of this NDA 204442 Class 2 resubmission, Titan sponsored a new Study PRO-814 to demonstrate the safety and efficacy of Probuphine®, a subdermal implant formulation of BPN for long-term maintenance treatment of opioid dependence. This study was audited at GCP inspections of four CI sites.

No significant GCP deficiencies were observed at all four sites. A Form FDA 483 was issued at Site 007 for deficiencies unlikely to be significant to the study outcome. Study conduct at all inspected sites appeared adequate, including IRB/sponsor oversight of study conduct. All audited data were verifiable among source records, CRFs, and NDA data listings. The data from the four study sites appear reliable as reported in the NDA resubmission.

Note: For Sites 002 and 005, the final EIR has not been received from the field office and the final inspection outcome remains pending. The inspection results presented in this Clinical Inspection Summary (CIS) are based on preliminary communication with the field investigator. Upon receipt and review of the EIR, an addendum will be forwarded to the review division if the final outcome changes from that reported in this CIS. Otherwise, close-out correspondence with the CI (copied to review division) indicates EIR review completion with no new significant findings and inspection outcome finalization as reported in this CIS without an addendum.

{See appended electronic signature page}

John Lee, M.D.

Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

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Good Clinical Practice Assessment Branch

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Office of Scientific Investigations

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/s/

JONG HOON LEE
02/03/2016

JANICE K POHLMAN
02/03/2016

KASSA AYALEW
02/03/2016



Food and Drug Administration
Office of Device Evaluation
White Oak Building 66
10903 New Hampshire Ave.
Silver Spring, MD 20993

Intercenter Consult Memorandum

CDER NDA 204442 - CDRH ICC1500524

Date: December 29, 2015

To: Swati Patwardhan
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP),
Office of Drug Evaluation II (ODEII),
Office of New Drugs (OND),
Center for Drug Evaluation and Research (CDER)

From: John McMichael
General Hospital Devices Branch (GHDB),
Division of Anesthesiology, General Hospital, Respiratory,
Infection Control, & Dental Devices (DAGRID),
Office of Device Evaluation (ODE),
Center for Devices and Radiological Health (CDRH)

Subject: CDRH Consult for any additional changes to product after CR

Recommendation: Adequate Information for Approval

Review Summary: The consultant was able to interact with the Sponsor via Information Requests (detailed in Section V) and adequately resolve all device related review issues. Therefore, the consultant has no remaining deficiencies within the scope of this review. The consultant notes that the Sponsor has agreed to incorporate and report performance testing on accelerated and real-time aged device samples as part of their stability protocol (see final IR under Section V for more details).

I. Purpose

CDER/OND/ODEII/DAAAP has requested CDRH/ODE's assistance in assessing the acceptability of any additional changes that have been made to the product after receiving a complete response from the sponsor on 08/27/15 in response to a complete response issued by the Agency in April of 2013.

II. Background

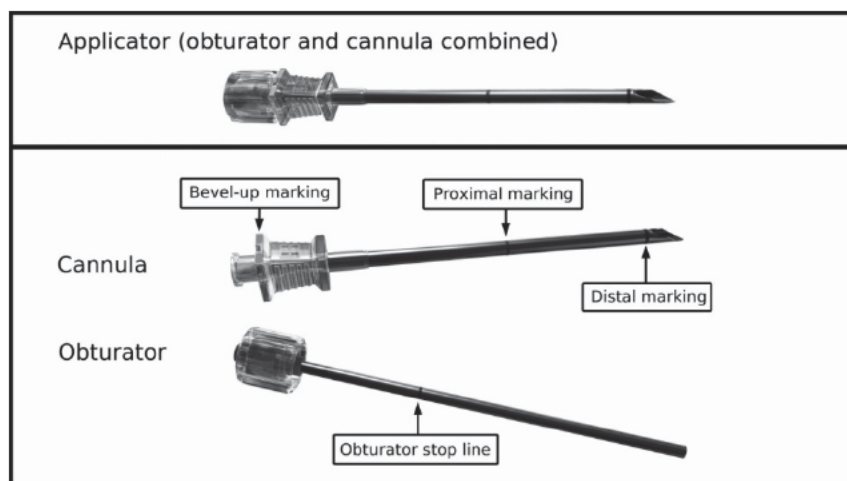
This memo is in response to an NDA resubmission submitted by Titan Pharmaceuticals in August 2015. CDRH/ODE was previously consulted and found the performance data adequate to support approval in April of 2013 before a CR was issued by the Agency. This combination product involves the subcutaneous implantation of 4 buprenorphine-EVA rods/implants via an applicator. The implantation procedure is to be executed by a trained health care provider. The drug is a buprenorphine hydrochloride USP designed for maintenance treatment of opioid dependence and is to be used as part of a complete treatment program to include counseling and psychosocial support. The scope of this review covers the device component of the combination product, which includes the Probuphine Applicator as well as the packaging of the implants and applicator.

III. Device Description

The Applicator being supplied for Probuphine administration is manufactured for the Sponsor by (b) (4) at their facility located at (b) (4), (b) (4). The Applicator comprises two components, a cannula and obturator, both of which are manufactured from 304 stainless steel. The cannula is a thin-walled 10 gauge needle, and the blunt ended obturator is a rod that can be easily inserted into the cannula. Cannula and obturator hubs are manufactured from polymeric materials (b) (4) respectively). The applicator design includes placement of an orientation marking on both the cannula and obturator, and a standard "B" bevel point on the cannula to facilitate the subdermal insertion of Probuphine. Each Applicator is intended for single patient use, individually packaged in a pouch (b) (4). The Applicator is sterilized (b) (4) validated by the manufacturer (b) (4). The Sponsor is supplying the Applicator only for use with Probuphine.

During the course of Probuphine development, the Sponsor introduced several variations of the disposable Applicator. The Applicator utilized in studies PRO-806, PRO-810, PRO-811 and PRO-814 represents the version that the Sponsor intends to market. The final Applicator design employs a standard "B" bevel (sharpened) point on the cannula to facilitate the subdermal insertion of Probuphine. This design modification of beveling, along with the modified surgical equipment (applicator and removal clamp), surgical techniques and implementation of a training program for the insertion and removal of the Probuphine implants, resulted in better tolerability of the implant and removal procedures. All Probuphine prescribers, including implanting healthcare providers, will be trained prior to the insertion or removal of Probuphine.

Figure 1: Probuphine Applicator and Components



IV. Proposed Device Parts of the Combination Product

Probuphine Applicator:

The Probuphine Applicator consists of three parts: (1) an insertable obturator (stylet rod), (2) a cannula needle, and (3) a needle guard which covers the entire cannula from hub to tip. Further descriptions of the device parts are below.

1. Obturator

Medical grade 304 stainless steel rod (Obturator) used to advance the Probuphine implants to the

proper subdermal position. The Stylet wire has a diameter of 0.110 in (2.79 mm), and a length of 3.5 mm \pm 0.79 mm with a blunt tip that can be easily inserted into the Cannula without catching or obstruction. The fit between the stylet wire and the cannula ensures that Probuphine will not remain in the barrel of the cannula if the stylet is inserted to the stop marker. There is a stop marker line 26 mm \pm 0.79 mm from the hub on the Stylet.

2. Cannula

Thin walled piercing needle, made of medical grade 304 stainless steel with a smooth inner surface, 10 gauge internal diameter and 60 mm length, in order to allow the passage of Probuphine (2.5 mm \times 2.5 mm diameter) without impediment. The needle has two depth orientation markers are 60 mm \pm 0.79 mm from the hub on the Cannula and 40 mm \pm 0.79 mm from tip of Cannula.

3. Needle Guard

The Needle Guard for the Applicator consisting of an LDPE sleeve which covers the entire Cannula from the hub to the tip. The Needle Guard protects the Applicator tip during transport and handling and as a safety measure during user handling (removal of the Applicator from packaging). The components of the Applicator are shown in (excluding the Cover). The Cannula and Stylet have interlocking hubs (referred to as Swivel Nuts) manufactured from biocompatible polymeric materials. The Applicator design includes guide and orientation marker visual aids to assist healthcare providers with the proper placement of the Probuphine implants. These markers include orientation markings on both the Cannula and Stylet to facilitate the proper depth of implant placement, and a foil stamp marking on the hub of the Cannula showing the correct "bevel up" position for the cannula which facilitates the correct subdermal insertion of Probuphine.

Packaging of Probuphine Applicator:

The Probuphine Applicator is packaged in a (b) (4) pouch (b) (4). The (b) (4) material has been verified to maintain sterility for up to (b) (4) months.

V. CDRH Review

This review is limited in scope to any apparent changes in the device component of the combination product from the previous submission reviewed by CDRH/ODE in April of 2013. It is noted that the performance testing, sterility, and biocompatibility of the device components are unchanged from the previous submission and have been evaluated under the previous CDRH review, which was submitted to DAARTS on 04/17/2013.


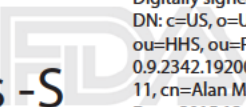

The following were concerns communicated from the reviewer to the Sponsor via Information Request on 10/26/2015. The Sponsor responded to the Information Request on 11/02/2015 and the response is documented in the GSR folder, Sequence No. 0040.

1. In 3.2.A Appendices Probuphine Product Applicator Product Requirements, tracking number 3.2 states that (b) (4) completed biocompatibility testing on a part with similar materials to your Applicator device; please provide a comparison table between the tested part and your Applicator, including material composition of the parts.

Sponsor Response:

12 Pages have been Withheld in Full as B4 (CCI/TS) immediately following this page

VI. Concurrence Table

Digital Signature Concurrence Table	
Reviewer Sign-Off	 John C. Date: 2015.12.29 Mcmichael -S 14:03:12 -05'00'
Team Lead Sign-Off	 Alan M. Digitally signed by Alan M. Stevens -S Stevens -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=13001892 11, cn=Alan M. Stevens -S Date: 2015.12.29 14:05:57 -05'00'
Branch Sign-Off	 Richard C. Chapman -S 2015.12.29 14:34:35 -05'00'

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

/s/

SWATI A PATWARDHAN

02/01/2016

On behalf of CDRH reviewer, John Mcmichael

Food and Drug Administration (FDA)
Center for Drug Evaluation and Research (CDER)
Office of New Drugs (OND)
Office of Drug Evaluation (ODE) III
Division of Bone, Reproductive, and Urologic Products (DBRUP)

Consult Review

Consult Tracking #: 151

Review Date: December 11, 2015

To: Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)

From: Catherine Sewell, M.D., M.P.H. – Medical Officer

Through: Christina Chang, M.D., M.P.H. – Clinical Team Leader
Audrey Gassman, M.D. – Deputy Division Director

Subject: NDA 204422 Probuphine (buprenorphine subdermal implants) for the treatment of opioid addiction -
Safety of Insertion and Removal Procedures for Probuphine Implants

1. Introduction

Probuphine, an implantable formulation of buprenorphine proposed to treat opioid addiction is under a second-cycle review in DAAAP. Each treatment cycle with Probuphine provides six months of continuous delivery of buprenorphine and consists of four buprenorphine-containing implants, 26 mm in length and 2.5 mm in diameter, that are surgically inserted in the inner side of the upper arm. Both the insertion and removal procedures can be accomplished in an outpatient setting. Because buprenorphine is a controlled substance, only providers who are DATA 2000-waived or who practice within an opioid treatment program will be eligible to perform insertion or removal procedures.

Because the insertion and removal procedures share some commonalities with those for implantable contraceptives (e.g, Norplant or implantable levonorgestrel), DBRUP is asked to provide a clinical perspective on the interpretation of the Human Factors Study (intended to demonstrate the effectiveness of a training program with simulated procedures) and the proposed training program and certification procedures for Probuphine insertion and removal. DAAAP has also requested that DBRUP provide comments on labeling and REMS components to promote safety with respect to the insertion and removal procedures. DBRUP has prepared this review as a follow-up to a previously completed consult during the original NDA review.

2. Regulatory Background

Illicit opioid drug use is a significant public health problem. A 2010 Survey on Drug Use and Health by the Substance Abuse and Mental Health Services Administration found that over 2.3 million

people in the United States (US) abuse or are dependent on opioids.¹ Prescription opioids are increasingly being used, misused, diverted, and abused. Although buprenorphine is approved in sublingual, buccal, injectable and transdermal formulations, there still is a need for abuse-deterrent opioid formulations. Subdermally implanted Probuphine was developed with the aim of simplifying the dosing regimen and deterring abuse and diversion.

In the first review cycle, DBRUP provided clinical perspectives on procedure-related safety issues, based on our experience with contraceptive implants and, with input from the Office of Surveillance and Epidemiology (OSE)'s Division of Pharmacovigilance II (DPVII) and Division of Medication Error Prevention and Analysis (DMEPA), summarized contraceptive implant-related adverse events. At the conclusion of the first review cycle, DAAAP issued a Complete Response (CR) on April 30, 2013. The main deficiency in the CR letter pertinent to this consult was the paucity of clinical experience with the insertion and removal procedures for the Probuphine rods. DAAAP was concerned that the proposed training program was not sufficient to impart the necessary skills to a variety of providers, who may not all have surgical experience. Hence, DAAAP recommended a Human Factors Usability Evaluation of the training associated with Probuphine's insertion and removal. The goal was to capture findings from which the Applicant could make program modifications in order to prevent improper implant insertion and/or removal. Further, the findings could validate the proposed training program's design and materials. On August 27, 2015, the applicant submitted a complete response to the April 30, 2013 CR letter. This submission includes a new Phase 3 study (PRO-814) and a human factors evaluation.

3. Review

3.1. Material Reviewed

This medical officer reviewed the following documents for this consult from NDA 204442/0000 and NDA 204442/0030:

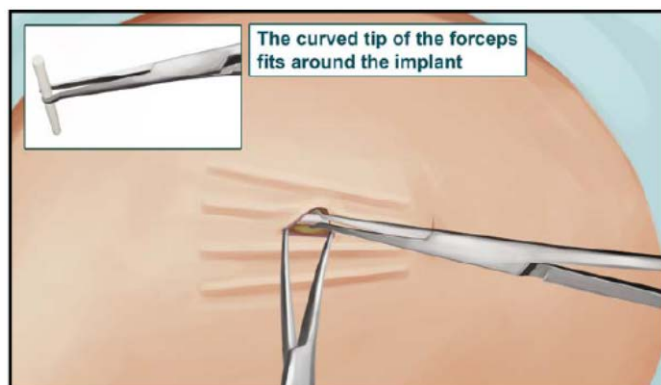
- a. Clinical Overview Addendum
- b. Summary of Clinical Safety
- c. Integrated Summary of Safety and the Integrated Summary of Safety Addendum
- d. Clinical Study Reports for PRO-807 and PRO-811
- e. Human Factors Study Report
- f. Proposed REMS and labeling
- g. DBRUP consult dated March 21, 2013

¹ Substance Abuse and Mental Health Services Administration. Results from the 2010 National Survey on Drug Use and Health: Summary of National Findings. Rockville, MD: Substance Abuse and Mental Health Services Administration, US Department of Health and Human Services; 2011. NSDUH Series H-41. HHS Publication No. (SMA) 11-4658.

3.2. Outstanding Issue From Last Review Cycle: U-Technique for Implant Removal

Among the concerns relating to the insertion/removal procedures identified in the first review cycle was the “U-technique” used for removal of the buprenorphine rods (see Figure 1). This technique is not commonly practiced in the US, and its adoption was a subject of questions raised by gynecology experts at the 2013 Advisory Committee meeting.

Figure 1. Incision for removal of Probuphine implants



Source: Figure 16, Probuphine Instruction for Insertion and Removal, Attachment B to the Response to FDA Information Request, dated November 10, 2015

Our research confirmed the validity of this U-technique. It was originally described in 1993 by Dr. Untung Praptohardjo for Norplant removal, and subsequently modified by Reynolds in 1995.^{2,3} In this technique, a 4 mm incision was made longitudinally between capsules 3 and 4, starting approximately 0.5 cm proximal to the distal ends of the capsules, rather than transversely at the base of the capsules. Forceps were inserted through the incision to grasp the Norplant capsule at right angles to its long axis and within 5 mm of the distal tip. The capsule was pulled to the incision, while the handle of the forceps was rotated toward the subject's shoulder, bringing the tip of the capsule into view in the incision. The fibrous capsule was cleaned off and the capsule was removed. This technique was shown to shorten removal times and was associated with less damage to the implants. Reynolds made minor modifications to the U-technique so the implants could be grasped anywhere along the shaft.

Reviewer Comment:

Compared to the U-technique, the applicant's training material describes a larger incision (7-10 mm) to be made, necessitating suturing for wound closure. The applicant has noted that the Probuphine implants appear to be "less forgiving" than Norplant implants; the larger incision proposed likely

² Praptohardjo U, Wibowo S. The "U" technique: a new method for Norplant@ implants removal. *Contraception* 1993;48:526-536.

³ Reynolds RD. The "modified U" technique: a refined method of Norplant removal. *J Fam Pract.* 1995;40(2):173-80.

allows greater potential for the ease of dissection and better access to the implant in the event of implant breakage.

It should be noted that, if the patient plans to continue with another treatment cycle with Probuphine, a separate incision would be needed for insertion at this visit. This is in contrast with contraceptive implants, where new implants, if requested by patients, are usually inserted through the same incision made for removal in the opposite direction to the implants previously placed. In DBRUP's assessment, the U-technique likely provides greater visualization of and access to the implants to facilitate removal and poses little additional risk.

3.3. Review of Procedure-Related Safety --Clinical Trials in NDA 204442

DBRUP reviewed procedure-related safety issues based on information provided in the Integrated Summary of Safety relating to the following clinical studies:

- 2 double-blind, placebo-controlled trials (Study PRO-805 and Study PRO-806) and 1 double-blind, active-controlled trial (PRO-814) where subjects receiving the active control product (sublingual buprenorphine) also received placebo implants
- 2 open-label, safety extension studies (PRO-807 and PRO-811)
- 1 open-label, comparative bioavailability study (PRO-810)
- 1 dose-finding pharmacokinetic study (TTP-100-02-01)

Of note, several modifications were made during development to the applicator used for the insertion of Probuphine implants, the number of implants inserted, and the insertion/removal procedures. DBRUP's safety review has taken these changes into account. With respect to the applicator, its original blunt-tip, which was associated with more encapsulation and implant fractures, was changed to a sharp one to reduce tissue damage, allow for closer placement of implants and easier removals. Additionally, for Studies PRO-806 (henceforth referred to as "806" for brevity), 811, and 814, the Probuphine Clinical Training and Certification program was implemented. Clinicians watched an Implant Insertion/Removal Training Video and were given written instructions for the proper, aseptic subdermal insertion and removal of Probuphine and placebo implants. Finally, subjects in the first two efficacy trials (Studies 805 and 806) initially received 4 implants but were allowed to receive a 1-implant dose increase (arriving at 5 implants total) if protocol dose increase criteria were met. All subjects in the third trial (Study 814) received 4 implants (either Probuphine or placebo); a fifth implant was not permitted.

To assess procedure-related safety, DBRUP pooled procedures performed across five trials – three efficacy trials (805, 806, 814) and two extension trials (807 and 811) in which subjects received a second treatment cycle. Cumulative exposure to the insertion/removal procedures among subjects who participated in these five trials is shown in Table 1 below:

Table 1. Pooled Extent of Exposure to Procedures

Number of subjects	Probuphine implants	Placebo implants	Total
Study 805	108	55	163
Study 806	114	54	168
Study 814	87	89	176
Study 807	62	N/A	62
Study 811	85	N/A	85
	456	198	654

Source: Extracted from Table 5, disposition of Subjects by Study, pages 31-32 of 153, ISS Addendum, Module 5.3.5.3; NDA 204442/0000: Table 10-1Disposition of Subjects (safety population) Clinical Study Report, page 65, Study Report Body PRO-807, Module 5.3.5.2; 204442/0000: Table 10-1Disposition of Subjects (safety population) Clinical Study Report, page 65, Study Report Body, Module 5.3.5.2204442/0000: Table 10-1Disposition of Subjects (safety population) Clinical Study Report, page 65, Study Report Body PRO-811, Module 5.3.5.2, page 65.

Reviewer Comment:

The extent of procedural exposure is small relative to the pre-approval exposure for contraceptive implant. For example, prior to approval, the Norplant clinical program included 849 removal procedures. The Jadelle (2 levonorgestrel implants) program had > 1100 removal procedures, whereas the Implanon (etonogestrel implants) and Nexplanon (radiopaque version of Implanon) programs had 942 and 296 removal procedures, respectively.⁴ Generalizability of adverse event profiles of contraceptive implants to Probuphine implants may be inferred if Probuphine providers have reasonably similar surgical expertise as providers of contraceptive implants.

As expected, commonly reported procedure-related adverse events (AEs) were mild and self-limiting, such as pain, pruritis, erythema at the incision/implant site. Procedure-related AEs of special interest are summarized in Table 2 below. Compared to contraceptive implants, higher incidences of bleeding (10.9%), complicated removals (3.2%), and implant site infection (4.0%) were noted in the Probuphine trials.

Of note, DBRUP disagreed with the applicant's categorization of AEs associated with "complication of device removal." In the applicant's individual study reports and the integrated safety summary, subjects who required a second attempt to remove all implants were not deemed to have "complicated removal." DBRUP considered a failure to remove all implants during the first attempt – thus necessitating imaging studies to locate all implants and a second removal attempt – to be a complication of the initial implant removal attempt.

⁴ DBRUP slide presentation to the 2013 Probuphine Advisory Committee.

Table 2. Key Procedure-Related Adverse Events by Trial

	Efficacy Studies			Extension Studies			
	Study 805 (N = 163)	Study 806 (N = 168)	Study 814 (N = 176)	Study 807 (N = 62)	Study 811 (N = 85)	Total # Events of Special Interest	AE incidence (% of Total # Procedures Performed, 654)
Implant expulsion \times	5 (3.1%)	2 (1.2%)	1 (0.6%)	2 (4.8%)	0	10	1.5%
Implant site infection*	9 (5.5%)	3 (1.8%)	6 (3.4%)	4 (6.4%)	4 (4.7%)	26	4.0%
Wound complications $^{\infty}$	4 (2.5%)	2 (1.2%)	2 (1.1%)	1 (1.6%)	1 (1.1%)	10	1.5%
Complication of removal or requiring multiple attempts	15 (9.2%)	0	7 (4.0%)	3 (4.8%)	2 (2.3%)	27	4.1%
Bleeding**	30 (18.4%)	19 (11.3%)	1 (0.6%)	16 (25.8%)	5 (5.9%)	71	10.9%

Source:

- For Study 805: extracted from Table 15/page 78 of Study Report, Table 2 and written response to Information Request dated 2/28/13 and 12/10/15
- For Study 806: extracted from Table 14.3.1.2 of Study Report, response to Information Request dated 2/28/13 and 12/10/15
- For Study 814: extracted from Table 30 of Study Report
- For Study 807: extracted from Table 14.3.1.2.1 of Study Report, response to Information Request dated 2/28/13
- For Study 811: extracted from Table 14.3.1.2 of Study Report, response to Information Request dated 2/28/13
- For Study 814: extracted from Table 30 of Study Report

 \times including implant expulsion and implant protrusion

*including AE terms of cellulitis, purulent discharge, implant site pruritus, incision site infection, and wound infection, implant site abscess, and subcutaneous abscess

 $^{\infty}$ including AE terms of incision site necrosis, wound dehiscence, incision site complication, postoperative wound complication, suture-related complication, wound complication, impaired healing

**including AE terms of implant site bleeding/hematoma/hemorrhage, and incision site hemorrhage

*Reviewer Comments:**Key implant site AEs in the database fall into the following broad categories:*

- *Pain*
- *Hemorrhage/hematoma*
- *Infection (includes general term infection, cellulitis, wound infection)*
- *Device expulsion*
- *Complicated removal (includes implants requiring more than one attempt at removal or missing implants never removed)*

- *Neuropathy (paresthesias, peripheral sensory neuropathy)*

Our review did not identify any long-term complications such as permanent disability due to nerve damage; it would be unlikely for such events to be observed in a clinical program of this size.

Two events types of special interest emerged from our review of procedure-related safety. First, pooled incidences of bleeding in the Probuphine program, including implant site hemorrhage/hematoma and incision site bleeding (10.9%) is much higher than that (of hematoma) observed in the Implanon clinical program (0.1%).⁵ Second, implant site infections were seen at a relatively high rate for a simple procedure in the setting of subdermal implant insertion (4.0% overall).

Two explanations may be plausible for such observations. First, the general health status of patients with addiction likely differs from that of young, generally healthy women who seek long-term contraceptive implants. Thus, greater AE incidences would be expected (and likely unavoidable) in the Probuphine program. Two, not all providers who performed the procedures in the Probuphine program were equally familiar with surgical care (both intra-operative/technical care and postoperative care); it is conceivable that providers who were less procedurally-oriented may have had worse surgical outcomes. For example, rates of hematoma and hemorrhage were higher when the procedures were performed by psychiatrists and family medicine practitioners than for surgical specialists in the Studies 805 and 806.⁶ It is possible that competency in pre-operative procedures, insertion and removal of such implants is expected to improve over time given sufficient surgical volume and continuing education/training. However, if Probuphine is approved, these safety findings suggest that provider qualification and training should be better defined. Furthermore, continued provider training and enhanced pharmacovigilance for procedure-related AEs should be considered.

Despite provider training implemented after Study 805, the incidences of patients who required more than one attempt for implant removal remained high (4.8% in Study 807, 2.3% in Study 811, and 4% in Study 814). One subject required three attempts at removal; successful removal of all implants was eventually achieved after referral to a surgeon. Additionally, there were implants which were never located by imaging and never removed during the study (subjects 007-026 and 015-003 who received placebo implants). For these two subjects, despite all four implants being palpated at the scheduled removal, only three were accounted for upon removal. Both subjects had ultrasound performed but the fourth implant was not located. The case report forms (CRFs) do not describe whether the implants were ever located or removed.

⁵ Implant label, section 6.1. http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/021529s0111bl.pdf

⁶ NDA 204442 Integrated Summary of Safety Attachment A Tables 1-4, pages 1-8/8.

3.4. Clinical Perspective--Human Factors Study

In the 2013 consult review, DBRUP summarized the profile of more serious safety concerns associated with contraceptive implants, including:

- Complicated removal due to deep placement or broken implants
- Migration of existing implants including to other sites in the arm or chest
- Nerve damage (from either deep placement or complicated removal), potentially resulting in permanent disability
- Partially removed implants, possibly due to encapsulation from fibrous tissue
- Inability to locate implants for removal, necessitating additional invasive surgery
- Infection
- Bleeding
- Spontaneous expulsion

In response to the 2013 Complete Response letter, the applicant developed training materials and Instruction for Use to mitigate these potential risks. The applicant conducted a series of human factors reviews and formative studies (collectively submitted as the “Human Factor study”), seeking to validate the effectiveness of a single training program in preparing healthcare providers to perform Probuphine insertion and removal procedures.

Components of the Human Factor Study include:

1. Formative study: Classroom instruction on implant procedures: slide presentation on the anatomy of the brachium, the insertion procedure, implant localization, removal procedure, wound care and voiding complications. The moderator instructed participants to review the Instruction for use (IFU) and view videos of both insertion and removal procedures. The participants then performed the procedures without assistance from trainers.
2. Effectiveness training: Live practicum of procedures using a simulated human arm (i.e. pork tenderloin), focus on proper techniques to avoid complications
 - a. To simulate the removal procedure, each piece of pork tenderloin had 4 placebo implants placed 1-4 prior to the practicum. One implant was intentionally fractured (into two pieces of equal size). Another implant had adhesive injected around it to simulate adherent/fibrotic tissue that would require dissection
3. Certification exam: Each participant was evaluated on implant insertion and removal procedure performance, and on responses to a series of knowledge-based questions on both insertion and removal procedures.
 - a. Metrics used to evaluate performance include:
 - i. Insertion Procedure
 1. Maintaining a sterile field
 2. Proper incision performance
 3. Proper Probuphine applicator usage
 4. Implant depth
 5. Implant distribution
 - ii. Removal Procedure

1. Identification of all four implants--with or without imaging assistance (Ultrasound or MRI)
 2. Maintaining a sterile field
 3. Proper incision performance
 4. Proper dissection technique (if necessary)
- b. Critical tasks and subtasks which may mitigate potential risks that were evaluated pertaining to patient screening, insertion, removal, and patient discharge.

The applicant's recruited for both "proceduralists" and "non-proceduralists" to participate, as intended providers of Probuphine did not appeared to be limited to only providers with surgical expertise. The human factor study qualified physicians and mid-level providers as "proceduralists" if they meet one of these two criteria:

- They had completed a medical residency or fellowship in a "procedural specialty" AND they currently practiced in that specialty. (A "procedural specialty" was defined as one in which practitioners perform invasive procedures involving injection of local anesthetic and use of sterile technique, including but are not limited to: anesthesia, surgery, obstetrics and gynecology, dermatology, emergency medicine, critical care, etc.)
- They had performed a sterile procedure in the last 3 months, defined as injecting local anesthetic AND using sterile technique to place sutures, insert a catheter, or make a skin incision. If a midlevel provider, nurse practitioners and physician assistants only.

Both proceduralists and non-proceduralists participated in the classroom instruction and formative user testing (using pork tenderloins) to assess the number of successful implant completion and implant depth. However, the applicant subsequently allowed only proceduralists to participate in the live practicum/certification portion of the human factor study. The live practicum portion enrolled 15 proceduralists with diverse backgrounds – physicians from multiple specialties (anesthesia, surgery, obstetrics and gynecology, dermatology, emergency medicine, critical care, etc.) as well as midlevel providers (nurse practitioners and physician assistants).

Reviewer comment:

The metrics, critical tasks and subtasks are adequate to capture deficiencies in preventing the AEs of concern. However, DBRUP has the following concerns with the overall design, and in turn the utility, of human factor study:

- *The pork tenderloin may be suitable as a model for demonstrating technical proficiency for the insertion procedure. However, it is not suitable for predicting whether certain procedure-related AEs - such as infection and bleeding – can be mitigated by training. As a consequence, the only pertinent task that can be assessed was "depth of implant placement," which on its own has limited clinical relevance.*
- *The scenarios designed to mimic complicated removals (from either breakage or densely adhered implants) appeared reasonable. However, the pork tenderloin is not adequate as a substitute for the removal procedure. Neither the pork tenderloin nor an artificial arm can provide an adequate representation of scarring after 6 months of foreign bodies in the*

- arm. In addition, neither substitute would allow for real-world scenarios in which patients may move, experience pain requiring more anesthesia, or have bleeding.*
- The applicant has not clearly articulated who the intended real-world “proceduralists” would be, but participants in the simulation/validation component of human factors study were all from specialties which involve doing procedures or surgery. Consequently, results of this human factor study are not generalizable to providers of other non-surgical specialties. If approved, DBRUP recommends that labeling and risk mitigation and evaluation strategies (REMS) specify the qualification of the providers who will be performing the insertion/removal procedures.*
 - The applicant should require mid-level providers to also be licensed and provide experience of “procedural specialty” as in many states mid-level providers work independently from physicians.*

Results of human factor study

Results of training with IFU/video viewing showed that physicians (both proceduralists and non-proceduralists) performed slightly better than mid-level practitioners (both non-proceduralists and non-proceduralists), as shown in Tables 3 and 4 below.

Table 3. Implant Depth and Distribution Correctness by Subgroup

User Subgroups	Implant 1 Depth Correctness	Implant 2 Depth Correctness	Implant 3 Depth Correctness	Implant 4 Depth Correctness	Distribution Correctness
Proceduralist - Physicians	7 of 8	7 of 8	6 of 8	5 of 8	6 of 8
Proceduralist - Midlevels	5 of 7	5 of 7	5 of 7	5 of 7	4 of 7
Nonproceduralist - Physicians	6 of 7	6 of 7	6 of 7	5 of 7	5 of 7
Nonproceduralist - Midlevels	5 of 8	5 of 8	5 of 8	4 of 8	3 of 8

Table 4. Implant Removal Performance

User Group	Incision Length Correctness	Incision Depth Correctness	Implants Removed and/or Appropriate Imaging Referral Initiated
Proceduralist - Physicians	5 of 8	7 of 8	4 of 8
Proceduralist - Midlevels	7 of 7	7 of 7	3 of 7
Nonproceduralist - Physicians	5 of 7	7 of 7	5 of 7
Nonproceduralist - Midlevels	4 of 8	5 of 8	2 of 8

The applicant acknowledged that “when users were provided with only the IFU and video materials to...prepare themselves for performing the insertion and removal of Probuphine, there was sub-optimal performance.” However, it is unclear why they proceeded to the live practicum/validation portion of the study only with proceduralists (both physicians and mid-level practitioners) as non-proceduralist physicians appeared to have performed better than proceduralists-midlevel practitioners.

Results of the live practicum/validation study are shown in Table 5 below. For the purposes of this review, this medical officer grouped salient subtasks according to the AE to be mitigated.

Table 5. Risks and Subtasks to Mitigate These Risks

Risk	Subtask	Insertion	Removal	Correctly Performed
Infection	Using aseptic technique, place applicator and four implants on the sterile field	Subtask #11		13/15 (corrected* to 15/15)
	Clean incision site area with chloraprep triple swab for up to 30 seconds	Subtask #13	Subtask #56	14/15 (corrected* 15/15)
	Unwrap surgical tray and place equipment in the sterile field		Subtask #54	14/15 (corrected* 15/15)
Deep placement(which could result in migration/ spontaneous expulsion/nerve damage/hemorrhage or hematoma)	Check applicator function by removing the obturator from the cannula and re-locking it	Subtask #12		13/15 (corrected* 15/15)
	While tenting, gently advance applicator			12/15 x 4 =48; 6 too shallow (<5mm); 6 too deep (5-7 mm) Corrected* 15/15 (60/60)
Bleeding	Make a 2.5-3mm length shallow incision at the marked insertion site	Subtask #17		15/15
Lost migrated implants Difficult/Incomplete Removal/Broken implant	Locate non-palpable implants with ultrasound or MRI		Subtask #48	14/15 (corrected* 15/15)
	Make a 7-10mm incision w/ the scalpel, parallel to the access of the arm, between the 2nd and third implants		Subtask #60	14/15 (midlevel providers made incisions 20-22 mm long)
	Lift skin edge with Adson toothed forceps		Subtask #61	14/15 (used mosquito clamp), corrected* 15/15

Risk	Subtask	Insertion	Removal	Correctly Performed
Fibrous encapsulation	Dissect away any tissue adhering to the implant w/ scissors or mosquito forceps		Subtask #62	14/15 (one closed incision without removing difficult implant; would send for imaging first)
	If implant is encapsulated, use scalpel to shave tissue sheath and carefully dissect the implant		Subtask #64	

After the live practicum, participants were asked follow-up questions to assess their performance and knowledge. The applicant concluded that the participants performed well on assigned tasks. However, a closer reading of the narratives yielded the following gaps in participants' responses, which DBRUP considers notable for having potential clinical ramifications:

On mitigating infection risks:

- 14/15 participants succeeded in inserting all 4 implants. One participant reported getting "flustered" and placed the 4th implant outside the sterile zone.⁷
- 14/15 participants cleaned incision site with antiseptic prior to insertion. One participant omitted this step despite acknowledging this instruction in training.⁸
- 14/15 participants properly placed sterile equipment on the sterile field. One participant broke sterile field while wearing a nonsterile glove despite knowing the importance of properly maintained sterile field.⁹

On mitigating the risks resulting from complicated removal:

- 7/15 participants succeeded in removing all 4 implants. The other 8 "followed proper safety protocol."¹⁰
- 1 mid-level practitioner was unable to remove all 4 implants but proceeded to close the incision. This participant indicated that it "would be prudent to close the incision, bandage up, and send the patient for imaging to return 2-3 weeks later).¹¹
- 14/15 participants correctly requested imaging studies (ultrasound or MRI) to locate non-palpable implants prior to making an incision for removal. A mid-level practitioner failed to request imaging prior to making an incision despite indicating that imaging would have been warranted. She indicated that "she would have followed that guideline in a real patient situation." The applicant interpreted her response as "correct" due to "study artifact."¹²

⁷ Page 55 of 193, human factor study report.

⁸ Page 57-58 of 193, human factor study report.

⁹ Page 57 of 193, human factor study report.

¹⁰ Page 61 of 193, human factor study report.

¹¹ Page 59 of 193, human factor study report.

¹² Page 57 of 193, human factor study report.

On proper use of instruments and surgical technique:

- 13/15 successfully confirmed that the applicator was functioning properly before initiating the procedure. Because all participants indicated that functionality of the applicator should be checked and the “low likelihood of applicator malfunction,” the applicant stated that knowledge “was transferred adequately” and that the two violations of this task “were not due to the training program deficiency.”¹³
- 12/15 participants correctly tented up the skin while advancing the applicator in the 60 implant attempts (4 per participants). As a result, some implants were placed either too shallow (6 of 12 attempts) or too deep (6 of 12 attempts) relative to the pre-specified and recommended subdermal level. The applicant attributed these as “slips” (presumably, from tenting).¹⁴

Reviewer comment:

Given the design of this human study, the subtasks and critical tasks identified appear appropriate. The study showed that most participants could adequately perform the tasks required to mitigate the risks of infection, bleeding and fibrous scar formation around implants. Nevertheless, the narratives of task failures captured above raise a number of issues:

- *The applicant appears to equate “receipt of knowledge” with the ability to adequately perform a surgical procedure. It is unclear how “transfer of knowledge” can mitigate the procedure-related safety concerns that were identified in the clinical trials. The applicant appears to assume, that once a provider recognizes their task failure, they would be able to perform this task correctly in subsequent procedures. However, by design, the human factor study provides no data to support such an assumption.*
- *There were three task failures relating to mitigating infection risks in this human factor study. Notably, the overall incidence of infection-related AEs (4.0%, of all procedures performed) in the clinical trials were already high for an outpatient procedure, aseptic technique and maintaining sterile field should be further addressed in the training program if Probuphine is approved.*
- *Not all participants were able to remove all implants in this practice session. The applicant has not adequately articulated how complicated removals—which will include non-localized, deep or broken implants—will be addressed in the real world setting. Based on postmarketing data on contraceptive implants, implants have been known to migrate great distances from the site of insertion. The Applicant should have a plan for localizing Probuphine implants that are not found with ultrasound or MRI of the upper arm. Further, postmarketing data indicate some contraceptive implants are never localized or removed. The Applicant should address follow-up if implants are never localized or removed.*
- *With regard to deep insertion, 6 of 60 (10%) of implants inserted were beyond the desired depth (5-7 mm); some implants were appropriately positioned and some too deep in any given insertion of 4. All of the deep placements were by midlevel providers. None reached or exceeded the depth of 10 mm which the Applicant associates with a risk of acute or chronic injury to a patient. While DBRUP concurs that insertion depth less than 10 mm is unlikely to*

¹³ Page 50-51 of 193, human factor study report.

¹⁴ Page 53-54 of 193, human factor study report.

result in injury, the finding suggests that the steps in the training program related to insertion depth should be reinforced.

4. Conclusions

- Based on the safety information for contraceptive implants and the Probuphine clinical development program, procedure-related risks are predominantly minor and self-limiting, such as localized infection, bleeding, pain at surgical site, swelling, pruritis, scarring, etc. Serious risks relating to insertion and removal of these devices include complications associated with improper placement of implants (e.g., distant migration; prolonged, difficult or incomplete removal; broken or partially removed implants) and nerve damage are rare but cannot be completely mitigated.
- Questions remain as to whether patients can use Probuphine for longer than 24 months, at which point, all the appropriate sites in both the non-dominant and dominant arms will have been exhausted. If a patient wishes to continue Probuphine for longer than 24 months, previously used, scarred sites will have to be re-used. The ease and safety of insertion and removal from such scars, as well as absorption/efficacy of the drug would have to be evaluated. This should be undertaken as a postmarketing requirement. Furthermore, should sites other than medial surface of the upper arms be necessary for chronic use, additional clinical data will likely be needed.
- The human factors study shows that most intended users of Probuphine comprehended the key procedural tasks after receiving classroom instruction, video instructions, and live practicum using pork tenderloin. However, given the inherent design limitations, DBRUP has significant reservations on the utility and adequacy of the human factor study because study results from an artificial setting are unlikely to offset concerns over increased infection and bleeding risks identified from the clinical program.
- The applicant's decision to exclude non-proceduralists (physicians and mid-level practitioners) from the validation phase of human factor study is unclear, but this decision has implication for labeling and design of risk mitigation and evaluation strategies (REMS).
 - Participants in the simulation/validation component of human factors study were all from specialties which involve doing procedures or surgery. Consequently, results of the validation/certification study are not generalizable to providers of other non-surgical specialties. If approved, DBRUP recommends that labeling and risk mitigation and evaluation strategies (REMS) specify the qualification of the providers who will be performing the insertion/removal procedures.
 - The human factor study has not adequately demonstrated that mid-level practitioners (regardless of whether defined as "proceduralists" by the applicant) can manage the procedures and their potential complications. If mid-level practitioners are intended users of Probuphine, additional data would be needed to document appropriate surgical proficiency in mid-level practitioners.

- The applicant should address how complicated removals—which will include non-localized, deep or broken implants—will be managed. Based on postmarketing data on contraceptive implants, implants have been known to migrate great distances from the site of insertion. The Applicant should have a plan for localizing Probuphine implants that are not found with ultrasound or MRI of the upper arm. Further, postmarketing data indicate some contraceptive implants are never localized or removed. The Applicant should address follow-up if implants are never localized or removed.
- If Probuphine is approved, the applicant should begin a postmarketing surveillance program that will capture adverse events and follow-up to determine whether additional modifications to the REMS or labeling is necessary.

5. Specific Recommendations on Labeling and Risk Evaluation and Mitigation Strategies (REMS)

If this application is approved, we have the following recommendations for labeling and REMS training materials:

- Consider specifying in the labeling and risk mitigation and evaluation strategies (REMS) qualification of the providers who will be performing the insertion/removal procedures.
- Enhanced pharmacovigilance may be needed for procedure-related adverse events such as bleeding, infection, and complicated removal. Modification of training materials may be warranted to mitigate these special events of interest.
- DBRUP recommends that mid-level providers not participate in Probuphine procedures unless they can demonstrate procedural experience equivalent to that of physicians who perform outpatient surgical procedures.

We have the following specific recommendations for the Instructive for Use (IFU) and/or training materials:

- Be more specific with regard to the confirmation that anesthesia is adequate prior to making any incision for insertion or removal and provide information on the maximum dose of local anesthetic it is safe to use at one time.
- Stress steps related to the depth of insertion: the slight 20° angle, tenting the skin with the tip of the applicator during insertion, palpation of the ends of the implants to check correct subdermal insertion.
- Emphasize aseptic surgical technique and maintenance of sterile surgical field during the procedures.
- Steps in the training program related to appropriate depth of insertion should be highlighted. The Human Factors Study showed that 10% of implants placed by midlevel providers were beyond the desired depth (5-7 mm) which can result in additional complications and removal difficulty.

- Provide specific post-procedure wound care instructions at discharge.
- Be more specific with regard to discharge instructions, specifically how much pain, swelling or redness for which a patient should call the provider.
- Provide a plan for localizing Probuphine implants that are not found with ultrasound or MRI of the upper arm and a plan to address follow-up if implants are never localized or removed. The applicant's training material currently instructs providers to call 1-800-xxx-yyyy "if ultrasound or MRI fail," but does not specify what further instructions will be given to the providers who call this number.
- If the applicant intends to provide surgical instruments to providers who do **not** routinely performed outpatient surgical procedures, the applicant should:
 - Provide educational materials and training to the providers on acceptable surgical pre-operative procedures such as aseptic surgical technique and maintenance of surgical field sterility
 - Specify whether these instruments will be for one-time or repeated use.
 - If the instruments are for one-time use, clarify disposal plans for biomedical waste (including blood-stained bandages, discarded surgical gloves, discarded surgical instruments, discarded needles used for anesthesia) that conform to pertinent local, state, and federal regulations.¹⁵
 - If the instruments are for repeated use, clarify what sterilization will be necessary.

¹⁵ Medical waste disposal is primarily regulated at the state level.

<http://www3.epa.gov/epawaste/nonhaz/industrial/medical/programs.htm>

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/s/

CATHERINE A SEWELL
12/11/2015

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12/11/2015

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12/11/2015

STUDY ENDPOINT CONSULT REVIEW

SEALD TRACKING NUMBER	AT 2014-014
IND/NDA/BLA NUMBER	NDA 204442
LETTER DATE/SUBMISSION NUMBER	January 22, 2014; SDN 29; ECTD# 0028
PDUFA GOAL DATE	N/A (Between cycle priority NDA)
DATE OF CONSULT REQUEST	January 23, 2014
REVIEW DIVISION	DAAAP
MEDICAL REVIEWER	Rachel Skeete
REVIEW DIVISION PM	Lisa Basham
SEALD REVIEWER(S)	Ashley Slagle
SEALD DIRECTOR	Sandy Kweder (acting)
REVIEW COMPLETION DATE	February 6, 2014
ESTABLISHED NAME	Buprenorphine implant
TRADE NAME	Probuphine
SPONSOR/APPLICANT	Titan Pharmaceuticals / Braeburn Pharmaceuticals
CLINICAL OUTCOME ASSESSMENT TYPE	 ^{(b) (4)}
ENDPOINT(S) CONCEPT(S)	
MEASURE(S)	
INDICATION	Maintenance treatment of opioid dependence in patients stabilized on sublingual buprenorphine
INTENDED POPULATION(S)	Adult outpatients with opioid dependence stabilized on sublingual buprenorphine

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ASHLEY F SLAGLE
02/07/2014

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02/07/2014

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Human Factors Study Memorandum

Date: January 6, 2014

Reviewer: Vicky Borders-Hemphill, Pharm.D.
Division of Medication Error Prevention and Analysis

Team Leader: Irene Chan, PharmD, BCPS
Division of Medication Error Prevention and Analysis

Drug Name/Strength: Probuphine (buprenorphine hydrochloride and
ethylene vinyl acetate) 80 mg implant

Application Type/Number: NDA 204442

Applicant/sponsor: Titan Pharmaceuticals, Inc.

OSE RCM #: 2013-2168

1 INTRODUCTION

This memorandum communicates the Division of Medication Error Prevention and Analysis' (DMEPA) responses to Titan Pharmaceuticals' responses to recommendations regarding Human Factors provided in the FDA's Preliminary Comments to the Type C meeting Briefing Package dated November 15, 2013.

2 BACKGROUND

On October 29, 2012, Titan Pharmaceuticals, Inc. submitted NDA 204442 for buprenorphine hydrochloride and ethylene vinyl acetate, a subdermal implant for the maintenance treatment of opioid dependence.

On April 30, 2013, the Applicant received a Complete Response (CR) letter requesting additional data to support the efficacy of Probuphine and to conduct a Human Factors study.

On September 13, 2013, the Applicant submitted the proposed summative protocol in preparation of a November 19, 2013, Type C meeting to discuss a strategy for response to the CR letter with the Applicant. On November 18, 2013, Titan Pharmaceuticals, Inc. submitted a reply to FDA's November 15, 2013, Preliminary Comments to the Type C meeting Briefing Package.

3 CONCLUSIONS AND RECOMMENDATIONS

Section 3.1 (Comment to the Applicant) includes DMEPA's original recommendations, then the Applicant's November 18, 2013, response to FDA's Preliminary Comments (in blue), followed by DMEPA's second response which were agreed to be conveyed after the November 19, 2013 Type C meeting.

3.1 COMMENTS TO THE APPLICANT

DMEPA agrees with your summative study plan, however, we have the following recommendations:

1. Two types of human factors validation testing must be performed: instructions for use effectiveness and training effectiveness. Ensure that the summative study validates both the effectiveness of the training and the effectiveness of the instructions for use including the instructional video.

Braeburn Response: The team will run 15 users through an instructions-for-use effectiveness study in addition to the training effectiveness study that is - as currently designed - scheduled to run two groups of 15. Does the FDA agree that this approach will be satisfactory?

DMEPA response: Validation of the Instructions for Use (IFU) can be conducted separately as you have indicated or be integrated as part of the validation of user performance in the insertion of implants. We recommend 30 users (15 for each user group) for validation of the IFU. Additionally, prior to your validation study, ensure that

appropriate labeling comprehension testing has occurred (see recommendation 2) to ensure that intended users understand the information on the labeling prior to validation.

2. Because the instructions are complicated and from the submission it appears as though the instructions for use have not been formerly assessed. Assess comprehension and usability of the instructions for use separate from and prior to the training validation study. So as not to bias the training validation study, select a separate set of user groups than those used for the training validation. Consider asking study participants to read the instructions for use and view the video then, based on their understanding of the information they read and viewed, ask the participants targeted questions related to their understanding of key concepts, such as the proper location to insert the implants or to locate inserted implants, etc.

Braeburn Response: The instructions for use were formerly assessed during our heuristic evaluation which resulted in numerous refinements. However, it appears that what is being requested is a formative comprehension study with intended users (not usability experts) on the instructions for use. If this is correct, then one can be performed prior to inclusion in the summative usability evaluation sessions (this will be in addition to the effectiveness validation study of the instructions for use described in the Braeburn response #1 above).

DMEPA response: We recommend the labeling comprehension study be conducted with at least 15 intended users that are not participating in the validation study.

3. Ensure that there are at least 15 users per group for the instructions for use validation testing and at least 15 users per group for the training validation testing.

Braeburn Response: As described in the Braeburn response #1, the plan is to use 15 users participating in a validation study of the instructions for use effectiveness, and 30 users (15 for each user group previously identified) participating in the training validation. Does the FDA agree that this approach will be satisfactory?

DMEPA response: See response to 1 above.

4. Ensure that intended users included in these summative studies are users that would most likely prescribe and or administer Probuphine. The user groups as presented in your submission need additional granularity based on level of training. As presented in your submission, the users assigned to the “Non-procedural specialist” group include Nurse Practitioners and Physician Assistants which may not have the same level of medical training as physicians listed in this group and should be evaluated as a separate user group. However, if the intent of including Nurse Practitioners and Physician Assistants in the group designated “non-procedural specialists” is to ensure that practitioners with this level of training can learn the procedure, then Nurse Practitioners and Physician

Assistants who are currently performing procedures as part of their professional practice should not be included.

Braeburn Response: We have re-shaped the definitions of our two distinct user groups (“proceduralist” and “nonproceduralist”) and added language to ensure that midlevel providers (such as physician assistants [PA], nurse practitioners [NP], nurse anesthetists, and nurse midwives) are placed into the appropriate group. Because the development of competency in procedures occurs during the post-graduate period, we have focused on the residency training and current practice environment of both physicians and midlevel providers. For example, many PAs and NPs (and all nurse anesthetists and nurse midwives) regularly perform procedures (such as suturing, line insertion, etc). Therefore ALL midlevel providers who perform insertions will be supervised by DATA 2000 qualified physicians.

A provider (including physicians and midlevel providers) will be considered a proceduralist if one of the following two criteria are met:

1. They have completed a medical residency or fellowship in a “procedural specialty” AND they currently practice in that specialty.
 - a. A “procedural specialty” is defined as one in which required competencies include invasive procedures which involve the injection of local anesthetic and the use of sterile technique.
 - b. These include (but are not limited to): anesthesia, surgery, obstetrics and gynecology, dermatology, emergency medicine, critical care, etc).
2. They have performed a sterile procedure in the last 3 months, defined as injecting local anesthetic AND using sterile technique to place sutures, insert a catheter, or make a skin incision.

All other providers that can attest to the original screening requirements will be considered nonproceduralists.

DMEPA response: We agree with this approach.

5. Ensure that summative study results include an in-depth analysis of all use errors or task failures to determine the root causes, the potential negative clinical consequences to the patient or clinician, and the possibility of reducing the risks through modification of the training program and/or the instructions for use and instructional video.

Braeburn Response: A comprehensive risk analysis was performed (failure mode and effects analysis of usage) which was recently submitted to the FDA per their request. The results of this risk analysis provided the foundation for the development of the summative study protocol and recommendations for training program refinements were made. All use errors and task failures that result during the summative study will be cross-checked with the risk analysis results in order to provide the in-depth analysis that is requested above.

DMEPA response: We agree with this approach.

6. Your submission identified several steps or processes in the formative use related risk analysis (such as Pre-Insertion Preparation, Implant Insertion, Dosage Increase, and Implant Removal). As presented in the summative protocol, it is not clear how the instructional meat lab will be designed to address all critical tasks for each process although many tasks may be repeated during a different process. Provide a more granular explanation of the design of the instructional meat lab by providing the specific tasks that will be assessed for each of the following processes (Pre-Insertion, Implant Insertion, Dosage Increase, and Implant Removal).

Braeburn Response: The purpose of the meat lab is to provide a step-by-step exercise in performing all steps in the four categories (Pre-insertion Preparation, Implant Insertion, Dosage Increase, and Implant Removal). Trainers will provide guidance and feedback on technique for all tasks with a special focus on all risk-related tasks and proper safety procedures.

DMEPA response: No comments. Thank you for the clarification.

7. Your submission did not address tasks related to the Pre-Insertion Preparation process in the summative protocol in spite of receiving a high severity (9-10) rating from the formative use related risk analysis. Please describe the tasks you plan to use for Pre-Insertion Preparation. Specifically, provide an explanation of how the instructional meat lab can capture the high severity rated task that ensures that the patient is properly positioned on their back with arm flexed and hand next to head. Consider using a mannequin and placing the arm substitute (meat tenderloin) on the appropriate area of the mannequin.

Braeburn Response: The pre-insertion preparation procedures are provided in list format at the very beginning of the instructions for use, and also presented at the beginning of the instructional video. Each user will be instructed to go through this list and determine if they have properly confirmed these issues. In order to ensure that users can properly position arms and identify the proper location of implantation, trainers will act as mock patients and guide each trainee how to position their arm and identify the location for implants. When these trainees move to the validation study, they will position the arm of one of the human factors experimenters and identify the location of where implants should go. The accuracy of this will be noted by experimenters and also video recorded.

DMEPA response: We agree with this approach, however, ensure that during the validation study that the user is not provided guidance or correction by the moderator.

8. Confirm if the arm substitute (meat tenderloin) to be used in instructional meat lab originates from beef or pork sources as previous studies have shown that the pork source closest resembles human skin.

Braeburn Response: Yes, we can confirm that pork tenderloins will be used for the meat lab and the validation study. Throughout the years of clinical trials and training development, many types of meats were evaluated for accurate simulation and the pork tenderloin was by far the best substitute. These pork tenderloins will be prepared prior to all labs and validation by members of the MedStar Health Simulation Training & Education Lab and human factors experts.

DMEPA response: We agree with this approach.

9. Your submission did not address tasks related to the Dosage Increase process in the summative protocol in spite of receiving a high severity (9-10) rating from the formative use related risk analysis. Please describe the tasks you plan to use for Dose Increase, as the following tasks appear to be critical based on our review of the formative study results:
 - a. Verify the exact location of each implant by palpation
 - b. Use sterile marker to mark the location of the fifth channel path by drawing a 4-6 mm line, medially adjacent to the other four implants
 - c. Mark the insertion site location, separate from original insertion site
 - d. Disinfect insertion site
 - e. Apply sterile drape
 - f. Anesthetize insertion site (ie: inject 5 cc of lidocaine 1%/ epinephrine 1:100,000, just under the skin along the planned channels of insertion)
 - g. Create an incision through the dermis at the marked insertion site
 - h. Insert the applicator at a 20° angle until you can no longer see the distal marking
 - i. Level the applicator and bevel up the skin

Braeburn Response: Use of a fifth implant has been withdrawn and will no longer be evaluated in the human factors summative evaluation.

DMEPA response: No additional comments.

10. Provide an explanation of how the instructional meat lab can capture the high severity rated task of locating implants with ultra sound or MRI, if they cannot be found with palpation.

Braeburn Response: Adjustments to the instruction and training material will be made to indicate that if a user is unable to locate one or more implants through palpation that the patient should be referred to radiology for identification and marking (e.g. ultrasound). This will mimic real-world practice. In training and in the validation study one of the four

implants will be positioned deeper than the others in order to make palpation difficult. This will likely simulate the need for the user to acknowledge and refer to radiology, in which case trainers and human factors experimenters will act as mock radiology personnel. They will then identify the location and return the tenderloin with the implant marked on the surface of the tenderloin.

DMEPA response: We agree with this approach.

11. Provide an explanation of how the instructional meat lab can capture the high severity rated task of user placement of sterile equipment on the sterile field of the mayo instrument stand.

Braeburn Response: The instructional meat lab will provide all of the necessary materials and equipment as the validation testing. All intended users will have been trained in sterile technique, and maintaining sterile technique will be an emphasis of evaluation during testing. As stated above, this is a high severity issue and will be evaluated closely.

DMEPA response: Infection may reduce wound healing which may precipitate implant expulsion or implant migration. To mitigate the risk of infection, ensure that there is a task included for the placement of sterile equipment in the sterile field during the validation study.

12. Your submission did not address the following tasks related to the Implant Insertion process in the summative protocol in spite of receiving a high severity (9-10) rating from the formative use related risk analysis. Please describe the tasks you plan to use for Implant Insertion process, as the following tasks appear to be critical based on our review of the formative study results:
 - a. Draw a line to mark insertion location
 - b. Draw lines for channel points in close, fan-shaped distribution, 4 cm long and 4-6mm apart
 - c. Apply sterile drape
 - d. Using counter traction, insert the applicator at a 20° angle until you can no longer see the distal marking
 - e. Level the applicator and bevel up the skin

Braeburn Response: All tasks associated with the Pre-insertion Preparation, Implant Insertion, and Implant Removal will be performed in the meat lab and tested during the validation testing. Participants will be instructed to perform all of the necessary steps to successfully insert four implants, and remove four implants. In summary, all tasks will be performed, not only the high RPN-related tasks.

DMEPA response: Ensure that aforementioned task successes, close calls, and failures are recorded. During post-study follow-up with the user, information should be collected to determine how and why the close call or failure occurred using post testing interviews.

13. Your submission did not address the following tasks related to the Implant Removal process in the summative protocol in spite of receiving a high severity (9-10) rating from the formative use related risk analysis. Please describe the tasks you plan to use for Implant Removal process, as the following tasks appear to be critical based on our review of the formative study results:
- a. Verify the exact location of each implant by palpation
 - b. Re-confirm location of all implants by palpation
 - c. Clean removal site with alcohol prep pad
 - d. Mark locations of implants with sterile marker
 - e. Unwrap surgical tray and place equipment in the sterile field on the mayo stand
 - f. Put on sterile gloves
 - g. Dis-infect insertion site
 - h. Apply sterile drape
 - i. Make a 7-10 mm incision w/ the scalpel, parallel to the access of the arm, between the 2nd and third implants
 - j. Confirm entire implant has been removed by measuring its length
 - k. If the entire implant has not been removed, remove the other segment following the same procedure
 - l. Clean incision site

Braeburn Response: Same response as above for #12.

DMEPA response: See our previous response for #12.

14. Since the instructions for use will be made available during the instructional meat lab of the training validation testing, observationally capture which parts of the instruction for use that users refer to during the simulation.

Braeburn Response: Agreed, recording the usage of the instructions for use and then comparing to usage in the validation test (and relating to overall performance) could potentially be a valuable measure. Our team will do this.

DMEPA response: We acknowledge your concurrence.

15. For improved readability, consider making the following modification based on DMEPA's review of the instructions for use in the insert labeling that were submitted to NDA 204442 in January, 2013. These comments were shared with FDA's Probuphine Review Team during the March, 2013 labeling meetings:

- a. Consider aligning all figures to appear adjacent to the instructions to which they refer in Section 2 (Dosage and Administration). This will improve readability of instructions and should allow there to be around 4 figures per page with pertinent instructions visible on the same page.

Braeburn Response: Agreed, this will be adjusted to reflect the recommendation.

DMEPA response: We acknowledge your concurrence.

- b. Consider deleting redundant figures that were used in section 2.4 (Insertion of Probuphine) and again for other sections and refer to the original figure in the text.

Braeburn Response: It is anticipated that the instructions for use will be used as a reference guide that contains independent sections. Each of these independent sections should stand alone and contain the necessary content and figures. It is recommended that this be left as is.

DMEPA response: We agree with this approach and will assess the success of this approach based on the results of the validation study.

- c. Consider adding a figure that depicts the suggested equipment laid out on the Mayo instrument stand. Align the figure to appear adjacent to the bulleted listing of equipment provided on page 5 for Section 2.4 (Insertion of Probuphine Four Implants), page 13 (Probuphine Implant Dose Increase: Fifth Implant Insertion), and page 19 (Probuphine Removal Procedure) of the insert labeling.

Braeburn Response: Agreed, this will be adjusted to reflect the recommendation

DMEPA response: We acknowledge your concurrence.

- d. Consider revising images of the cannula and obturator in Figure 1 (the applicator and its parts) to increase the visibility of the cannula's bevel-up marking, proximal marking and distal marking, and the obturator's stop line.

Braeburn Response: Agreed, this will be adjusted to reflect the recommendation

DMEPA response: We acknowledge your concurrence.

- e. Consider including a depiction of the patient's head in Figure 2 (for insertion of Probuphine 4 implants) and Figure 14 (for Probuphine implant dose increase: fifth implant insertion) since the patient's head is used as a reference point for the hand position.

Braeburn Response: This issue of orientation and position were identified during the heuristic evaluation, and adjustments to the descriptions and visuals will be adjusted to make things more clear and reduce confusion.

DMEPA response: We agree with this approach and will assess the success of this approach based on the results of the validation study.

- f. Consider removing the last paragraph of the instructions in step 2 that refer to Figure 3 and reads “The implants should be inserted subdermally just under the skin to avoid large blood vessels...” as it is redundant with information already provided previously under Figure 1.

Braeburn Response: This issue was identified during the heuristic evaluation and the change is currently underway in the next iteration.

DMEPA response: We agree with this approach and will assess the success of this approach based on the results of the validation study.

- g. Consider combining steps 2, 3, and 4 (for insertion of Probuphine 4 implants) into a single step that refers to Figure 3 to provide concise information about the insertion site as follows: “Step 2. Identify the insertion site, which is at the inner side of the upper arm about 8-10 cm (3-4 inches) above the medial epicondyle of the humerus. Instructing the patient to flex the bicep muscle may facilitate the identification of the site. Clean the insertion site with alcohol prep pad then mark the insertion site using a sterile marker (Figure 3).”

Braeburn Response: Agreed, combining these steps will allow a user to properly prepare an alcohol prep pad and sterile marker so that once the site is identified with one hand, he/she does not have to take their finger/hand from that location in order to open/procure the other equipment potentially resulting in the need to re-identify the site.

DMEPA response: We acknowledge your concurrence.

- h. Consider adding an early description of the size of the incision to the instructions for Figure 3 as follows: “The implants will be inserted through a small 2.5 to 3 mm subdermal incision.” This will facilitate instructional flow for the next figure and set of instructions.

Braeburn Response: Agreed, this will be added.

DMEPA response: We acknowledge your concurrence.

- i. Consider revising the Step 5 (for insertion of Probuphine 4 implants) to include a description of the distance between the implants, the length of the marking for the channel tracks, the distance between the incision and the implant once subdermally positioned, and the direction of the opening of the fan shaped lines to read as follows: “Using a sterile marker, mark the channel tracks where each implant will be inserted by drawing 4 lines with each line 4 cm in length. The implants will be positioned in a fan shaped distribution 4-6 mm apart with the fan opening towards the shoulder (Figure 4). The closer the implants lie to each other at the time of insertion, the more easily they can be removed.” Consider adding the statement “There should be at least 5 mm between the incision and the

implant when the implant is properly positioned.” to instructions referring to figure 4.

Braeburn Response: Agreed, this adjustment will be made.

DMEPA response: We acknowledge your concurrence.

- j. Consider adding measure lines for the distance between the marked incision site and channel tracks, the distance between the implants, as well as the length of the marking for the channel tracks to Figure 4 (for insertion of Probuphine 4 implants).

Braeburn Response: Agreed, these adjustments will be made.

DMEPA response: We acknowledge your concurrence.

- k. Consider combining steps 7 (clean insertion site) and 8 (apply sterile drape) into one single step (for insertion of Probuphine 4 implants and for Probuphine implant dose increase: fifth implant insertion).

Braeburn Response: In order to maintain aseptic conditions, it is important that these steps remain separated. If they were combined, a user may try and prepare both the antiseptic solution and the sterile drape at the same time, then realize they need to set the drape down while they clean the site potentially soiling the sterile drape.

DMEPA response: We agree with this approach.

- l. Describe the volume of Lidocaine 1% with epinephrine 1:100,000 in milliliters in step 9 (for insertion of Probuphine 4 implants and for Probuphine implant dose increase: fifth implant insertion) and in step 8 (for removal procedure). The metric volume cubic centimeter or “cc” is on the Institute for Safe Medication Practice’s List of Error-Prone Abbreviations, Symbols and Dose Designations for commonly being misinterpreted as “u” units.

Braeburn Response: Agreed, this adjustment will be made.

DMEPA response: We acknowledge your concurrence.

- m. Consider revising the sentence in step 10 (for insertion of Probuphine 4 implants and for Probuphine implant dose increase: fifth implant insertion) to provide the incision length and depth as follows: “After determining that anesthesia is adequate and effective, make a 2.5 to 3 mm in length shallow incision through the dermis.”

Braeburn Response: Agreed, this adjustment will be made

(b) (4)

DMEPA response: We agree with this approach and will assess the success of this approach based on the results of the validation study.

- n. Consider identifying the position of the bevel up marking by revising the second sentence of step 11 (for insertion of Probuphine 4 implants and for Probuphine implant dose increase: fifth implant insertion) as follows:
“While applying counter-traction to the skin, insert only the tip of the applicator at a slight angle (no greater than 20 degrees) into the subdermal space with the bevel up marking on the cannula facing upwards and visible and with the obturator locked fully into the cannula”.

Braeburn Response: Agreed, this adjustment will be made.

DMEPA response: We acknowledge your concurrence.

- o. The shaded area that designates the 20 degree angle in Figure 5 (for insertion of Probuphine 4 implants) and Figure 16 (for Probuphine implant dose increase: fifth implant insertion) may be mistaken for tented skin. Consider revising the shaded area by removing the dark lines and grey shade.

Braeburn Response: Agreed, this figure will be adjusted to be more clear.

DMEPA response: We acknowledge your concurrence.

- p. Consider designating the sentence that refers to Figure 6 (for insertion of Probuphine 4 implants) and Figure 17 (for Probuphine implant dose increase: fifth implant insertion) - “Lower the applicator to a horizontal position, lift the skin up with the tip of the applicator but keep the cannula in the subdermal connective tissue.” as the next numerical step in sequence occurring after and separate from step 11 and placing it adjacent to Figure 6 (for insertion of Probuphine 4 implants) and Figure 17 (for Probuphine implant dose increase: fifth implant insertion).

Braeburn Response: Agreed, this adjustment will be made.

DMEPA response: We acknowledge your concurrence.

- q. Consider revising Figure 6 (for insertion of Probuphine 4 implants) to depict proper placement and angle of the applicator as the current figure does not clearly convey that the applicator is in a horizontal position with the skin lifted.

Braeburn Response: Agreed, the main picture will be adjusted. In addition, we propose using a small subpicture (similar to Figure 7) to add to this figure in order to show proper horizontal positioning of the applicator. This will improve consistency with Figure 7 and reduce potential for confusion of proper placement angle.

DMEPA response: We agree with this approach and will assess the success of this approach based on the results of the validation study.

- r. Consider designating the sentence that refers to Figure 7 (for insertion of Probuphine 4 implants) and Figure 17 (for Probuphine implant dose increase: fifth implant insertion) - “While tenting (lifting), gently advance the applicator subdermally along the channel marking on the skin until the proximal marking on the cannula just disappears into the incision.” as the next numerical step in sequence occurring after and separate from step 11 and placing it adjacent to Figure 7 (for insertion of Probuphine 4 implants) and Figure 17 (for Probuphine implant dose increase: fifth implant insertion).

Braeburn Response: Agreed, this adjustment will be made.

DMEPA response: We acknowledge your concurrence.

- s. The applicator in the subpicture of Figure 7 (for insertion of Probuphine 4 implants) and Figure 17 (for Probuphine implant dose increase: fifth implant insertion) appears to better convey the angle described in the instructions associated with these figures and appear to be at an angle different from that which is depicted in the main picture of these figures. Consider revising the main picture of these figures to depict the tented skin with advanced placement of the applicator’s proximal marking just beneath the incision.

Braeburn Response: Agreed, the main pictures will be adjusted and subpictures will be added.

DMEPA response: We acknowledge your concurrence.

- t. Consider combining steps 12 and 13 (for insertion of Probuphine 4 implants and for Probuphine implant dose increase: fifth implant insertion) into a single step and designating these two sentences as instructions that refer to Figure 8 and Figure 18, respectively, as follows: “While holding the cannula in place, unlock the obturator and remove the obturator. Insert one implant into the cannula.” Make this the next numerical step in sequence and placing it adjacent to Figure 8 and Figure 18.

Braeburn Response: Agreed, this adjustment will be made.

DMEPA response: We acknowledge your concurrence.

- u. Consider beginning the next step in sequence with the remaining instructions from step 13 (for insertion of Probuphine 4 implants and for Probuphine implant dose increase: fifth implant insertion) - “re-insert the obturator, and gently push the obturator forward (mild resistance should be felt) until the obturator stop line is level with the bevel-up marking, which indicates the implant is positioned at the tip of the cannula. Do not

force the implant beyond the end of the cannula with the obturator. There should be at least 5 mm between the incision and the implant when the implant is properly positioned.” and placing these instructions adjacent to Figure 9 (for insertion of Probuphine 4 implants) and Figure 19 (for Probuphine implant dose increase: fifth implant insertion).

Braeburn Response: Agreed, this adjustment will be made.

DMEPA response: We acknowledge your concurrence.

- v. Consider revising Figure 10 (for insertion of Probuphine 4 implants) and Figure 20 (for Probuphine implant dose increase: fifth implant insertion) to depict the movement of the cannula by replacing the white arrow from above the obturator to a location above the cannula.

Braeburn Response: Agreed, this adjustment will be made.

DMEPA response: We acknowledge your concurrence.

- w. Clarify why pressure may need to be applied to the incision site for approximately 5 minutes in step 18 (for insertion of Probuphine 4 implants) and step 17 (for Probuphine implant dose increase: fifth implant insertion)

Braeburn Response: Agreed, this adjustment will be made.

DMEPA response: We acknowledge your concurrence.

- x. Clarify when and how long after the procedure and how often the patient should palpate the implants in the instructions in step 20 (for insertion of Probuphine 4 implants) and step 19 (for Probuphine implant dose increase: fifth implant insertion).

Braeburn Response: The recommendation that patients palpate the implants is being removed in order to avoid non-sterile hands from touching the implant site. The instructions for use and training is being adjusted to reflect.

DMEPA response: We agree with this approach and will assess the success of this approach based on the results of the validation study.

- y. Consider combining steps 22 and 24 (for insertion of Probuphine 4 implants) as well as combining steps 21 and 23 (for Probuphine implant dose increase: fifth implant insertion) as both steps refer to the provision of instructions for the patient as follows: “Complete the PATIENT IDENTIFICATION CARD and give it to the patient to keep. Also, complete the PATIENT CHART LABEL and affix it to the patient medical record. Provide the patient with the Medication Guide and explain proper care of the insertion site. Instruct the patient to apply an ice pack on

his/her arm for 40 minutes every two hours for first 24 hours and as needed.”

Braeburn Response: Agreed, this adjustment will be made. Also being made is a change to the ice pack recommendation which will read "Instruct the patient to apply an ice pack on his/her arm as needed."

DMEPA response: We agree with this approach and will assess the success of this approach based on the results of the validation study. Additionally, consider providing detailed frequency of ice application.

- z. Consider revising step 2 (for Probuphine implant dose increase: fifth implant insertion) to provide the purpose of this step as follows: “Identify the insertion site by first locating four implants in the arm verified by palpation. If you cannot feel each of the four implants or are in doubt of their presence use other methods to confirm the presence of the implant. Suitable methods to locate are: Ultrasound with a high frequency linear array transducer (10 MHz or greater) or Magnetic Resonance Imaging (MRI). Please note that the PROBUPHINE implants are not radiopaque and cannot be seen by X-ray or CT scan. *If ultrasound and MRI fail call 1-800-XXXX.*”

Braeburn Response: Use of a fifth implant has been withdrawn and will no longer be evaluated in the human factors summative evaluation.

DMEPA response: No additional comments.

- aa. Consider combining steps 3, 4, and 5 (for Probuphine implant dose increase: fifth implant insertion) into a single step that refers to Figure 15 to provide concise information about the insertion site and the channel track consistent with the training video transcript as follows: “Step 3. Clean the insertion site with alcohol prep pad then mark the insertion site using a sterile marker.” Consider adding the statement “The insertion site should be separate from the original incision. There should be at least 5 mm between the insertion incision and fifth implant.” to instructions referring to figure 15.

Braeburn Response: Use of a fifth implant has been withdrawn and will no longer be evaluated in the human factors summative evaluation.

DMEPA response: No additional comments.

- bb. Consider adding an early description of the size of the incision to the instructions for Figure 15 (for Probuphine implant dose increase: fifth implant insertion) as follows: “The fifth implant will be inserted through a small 2.5 to 3 mm subdermal incision.”

Braeburn Response: Use of a fifth implant has been withdrawn and will no longer be evaluated in the human factors summative evaluation.

DMEPA response: No additional comments.

- cc. Additionally for instructions pertaining to Figure 15 (for Probuphine implant dose increase: fifth implant insertion), consider including a description of the distance between the 4 implants and the fifth implant, the length of the marking for the fifth implant channel track, the distance between the incision and the implant once subdermally positioned, and the direction of the opening of the fan shaped lines to read as follows: “Using a sterile marker, mark the channel track where the fifth implant will be inserted by drawing one line approximately 4 cm in length and 4-6 mm adjacent and medial to the previously inserted four implants. The fifth implant will be positioned in the same fan shaped distribution with the fan opening towards the shoulder (Figure 15). The closer the implants lie to each other at the time of insertion, the more easily they can be removed.”

Braeburn Response: Use of a fifth implant has been withdrawn and will no longer be evaluated in the human factors summative evaluation.

DMEPA response: No additional comments.

- dd. Consider deleting the sentence referring to Figure 15 (for Probuphine implant dose increase: fifth implant insertion) “The implant should be inserted subdermally just under the skin to avoid the large blood vessels and nerves that lie deeper in the subcutaneous tissues in the sulcus between the triceps and biceps muscles.” to reduce redundant language.

Braeburn Response: Use of a fifth implant has been withdrawn and will no longer be evaluated in the human factors summative evaluation.

DMEPA response: No additional comments.

- ee. Consider adding measure lines for the distance between the marked incision site and channel tracks, the distance between the implants, as well as the length of the marking for the channel tracks to Figure 15 (for Probuphine implant dose increase: fifth implant insertion).

Braeburn Response: Use of a fifth implant has been withdrawn and will no longer be evaluated in the human factors summative evaluation.

DMEPA response: No additional comments.

- ff. Consider combining steps 6 (clean insertion site) and 7 (apply sterile drape) into one single step (for removal procedure).

Braeburn Response: When using betadine, it is necessary to allow it to sit which further justifies that these steps should remain separate. In addition in order to maintain aseptic conditions, it is important that these steps remain separated. If they were combined, a user may try and prepare both the antiseptic solution and the sterile drape at the same time, then realize they need to set the drape down while they clean the site potentially soiling the sterile drape.

DMEPA response: We agree with this approach and will assess the success of this approach based on the results of the validation study.

- gg. Consider designating the sentence that refers to Figure 25 (for removal procedure) - “Grasp the center of the implant with the X-plant clamp and apply gentle traction. Use the technique of spreading and closing with either the iris scissors or mosquito forceps to separate the fibrous tissue” as the next numerical step in sequence occurring after and separate from step 10 and placing it adjacent to Figure 25.

Braeburn Response: Agreed, this adjustment will be made.

DMEPA response: We acknowledge your concurrence.

- hh. Figures 24 and 25 appear to be the same and use the same instrument. Consider deleting Figure 24 or revising it to depict the instructions to which it refers.

Braeburn Response: These two figures do appear similar with small differences that aren't easily perceived. We will adjust these figures, or create a new single figure, that will make it more clear what tools should be used for which steps.

DMEPA response: We agree with this approach and will assess the success of this approach based on the results of the validation study.

If you have further questions or need clarifications, please contact Mark Liberatore, project manager, at 301-796-2221.

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

/s/

BRENDA V BORDERS-HEMPHILL
01/06/2014

LUBNA A MERCHANT on behalf of IRENE Z CHAN
01/06/2014



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Pediatric and Maternal Health Staff
Office of New Drugs
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Food and Drug Administration
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**PEDIATRIC AND MATERNAL HEALTH STAFF,
MATERNAL HEALTH TEAM MEMORANDUM**

Date: 07-19-2013

From: Leyla Sahin, M.D.
Medical Officer,
Pediatric and Maternal Health Staff, Maternal Health Team

Through: Melissa S Tassinari, PhD.
Acting Team Leader,
Pediatric and Maternal Health Staff, Maternal Health Team

Through: Lynne P Yao, M.D.
Associate Director, Office of New Drugs
Pediatric and Maternal Health Staff

To: Division of Anesthesia, Analgesia and Addiction Products

Drug: Probuphine (buprenorphine) subdermal implant; NDA 204 442

Applicant: Titan Pharmaceuticals

Subject: Labeling for Pregnancy and Nursing Mothers

Materials Reviewed: Applicant labeling

Consult Question: Please review the proposed labeling for Pregnancy and Nursing Mothers

MEMORANDUM

Titan Pharmaceuticals had submitted an NDA for Probuphine (buprenorphine) subdermal implant, a new formulation for the maintenance treatment of opioid dependence. The application was granted priority review due to the claim of improved treatment compliance, reduced risk of abuse, diversion, overdose, and accidental pediatric exposure. The application was issued a complete response on May 1, 2013 (Appendix A) by The Division of Anesthesia, Analgesia, and Addiction Products (DAAAP); therefore the Pediatric and Maternal Health Staff, Maternal Health Team (PMHS-MHT) did not provide labeling recommendations at this time.

APPENDIX A- Complete Response Letter

Titan Pharmaceuticals, Inc.
c/o: Allene M, Dodge; Regulatory Affairs Consultant
PO Box 711
Fox Island, WA 98333

Dear Ms. Dodge:

Please refer to Titan Pharmaceuticals' New Drug Application (NDA) dated October 29, 2012, received October 31, 2012, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Probuphine (buprenorphine hydrochloride implant) for subdermal use.

We acknowledge receipt of your amendments dated November 13, 15, and 16, and December 19 and 24, 2012, and January 11, 24, and 30, February 15 and 28, March 13, 18 (letter says 15), 27, and 29, and April 2, 5, 9, 16, and 25, 2013.

We also acknowledge receipt of your amendment dated April 2, 2013, which was not reviewed for this action. You may incorporate applicable sections of the amendment by specific reference as part of your response to the deficiencies cited in this letter.

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

1. The clinical benefit that would be associated with the minor changes in drug taking behavior that were observed in the clinical trials has not been established. Provide additional data supporting the efficacy of Probuphine, including:
 - a. Opioid blockade study
Conduct a study to evaluate the ability of Probuphine to provide opioid blockade of relevant doses of agonists, in order to identify an effective opioid-blocking dose to be studied in future clinical trials.
 - b. Study of higher doses of Probuphine
Study substantially higher doses of Probuphine, ideally doses more closely approximating the plasma levels associated with sublingual doses of 12 to 16 mg/day. Examine factors such as Body Mass Index (BMI) and/or body weight as part of your dose finding exploration to ensure that a dose appropriate for a range of patient body types is identified. Ideally, the study should be a double-blind, double-dummy

comparison to sublingual buprenorphine, which should be provided under dosing conditions that more closely approximate the way treatment is usually provided.

Alternatively, if you are aware of data showing the clinical benefit of minor changes in drug use behavior, provide the data and a rationale supporting the clinical benefit of the patterns of drug use that were typically observed in the clinical trials.

2. Human Factors Usability Evaluation

There is a paucity of clinical experience with the insertion and removal procedures for the Probuphine rods. Since the “U-technique” for removal is not a commonly used procedure with implantable contraceptives, there is limited experience with this removal procedure. The proposed training that practitioners will receive to perform the procedures will provide only minimal experience for insertion and removal of the implants. Unlike the practitioners who perform procedures for implantable contraceptives, who are generally surgeons, the training program must be sufficient to impart the necessary skills to a variety of providers, who may not have surgical experience.

Therefore, you must conduct Human Factors testing of the training associated with Probuphine’s insertion and removal. These studies will capture findings which may suggest program modifications to prevent improper implant insertion and/or removal. In addition, they will validate the proposed training program’s design and materials. Conduct a comprehensive use-related risk analysis. This risk analysis should include: a comprehensive evaluation of all the steps involved in using the device, the errors that users might commit or the tasks they might fail to perform, the potential negative clinical consequences of use errors and task failures, the risk-mitigation strategies employed to reduce any moderate or high risks to acceptable levels, and the method of validating the risk-mitigation strategies.

LABELING

1. We reserve comment on the proposed labeling until the application is otherwise adequate.

If you revise labeling, your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>.

2. Please submit draft carton and container labeling revised as follows: A. General Comments

1. Per 21 CFR 201.15(b)(1) and 201.56(a)(2), remove (b) (4)
2. Revise the established name to read buprenorphine hydrochloride implant.
3. Revise the strength statement to read 80 mg buprenorphine hydrochloride.

4. Ensure that the strength statement appears directly below the established name on the principal display panel of all product labels and labeling to consistently convey this critical information. For example:

Probuphine
(buprenorphine hydrochloride implant)
80 mg per implant
5. Relocate the scheduled drug designation (CIII) away from the established name.

Ensure there is adequate white space between the established name and the CIII designation so that the CIII designation does not interfere with the readability of the established name.
6. Add the lot number and expiration date to the outside box.
7. If the model of care for this product ultimately changes to one where the patient may in fact handle this product at any portion of the use system, add the statement “Keep out of reach of children” on the container labels and carton labeling.

B. Pouch Container Label

1. Revise the contents statement to read “Contents: One implant containing 80 mg buprenorphine hydrochloride.”
2. Add a statement that reads “Sterile unless pouch is damaged or opened” so that practitioners understand that the pouches ensure the sterility of each individual rod.
3. Add a route of administration statement that reads “For Subdermal Administration Only.” Ensure the route of administration statement appears below the strength statement, “80 mg per implant” and before the “Contents” statement.
4. Relocate the “Rx only” statement to the bottom portion of the label away from the proprietary name, established name, and strength statement.

C. Kit Carton Labeling ((b) (4) Implant Kit (b) (4))

1. On the principal display panel, list the contents as follows: Contents:
Four Probuphine implants, 80 mg buprenorphine hydrochloride per implant
One applicator Prescribing information Medication guide
2. Back Panel:
 - i. Add a statement that reads “Active ingredients: 80 mg buprenorphine hydrochloride per implant.”
 - ii. Add a statement that lists all inactive ingredients.

iii. Add the Dosage and Administration statement that reads: “A single use, sterile and disposable applicator is provided. Do not use if the package has been opened, or if the sterile barrier has been otherwise compromised. Please refer to package insert for complete product information. Insert Probuphine no later than the date printed on the Probuphine pouch container label.”

iv. Add a statement that reads: “For the Healthcare Provider: All health care providers who insert and/or remove Probuphine must receive instruction and training and, where appropriate, supervision prior to inserting or removing Probuphine.”

D. Applicator Container Label and Carton Labeling

Revise the presentation of the information to highlight the applicator device. The title of “applicator” should have equal or greater prominence to that of the proprietary name. Revise the statement of identity to appear similar to “Applicator for Probuphine (buprenorphine hydrochloride implant)” (b) (4)

E. Patient Chart Label

We note the Patient Chart Label is not listed in the contents section of the Implant Kit labeling (b) (4). Please provide an explanation how the Patient Chart Label will be provided to the physician.

F. Patient Identification Card

We note the Patient Identification Card is not listed in the contents section of the Implant Kit labeling (b) (4). Please provide an explanation how the Patient Identification Card will be provided to the physician and patient.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the FDCA authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS) if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)].

We acknowledge receipt of your proposed REMS, included in your submission dated October 29, 2012, and amended on March 13, 2013 and April 2, 2013, which contains a Medication Guide, communication plan, elements to assure safe use, implementation system and a timetable for submission of assessments of the REMS. In accordance with section 505-1 of the FDCA, we agree that a REMS will be necessary for Probuphine (buprenorphine hydrochloride implant), if it is approved, to ensure that the benefits of the drug outweigh the risks of complications that could result from improper technique associated with the implantation/removal procedure of Probuphine (buprenorphine hydrochloride implant) and the risks of misuse, abuse, and accidental overdose associated with Probuphine treatment.

The REMS, should it be approved, will create enforceable obligations. We will continue discussion of your proposed REMS after your complete response to this action letter has been submitted.

Under 21 CFR 208.24(d), you are responsible for ensuring that the label of each container or package includes a prominent and conspicuous instruction to authorized dispensers to provide a Medication Guide to each patient to whom the drug is dispensed, and states how the Medication Guide is provided. You should submit marked up carton and container labels of all strengths and formulations with the required statement alerting the dispenser to provide the Medication Guide. We recommend one of the following statements, depending upon whether the Medication Guide accompanies the product or is enclosed in the carton (for example, unit of use):

- f* “Dispense the enclosed Medication Guide to each patient.” or
- f* “Dispense the accompanying Medication Guide to each patient.”

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.
2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
 - Present new safety data from the studies/clinical trials for the proposed indication using the same format as the original NDA submission.
 - Present tabulations of the new safety data combined with the original NDA data.
 - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
 - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.
3. Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.
4. Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.
5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

6. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).
7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.
8. Provide English translations of current approved foreign labeling not previously submitted.

POSTMARKETING REQUIREMENTS UNDER 505(o)(3)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

FDA has determined that, if NDA 204442 is approved, an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess the unexpected serious risk of QT prolongation with Probuphine (buprenorphine hydrochloride implant).

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk.

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess this serious risk.

Therefore, based on appropriate scientific data, FDA has determined that, if NDA 204442 for Probuphine (buprenorphine hydrochloride implant) for subdermal use is approved, you will be required to conduct the following:

Conduct a clinical trial to assess the risk of QT prolongation with subdermal buprenorphine, i.e., a thorough QT (tQT) trial.

Any additional specific details of this required postmarketing clinical trial, including a timetable and annual reporting requirements, will be described more fully in the approval letter for this application, if it is approved.

If you complete this trial prior to re-submitting your application, you may include the final report and relevant data sets in your Complete Response submission to facilitate review of the information.

ADDITIONAL COMMENTS:

1. As already discussed at your pre-NDA meeting, you should evaluate the effect of scarring or inflammation at previously implanted sites on the re-implantation and bioavailability of Probuphine. Probuphine has never been administered in an implant site that was previously used. Scarring or other local tissue changes may have an impact on drug delivery, or on the

feasibility of re-implantation. Because opioid addiction is a chronic, relapsing disorder, it is conceivable that long-term or even life-long pharmacologic treatment will be required by some patients.

Should this evaluation reveal that sites cannot be re-used, study implantation sites other than the arm.

2. Consider conducting a study of Probuphine in patients with lower sublingual buprenorphine requirements. The current dosing regimen of Probuphine may well be appropriate for some patients. In particular, it may provide an adequate dose for patients who are in long-term, stable, recovery and are maintained on low (6 mg or less) doses of sublingual buprenorphine. These patients require less close clinical supervision and clinical interaction than patients early in treatment, and are likely to be the ideal candidates for a drug product which permits very infrequent contact with the treatment provider.

3. Consider modifying the implant to include a radio-opaque marker to facilitate removal when the implants cannot be palpated, or migrate from the implantation site.

4. We do not believe the mg/m² body surface area-derived safety margins modified from the reference sublingual label as described in the Pregnancy, (b) (4) and Fertility sections of the proposed label are appropriate.

In order to support nonclinical labeling of Probuphine doses which produce exposures within or in excess of the exposure levels of the listed drug during any portion of the implants usage you will need to provide a persuasive exposure-based scientific justification for safety margins described in nonclinical sections which may require bridging toxicokinetic studies. Otherwise you will need to conduct reproductive toxicology studies necessary to support sections 8.1 *Pregnancy* and carcinogenicity studies described in 13.1 *Carcinogenesis, Mutagenesis, and Impairment of Fertility*.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA Guidance for Industry, "Formal Meetings Between the FDA and Sponsors or Applicants," May 2009 at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf>.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, call Lisa E. Basham, Senior Regulatory Health Project Manager, at (301) 796-1175.

Sincerely,

{See appended electronic signature page}

Bob A. Rappaport, M.D. Director
Division of Anesthesia, Analgesia, and Addiction
Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

LEYLA SAHIN
07/19/2013

MELISSA S TASSINARI
07/22/2013

LYNNE P YAO
07/22/2013

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

******Pre-decisional Agency Information******

Memorandum

Date: May 30, 2013

To: Lisa Basham, Regulatory Project Manager
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)

From: L. Sheneé Toombs, Regulatory Review Officer (OPDP)

CC: Olga Salis, Senior Regulatory Health Project Manager (OPDP)
Michael Wade, Regulatory Health Project Manager (OPDP)

Subject: NDA 204442
OPDP labeling comments for Buprenorphine implant

OPDP acknowledges receipt of your November 14, 2012, consult request for the proposed Package Insert, Carton/Container Labeling, and Medication Guide for Buprenorphine implant. Reference is made to the April 30, 2013 complete response letter. As a result, OPDP will provide comments regarding labeling for this application during a subsequent review cycle. OPDP requests that DAAAP submit a new consult request during the subsequent review cycle.

Thank you for the opportunity to comment on these proposed materials.

If you have any questions, please contact Sheneé' Toombs at (301) 796-4174 or latoya.toombs@fda.hhs.gov.

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/s/

LATOYA S TOOMBS
05/30/2013

Internal Consult

****Pre-decisional Agency Information****

Please Note: The following review is for DRISK only and should not be used to provide comments to the sponsor.

To: Joan E. Blair, Risk Management Analyst, DRISK

From: L. Shenee' Toombs, Regulatory Review Officer

CC: L. Shenee' Toombs, Regulatory Review Officer
Sam Skariah, Team Leader
Lisa Skarupa, SRPM, OSE
Kimberly Lehrfeld, Team Leader, DRISK
Donella Fitzgerald, Risk Management Analyst, DRISK
Carole Broadnax
CDER-OPDP-RPM
Michael Wade

Date: May 6, 2016

Re: NDA # 204442
PROBUPHINE[®] (buprenorphine)
Comments on draft Risk Evaluation and Mitigation Strategies (REMS)
Materials (Submission date: May 4, 2016 and May 5, 2016)

Materials Reviewed

OPDP has reviewed the following proposed REMS materials for Probuphine:

- Healthcare Provider (HCP) REMS Materials:

- Probuphine REMS Program Healthcare Provider Who Prescribes Enrollment Form
 - Probuphine REMS Program Healthcare Provider (b) (4) Enrollment Form
 - Probuphine REMS Program Healthcare Provider Dual Enrollment Form
 - Probuphine REMS Program Live Training: Lecture Slides
 - Probuphine REMS Program Knowledge Assessment
 - Probuphine REMS Program Criteria for Procedural Competency: Insertion
 - Probuphine REMS Insertion/Removal Log Form
 - Probuphine REMS Website: Healthcare Providers
 - Probuphine REMS Program Procedure Record for Recertification
 - Probuphine REMS Program Healthcare Provider (b) (4) Recertification Form
 - Probuphine REMS Program Insertion/Removal Recertification Video
- Direct-to-Consumer (Patient) REMS Materials:
 - What You Need to Know About Probuphine: A Patient's Guide
 - Probuphine REMS Website: Patients

The version of the draft REMS materials used in this review were provided by DRISK (Joan Blair) via email on May 5, 2016 and they are attached to the end of this review.

OPDP offers the following comments on these draft REMS materials for Probuphine,

General Comment

Please remind Braeburn that REMS materials are not appropriate for use in a promotional manner.

OPDP notes the link www.ProbuphineREMS.com and toll free numbers such as 1-844-859-6341. OPDP recommends that these items represent a direct link to only REMS related information and not be promotional in tone. Furthermore, we remind the sponsor that the REMS specific website should not be the sole source of approved REMS materials.

OPDP notes that the Probuphine PI and Medication Guide are still being reviewed and modified. Therefore, we recommend that the REMS materials be revised, as appropriate, to reflect all changes in the final approved Probuphine PI and Medication Guide.

REMS Materials

OPDP does not object to including the following materials in the REMS program (please see Specific Comment[s] below):

- Healthcare Provider (HCP) REMS Materials:

- Probuphine REMS Program Healthcare Provider Who Prescribes Enrollment Form
 - Probuphine REMS Program Healthcare Provider (b) (4) Enrollment Form
 - Probuphine REMS Program Healthcare Provider Dual Enrollment Form
 - Probuphine REMS Program Live Training: Lecture Slides
 - Probuphine REMS Program Knowledge Assessment
 - Probuphine REMS Program Criteria for Procedural Competency: Insertion
 - Probuphine REMS Insertion/Removal Log Form
 - Probuphine REMS Website: Healthcare Providers
 - Probuphine REMS Program Procedure Record for Recertification
 - Probuphine REMS Program Healthcare Provider (b) (4) Recertification Form
 - Probuphine REMS Program Insertion/Removal Recertification Video
- Direct-to-Consumer (Patient) REMS Materials:
 - What You Need to Know About Probuphine: A Patient's Guide
 - Probuphine REMS Website: Patients

Specific Comment[s]

OPDP recommends the following revisions or deletions for the following REMS pieces:

Probuphine REMS Program Live Training: Lecture Slides

- The proposed lecture slides minimize the risk concepts related to the goals of the REMS. Specifically, the proposed lecture slides fail to include important material risk information from the PI. According to the WARNINGS AND PRECAUTIONS section of the PI (underlined emphasis added):

(b) (4) complications including nerve damage and migration resulting in embolism and death may result from improper insertion of drug implants inserted in the upper arm.

Insert PROBUPHINE in accordance with the instructions...It is essential to insert PROBUPHINE subdermally so that each implant is palpable after insertion. If PROBUPHINE is inserted too deeply (intramuscular or in the fascia), neural or vascular injury may occur.

Incomplete insertions or infections may lead to protrusion or expulsion...Accidental exposures to PROBUPHINE can result from protrusion or expulsion of the implants...

Improper insertion may lead to complicated removal if the implant is inserted too deeply, is not palpable, or has migrated. Deep insertions may lead to difficulty localizing the implant; additional surgical procedures may

be required in order to remove the implant...Injury to deeper neural or vascular structures in the arm may occur when removing deeply inserted implants.

OPDP recommends revising the proposed lecture slides to include this material information.

In addition, page 19 of the proposed lecture slides include patient information on the potential risks associated with the insertion and removal of Probuphine. However, the presentation fails to include risk information regarding migration. According to the **“What is the most important information I should know about PROBUPHINE?”**(bolded emphasis original) section of the Medication Guide:

- Movement of implant (migration). PROBUPHINE or pieces of it can move into blood vessels and to your lung, (b) (4) and could lead to death.

OPDP recommends revising the proposed lecture slides to include this important risk information.

- Page 20 of the proposed lecture slides include the statement, “If there are symptoms suggesting the implant has (b) (4) such as weakness or numbness in the arm, or shortness of breath”(underlined emphasis added). OPDP notes that this statement is inconsistent with the PI. The Patient Counseling Information section of the draft PI states, “Inform patients to call a Healthcare professional immediately if they experience any of the following...Symptoms suggesting the implant has migrated, such as numbness or weakness, or shortness of breath” (underlined emphasis added). OPDP recommends revising this statement for consistency with the PI.

Probuphine REMS Website: Patients

- The proposed website includes the following presentation (bolded emphasis original):
 - **“What is Probuphine?”**
 - (b) (4)
Probuphine implants contain the opioid buprenorphine, which may cause physical dependence.
 - ...
 - (b) (4)

This presentation is an inadequate communication of the indication - we recommend that it be revised to include the approved indication as presented in the Medication Guide.

- The proposed website minimizes the risk concepts related to the goals of the REMS. Specifically, the proposed website fails to include important material risk information from the Medication Guide. According to the **“What is the most important information I should know about PROBUPHINE?”** (bolded emphasis original) section of the Medication Guide:

- Movement of implant (migration). PROBUPHINE or pieces of it can move into blood vessels and to your lung, (b) (4) and could lead to death.

OPDP recommends revising the proposed website to include this important risk information.

What You Need to Know About Probuphine: A Patient’s Guide

- The proposed patient guide includes the following presentation (bolded emphasis original):

- **“What is Probuphine?”**

(b) (4)

This presentation is an inadequate communication of the indication - we recommend that it be revised to include the approved indication as presented in the Medication Guide.

- The proposed patient guide includes a presentation titled, (b) (4) (bolded emphasis original). This presentation is misleading (b) (4) (b) (4) (b) (4) OPDP recommends revising this presentation to accurately reflect the content of this section. For example, consider revising to state, “What are the Risks Related to Insertion and Removal of Probuphine implants?”

- The proposed patient guide minimizes the risk concepts related to the goals of the REMS. Specifically, the proposed patient guide fails to include important material risk information from the Medication Guide. According to the **“What is the most important information I should know about PROBUPHINE?”** (bolded emphasis original) section of the Medication Guide:

- Movement of implant (migration). PROBUPHINE or pieces of it can move into blood vessels and to your lung, (b) (4) and could lead to death.

OPDP recommends revising the proposed patient guide include this important risk information.

We have no additional comments on these proposed REMS materials at this time.

Thank you for your consult.

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/s/

LATOYA S TOOMBS
05/06/2016

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs**

REVIEW DEFERRAL MEMORANDUM

Date: May 1, 2013

To: Bob A. Rappaport, MD
Director
**Division of Anesthesia, Analgesia, and Addiction
Products (DAAAP)**

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Barbara Fuller, RN, MSN, CWOCN
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Nathan Caulk, MS, BSN, RN
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Subject: Review Deferred: Medication Guide (MG)

Drug Name (established name): Probuphine (buprenorphine hydrochloride/ethylene vinyl acetate)

Dosage Form and Route: Subdermal implant

Application Type/Number: NDA 204-442

Applicant: Titan Pharmaceuticals Inc.

1 INTRODUCTION

On October 31, 2012, Titan Pharmaceuticals Inc. submitted for the Agency's review an original New Drug Application (NDA) 204-442 for Probuphine (buprenorphine hydrochloride/ethylene vinyl acetate) Subdermal implant with the proposed indication for the maintenance treatment of opioid dependence. On November 14, 2012, the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) requested that the Division of Medical Policy Programs (DMPP) review the Applicant's proposed Medication Guide (MG) for Probuphine (buprenorphine hydrochloride/ethylene vinyl acetate) Subdermal implant.

This memorandum documents the DMPP review deferral of the Applicant's proposed Medication Guide (MG) for Probuphine (buprenorphine hydrochloride/ethylene vinyl acetate) Subdermal implant.

2 CONCLUSIONS

Due to outstanding clinical deficiencies, DAAAP issued a Complete Response (CR) letter on April 30, 2013. Therefore, DMPP defers comment on the Applicant's patient labeling at this time. A final review will be performed after the Applicant submits a complete response to the Complete Response (CR) letter. Please send us a new consult request at such time.

Please notify us if you have any questions.

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/s/

NATHAN P CAULK
05/01/2013

BARBARA A FULLER
05/01/2013

LASHAWN M GRIFFITHS
05/01/2013

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Label, Labeling and Packaging Review

Date: April 25, 2013

Reviewer: Vicky Borders-Hemphill, Pharm.D.
Division of Medication Error Prevention and Analysis

Team Leader: Jamie Wilkins Parker, Pharm.D.
Division of Medication Error Prevention and Analysis

Associate Director: Scott Dallas, RPh
Division of Medication Error Prevention and Analysis

Drug Name/Strength: Probuphine (buprenorphine hydrochloride and
ethylene vinyl acetate) 80 mg implant

Application Type/Number: NDA 204442

Applicant/sponsor: Titan Pharmaceuticals, Inc.

OSE RCM #: 2012-2725

*** This document contains proprietary and confidential information that should not be released to the public.***

Contents

1	Introduction.....	1
1.1	Regulatory History	1
1.2	Product Information	1
2	Methods and Materials Reviewed.....	2
2.1	Selection of Medication Error Cases.....	2
2.2	Literature Search	3
2.3	Labels and Labeling	3
3	Medication Error Risk Assessment.....	3
3.1	Medication Error Cases.....	3
3.2	Integrated Summary of Medication Error Risk Assessment.....	4
4	Conclusions.....	5
5	Recommendations.....	5
	Appendices.....	13
	Appendix A. Database Descriptions.....	13
	Appendix B: Pouch Container Labels	14
	Appendix C: Applicator Container Labels	15
	Appendix D: Applicator Carton Labeling	16
	Appendix E: Kit Carton Labeling (Implant Kit (b) (4))	17
	Appendix F: Patient Chart Label	21
	Appendix G: Patient Identification Card.....	22
	Appendix H: Case numbers discussed in this review	23

1 INTRODUCTION

This review evaluates the proposed pouch and applicator container labels, applicator and kit carton labeling, insert labeling, Patient chart label, and Patient identification card for Probuphine, NDA 204442 for areas of vulnerability that could lead to medication errors.

1.1 REGULATORY HISTORY

On October 29, 2012, Titan Pharmaceuticals, Inc. submitted NDA 204442 for buprenorphine hydrochloride and ethylene vinyl acetate, a subdermal implant for the maintenance treatment of opioid dependence.

On March 21, 2013, a Psychopharmacologic Drugs Advisory Committee meeting was held to discuss safety of Probuphine and lessons learned from contraceptive implants (Norplant and Implanon); and efficacy as well as the proposed model of care submitted to the Risk Evaluation and Mitigation Strategy for Probuphine. The panel voted 10-4 in favor of recommending approval of Probuphine with one abstention, however expressed concerns regarding continued appropriate dose finding for this product.

1.2 PRODUCT INFORMATION

The following product information is provided in the November 15, 2012 proprietary name submission.

- Active Ingredient: buprenorphine hydrochloride
- Established name: buprenorphine implant
- Indication of Use: for the maintenance treatment of opioid dependence
- Route of Administration: inserted subdermally at the inner side of the upper arm about 8-10 cm (3-4 inches) above the medial epicondyle of the humerus
- Dosage Form:
 - Subdermal Implant [a sterile, single, off-white, soft, flexible, ethylene vinyl acetate (EVA) implant]
 - Implant size: rod shaped 26 mm in length and 2.5 mm in diameter
- Strength: each implant contains 80 mg of buprenorphine
- Dose and Frequency:
 - 4 implants inserted every 6 months (alternating arms) initiated after at least 3 days of buprenorphine sublingual tablet (Subutex) titration to a daily dose range of 12-16 mg; sublingual buprenorphine to be discontinued 12 hours to 24 hours prior to the insertion of the implant to avoid potential overdose. Patients requiring greater than three days per week of supplemental sublingual buprenorphine for two consecutive weeks or eight days total over four consecutive weeks are eligible to receive one additional implant at any time after two weeks from the initial insertion date. The 5th implant is to be inserted into the same arm/location

as the initial four implants. All implants must be removed within six months of the original four implant insertion date.

- How Supplied: two planned configurations:
 - four individually pouched implants in a carton co-packaged with one single sterile disposable applicator and
 - single pouched implant co-packaged with a single sterile disposable applicator (b) (4)
- Storage: 20 to 25°C (68 to 77°F), with excursions permitted to 15 to 30°C (59-86°F) [see USP Controlled Room Temperature
- Container Closure System: laminated foil pouch

2 METHODS AND MATERIALS REVIEWED

In support of the Division of Reproductive and Urologic Products presentation at the March 21, 2013, Psychopharmacologic Drugs Advisory Committee meeting, on lessons learned from contraceptive implants, DMEPA searched the FDA Adverse Event Reporting System (FAERS) database for medication error reports of a similar product, Norplant (levonorgestrel).

We also reviewed the Probuaphine container labels, and carton and package insert labeling submitted by the Applicant.

2.1 SELECTION OF MEDICATION ERROR CASES

We searched the FAERS database using the strategy listed in Table 1, focusing on cases of deeply placed implants or migrated implants.

Table 1. FAERS Search Strategy	
Date	December 10, 1990 through February 1, 2013
Drug Names	Product name 'Norplant'
MedDRA Search Strategy	Complication Of Device Insertion (PT) Complication Of Device Removal (PT) Device Dislocation (PT) Product Quality Issue (PT) Device Expulsion (PT) Device Extrusion (PT) Medication error (PT) Medical Device Complication (PT) Procedural Complication (PT) Incorrect Drug Administration duration (PT)

The FAERS database search identified 2302 cases. We reviewed a sampling of these cases to identify unusual cases of deeply placed implants or migrated implants.

2.2 LITERATURE SEARCH

We searched PubMed on October 26, 2013, for additional cases and actions concerning Norplant. The incidence and description of Norplant removal complications can be found throughout published literature. Specifically, Dunson, et al. described complications at the removal of Norplant from 3416 users from 11 countries who participated in preintroductory clinical trials with a 4.5% incidence of removal complications related to broken or deeply placed implants.¹ The authors indicated that displaced implants have been associated with using the wrong implantation technique by inserting the trocar too far at insertion thus creating a channel through which the implants migrate. These removal complications included pieces of the implant being left in 3 of the 57 broken implant cases (1.7% overall incidence rate). They also described “not found” as a removal complication with an incidence rate of 0.2%. Additionally, Wysowski, et al reviewed Medwatch reports from February 1991 to December 1993 and found that three women had expelled Norplant implants, and 14 women were hospitalized or disabled for removal difficulties which appeared to result from inability to locate implants because they had migrated or were embedded too deeply.²

2.3 LABELS AND LABELING

Using the principles of human factors and Failure Mode and Effects Analysis,³ along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Pouch and Applicator container labels, Applicator and Kit carton labeling, Patient chart label, and Patient identification card submitted February 14, 2013 (Appendices B through G)
- Insert Labeling submitted January 11, 2013

3 MEDICATION ERROR RISK ASSESSMENT

The following sections describe the results of our FAERS search and the risk assessment of the Probuphine product design as well as the associated label and labeling.

3.1 MEDICATION ERROR CASES

Examination of a sampling of the FAERS cases found reports of Norplant implant migration, expulsion, and extrusion similar to what has been reported in the literature.

¹ Dunson TR, et al. Complications and risk Factors Associated with the Removal of Norplant Implants. *Obstet Gynecol* 1995;85:543-8.

² Wysowski D, Green L. Serious adverse events in Norplant Users reported to the Food and Drug Administration's MedWatch Spontaneous Reporting System. *Obstet gynecol.* 1995;85:538-42.

³ Institute for Healthcare Improvement (IHI). *Failure Modes and Effects Analysis*. Boston. IHI:2004.

FAERS cases described the implant migrating deep into muscle, fat, on or near bone, near nerves, and near veins. This migration reportedly occurred anywhere from 3 weeks to 2 years following insertion. Some cases indicate that once migration occurred the implant could not be located via palpation, by radiograph, ultrasound, or other technologies making it difficult to remove. In some cases it was reported that up to 5 of the 6 implants remained in the patient. Due to the migration the removal of the implant resulted in a lengthy procedure (several hours) or required the need for multiple removal attempts. Cases describe patients not returning for the second attempt at removal. Other cases reported the need for surgical removal of the implant in the operating room under general anesthesia. Other cases describe extrusion (poking out of skin) and expulsion (coming out of arm) of the implant. The time to complete expulsion from arm after insertion of Norplant varied from 3 days to 2 years. Table 2 (Appendix H) provides a listings of case samples descriptive of deeply placed Norplant implants or migrated Norplant implants.

3.2 INTEGRATED SUMMARY OF MEDICATION ERROR RISK ASSESSMENT

At the March 21, 2013, Psychopharmacologic Drugs Advisory Committee meeting, the Division of Reproductive and Urologic Products provided a presentation on lessons learned from contraceptive implants including complications reported at removal from the literature and from a sampling of FAERS cases retrieved by DMEPA. Cases obtained from the FAERS database search support findings provided in the literature and help to characterize cases of deeply placed and/or migrated Norplant implants. Complications at Norplant implant removal describe difficulty in the removal being related to improper insertion technique. Norplant and Probughine have a similar dosage form, route of administration, and insertion and removal techniques. As experienced with Norplant implants, Probughine implants may be subject to implant expulsion prior to the end of the dosing period resulting in patient underdosing. Probughine implants may also be subject to the implant migrating further into the insertion site impeding the removal of the implant at the end of the dosing period resulting in a dose greater than the prescriber intended or a dosing period greater than the prescriber intended. Thus, we recommend that the training program implemented to train healthcare providers on Probughine insertion and removal be validated using principles of human factors and Failure Mode and Effects Analysis to capture findings that suggest program modifications which may prevent improper implant insertion techniques.

DMEPA provided comments on the proposed insert labeling for review division consideration during March 2013 insert labeling meetings. The proposed insert labeling contains numerous figures with corresponding text as step instructions for insertion and removal of Probughine implants in section 2.4 (Insertion of Probughine) and section 2.5 (Removal of Probughine). While it is important that this information be made accessible to healthcare providers responsible for insertion and removal of Probughine, the review team expressed concern that the location of the figures delayed access to other areas of the insert labeling and provided detailed instructions intended those formally trained in the insertion and removal of Probughine. DMEPA has a substantial amount of recommended changes to these figures and corresponding text (Section 5 Recommendations) but defers to the Study Endpoint and Labeling Development (SEALD) team and the division for the proper placement of these instructions to satisfy

Structured Product Labeling (SPL) requirements. The SEALD team suggested that since these figures exceed the size that satisfies the SPL requirements of each individual figure being less than 1 MB (no limit in the number of figures), the division may consider including all administration information and instructing the Applicant to revise the size of the figures to satisfy SPL requirements or to summarize the key elements of the Dosage and Administration instructions, develop a manufacturer's non-promotional website for these Physician instructions for use, and cross-reference the website address in the Dosage and Administration section of the approved insert labeling. If the latter option is chosen, then the Applicant should be advised that the Office of Prescription Drug Promotion has the authority to take enforcement action against any manufacturer website that is false or misleading.

The following summarize the insert labeling recommendations provided at insert labeling meeting:

- Delete redundant text in the Highlights of Prescribing Information section and Section 2 (Dosage and Administration)
- Consider aligning all figures to appear adjacent to the instructions to which they refer in Section 2 (Dosage and Administration) to improve readability of instructions.
- Consider revising figures to improve visibility of images

DMEPA reviewed the proposed pouch and applicator container labels, applicator and kit carton labeling, insert labeling, Patient chart label, and Patient identification card and comments are provided below (Section 5 Recommendations).

4 CONCLUSIONS

DMEPA concludes that the proposed pouch and applicator container labels, applicator and kit carton labeling, insert labeling, Patient chart label, and Patient identification card can be improved to increase the readability and prominence of important information on the label to promote the safe use of the product and to clarify information.

5 RECOMMENDATIONS

Comments to the Division

These insert labeling comments are based upon a review of the insert labeling for NDA 204442 submitted January, 2013. These comments were shared with the Review Team during the March, 2013 labeling meetings, and are reiterated here.

A. Instructions for use (Insert Labeling)

1. Consider deleting the first bullet under the Highlights of Prescribing Information Dosage and Administration section to highlight the dose of Probuphine. (b) (4)
2. Consider deleting the 5th bullet under Warnings and Precautions as it is redundant with the first bullet of this same section. (b) (4)

3. Consider moving section 2.2 (Dose Titration) and section 2.3 (Continuation of Therapy) to be placed after section 2.4 (Insertion of Probuphine) to follow the sequence of events in which they will occur.
4. Consider aligning all figures to appear adjacent to the instructions to which they refer in Section 2 (Dosage and Administration). This will improve readability of instructions and should allow there to be around 4 figures per page with pertinent instructions visible on the same page.
5. Consider deleting redundant figures that were used in section 2.4 (Insertion of Probuphine) and again for other sections and refer to the original figure in the text.
6. Consider adding a figure that depicts the suggested equipment laid out on the Mayo instrument stand. Align the figure to appear adjacent to the bulleted listing of equipment provided on page 5 for Section 2.4 (Insertion of Probuphine Four Implants), page 13 (Probuphine Implant Dose Increase: Fifth Implant Insertion), and page 19 (Probuphine Removal Procedure) of the insert labeling.
7. Consider revising images of the cannula and obturator in Figure 1 (the applicator and its parts) to increase the visibility of the cannula's bevel-up marking, proximal marking and distal marking, and the obturator's stop line.
8. Consider including a depiction of the patient's head in Figure 2 (for insertion of Probuphine 4 implants) and Figure 14 (for Probuphine implant dose increase: fifth implant insertion) since the patient's head is used as a reference point for the hand position.
9. Consider removing the last paragraph of the instructions in step 2 that refer to Figure 3 and reads "The implants should be inserted subdermally just under the skin to avoid large blood vessels..." as it is redundant with information already provided previously under Figure 1.
10. Consider combining steps 2, 3, and 4 (for insertion of Probuphine 4 implants) into a single step that refers to Figure 3 to provide concise information about the insertion site as follows: "Step 2. Identify the insertion site, which is at the inner side of the upper arm about 8-10 cm (3-4 inches) above the medial epicondyle of the humerus. Instructing the patient to flex the bicep muscle may facilitate the identification of the site. Clean the insertion site with alcohol pred pad then mark the insertion site using a sterile marker (Figure 3)."
11. Consider adding an early description of the size of the incision to the instructions for Figure 3 as follows: "The implants will be inserted through a small 2.5 to 3 mm subdermal incision." This will facilitate instructional flow for the next figure and set of instructions.
12. Consider revising the Step 5 (for insertion of Probuphine 4 implants) to include a description of the distance between the implants, the length of the marking for the channel tracks, the distance between the incision and

the implant once subdermally positioned, and the direction of the opening of the fan shaped lines to read as follows: “Using a sterile marker, mark the channel tracks where each implant will be inserted by drawing 4 lines with each line 4 cm in length. The implants will be positioned in a fan shaped distribution 4-6 mm apart with the fan opening towards the shoulder (Figure 4). The closer the implants lie to each other at the time of insertion, the more easily they can be removed.” Consider adding the statement “There should be at least 5 mm between the incision and the implant when the implant is properly positioned.” to instructions referring to figure 4.

13. Consider adding measure lines for the distance between the marked incision site and channel tracks, the distance between the implants, as well as the length of the marking for the channel tracks to Figure 4 (for insertion of Probuphine 4 implants).
14. Consider combining steps 7 (clean insertion site) and 8 (apply sterile drape) into one single step (for insertion of Probuphine 4 implants and for Probuphine implant dose increase: fifth implant insertion).
15. Describe the volume of Lidocaine 1% with epinephrine 1:100,000 in milliliters in step 9 (for insertion of Probuphine 4 implants and for Probuphine implant dose increase: fifth implant insertion) and in step 8 (for removal procedure). The metric volume cubic centimeter or “cc” is on the Institute for Safe Medication Practice’s List of Error-Prone Abbreviations, Symbols and Dose Designations for commonly being misinterpreted as “u” units.
16. Consider revising the sentence in step 10 (for insertion of Probuphine 4 implants and for Probuphine implant dose increase: fifth implant insertion) to provide the incision length and depth as follows: “After determining that anesthesia is adequate and effective, make a 2.5 to 3 mm in length shallow incision through the dermis.”
17. Consider identifying the position of the bevel up marking by revising the second sentence of step 11 (for insertion of Probuphine 4 implants and for Probuphine implant dose increase: fifth implant insertion) as follows: “While applying counter-traction to the skin, insert only the tip of the applicator at a slight angle (no greater than 20 degrees) into the subdermal space with the bevel up marking on the cannula facing upwards and visible and with the obturator locked fully into the cannula”.
18. The shaded area that designates the 20 degree angle in Figure 5 (for insertion of Probuphine 4 implants) and Figure 16 (for Probuphine implant dose increase: fifth implant insertion) may be mistaken for tented skin. Consider revising the shaded area by removing the dark lines and grey shade.
19. Consider designating the sentence that refers to Figure 6 (for insertion of Probuphine 4 implants) and Figure 17 (for Probuphine implant dose

increase: fifth implant insertion) - “Lower the applicator to a horizontal position, lift the skin up with the tip of the applicator but keep the cannula in the subdermal connective tissue.” as the next numerical step in sequence occurring after and separate from step 11 and placing it adjacent to Figure 6 (for insertion of Probuphine 4 implants) and Figure 17 (for Probuphine implant dose increase: fifth implant insertion).

20. Consider revising Figure 6 (for insertion of Probuphine 4 implants) to depict proper placement and angle of the applicator as the current figure does not clearly convey that the applicator is in a horizontal position with the skin lifted.
21. Consider designating the sentence that refers to Figure 7 (for insertion of Probuphine 4 implants) and Figure 17 (for Probuphine implant dose increase: fifth implant insertion) - “While tenting (lifting), gently advance the applicator subdermally along the channel marking on the skin until the proximal marking on the cannula just disappears into the incision.” as the next numerical step in sequence occurring after and separate from step 11 and placing it adjacent to Figure 7 (for insertion of Probuphine 4 implants) and Figure 17 (for Probuphine implant dose increase: fifth implant insertion).
22. The applicator in the subpicture of Figure 7 (for insertion of Probuphine 4 implants) and Figure 17 (for Probuphine implant dose increase: fifth implant insertion) appears to better convey the angle described in the instructions associated with these figures and appear to be at an angle different from that which is depicted in the main picture of these figures. Consider revising the main picture of these figures to depict the tented skin with advanced placement of the applicator’s proximal marking just beneath the incision.
23. Consider combining steps 12 and 13 (for insertion of Probuphine 4 implants and for Probuphine implant dose increase: fifth implant insertion) into a single step and designating these two sentences as instructions that refer to Figure 8 and Figure 18, respectively, as follows: “While holding the cannula in place, unlock the obturator and remove the obturator. Insert one implant into the cannula.” Make this the next numerical step in sequence and placing it adjacent to Figure 8 and Figure 18.
24. Consider beginning the next step in sequence with the remaining instructions from step 13 (for insertion of Probuphine 4 implants and for Probuphine implant dose increase: fifth implant insertion) - “re-insert the obturator, and gently push the obturator forward (mild resistance should be felt) until the obturator stop line is level with the bevel-up marking, which indicates the implant is positioned at the tip of the cannula. Do not force the implant beyond the end of the cannula with the obturator. There should be at least 5 mm between the incision and the implant when the implant is properly positioned.” and placing these instructions adjacent to

Figure 9 (for insertion of Probuphine 4 implants) and Figure 19 (for Probuphine implant dose increase: fifth implant insertion).

25. Consider revising Figure 10 (for insertion of Probuphine 4 implants) and Figure 20 (for Probuphine implant dose increase: fifth implant insertion) to depict the movement of the cannula by replacing the white arrow from above the obturator to a location above the cannula.
26. Clarify why pressure may need to be applied to the incision site for approximately 5 minutes in step 18 (for insertion of Probuphine 4 implants) and step 17 (for Probuphine implant dose increase: fifth implant insertion)
27. Clarify when and how long after the procedure and how often the patient should palpate the implants in the instructions in step 20 (for insertion of Probuphine 4 implants) and step 19 (for Probuphine implant dose increase: fifth implant insertion).
28. Consider combining steps 22 and 24 (for insertion of Probuphine 4 implants) as well as combining steps 21 and 23 (for Probuphine implant dose increase: fifth implant insertion) as both steps refer to the provision of instructions for the patient as follows: “Complete the PATIENT IDENTIFICATION CARD and give it to the patient to keep. Also, complete the PATIENT CHART LABEL and affix it to the patient medical record. Provide the patient with the Medication Guide and explain proper care of the insertion site. Instruct the patient to apply an ice pack on his/her arm for 40 minutes every two hours for first 24 hours and as needed.”
29. Consider revising step 2 (for Probuphine implant dose increase: fifth implant insertion) to provide the purpose of this step as follows: “Identify the insertion site by first locating four implants in the arm verified by palpation. If you cannot feel each of the four implants or are in doubt of their presence use other methods to confirm the presence of the implant. Suitable methods to locate are: Ultrasound with a high frequency linear array transducer (10 MHz or greater) or Magnetic Resonance Imaging (MRI). Please note that the PROBUPHINE implants are not radiopaque and cannot be seen by X-ray or CT scan. *If ultrasound and MRI fail call 1-800-XXXX.*”
30. Consider combining steps 3, 4, and 5 (for Probuphine implant dose increase: fifth implant insertion) into a single step that refers to Figure 15 to provide concise information about the insertion site and the channel track consistent with the training video transcript as follows: “Step 3. Clean the insertion site with alcohol prep pad then mark the insertion site using a sterile marker.” Consider adding the statement “The insertion site should be separate from the original incision. There should be at least 5 mm between the insertion incision and fifth implant.” to instructions referring to figure 15.

31. Consider adding an early description of the size of the incision to the instructions for Figure 15 (for Probuphine implant dose increase: fifth implant insertion) as follows: “The fifth implant will be inserted through a small 2.5 to 3 mm subdermal incision.”
32. Additionally for instructions pertaining to Figure 15 (for Probuphine implant dose increase: fifth implant insertion), consider including a description of the distance between the 4 implants and the fifth implant, the length of the marking for the fifth implant channel track, the distance between the incision and the implant once subdermally positioned, and the direction of the opening of the fan shaped lines to read as follows: “Using a sterile marker, mark the channel track where the fifth implant will be inserted by drawing one line approximately 4 cm in length and 4-6 mm adjacent and medial to the previously inserted four implants. The fifth implant will be positioned in the same fan shaped distribution with the fan opening towards the shoulder (Figure 15). The closer the implants lie to each other at the time of insertion, the more easily they can be removed.”
33. Consider deleting the sentence referring to Figure 15 (for Probuphine implant dose increase: fifth implant insertion) “The implant should be inserted subdermally just under the skin to avoid the large blood vessels and nerves that lie deeper in the subcutaneous tissues in the sulcus between the triceps and biceps muscles.” to reduce redundant language.
34. Consider adding measure lines for the distance between the marked incision site and channel tracks, the distance between the implants, as well as the length of the marking for the channel tracks to Figure 15 (for Probuphine implant dose increase: fifth implant insertion).
35. Consider combining steps 6 (clean insertion site) and 7 (apply sterile drape) into one single step (for removal procedure).
36. Consider designating the sentence that refers to Figure 25 (for removal procedure) - “Grasp the center of the implant with the X-plant clamp and apply gentle traction. Use the technique of spreading and closing with either the iris scissors or mosquito forceps to separate the fibrous tissue” as the next numerical step in sequence occurring after and separate from step 10 and placing it adjacent to Figure 25.
37. Figures 24 and 25 appear to be the same and use the same instrument. Consider deleting Figure 24 or revising it to depict the instructions to which it refers.

Comments to the Applicant

DMEPA provides the following recommendations to be implemented prior to approval of the NDA:

A. General Comments

1. Ensure that the strength statement appears directly below the established name on the principal display panel of all product labels and labeling to

consistently convey this critical information. For example:

Probuphine
(buprenorphine hydrochloride implant)
80 mg per implant

2. Relocate the scheduled drug designation (CIII) away from the established name. Ensure there is adequate white space between the established name and the CIII designation so that the CIII designation does not interfere with the readability of the established name.
3. If the model of care for this product ultimately changes to one where the patient may in fact handle this product at any portion of the use system, add the statement “Keep out of reach of children” on the container labels and carton labeling.

B. Pouch Container Label

1. Revise the contents statement to read “Contents: One implant containing 80 mg buprenorphine”
2. Add a statement that reads “Sterile unless pouch is damaged or opened” so that practitioners understand that the pouches ensure the sterility of each individual rod.
3. Add a route of administration statement that reads “For Subdermal Administration Only”. Ensure the route of administration statement appears below the strength statement, “80 mg per implant” and before the “Contents” statement.
4. Relocate the “Rx only” statement to the bottom portion of the label away from the proprietary name, established name and strength statement.

C. Kit Carton Labeling (Implant Kit (b) (4))

1. On the principal display panel, list the contents as follows:

Contents:

Four Probuphine implants, 80 mg per implant

One applicator

Prescribing information

Medication guide
2. Back Panel:
 - i. Add a statement that reads “Active ingredients: 80 mg buprenorphine per implant”
 - ii. Add a statement that lists all inactive ingredients
 - iii. Add the Dosage and Administration statement that reads: “A single use, sterile and disposable applicator is provided. Do not use if the package has been opened, or if the sterile barrier has been

otherwise compromised. Please refer to package insert for complete product information. Insert Probuphine no later than the date printed on the Probuphine pouch container label.”

- iv. Add a statement that reads: “For the Healthcare Provider: All health care providers who insert and/or remove Probuphine must receive instruction and training and, where appropriate, supervision prior to inserting or removing Probuphine.

D. Applicator Container Label and Carton Labeling

1. Revise the presentation of the information to highlight the applicator device. The title of “applicator” should have equal or greater prominence to the proprietary name. Revise the statement of identity to appear similar to “Applicator for Probuphine (buprenorphine hydrochloride implant)”

(b) (4)

E. Patient Chart Label

1. We note the Patient Chart Label is not listed in the contents section of the Implant Kit labeling (b) (4) Please provide an explanation how the Patient Chart Label will be provided to the physician.

F. Patient Identification Card

1. We note the Patient Identification Card is not listed in the contents section of the Implant Kit labeling (b) (4) Please provide an explanation how the Patient Identification Card will be provided to the physician and patient.

If you have further questions or need clarifications, please contact Mark Liberatore, project manager, at 301-796-2221.

APPENDICES

APPENDIX A. DATABASE DESCRIPTIONS

FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FDA implemented FAERS on September 10, 2012, and migrated all the data from the previous reporting system (AERS) to FAERS. Differences may exist when comparing case counts in AERS and FAERS. FDA validated and recoded product information as the AERS reports were migrated to FAERS. In addition, FDA implemented new search functionality based on the date FDA initially received the case to more accurately portray the follow up cases that have multiple receive dates.

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

9 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

APPENDIX H: CASE NUMBERS DISCUSSED IN THIS REVIEW

FAERS Case #	ISR Number(s)	Version Number	Narrative
3431147	3455077	1	Norplant inserted for 3 years (b) (6) (b) (6) Norplant implants were removed with some difficulty as evidenced by unusually deep placement (difficult palpation), extensive scar tissue with one implant partially fixed to the bicep muscle at the most superior pole of the implant, and need for extension of incision which required seven 4-0 Prolene sutures for closure
5223794	1568586	1	Four implants were previously removed. X-ray examination of left arm located 5th implant in soft tissue and removed under intravenous sedation. Sixth implant visualized near axilla via X-ray but could not be palpated for removal. Patient referred to orthopedic surgeon.
5224754	1569593	1	Norplant system inserted in left arm approximately two years...had two unsuccessful removal procedures with a total of four implants retrieved...[and] the remaining two implants were close to the bone and patient to require surgery under general anesthesia [for removal]. Patient was referred to a surgeon by clinic physician.
5359130	1708955	1	Norplant in place for eighteen months, experienced arm discomfort when one implant migrated causing a lump in arm. Five implants were successfully removed, however, the sixth implant had migrated to the antecubital fossa (adjacent to the antecubital vein) and required removal by a surgeon because of increased vascularity. Patient tolerated the procedure and there were no complications.
5552622	1908305	1	Four implants removed (b) (6) during 25-30 minute procedure; remaining 2 implants located via x-ray and were reported to be deep within the bicep muscle and to remain in place indefinitely

FAERS Case #	ISR Number(s)	Version Number	Narrative
3150359	1	2/6/1998	Patient experienced movement of implant close to surface of skin and appeared as if they might expel after nearly 2 years of Norplant system use. Patient to have Norplant system checked by physician.
3432327	1	2/9/2000	Therapy with Norplant system first set began (b) (6) and ceased on (b) (6) [for 7 years] with second set or six implants inserted the same day. Two implants expelled on (b) (6) [3 days later]. The remaining implants from second set were removed (b) (6)
3174367	3120188	1	Complaint of left arm pain and numbness including fingers following second set of Norplant implant inserted (b) (6) in downward fan pattern below original incision; migration of implants occurred and 2 implants crossed or touched at one point; shallow insertion of third implant, physician expecting implant was touching ulnar nerve. Implants were removed and third set was inserted.
3447569	3454813	1	Patient had Norplant system inserted in (b) (6) and removed in (b) (6) due to menometrorrhagia. One implant was broken and a fragment of that implant remained implanted. Within a few weeks of removal attempt the patient reported difficulty lifting arm due to arm pain.
3804155	3869531	1	Therapy with the Norplant system began in (b) (6) and ceased on (b) (6) with one implant removed. The dose regimen included six. No further outcome was reported.

FAERS Case #	ISR Number(s)	Version Number	Narrative
5210595	1554923	1	Patient had Norplant system in for approximately 10 months was diagnosed pregnant. The first attempt at removal used a cross cut incision and took 3 hours to remove 3 implants. The following day the patient went to an outpatient surgical room for a second procedure which lasted two hours and one additional capsule was removed. Two capsules could not be located and remain in place. The patient had approximately 13 stitches in the arm with resultant severe scarring.
5218282	1562870	1	The patient previously had the Norplant system removed and reinserted in her left arm through the same incision (at the patients request for cosmetic reasons). The patient requested to have it removed. She experienced six unsuccessful removal procedures. The first attempt was unsuccessful and lasted three hours. The second attempt required three incisions and X-ray and removed one implant. Four additional attempts were made and resulted in second implant removed. The patient was subsequently referred to a plastic surgeon and hospitalized. The final removal procedure was performed under general anesthesia and lasted approximately 65 minutes. The remaining four implants were removed with the fifth and sixth located and removed from muscle.
5225984	1570876	1	Approximately 3 weeks after Norplant system insertion, the patient experienced implant migration with pain/irritation at the insertion site. Symptoms have resolved.
5359124	1708949	1	Approximately one month after insertion the patient developed a rash which resolved with topical medication. Unsuccessful implant removal procedure occurred. Approximately two and a half years after insertion the patient reportedly noted a two inch implant migration.

FAERS Case #	ISR Number(s)	Version Number	Narrative
5372397	1722505	1	First removal attempt (b) (6) two implants were removed. Second removal attempt (b) (6) three implants removed. Third removal attempt (b) (6) and fourth removal attempt (b) (6) (u) (d) unsuccessful. Fifth removal attempt (b) (6) CT scan showed a foreign body on medial surface of humerus. Excision biopsy of [implant] found it directed towards tricep muscle deep in fat of left arm. On (b) (6) the patient was hospitalized for excisional debridement of left arm with diagnoses of cellulitis of left upper extremity.
5549133	1904715	1	Removal of Norplant System on (b) (6) (b) (6) 2 implants fractured; one-2 mm implant fragment remains in patients arm; patient opted not to attempt repeat removal of fragment
5223208	1567988	1	Patient had Norplant system removed after six months (reason unspecified). Only one implant was retrieved and five remain in place. The report (nurse practitioner) noted the remaining implants are difficult to remove.

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/s/

BRENDA V BORDERS-HEMPHILL
04/25/2013

JAMIE C WILKINS PARKER
04/26/2013

SCOTT M DALLAS
04/26/2013

**DEPARTMENT OF HEALTH AND HUMAN SERVICES****M E M O R A N D U M**

Food and Drug Administration
Center for Devices and
Radiological Health
Office of Device Evaluation
White Oak Building 66
10903 New Hampshire Avenue
Silver Spring, MD 20993

Date: April 5, 2012

From: Jacqueline Ryan, Combination Products Team Leader, WO66, RM 1257
General Hospital Devices Branch, DAGID, ODE, CDRH

To: Lisa Basham, Senior RPM, OMPT/CDER/OND/ODEII/DAAAP

Subject: CDRH Consult, NDA 204442, Trochar to deliver Probuphine implants

1. Issue

The Center for Drug Evaluation and Research (CDER) has requested a consult from the Center for Devices and Radiological Health (CDRH), regarding NDA 20442. The device constituent of this combination product consists of a Trochar to deliver Probuphine implants.

2. Drug Background

Probuphine® (buprenorphine implant) drug product is a subdermal implant containing 80 mg buprenorphine hydrochloride USP (BPN) in an ethylene vinyl acetate copolymer (EVA) matrix. Each implant measures 26 mm in length and 2.5 mm in diameter. The total weight of each implant is 112 mg. Implants are individually packaged in laminated foil pouches. The pouches are terminally sterilized using gamma irradiation. Probuphine is indicated for maintenance treatment of opioid dependence and should be used as part of a complete treatment program to include counseling and psychosocial support. Probuphine is a long-acting (up to 6 months) treatment for opioid dependence. Four implants are administered subdermally in the inner side of the patient's upper arm. Patients may receive a fifth implant, if an increased dose is required. Probuphine must be removed by the end of the sixth month and may be replaced by new implants, in the opposite arm, at the time of removal, if continued treatment is desired. The matrix formulation of the implants results in a steady-state delivery of BPN that maintains a stable plasma level of the drug for 6 months.

3. Device Description

Probuphine® in the subdermal space of the body, by trained healthcare providers. Probuphine (buprenorphine hydrochloride/ethylene vinyl acetate) is an implantable formulation of buprenorphine hydrochloride developed for up to 6 months of maintenance treatment of opioid dependence. Probuphine must be removed by the end of the sixth month and may be replaced with new implants at the time of removal, if continued treatment is desired.

The Applicator is comprised of three (3) main components which are detailed below:

1. Cannula Needle: Thin walled piercing needle, made of medical grade 304 stainless steel with a smooth inner surface, 10 gauge internal diameter and 60 mm length, in order to allow the passage of Probuphine (2.5 mm + 2.5 mm diameter) without impediment. The needle has two depth orientation markers are 60 mm \pm 0.79 mm from the hub on the Cannula and 40 mm \pm 0.79 mm from tip of Cannula.

2. Insertable Stylet Rod: Medical grade 304 stainless steel rod (Obturator) used to advance the Probuphine implants to the proper subdermal position. The Stylet wire has a diameter of 0.110 in (2.79 mm), and a length of 3.5 mm \pm 0.79 mm with a blunt tip that can be easily inserted into the Cannula without catching or obstruction. The fit between the stylet wire and the cannula ensures that Probuphine will not remain in the barrel of the cannula if the stylet is inserted to the stop marker. There is a stop marker line 26 mm \pm 0.79 mm from the hub on the Stylet.

3. Cover (Needle Guard): The Needle Guard for the Applicator consisting of an LDPE sleeve which covers the entire Cannula from the hub to the tip. The Needle Guard protects the Applicator tip during transport and handling and as a safety measure during user handling (removal of the Applicator from packaging).

The components of the Applicator are shown in (excluding the Cover). The Cannula and Stylet have interlocking hubs (referred to as Swivel Nuts) manufactured from biocompatible polymeric materials. The Applicator design includes guide and orientation marker visual aids to assist healthcare providers with the proper placement of the Probuphine implants. These markers include orientation markings on both the Cannula and Stylet to facilitate the proper depth of implant placement, and a foil stamp marking on the hub of the Cannula showing the correct "bevel up" position for the cannula which facilitates the correct subdermal insertion of Probuphine.

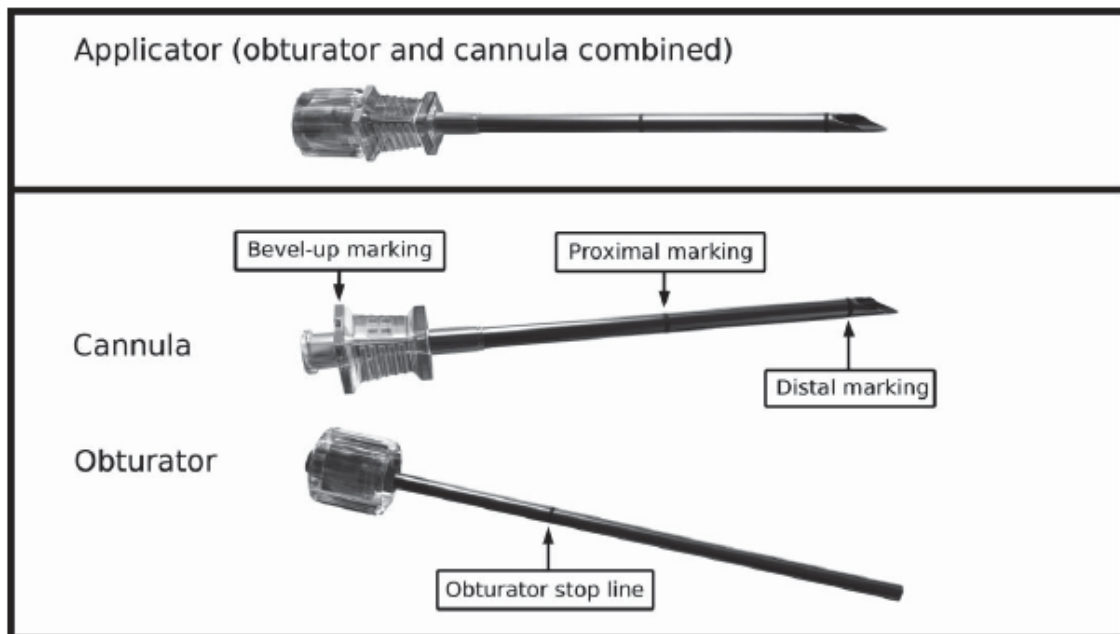


Figure 1: Probuphine Applicator Components

The insertion procedure involves a brief in-office procedure under local anesthetic and aseptic technique. Using the Probuphine Applicator, four Probuphine implants are inserted subdermally in the upper arm in patients who have been initially inducted using sublingual buprenorphine tablets.

During insertion, the Cannula of the Applicator is subdermally inserted through a small incision in the inner side of the non-dominant upper arm, to the 40 mm mark (see Figure 2). A sterile Probuphine implant is inserted into the Cannula and the Stylet is used to advance the implant to the correct position under the skin. The Cannula is withdrawn to the 60 mm mark to allow insertion of the next implant. This process is repeated until the 4 Probuphine implants are inserted at which time the Cannula is removed.

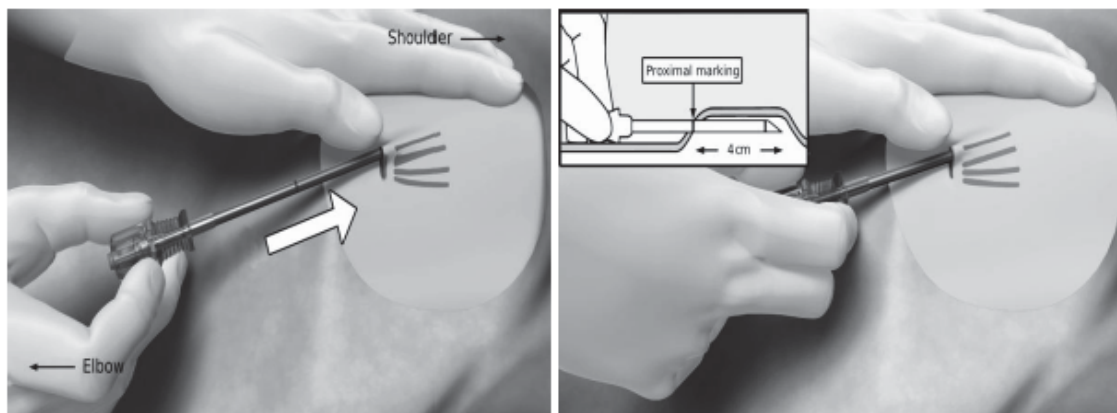


Figure 2: Applicator Insertion

4. CDRH Review

CDRH's Review of the device constituent for this Combination Product consisted of a review of Device Performance, Biocompatibility, and Sterility

Performance

Stylet dimensional and pull testing is conducted to verify that the Stylet component design meets visual, dimensional and pull strength requirements per ISO 11070 - Sterile Single-use Intravascular Catheter Introducers, Section 5.4.2 (Strength of Union of Needle Tube and Needle Hub) for the Probuphine Applicator's intended use.

Cannula dimensional, pull and leakage testing is conducted to verify that the Cannula component design meets visual, dimensional and pull strength requirements per ISO 11070 - Sterile Single use Intravascular Catheter Introducers, Section 5.4.2 (Strength of Union of Needle Tube and Needle Hub), and leakage requirements per ISO 594-1 Section 4.2 (Liquid Leakage) requirements when test method process is performed according to ISO 594-2 Section 5.2 (Liquid leakage from fitting assembly under pressure) for the Probuphine Applicator's intended use.

Swivel nut/hub bench test is conducted to verify that the Swivel Nut/Hub component design (without Stylet or Cannula) meets visual specifications for the Probuphine Applicator's intended use.

The Probuphine Applicator bench test is conducted to verify that the fully assembled Probuphine Applicator meets the requirements of ISO 594-Conical Fitting with a 6% (Luer) Taper for Syringes, Needles and Certain Other Medical Equipment Part 1: General Requirements, for its intended use. The acceptance criteria for the testing and test results for manufactured Lot #D3K3.#D05L were provided and all devices met criteria .

Section 2.6.2, Clinical Summary Probuphine Applicator provides confirmation of the Applicator's performance in real-use including:

- Obturator Compatibility
- Insertion & Cannula Stability
- Insertion testing
- Applicator Handle Strength Testing
- Torque and Tensile Strength Testing
- Delivery Testing
- Implant Removal Force Testing

Reviewer's comment:

The test matrix was complete and comprehensive for the potential failure modes of the device. Test methods and acceptance criteria were clearly stated and described and all devices met acceptance criteria

Biocompatibility

The component materials and their route of contact with the patient were provided and testes using a risk management approach according to ISO 10993-1. .

Further, (b) (4) conducted biocompatibility testing on a procedural needle made of the same materials as the Probuphine Applicator (304 Stainless Steel, electrochemical markings (b) (4)) in 2005. Sterilization Validation.

Reviewer's comment:

The materials of construction as well as markings are identical to the reference device. Sterilized, tested devices met acceptance criteria for Cytotoxicity, Sensitization, and Intracutaneous reactivity according to ISO 10993..

Sterility

The Probuphine Applicator is packaged in a (b) (4) pouch (b) (4) (b) (4)

(b) (4)

(b) (4) Due to historical longevity of the pouch materials and the durability of Applicator materials, it is anticipated that the device, when kitted with the Probuphine drug product is expected to meet a shelf life (b) (4)

Packaging Tensile Test TM-009

Packaging tensile test TM-009 is conducted to verify that Probuphine Applicator primary packaging (b) (4) meets the required tensile strength. Table 5 in the submission presents the acceptance criteria for the testing and test results for manufactured Lot D40T.

Ship Test of Final Package design

Packaging tests will be performed according to ASTM standards to ensure the product and package creates a complete system where the device and the drug will perform efficiently, safely, and effectively in the hands of the user. The final package will accommodate the Probuphine drug product, and an Applicator. (b) (4)

(b) (4) This package configuration will be validated to provide assurance that there is no damage to the Applicator pouch that might compromise the sterility of the device. The testing will include exposure to environmental conditions to confirm the ability of the package to sustain the product through variations in temperature and humidity and potential for rough handling (or normal shipping and distribution). The test protocol can include several of the following: ASTM D4169: Standard Test Method for Testing of Shipping Containers and Systems, ASTM F1886-Visual Inspection Test, ASTM F88-Peel Strength Test, ASTM F1140-Burst Test, ASTM F1929-Dye Penetration Test, ASTM F2096 – Bubble Emission Test, ASTM D-5264-98 (2004)- Label Abrasion Test or others.

Reviewer's comments:

Sterilization has been validated for the final package conformation with acceptable (b) (4) per ISO (b) (4) Package integrity has been tested according to ASTM D4169: Standard Test Method for Testing of Shipping Containers and Systems, ASTM F1886-Visual Inspection Test, ASTM F88-Peel Strength Test, ASTM F1140-Burst Test, ASTM F1929-Dye Penetration Test, ASTM F2096 – Bubble Emission Test, ASTM D-5264-98 (2004)- Label Abrasion Test All devices met acceptance criteria.

Safety

Safety of the Applicator is demonstrated by an overall low incidence of events and minimal clinical consequences from the insertion procedure. Out of 317 procedures performed with the Probuphine Applicator, there were 60 (18.9%)

Adverse Events determined to be related or possibly related to the insertion procedure where the Probuphine Applicator is utilized. The most often occurring events associated with the insertion procedures were hematoma (15/60, 25%), implant site pain (10/60, 16.7%), hemorrhage (7/60, 11.7%) and pruritis (7/60, 11.7%).

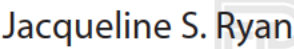

Reviewer's comments:

Clinical safety data were reviewed and deemed acceptable to CDRH, but CDRH will defer to CDER regarding the clinical safety data. Training and instructions for use were reviewed by CDR Human Factors Team.

5. CDRH Comments

Based on our review, the performance data supplied is adequate to support approval of the NDA from a device evaluation perspective. The sponsor has submitted the necessary data to evaluate the insertion device for safety and efficacy when inserted by individuals with the requisite training and skills.

If you have any questions, please contact Jacqueline Ryan at 301-796-9599.

Digital Signature Concurrence Table	
Reviewer Sign-Off	<div> Digitally signed by Jacqueline S. Ryan DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000570293, cn=Jacqueline S. Ryan Date: 2013.04.16 14:56:26 -04'00'</div>
Branch Chief Sign-Off	<div> Richard C. Chapman 2013.04.17 10:32:36 -04'00'</div>

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

/s/

LISA E BASHAM

04/17/2013

entered into DARRTS for Jacqueline Ryan, M.D.-CDRH review of applicator for Probuphine NDA
204442

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: April 15, 2013

TO: Rachel Skeete, M.D., Clinical Reviewer
Celia Winchell, M.D., Clinical Team Leader
Lisa Basham, Senior Regulatory Project Manager
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)

FROM: Cynthia F. Kleppinger, M.D.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH: Janice Pohlman, M.D., M.P.H.
Team Leader
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

Susan D. Thompson, M.D.
Acting Branch Chief
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 204442

APPLICANT: Titan Pharmaceuticals

DRUG: Buprenorphine HCl/ethyl vinyl acetate (Probuphine)

NME: No

THERAPEUTIC CLASSIFICATION: Priority Review

INDICATIONS: Treatment of opioid dependence

CONSULTATION REQUEST DATE: December 14, 2012

CLINICAL INSPECTION SUMMARY GOAL DATE: April 10, 2013

DIVISION ACTION GOAL DATE: April 30, 2013

PDUFA DATE: April 30, 2013

I. BACKGROUND

Titan Pharmaceuticals is seeking approval of Probuphine (buprenorphine hydrochloride/ethylene vinyl acetate) for treatment of opioid dependence. Probuphine is an implantable formulation of buprenorphine hydrochloride (BPN) inserted subdermally into the inner side of the subject's upper arm (or an alternate location if deemed medically necessary by the implanting clinician) designed to provide sustained release of BPN for 6 months. The application is based on the results of two multicenter, randomized, double-blind, placebo-controlled Phase 3 trials:

- PRO-805: A Randomized, Double-Blind, Placebo-Controlled, Multi-Center Study of Probuphine in Patients with Opioid Dependence
- PRO-806: A Randomized, Placebo and Active-Controlled, Multi-Center Study of Probuphine in Patients with Opioid Dependence

PRO-805 initiation date was April 2, 2007; completion date was June 19, 2008. The study involved 18 U.S. sites (plus 4 sites that did not randomize a subject). 163 subjects were randomized; 88 subjects completed the study. The protocol-defined study period was 24 weeks. Following the randomization visit, there were approximately 88 scheduled visits: 16 study visits and 72 urine collection visits.

The primary objective was to determine the efficacy of Probuphine versus placebo in the treatment of subjects with opioid dependence over 16 weeks of treatment. The primary efficacy endpoint was assessed by examining urine toxicology results for illicit opioids. Specimens were sent to a central lab (b) (4). The primary efficacy variable was the cumulative distribution function (CDF) of the percent of urine samples that were negative for illicit opioids for Weeks 1-16.

Only subjects who successfully underwent induction with sublingual (SL) BPN and reached a target dose of 12-16 mg/day for at least 3 consecutive days immediately prior to randomization and within 10 days of the start of induction were eligible for randomization to treatment. Subjects who underwent induction with SL BPN to a dose < 12 mg/day or > 16 mg/day were not eligible. Of note, missed visits/samples were considered positive, and after a subject was withdrawn from study, their urine samples from that point onward were considered positive.

Study data were entered on electronic case report forms (eCRFs) through the electronic data capture (EDC) system. The contract research organization (CRO) (b) (4) performed data management and monitoring. The decision was made not to inspect this CRO for this application as it had undergone satisfactory inspection two months earlier for another application.

PRO-806 initiation date was April 22, 2010; completion date May 12, 2011. The study involved 20 U.S. sites. There were 301 subjects randomized; 287 subjects received at least one dose of study drug; 163 subjects completed the study. The protocol-defined study period was 24 weeks. Following the randomization visit, subjects in the implant groups (A and B) were seen for a total of approximately 77 visits: 18 study visits and 59 unique thrice-weekly urine collection visits. Subjects in the Suboxone® (buprenorphine) sublingual tablets (SL BPN) group (Group C) were seen for a total of approximately 76 visits: 17 study visits and 59 unique thrice-weekly urine collection visits.

The primary objective was to confirm the efficacy of Probuphine versus placebo in adult subjects with DSM-IVTR defined opioid dependence, over weeks 1–24 of outpatient treatment, through the assessment of thrice-weekly urine toxicology results. The primary efficacy endpoint was assessed by examining urine toxicity results for illicit opioids without and with imputation of positive values based on subject self-reported data in the Probuphine and placebo groups from Weeks 1 through 24.

Only subjects who successfully underwent induction with SL BPN and reached a target dose of 12-16 mg/day for at least 3 consecutive days immediately prior to randomization and within 16 days of the start of induction were eligible for randomization to treatment. Of note, missed visits/samples were considered positive, and after a subject was withdrawn from study, their urine samples from that point onward were considered positive.

Study data were entered on electronic case report forms (eCRFs) through the electronic data capture (EDC) system. The CRO, (b) (4), supplied IVRS randomization, data management, and monitoring.

A data safety monitoring board (DSMB) was established for both studies to safeguard the interests and safety of study participants.

These inspections were conducted as part of the routine PDUFA pre-approval clinical investigation data validation in support of NDA 204442 in accordance with Compliance Program 7348.811. General instructions were also provided with the assignment.

II. RESULTS (by Site):

Name of CI/ Site #, for Studies 805 and 806, respectively	Protocol # and # of Subjects Randomized	Inspection Dates	Final Classification
Scott D. Segal, MD Sites 17 & 31	PRO-805 Enrolled 15 PRO-806 Enrolled 19	January 14-18, 2013	Pending Preliminary classification VAI
David H. Flaherty, DO Sites 6 & 32	PRO-805 Enrolled 10	March 19-April 1, 2013	Pending Preliminary classification NAI

	PRO-806 Enrolled 16		
Amit Vijapura, MD Sites 26 & 20	PRO-805 Enrolled 12 PRO-806 Enrolled 17	February 13, February 19-21, 25, 26, 28, March 1 & 6, 2013	Pending Preliminary classification NAI
Ashwin Patkar, MD Sites 11 & 13	PRO-805 Enrolled 11 PRO-806 Enrolled 21	February 4- March 1, 2013	Pending Preliminary classification VAI
Jorg J. Pahl, MD Site 25	PRO-805 Enrolled 13	March 26-April 4, 2013	Pending Preliminary classification VAI
Kyle M. Kampman, MD Sites 19 and 9	PRO-805 Enrolled 18 PRO-806 Enrolled 17	February 5-21, 2013	Pending Preliminary classification NAI
Sponsor: Titan Pharmaceuticals	PRO-805 sites reviewed <ul style="list-style-type: none"> • Segal Site 31 • Flaherty Site 32 • Vijapura Site 26 • Patkar Site 11 • Pahl Site 25 • Kampman Site 19 PRO-806 sites reviewed <ul style="list-style-type: none"> • Segal Site 17 • Flaherty Site 6 • Vijapura Site 20 • Patkar Site 13 • Kampman Site 9 	February 21- March 01, 2013	Pending Preliminary classification NAI

Key to Classifications

NAI = No deviation from regulations

VAI = Deviation(s) from regulations

OAI = Significant deviations from regulations; data unreliable.

Pending = Preliminary classification based on information in 483, preliminary communication with the field, and/or review of EIR; final classification is pending.

1. Scott D. Segal, MD

Scientific Clinical Research, Inc.

1065 Northeast 125th Street, Suite 417

North Miami, FL 33161

- a. What was inspected:** The subjects' records consisted of an e-case report file and a study source document chart. The inspection covered, but was not limited

to, the review of all signed informed consent forms on file and screened/enrolled subjects' study records for PRO-805 and PRO-806, IRB/Sponsor generated correspondence, drug accountability records, collection of urine toxicological samples, and corresponding laboratory testing results related to the primary endpoint of the audited studies. Also reviewed was documentation on file pertaining to the site's participating clinicians' credentials and corresponding training received by the site's staff related to their assigned areas of responsibility. Per protocol requirement, the site was to remain blinded to the urine toxicological results. Upon request, the central lab provided the ORA field investigators with a CD-ROM containing the referenced urine testing results pertaining to Dr. Segal's site.

ORA field investigators addressed specific concerns related to the procedures followed at the site to ensure the staff performing the required study assessments were maintained blinded with respect to the drug treatment allocated to the participating subjects. They also addressed activities performed by sub-investigator Dr. Steven Chavoustie during the period of time when he acted as the Sponsor's Implant Medical Monitor for study PRO-806.

Upon completion of the studies, the Sponsor provided the site with a DVD containing copies of the e-case report forms completed for each of the participating subjects.

- b. General observations/commentary:** This site has been involved in over 100 INDs with no prior inspection history. (b) (4)
(b) (4) with many co-investigators/sub-investigators and is one of eight operating clinical trial sites pertaining to Segal Institute for Clinical Research, a subsidiary of Compass Health Systems. Dr. Segal is listed as the founder/president of both.

The Sponsor's Implant Medical Monitor for Study 806 was Steven Chavoustie, M.D.. He was located at the same site (Segal Institute) as the site PI Scott Segal, M.D.. (The appointed Implant Medical Monitor for PRO-805 was (b) (4)). Dr. Chavoustie was not listed on the Delegation of Authority Log, but received training and agreed to maintain the blind and perform the implant procedures on enrolled subjects. He was also designated as the training monitor at Segal Research Institute and trained other implant physicians on performing the implant insertion and removal procedures. Documentation on file revealed that he received at least 100 prototype implants and 3 applicators for a training session he was to conduct.

During Dr. Chavoustie's tenure as the Sponsor Implant Medical Monitor, he reported having held periodic conference calls with the other participating sites' implant physicians to discuss and provide resolution of implant issues and concerns. He also reviewed adverse events reported by participating sites related to the implantations and removals.

Dr. Chavoustie conducts studies under Fidelity Clinical Research, Inc (b) (4)

He confirmed by interview that he was the un-blinded staff member who performed all implant insertions and removals at both Dr. Segal's and Dr. Flaherty's trial sites. Dr. Chavoustie reported that the implantation and removal procedures were conducted at his private practice located on the second floor in the same building where Dr. Segal's research site is located. Subjects' records on file indicated that this was the only activity in which he was involved concerning the PRO-805 study.

Based on interviews held with Dr. Chavoustie and review of study records on file at the site, there were no apparent instances in which the study blind could have been compromised. The site maintained the confirmation randomization notifications obtained from the Interactive Voice Response System (IVRS) and it was confirmed that the correct allocated drug treatment was provided to each of the participating subjects.

For PRO-805, 24 subjects were screened, 15 randomized, and 10 completed the study. In general terms, the subjects' records were observed to be properly organized and legible. There were no translated documents and only English speaking subjects were allowed to enroll.

The following subjects were ordered to receive a fifth implant (Implant Dose Increase) as allowed by the protocol: (b) (6)
(b) (6) Subject (b) (6) refused to have the fifth implant ordered by Dr. Segal and withdrew his consent. The site maintained accountability logs for all study drugs and no issues or discrepancies were disclosed during the inspection.

One subject experienced a Serious Adverse Event (b) (6). The subject did not return for follow-up and had been incarcerated for possession of heroin and was later hospitalized for respiratory failure due to pneumonia. The subject did not return to have his implant removed. There was one AE not reported during the review of subject files. Subject (b) (6) reported (b) (6) pain at the surgical site. This event was not documented on the log and/or e-CRF.

For PRO-806, the site did not maintain a Master Patient Log as required by the Manual of Procedures. An electronically-generated screening and enrollment log generated by the CRO, (b) (4) were presented upon request. Twenty-six subjects were screened, 19 randomized, and 13 completed the study. In general terms, the subjects' records were observed to be properly organized and legible. There were English and Spanish translations of informed consents.

The site disclosed during the initial IRB site submission on 1/19/10 that there were no financial interests held greater than those identified in the submission document. (b) (4)

(b) (4) The site failed to disclose this on the subsequent Study Status Reports dated 9/8/10, 1/11/11, and 6/21/11.

The site maintained accountability logs for all study drugs and no issues or discrepancies were disclosed during the inspection. Although there were some broken implants in PRO-805, there were no reported broken implants at this site for PRO-806.

Review of subject source documents revealed all subjects that were eventually randomized underwent successful induction with SL BPN, reaching a fixed dose of 12-16 mg/day for at least 3 consecutive days immediately prior to randomization. The review did not reveal any instances wherein any subject randomized to Group A or B treatment arms received an implant dose increase.

As per the protocol Section 10.4.1, all missing urine toxicological results found in the subject records were reported as positive by the central laboratory.

Subject (b) (6) was withdrawn secondary to missing 9 consecutive urine samples. Per exclusion criterion #7, this subject was taking Atripla (emtricitabine/tenofovir/efavirenz), which was an exclusionary medication, and the subject should not have been enrolled. The PI reported that the Sponsor Medical Monitor had granted a waiver, although this was not documented.

At the conclusion of the inspection, a Form FDA 483 was issued for the following:

1. Updated financial information was not provided to the study Sponsor when relevant changes occurred during the course of the investigation. Specifically,

The Financial Disclosure Forms on file submitted by the PI and sub-investigator were not updated to reflect financial compensation received for providing consulting services by Dr. S.E.C. to serve as the Implant Monitor (b) (4)

In a formal response to the inspectional observation, Dr. Segal and Dr. Chavoustie provided Titan with updated Financial Disclosure Forms for all payments received for PRO-805, PRO-806, PRO-807, PRO-810 and PRO-811. Titan subsequently submitted to FDA Forms 3455 for each of the applicable Probuphine studies disclosing these payments for both Dr. Segal and Dr. Chavoustie to NDA 204442. Titan also confirmed that Dr. Chavoustie was not involved with any safety or efficacy assessments.

(b) (4)

(b) (4)

Titan is implementing processes to ensure that, in the future, disclosures will be submitted in accordance with applicable regulations. Furthermore, Dr. Segal stated that a written Standard Operating Procedure will be developed to ensure such payments are documented and reported to the study Sponsor; it will be implemented by September 2013, and all applicable staff will be trained on the new policy.

OSI Reviewer comment: Response is adequate.

2. Record Keeping and Retention. Specifically, The Study Master Patient Log was not available for review during the inspection.

In a formal response to the inspectional observation, Dr. Segal stated that he was under the impression from the CRO (b) (4) that the Patient Log would be generated through the IWRS system for placement in the Site Trial Master Files for PRO-806. In the future, he will utilize an internal patient log when the Sponsor does not provide one and/or the Sponsor requested them to be electronic.

OSI Reviewer comment: Response is adequate.

- c. **Assessment of data integrity:** The full Establishment Inspection Report (EIR) was submitted for review. Although regulatory violations were noted as described above, they are unlikely to significantly impact primary safety and efficacy analyses. Data from this site appear acceptable.

2. David H. Flaherty, DO

Behavioral Clinical Research
1065 NE 125th Street, Suite 221
North Miami, FL 33161

- a. **What was inspected:** The subjects' records consisted of an e-case report file and a study source document chart. The inspection covered but was not limited to the review of all signed informed consent forms on file and screened/enrolled subjects' study records for PRO-805 and PRO-806. One signed informed consent form was temporarily missing and found in another folder where all the consents had been filed. Also inspected were the IRB/Sponsor correspondence files, drug accountability records, collection of urine toxicological samples, and

corresponding laboratory testing results related to the primary endpoint of the audited studies. Per protocol requirement, the site was to remain blinded to the urine toxicological results. Upon request, the central lab provided the ORA field investigators with a CD-ROM containing the referenced urine testing results pertaining to Dr. Flaherty's site.

- b. General observations/commentary:** The PI has been involved with multiple INDs at multiple sites with no previous inspection history. The site is part of an SMO-type setting listing many co-investigators/sub-investigators. Most of the items found during the earlier inspection of Dr. Segal's site were corrected before the inspection began for Dr. Flaherty's site.

For PRO-805, 18 subjects were screened, 10 subjects were randomized, and 5 subjects completed the study. All subject records were reviewed. There was no evidence of under-reporting of adverse events and the primary efficacy endpoint data was verifiable. The site maintained accountability logs for all study drugs and no issues or discrepancies were disclosed during the inspection. However, one of the subject's drug pharmacy logs was not contemporaneous; the dates were not in sequence and it was difficult to review.

For PRO-806, 35 subjects were screened, 16 subjects were randomized, and 7 subjects completed the study. All subject records were reviewed. There was no evidence of under-reporting of adverse events and the primary efficacy endpoint data was verifiable. The site maintained accountability logs for all study drugs and no issues or discrepancies were disclosed during the inspection.

A review of records did not reveal concerns related to data capture at this site. The inspectional findings indicate adequate adherence to good clinical practice regulations and the study protocol. There were no objectionable conditions noted and no Form FDA 483, Inspectional Observations, was issued.

- c. Assessment of data integrity:** The full Establishment Inspection Report (EIR) was not available for review. Preliminary inspection results were communicated by the FDA ORA field investigator. Data from this site appear acceptable. The audit did not indicate serious deviations/findings that would impact the validity or reliability of the submitted data.

3. Amit Vijapura, MD

9141 Cypress Green Dr., Suite 1
Jacksonville, FL 32256

- a. What was inspected:** All 12 enrolled subjects' records for PRO-805 were reviewed and eleven (of 17) enrolled subjects' records for PRO-806 were reviewed. In addition, IRB, monitor and Sponsor correspondences, drug accountability, adverse events, informed consents, protocol adherence, financial disclosure, safety reports, signature log, monitor log, source documents and electronic case report forms were reviewed.

Upon request, the central lab provided the ORA field investigators with a CD-ROM containing the referenced urine testing results pertaining to Dr. Vijapura's site.

- b. General observations/commentary:** For PRO-805, 18 subjects were screened, 12 subjects were randomized, and 8 subjects completed the study. For PRO-806, 24 subjects were screened, 17 were randomized, and 8 subjects completed the study.

For both studies, the subjects were consented prior to beginning the study and there was no evidence of un-blinding in the studies. Documentation of the implanting physicians' training was available, and there were no cases where the implanting physician and implanting staff participated in subject efficacy evaluations. The implanting physicians did document the procedure in both studies and in Study PRO-806, forms for AEs and medications of the implant/explant procedure were used.

For PRO-805, there were a few minor adverse events found that were not captured. For PRO-806, there was no under-reporting of AEs upon review of the records.

For both studies, the primary efficacy endpoints were verifiable. The site had discs provided by the sponsor with the laboratory data for the urine collections and the eCRFs for both studies. The urine collections for all of the subjects of both studies were reviewed and then a random review for both studies was done to check the laboratory results from the urine samples.

For PRO-805, Subject (b) (6) sample (b) (6) appears to have been run twice by the laboratory. There were two results noted for each of the tests for this sample. The source data results and the sponsor data line listings were identical. This was the only subject that this issue was seen for both of the studies.

For PRO-806, the laboratory source data contained the screening visit urine sample results for one subject. The protocol states that an in-office urine toxicology kit should be used and the results reviewed prior to starting induction. The results should have been at the site; the urine sample should not have been sent to the central lab.

A Form FDA 483 was not issued at the close of the inspection, but some verbal observations were discussed with Dr. Vijapura which included the following:

PRO-805

1. Three AEs for one subject (b) (6) noted at a post implant visit were not reported, and Dr. Vijapura indicated that this was an error, and they should have been reported.

2. Some AEs noted at the post implant visit (one day after implant) for the evaluation of the surgical implant site for edema, redness, etc., were not reported (Subject (b) (6) and Subject (b) (6)). According to Dr. Vijapura, normal edema or other conditions after a surgical incision are expected and they were instructed by the Sponsor to report these only if the conditions were excessive and not a normal result of a surgical incision. The Sponsor representative present at the site during the inspection verified this to be accurate.
3. The site missed performing four laboratory collections (Subjects (b) (6) at Week 1; Subject (b) (6) at Week 12; and Subject (b) (6) at Week 16) and two ECGs (Subject (b) (6) and Subject (b) (6) for the Week 4 visit) for this study.
4. All of the urine collections for all of the subjects were reviewed for this study. The PRO-805 urine collection log was a sheet of paper where staff could list the urine samples collected; the sample dates were not always listed consecutively by the dates of the collections. Verification of the urine collections found that the source documents were consistent except in three instances. There were three missed collections on the urine collection log for Subject (b) (6) for (b) (6); Subject (b) (6) for (b) (6); and Subject (b) (6) for (b) (6) however, the laboratory requisition paperwork and the eCRF indicated that the urines had been collected for those dates.
 - There are records to show that Subject (b) (6) was at the site on (b) (6) for Visit 6. The urine log for Subject (b) (6) at the site indicated a missed appointment on (b) (6). The eCRF shows the site study coordinator changed the urine log data in the electronic record to correct the error.
 - The urine log for Subject (b) (6) shows no urine collection entry on (b) (6), but the subject did have a urine collection on (b) (6) recorded; in addition, there was a laboratory report showing the collection of (b) (6) at 13:05. The eCRF for this case shows the (b) (6) collection with notes in the error section indicating that the end of treatment visit was on (b) (6) but there was no urine collection; the site study coordinator added the (b) (6) collection date to the eCRF on 5/9/08.
 - The urine log for Subject (b) (6) indicates a missed appointment on (b) (6) but there was a urine toxicology laboratory requisition form showing a urine collection at the site on (b) (6) – the eCRF has notes in the error section dated 7/9/08 for the site to confirm information as the lab results were available for this date and on 7/10/08, the site study coordinator corrected the information in the eCRF to show the collection on this date.

The eCRF also indicated that the data was revised to show the collections had actually occurred. This was discussed at the close of the inspection with the CI.

The logs for the second study PRO-806 were forms where each study week was pre-listed and there were 3 spaces under each week indicating the 3 urine samples to be collected so the study coordinator would just add in the date of the collection when it occurred and could readily see what was needed for each week.

PRO-806

1. The protocol indicated that supplemental SL BPN after dosing was to be given to the subjects if the Clinical Opiate Withdrawal Scale (COWS) was > 12, the Opioid Craving Visual Analog Scale (VAS) was > 20, and the request for supplemental dosing was deemed appropriate by the physician. The protocol also allowed for the dispensing of take home supplemental SL BPN for weekends, holidays, or other circumstances at the discretion of the investigator. It was discussed with Dr. Vijapura that on one occasion, a supplemental dose of SL BPN was given to the subject (b) (6) without fulfilling the criteria and without the PI signature for approval (the worksheet for the Supplemental SL BPN was not completed); on three dates (Subject (b) (6) on (b) (6) and Subject (b) (6) on (b) (6), the supplemental BPN was given as take home dosing and there was documentation of a reason/circumstance that the dose was needed but the scales were not done and there was no PI signature; and two cases (Subject (b) (6) on (b) (6)) where the COWS criteria was not met but the supplemental dose was approved with the PI signature without the reason/circumstance for the dose. According to the Sponsor representative at the site during the inspection, this medical practice of supplementation is standard of care in outpatient treatment of opioid dependence, and this supplementary dosing was provided in the protocol for subject safety to alleviate the subjects' symptoms of withdrawal if they occurred. The Sponsor stated that if the PI deemed the take home dose to be clinically indicated, then it was not necessary or feasible to complete the COWS and VAS scales. Dr. Vijapura stated that the protocol gave permission for PI judgment for dispensing the supplemental dose. It was discussed that better documentation was needed regarding the approval and reason/circumstance for this supplemental dosing.

OSI Reviewer Note: *The protocol, Section 5.5.1 clearly states that in order to provide consistency regarding criteria for Investigators to prescribe supplemental SL BPN, subjects should meet all of the criteria. It also states that "The primary reason for the administration of supplemental SL BPN should be recorded in the CRF".*

2. The protocol exclusion criterion #3 indicates exclusion of subjects with chronic pain requiring opioids for treatment. It was discussed that the PI did not adequately document the treatment and medical care for chronic back pain for one subject (b) (6). This subject was included in the study and the source records documented that the subject had ongoing chronic back pain taking oxycodone and ibuprofen. A note was added that the "Subject is willing to go without medicine to get off opioids." According to the physician, at the time of this study the subject was not being treated by a physician for the back pain and did not need opioids for the condition; other treatments were thought to be fine.
3. Some of the forms used by the implanting physician to document the post (implant, dose increase implant, and explant) procedure vital signs (at 15 and 30 minutes after the procedure) did not have a space to document the time the vital signs were taken. It was explained that it was still the CI's responsibility to have a method to obtain needed times for the study even if a provided form did not request it.

The inspectional findings indicate adequate oversight and adherence to good clinical practice regulations.

- c. **Assessment of data integrity:** The full Establishment Inspection Report (EIR) was not available for review. Preliminary inspection results were communicated by the FDA ORA field investigator. Data from this site appear acceptable. The audit did not indicate serious deviations/findings that would impact the validity or reliability of the submitted data.

4. Ashwin Patkar, MD

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- a. **What was inspected:** A total of 18 informed consents (100% of available files) for PRO-805 and 27 informed consents (100% of available files) for PRO-806 were reviewed for randomized subjects and non-randomized screen failures during the inspection. The subjects' records consisted of an e-case report file and a study source document chart. Also inspected were the IRB/Sponsor correspondence files, drug accountability records, collection of urine toxicological samples, and corresponding laboratory testing results related to the primary endpoint of the audited studies. Per protocol requirement, the site was to remain blinded to the urine toxicological results. Upon request, the central lab provided the ORA field investigators with a CD-ROM containing the referenced urine testing results pertaining to Dr. Patkar's site.
- b. **General observations/commentary:** For PRO-805, 19 subjects were screened,

11 subjects were randomized, and 5 completed the study. One screen failure subject file (b) (6) could not be located at the site (screened on (b) (6)). For PRO-806, 27 subjects were screened, 21 randomized, and 11 completed the study.

The first randomized study subject was screened on (b) (6) for Protocol 805 and (b) (6) for Protocol 806. The last subject was consented on (b) (6) for Protocol 805 and on (b) (6) for Protocol 806. Both studies have been completed. Study 805 was completed on (b) (6) and Study 806 was completed on (b) (6) (close out visit).

The Duke University Medical Center (DUMC) Institutional Review Board (IRB) initially approved the protocol and informed consent form (ICF) documents for Studies 805 and 806 prior to the start of subject enrollment (dated 5/31/07 for Study 805 and 10/13/10 for Study 806). The latest IRB approved ICF for Study 805 was dated 12/17/2007. There were also versions of informed consent/revisions approved by DUMC IRB with approval dates 10/24/2007 for PRO-805 and 04/24/10 for PRO-806 in the regulatory binders.

It was confirmed that Clinical trials.gov language is in the ICFs dated July 2010, and informed consent procedures were also addressed in an Informed Consent Action Plan.

All training documentation for study personnel were available and acceptable, as well as CVs and medical licenses for key study personnel.

According to study staff, subject identities were verified using social security numbers for reimbursement. IDs were also checked, but were not copied to protect subject identity.

There were a few adverse events noted for PRO-805 that were not captured. Subject (b) (6) file notes indicated that there were implants possibly poking through that were not listed on the AE log. Subject (b) (6) Vital Signs form has comments relating to a bacterial infection at the implant site but the AE source log did not have bacterial infection listed.

“Taper doses” were observed on SL BPN logs in the files of some subjects at completion of the PRO-806 study. Staff explained that these had been dispensed from the study supply and had been accounted for by adding them to the list of concomitant medications at the recommendation of the monitor. The source list of concomitant medications for Subject (b) (6) was checked, and observed to contain the taper dose.

Monitoring was conducted by the CRO, (b) (4) for Study 805 and by the CRO, (b) (4) for Study 806. This site was also audited by the Sponsor for

PRO-806.

Review of the available subject files revealed that Subject # (b) (6) had a PK sample drawn too soon after the last induction dose of SL BLPN. This subject also had a pregnancy test result recorded as positive in the source documents and negative in the eCRF.

According to Dr. Patkar and staff, the pregnancy recorded on the source document had been a false positive. The subject was referred to DUMC where additional follow-up revealed a negative result. PK samples were taken after asking the subject when they took their last dose.

Delegation log for PRO-805 had study personnel delegated to assist with the implant procedure and also perform other study related duties. The implanting physician was also delegated to conduct assessment scales.

Dr. Patkar stated that people being on the delegation log did not mean they conducted the procedures. Some people were delegated so that in case of an emergency there would be someone available who could conduct the procedures. The implant vital signs were taken by study staff before the procedure when the implanting physician was not present and again after the procedure when the implanting physician was not for both studies. Neither implanting physician had a separate staff to assist. No one from the study staff was present during the procedure. People who took implant vitals were not doing efficacy assessments to the extent possible. The scales and assessments for PRO-806 were done by Dr. Patkar and the ones for PRO-805 were done by the study coordinators.

At the end of the inspection, a Form FDA 483 was issued for the following:

1. An investigation was not conducted in accordance with the signed statement of the investigator and investigational plan. Specifically,
 - a. The investigator failed to report the removal of implants under general anesthesia of Subject (b) (6) to the Sponsor or designee as an adverse event as required by the Form 1572 and the protocol. Additionally, the investigator failed to follow the study protocol in that the reason for early termination for Subject (b) (6) was reported as "Patient Request" to the Sponsor. Source documents including End of Treatment Physical Exam dated (b) (6) and Patient Disposition dated (b) (6) list the subject as a "treatment failure". A report to the IRB signed and dated by the investigator on 1/28/2008 in regards to the adverse event mentioned above lists the subject as a treatment failure.

Dr. Patkar reported that Subject (b) (6) was not doing well during the study, and wanted the implants removed. Dr. Manelli removed the implants, and the patient became uncooperative during the explant procedure. General anesthesia was used because the subject was uncooperative, and the remaining implants were removed in an outpatient setting. The subject had been reporting to emergency rooms during the study requesting pain medication. She had been considered a treatment failure because she had been seeking additional opiates. Dr. Patkar said that data management may have requested the change because the subject had been a treatment failure first and had then wanted the implants removed when she was told that she was not doing well in the study. He said that the IRB told the site not to consider the situation a severe adverse event.

- b. The investigator failed to follow the study protocol in that Subjects (b) (6) completed the study although records indicate that they both were no shows for 9 consecutive urine toxicology collection visits for the dates noted in the following table.

OSI Reviewer Note: *According to the study protocol this was criteria for withdrawal from the study. This criterion was added in Amendment 1 dated September 1, 2006 “Sections 7.4, 8.2, 9.1.13, 9.2: Additional criteria for early withdrawal: If a patient misses 6 consecutive counseling sessions after Baseline Visit, the patient will be considered non-compliant and will be withdrawn from the study.”*

Additionally, these subjects received counseling on the same day they were recorded as no shows on the urine toxicology log for the dates listed in the following table:

Subject #	Date	Urine Toxicology	Counseling Session
(b) (6)		“No Show”	45 mins
		“No Show”	
		“No Show”	
		“No Show”	45 mins
		“No Show”	
		“No Show”	
		“No Show”	45 mins
		“No Show”	
		“No Show”	45 mins

(b) (6)	"No Show"	
	"No Show"	
	"No Show"	45 mins
	"No Show"	
	"No Show"	
	"No Show"	45 mins
	"No Show"	
	"No Show"	45 mins

OSI Reviewer Note: *Both subjects had entries made to the counseling logs on dates the urine collection appointments were missed. Information found in progress notes indicated that both of these subjects were possibly incarcerated. Both subjects also provided information in the Addiction Severity Index (ASI) that they were awaiting charges, trial, or sentence related to the charges.*

Dr. Patkar and staff were unsure how Subjects (b) (6) failed to provide urine samples and still received counseling. They said that the two subjects usually came in together for study visits. At some point Subject (b) (6) began coming in without Subject (b) (6). They said the completed status (counseling/urine sample) had been a study staff error, and that the subjects may have been asked to come back later to provide urine samples and did not come back as instructed.

The investigator failed to follow the study protocol in that Subject (b) (6) also completed the study although records indicate that 6 consecutive counseling sessions were missed during Weeks 18-24. Per protocol, subjects were to receive counseling sessions once per week during Weeks 12-24. The last recorded counseling session for Subject (b) (6) occurred on (b) (6) (Week 17) and subject disposition date is recorded as (b) (6). Subject (b) (6) also received greater than or equal to 8 days of supplemental SL BPN over 4 consecutive weeks, as follows:

Administration Date	Time (24 Hour Clock)	Dose (mg)
(b) (6)	11:15	16
	11:15	16
	14:30	16
	15:50	16
	15:30	16

(b) (6)	15:00	16
	09:30	16
	15:00	16

Dr. Patkar stated that the patient disposition was reported as completed due to a study staff error.

2. Failure to prepare or maintain accurate case histories with respect to observations and data pertinent to the investigation and informed consent. Specifically,
 - a. The following subjects did not sign updated informed consent documents during the study after approval on 12/07/2007 by the IRB. The only version signed by these subjects was the earlier version dated 5/31/2007.

Subject #	Visit date
(b) (6)	(b) (6) (V11)
	(b) (6) (V10)
	(b) (6) (V8)
	(b) (6) (V6)
	(b) (6) (V6)
	(b) (6) (V6)
	(b) (6) (Implant Dose Increase)
	(b) (6) (V4)
	(b) (6) (V4)
	(b) (6) (V4)

The following subjects were screened and initially signed informed consent dated 5/31/2007, after a version dated 10/24/2007 had been approved by the IRB. These subjects were classified as screen failures.

Subject #	Screening Date
(b) (6)	

Dr. Patkar said that the changes to the informed consent did not involve an increased safety risk but the decision had been made to re-obtain informed consent anyway per the IRB. The counselors (involved with the protocol required manual-guided psychosocial counseling) did not pass on the information to re-

obtain informed consent subjects during their transition, and the repeat informed consent was not obtained.

Subject (b) (6) screened on (b) (6), did not have a signed informed consent form on file. This subject was classified as a screen failure.

As noted earlier, one screen subject failure file (b) (6) could not be located at the site. Dr. Patkar said that Subject (b) (6) had been looking for a short term detox program and had left before being seen by the PI. The study coordinator had begun interviewing the subject, but no physical exam had been done. The records for this subject were missing and could not be obtained. He stated that the subject had most likely signed an informed consent form, but it is missing from the study records. The form could not be retrieved from the archives.

- b. Two randomization qualifying Induction doses were manually altered to misrepresent the actual Induction dose for Subject (b) (6) administered on (b) (6). The authentic data did meet randomization criteria; however, the altered data would have made Subject (b) (6) ineligible for randomization. They are as follows:

Administration Date	Authentic Data	Altered Data
(b) (6)	11:00 8 mg	16 mg
	11:00 4 mg	16 mg
<i>Total Dose:</i>	12 mg	32 mg

Subject (b) (6) was randomized on (b) (6) and lost to follow up on (b) (6)

OSI Reviewer Note: *Two randomization qualifying Induction doses did not reflect the actual Induction dose for Subject (b) (6) administered on (b) (6). The ORA field investigator stated that the doses “were manually altered to misrepresent the actual Induction dose”. It is not clear if this was intentional or human error. The altered data rendered the subject ineligible for randomization so there is no immediate explanation as to why this would have been done intentionally. It is most likely a recordkeeping error.*

Dr. Patkar stated that the dose corrected to a double dose (32 mg) on the induction log for Subject (b) (6) was a correction that was made in error; he would never prescribe that much in one day.

The site attempted to locate the subject (lost to follow up without having the implants removed). At least three documented phone attempts were made and then certified letters were sent.

3. Investigational drug disposition records are not adequate with respect to dates, quantity, and use by subjects. Specifically,
 - a. The investigator or responsible party did not maintain an accountability log for the study drug (implant kits) showing receipt and dispensing to subjects, as well as used and unused study drug (implant kits) returned to the Sponsor for PRO-805.

OSI Reviewer Note: *Test article accountability logs were to be maintained for both studies. A log was contained in the regulatory binder for Study 806, but no accountability log could be located for Study 805. Bulk Logs from the pharmacy were not kept at the site for Study 805.*

Dr. Patkar was not sure how the inventory was done for PRO-805. Only individual patient forms were found. No overall implant accountability log could be located for the study. They said that the logs may have still been in storage. The Bulk Logs were most likely destroyed by the Division of Pharmacy after 5 years.

- c. **Assessment of data integrity:** The full Establishment Inspection Report (EIR) was submitted for review. As noted above, there were several isolated observations due to human error and the population involved with no overall pattern for concern. The audit did not indicate serious deviations/findings that would impact the validity or reliability of the submitted data.

5. Jorg J. Pahl, MD

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- a. **What was inspected:** Eleven subjects' records for PRO-805 were reviewed. In addition, IRB, monitor and sponsor correspondences, drug accountability, adverse events, informed consents, protocol adherence, financial disclosure, safety reports, signature log, monitor log, source documents and electronic case report forms were reviewed. Upon request, the central lab provided the ORA field investigators with a CD-ROM containing the referenced urine testing results pertaining to Dr. Pahl's site.
- b. **General observations/commentary:** For PRO-805, there were 17 subjects screened, 13 randomized, and 8 completed the study.

In 5 of the 13 subjects at this site who were randomized, the Sponsor granted

waivers when a subject did not meet randomization criteria due to an elevated Opioid Craving Visual Analog Scale (VAS) because the last induction dose was outside of the 24-hour window. For the 8 subjects that did not get a waiver, the 12-24 hour window between the last induction dose and the implantation was less than 12 hours. The decrease in time potentially caused the VAS to be lower than what it would have been if the window was met.

There was no under-reporting of AEs upon review of the records.

The primary efficacy endpoint was verifiable. The site had discs provided by the sponsor with the laboratory data for the urine collections and the eCRFs. The urine collections for 11 subjects were reviewed.

At the conclusion of the inspection, a Form FDA 483 was issued for the following:

1. An investigation was not conducted in accordance with the signed statement of investigator and investigational plan. Specifically,
 - a. Protocol Section 7.2, titled “EXCLUSION CRITERIA (PRIOR TO INDUCTION)” states that patients are not eligible for the study if on a current anti-coagulant therapy (such as warfarin) or has an INR > 1.2 prior to induction. However, Subject (b) (6) was documented as having an elevated exclusionary INR of 1.4 at screening on (b) (6) and on retest on (b) (6), but was randomized into the study on (b) (6).
 - b. Protocol Section 7.3, titled “RANDOMIZATION CRITERIA” states that prior to randomization in the study, patients must have no significant cravings for opioids (defined as a score ≤ 20 mm on the 100-mm Opioid Craving VAS). However, Subjects (b) (6) failed to meet protocol defined randomization criteria due to a VAS score > 20 mm on the day of randomization.
 - c. Protocol Section 9.3.2, titled, “BASELINE VISIT”, states that prior to randomization and on the day of randomization, a VAS should be done. However, there is no documentation that the VAS was determined for 2 of the 13 subjects on the day of randomization.
 - Subject (b) (6) did not have a documented VAS determined on the day of randomization on (b) (6). Last documented VAS was determined on (b) (6).
 - Subject (b) (6) did not have a documented VAS determined on the day of randomization on (b) (6). Last documented VAS was determined on (b) (6).
 - d. Protocol Section 7.3, titled “RANDOMIZATION CRITERIA”

states that prior to randomization in the study, patients must have undergone induction with SL BPN to a dose of 12-16 mg/day as clinically appropriate within 10 days of screening (and received a fixed dose of 12-16 mg/day SL BPN for at least three consecutive days immediately prior to randomization) and that patients who undergo induction with SL BPN to a dose < 12 mg/day or > 16 mg/day are not eligible. However, 4 of the 13 subjects failed to meet protocol defined fixed induction doses of 12-16 mg/day during the last three days of induction prior to implantation but were randomized into a treatment group.

- Subject (b) (6) was randomized into a treatment group on (b) (6) and received the last documented induction dose of 6 mg on (b) (6)
- Subject (b) (6) was randomized into a treatment group on (b) (6) and received the last documented induction dose of 6 mg on (b) (6)
- Subject (b) (6) was randomized into a treatment group on (b) (6) and received the last documented induction dose of 8 mg on (b) (6)
- Subject (b) (6) was randomized into a treatment group on (b) (6) and received the last documented induction dose of 8 mg on (b) (6)

e. Protocol Section 9.3.3, titled “Implant Visit” states that for the Initial Implant, the sublingual BPN should be discontinued 12-24 hours prior to implantation. However, 9 of the 13 subjects failed to meet the 12-24 hour window.

- Subject (b) (6) was documented as receiving the last induction dose on (b) (6) at 9:30 am and was documented as being implanted 55 hours later on (b) (6) at 16:30.
- Subject (b) (6) was documented as receiving the last induction dose on (b) (6) at 10:30 am and was documented as being implanted 7 hours 14 minutes later on (b) (6) at 17:44.
- Subject (b) (6) was documented as receiving the last induction dose on (b) (6) at 10:30 am and was documented as being implanted 7 hours later on (b) (6) at 17:30.
- Subject (b) (6) was documented as receiving the last induction dose on (b) (6) at 8:30 am and was documented as being implanted 33 hours 15 minutes later on (b) (6) at 17:45.
- Subject (b) (6) was documented as receiving the last induction dose on (b) (6) at 9:30 am and was documented as being implanted 4 hours 15 minutes later on (b) (6) at 13:45.

- Subject (b) (6) was documented as receiving the last induction dose on (b) (6) at 9:30 am and was documented as being implanted 7 hours 20 minutes later on (b) (6) at 16:50.
 - Subject (b) (6) was documented as receiving the last induction dose on (b) (6) at 9:00 am and was documented as being implanted unknown hours later on (b) (6) at an undocumented time.
 - Subject (b) (6) was documented as receiving the last induction dose on (b) (6) at 8:15 am and was documented as being implanted unknown hours later on (b) (6) at an undocumented time.
 - Subject (b) (6) was documented as receiving the last induction dose on (b) (6) at 8:30 am and was documented as being implanted 9 hours later on (b) (6) at 17:30.
- f. Protocol Section 9.3.6, titled TREATMENT VISITS WEEKS 1, 2, 4, 6, 8, 10, 12, 14, 16, 18 AND 20” states that the Week 1 visit should be performed on Day 7 \pm 2 days from the Implant Visit, and on Day 7 \pm 2 days after the Implant Dose Increase. Subsequent treatment visits should also be performed within \pm 2 days. However, 48% of the 114 eligible Week 1 through Week 20 follow-up visits were outside the \pm 2 days window. Visits were up to 33 days outside of the visit window with an average of 8 days. Examples include the following:
- Subject (b) (6) was outside the visit window on 6 of the 11 visits with a maximum of 28 days and an average of 21 days.
 - Subject (b) (6) was outside the visit window on 6 of the 11 visits with a maximum of 33 days and an average of 17 days.
 - Subject (b) (6) was outside the visit window on 6 of the 11 visits with a maximum of 13 days and an average of 7 days.
- g. Protocol Section 6.5.2, titled “ADDITIONAL DOSING: IMPLANT DOSE INCREASE” states that patients who require \geq 3 days per week of Supplemental SL BPN for 2 consecutive weeks or \geq 8 days of Supplemental SL BPN over 4 consecutive weeks will receive 1 additional implant any time after the first 2-4 weeks following the initial insertion of 4 implants. However, Subject (b) (6) received a dose increase on (b) (6) but met the protocol defined criteria for dose increase 3 supplemental doses earlier on (b) (6) after receiving 6 supplemental doses during a 10-day period between (b) (6) and (b) (6).
2. Failure to prepare or maintain adequate and accurate case histories with respect to observations and data pertinent to the investigation.

Specifically,

- a. Failure to collect and document the time of the test article implantation
 - Subject (b) (6) was implanted on (b) (6)
 - Subject (b) (6) was implanted on (b) (6)
 - Subject (b) (6) was implanted on (b) (6)
 - b. Failure to collect and document the time of the last induction dose.
 - Failure to document the fixed induction doses for Subject (b) (6) for the three days prior to randomization on (b) (6). The subject was dispensed 16 mg for (b) (6) through (b) (6) as take home doses, but there was no documentation that those doses were taken.
 - Failure to document the fixed induction doses for Subject (b) (6) for the three days prior to randomization on (b) (6). The subject was dispensed 16 mg for (b) (6) and (b) (6) as take home doses but there was no documentation that those doses were taken.
 - Failure to document the fixed induction doses for Subject (b) (6) for the three days prior to randomization on (b) (6). The subject was dispensed 16 mg for (b) (6) and (b) (6) as take home doses but there was no documentation that those doses were taken.
 - c. **Assessment of data integrity:** The full Establishment Inspection Report (EIR) was not available for review. Preliminary inspection results were communicated by the FDA ORA field investigator, along with review of the Form FDA 483. The audit did not indicate serious deviations/findings that would impact the validity or reliability of the submitted data. Deviations noted appear to be isolated in nature and are unlikely to significantly impact primary safety or efficacy analyses. In addition, it does not appear that the rights, safety, or welfare of subjects was compromised. With the exception of issues noted above, the study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.
- 6. Kyle M. Kampman, MD**
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Philadelphia, PA 19104
- a. **What was inspected:** Subjects' records were comprised of a source documentation binder, a copy of the completed case report forms and a medical chart. All subject records were reviewed for both studies. The 1572s, CVs, financial disclosures, and credentials of the PI and key study staff were

reviewed as well as training materials and confirmation of all training. In addition, IRB, monitor and Sponsor correspondences, drug accountability, adverse events, informed consents, protocol adherence, safety reports, signature log, monitor log, source documents and electronic case report forms were reviewed. Upon request, the central lab provided the ORA field investigators with a CD-ROM containing the referenced urine testing results pertaining to Dr. Kampman's site.

- b. General observations/commentary:** For PRO-805, 45 subjects were screened, 18 were randomized, and 13 completed the study. The first subject (b) (6) signed informed consent on (b) (6) and was administered test article on (b) (6). The last follow-up visit (for Subject (b) (6) was on (b) (6).

For PRO-806, 25 subjects were screened, 17 subjects were randomized, and 10 completed the study. The first subject (Subject (b) (6)) signed the informed consent on (b) (6) and was administered test article on (b) (6). The last follow-up visit for Subject (b) (6) was on (b) (6).

Multiple versions of informed consent documents were used during the course of these studies. All were submitted to and approved by the University of Pennsylvania IRB.

The site does not require a picture ID to verify the identity of a subject. Subjects (b) (6) dropped out of the study and never returned for the removal of the implants.

Dr. Elmer Yu, M.D. was the site Implant Physician. He completed all required training provided by the Sponsor. He and his staff did not participate in the subject's efficacy evaluations or discuss with other study staff information regarding the implants in reference to the subjects.

There were a few minor data discrepancies for PRO-805:

- The "PRO-805 Patient Severity Profile and Composite Scores" documents that the visit was dated (b) (6) however, the eCRF documents the visit date to be (b) (6).
- The PRO-805 record for subject (b) (4) states "Informed consent version dated: (b) (6)" but the subject actually signed IC version 2, dated (b) (6).

There were a few minor data discrepancies for PRO-806:

- The insertion examination record dated (b) (6) for subject initials (b) (6) documents the subject number (b) (6). However, the extraction examination record dated (b) (6), for subject initials (b) (6), documents the subject number (b) (6).

- The “Implant Site Examination/Treatment Compliance-Groups A & B only” documents the visual site assessment conducted after implant and removal. The staff could not locate the examination records for subjects

(b) (6)

Investigational drug disposition records were adequate with respect to dates and quantity.

There were no SL BPN dose reductions during the Study PRO-806 for subjects in Group C in response to an AE. There was no under-reporting of AEs and all SAEs were reported as required.

The “PRO-805 Urine Toxicology Log” for Subject (b) (6) was compared to the lab records and there was no documented evidence for urine samples collected on (b) (6)

Upon completion of the studies, the Sponsor provided the site with a DVD containing copies of the e-case report forms completed for each of the participating subjects.

The inspectional findings indicate adequate oversight and adherence to good clinical practice regulations. There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, was issued.

- c. Assessment of data integrity:** The full Establishment Inspection Report (EIR) was not available for review. Preliminary inspection results were communicated by the FDA ORA field investigator. Data from this site appear acceptable. The audit did not indicate serious deviations/findings that would impact the validity or reliability of the submitted data.

7. Titan Pharmaceuticals

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- a. What was inspected:** The inspection covered the firm’s management of the two studies, PRO-805 and PRO-806, at six clinical investigator sites (noted above). All sponsor responsibilities had been transferred to contract vendors. The trial master file (TMF) for each site was maintained by the respective CRO for each study and transferred to Titan at the close of the trial. Therefore, the inspection concentrated on the Sponsor’s oversight of all its vendors and records were reviewed pertaining to the two studies at the above mentioned sites. These included the site agreement, signature/delegation of authority log, Form FDA 1572 (Statement of Investigator), financial disclosures, site personnel curriculum vitae (CV) and licensures, training, implant physicians’ signed agreements to maintain the study blind, Institutional Review Board (IRB) correspondence, laboratory urine receipt documentation, investigational

product (IP) accountability, site enrollment/screening log, monitoring log and reports, and communications to the site.

Titan reviewed the Certificates of Analysis for the Probuphine implants prior to release for final packaging and distribution and generated the blinded batch number. The Certificates of Analysis for the three lots manufactured for the studies were inspected as well as the test article pouch labeling and kit labeling.

The three member DSMB CVs and files for both protocols were reviewed.

The records regarding the two subjects found in PRO-806 that enrolled at multiple sites were reviewed.

- b. General observations/commentary:** For both Protocols 805 and 806, all required 1572s and financial disclosures were present. IRB correspondence for initial protocol and informed consent approval, continuing review, and study closure were present. Monitoring logs and reports were consistent. One IP accountability discrepancy found for Site 32 was resolved by obtaining return kit documentation from the vendor (b) (4)

As noted, all Sponsor responsibilities had been transferred to contract vendors for Protocols 805 and 806. A list of vendors for both studies was obtained. All Transfer of Responsibility letters were reviewed, as well as major vendor contracts and responsibilities.

Titan's relevant SOPs were reviewed. For PRO-805, (b) (4) and Titan management jointly selected the clinical investigators. For PRO-806, the clinical investigators were selected by Titan. Each site selected was provided with all the necessary information prior to initiation of the clinical trial, including the Investigator Brochure. Each site had a Site Initiation Visit (SIV).

The Sponsor conducted an investigator meeting including implant physician training for PRO-805. Probuphine Clinical Training provided training and information for the clinicians performing insertion and removal of the Probuphine implants and additional training for PRO-806. Each site had 1-2 implant physicians. Each had documented training at the Investigator Meeting or Site Initiation Visit. The TMFs had implant physician training certificates or documentation of training in a monitoring correspondence report. Also present were signed agreements by the implanting physicians to maintain the blind.

It was verified that Dr. Chavoustie was a sub-investigator serving as the implant physician for Dr. Segal's site for both PRO-805 and PRO-806. Dr. Chavoustie also provided consulting and implant procedure medical monitoring for both protocols. (b) (4)

His role as the implant physician

at Dr. Segal's site

(b) (4)

Monitoring was contracted to the CROs. The CROs made efforts to bring sites with higher number of protocol deviations into compliance. No sites were closed. The Sponsor held weekly teleconferences with the CROs to monitor the progress and issues of the clinical studies. Titan has no QA department and hires contract auditors to audit investigational sites. Dr. Jorg Pahl and Dr. Amit Vijapura were audited for Study PRO-805. Dr. Ashwin Patkar and Dr. Amit Vijapura were audited for Study PRO-806. The audit reports were not reviewed. The Titan VP of Clinical Operations discovered the duplicate subject enrollment while co-monitoring and reviewing consent forms at Site 14 (Dr. Rosenthal) and Site 4 (Dr. Casadonte). The IVRS routinely performs a cross check of birthdates and initials across all sites and flags potential duplicates. It did not work in the two cases because the initials were entered differently at the 2 sites (on purpose by the subjects). After this discovery, Titan notified all site study coordinators to check government issued identification to verify that birthdates and initials correspond to what is reported by the subjects at the screening visit.

ClinicalTrials.gov registration and information was also confirmed for both studies.

Upon completion of the studies, the Sponsor provided each site with a DVD containing copies of the e-case report forms completed for each of the participating subjects.

No significant observations were noted during the inspection.

The inspectional findings indicate adequate oversight and adherence to good clinical practice regulations. There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, was issued.

- c. Assessment of data integrity:** The full Establishment Inspection Report (EIR) was submitted for review. The audit did not indicate serious deviations/findings that would impact the validity or reliability of the submitted data

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The inspection for this NDA consisted of 6 domestic clinical sites representing a total of 11 protocol sites as well as the Sponsor.

Three clinical sites inspected, Dr. Segal, Dr. Patkar, and Dr. Pahl, were each issued a Form FDA 483 citing inspectional observations and preliminary classifications for each of these inspections are Voluntary Action Indicated (VAI). Although regulatory violations were noted as described above for all three sites inspected, they are unlikely to significantly impact primary safety and efficacy analyses. The overall data in support of this application may be

considered reliable based on available information.

Drs. Flaherty, Vijapura, and Kampman and Sponsor Titan were not issued a Form FDA 483; the preliminary classifications are all NAI (No Action Indicated). Data from these sites are considered reliable based on the available information.

In general, based on the inspection of the six clinical study sites (representing 11 protocol sites) and the Sponsor, the inspectional findings support validity of data as reported by the Sponsor under this NDA.

Observations noted above for Drs. Segal, Patkar, and the Sponsor, Titan, are based on the preliminary review of the Establishment Inspection Reports and review of the Form FDA 483 for Drs. Segal and Patkar. Observations noted above for Drs. Flaherty, Vijapura, Pahl, and Kampman are based on communications from the field investigator and review of the Form FDA 483 for Dr. Pahl. An inspection summary addendum will be generated if conclusions change upon OSI final classification.

{See appended electronic signature page}

Cynthia F. Kleppinger, M.D.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

CONCURRENCE:

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Janice Pohlman, M.D., M.P.H.
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Susan D. Thompson, M.D.
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Office of Scientific Investigations

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

/s/

CYNTHIA F KLEPPINGER
04/16/2013

JANICE K POHLMAN
04/16/2013

SUSAN D THOMPSON
04/16/2013

RESPONSE TO CONSULT REQUEST

(Tracking Number – 400)

From: Barbara Wesley, M.D., M.P.H.
Medical Officer
Division of Reproductive and Urologic Products, (DRUP)
Office of Drug Evaluation III
Office of New Drugs

Vicky Borders-Hemphill, Pharm. D.
Safety Evaluator
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Surveillance and Epidemiology (OSE)

Adrienne Rothstein, Pharm.D.
Team Leader
Division of Pharmacovigilance II (DPV II)
OSE

Through: Christina Chang, M.D., M.P.H.
Acting Clinical Team Leader, DRUP, ODE III, OND

Audrey Gassman, M.D.
Deputy Division Director, DRUP, ODE III, OND

Hylton Joffe, M.D.
Division Director, DRUP, ODE III, OND

To: Lisa Basham

Division of Anesthesia, Analgesia, and Addiction Products
(DAAAP)

Date of Request: February 1, 2013

Completion Date: March 21, 2013

Subject: NDA 204-442, Probuphine (Buprenorphine HCl) Subdermal
Implant

Consult Instructions:

Probuphine is a surgically implanted product which delivers buprenorphine over six months. It is intended for use as a treatment of opioid dependence. The product must be surgically implanted and removed in a manner similar to Norplant. Please provide input on the risks of surgically implanted drug/device combinations, with reference to experience with implantable contraceptives such as Norplant, to assist us in assessing the risks of the implantation procedure used with the Probuphine implant. Provide expert

input into the review of the REMS and training procedures, and present information about risks of surgically implanted contraceptives to inform discussion at the Advisory Committee meeting.

Response to Consult:

DRUP, DMEPA, and DPV II provided input weekly to the NDA review team, in preparation for a presentation to the REMS Oversight Committee. In addition, our review of device-related safety data in the literature and from FDA's Adverse Event Reporting System (FAERS) was summarized in the background document and slide presentation for the Advisory Committee. Both the background document and slide presentation are attached.

Contraceptive Implants – Regulatory History and Lessons Learned

Background

All implantable methods of contraception offer long-acting reversible contraception and are > 99% effective in preventing pregnancy. Four iterations of contraceptive implants have been approved for marketing in the United States, with each new generation featuring product designs aimed at improving tolerability. These implants contain a progestin (either levonorgestrel or etonorgestrel), which is released over time.

Regulatory and Marketing History of Implantable Contraceptives

Norplant, the six-capsule levonorgestrel contraceptive implant system, was the first contraceptive implant to be approved in the U.S. in 1990; it was approved for up to 5 years of continuous use. Norplant consists of six, sealed silicone capsules which are placed in a fan shaped pattern in the medial aspect of the upper arm. Each capsule is 2.4 mm in diameter and 34 mm long.

In Norplant's first full year on the U.S. market, insertions were running at about 800 per day; by the beginning of 1993, one million U.S. women had become Norplant users.¹ In March 1994, negative media coverage on Norplant removal difficulties began to affect usage.² By 1996, annual U.S. Norplant insertions had decreased by 90 percent.³ U.S. marketing of Norplant was discontinued in 2002. In contrast, Norplant continues to be marketed in developing countries.^{4,5}

Norplant II (Jadelle), is a two-capsule levonorgestrel implant approved by the FDA for 3 years continuous use in 1996. The dosing duration was expanded to 5 years of continuous use in 2002. Despite the FDA approval, Norplant II has never been marketed in the U.S.

In 2006, the first single-capsule contraceptive implant (Implanon) was approved. Implanon was replaced by Nexplanon (Implanon NXT) in 2011. In Nexplanon, the capsule is made of ethylene vinylacetate copolymer; each is 2 mm in diameter and 40 mm long. Nexplanon is approved for up to 3 years of continuous use. It has 15mg of barium sulphate added to the core, so it is detectable by X-ray. Nexplanon also has a pre-

¹ Kolata G. Will the lawyers kill off Norplant? After breast implants. American Home Products' birth-control device is this year's target. *New York Times*. 28 May 1995.

² Contraceptive Research, Introduction, and Use: Lessons From Norplant, Institute of Medicine, 1998.

³ The Economist. On the needless hounding of a safe contraceptive, 2 September 1995; Freundlich, op. cit., 1997.

⁴ Contraceptive Maker Wins Woman's Suit Over Side Effects". *The New York Times*: A.7. September 5, 1998

⁵ Morrow, David J. "Maker of Norplant Offers a Settlement in Suit Over Effects". *The New York Times*, August 27, 1999.

loaded applicator for easier insertion. Currently, Nexplanon is the only contraceptive implant marketed in the U.S.

The subdermal implant system utilized for delivering buprenorphine (Probuphine) is similar to the Norplant system.

Description of Insertion and Removal Procedures

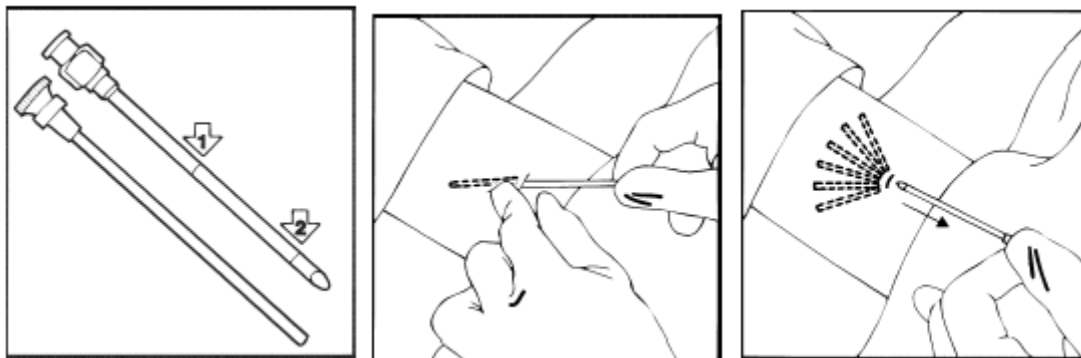
Norplant

Insertion:

The patient lies on her back on the exam table with her non-dominant arm flexed at the elbow and externally rotated so that her hand is at the level of her head. After cleaning the area with antiseptic solution and applying local anesthesia, the six capsules are inserted subdermally through a 2-mm incision and positioned in a fanlike manner with the fan opening towards the shoulder. The optimal insertion area is on the medial side of the upper arm, about 8 to 10 cm above the elbow crease.



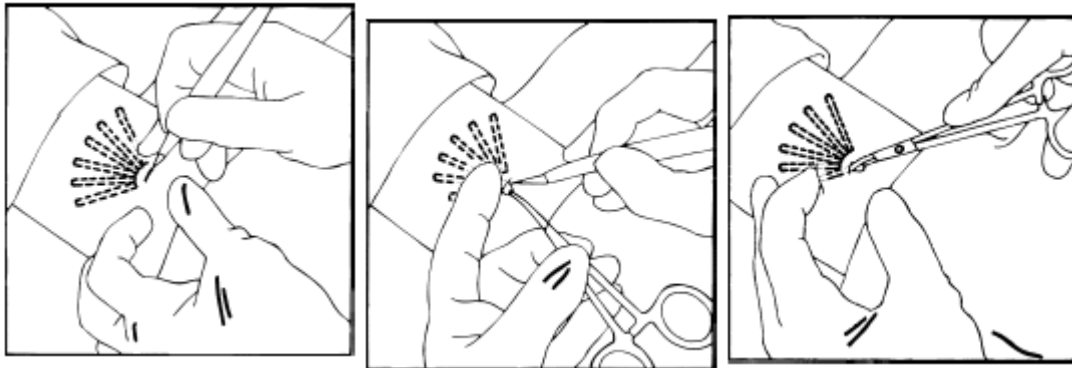
The six capsules are placed subdermally, one at a time, via a trocar. The trocar has two markings on it: the first mark is closer to the hub and indicated how far the trocar should be introduced under the skin before the loading of each capsule; the second mark is close to the tip and indicates how much of the trocar should remain under the skin following the insertion of each implant. The bevel of the trocar is oriented up toward the skin to keep the capsule in a superficial plane.



The trocar is not removed from the incision until all capsules have been inserted. The correct position of the capsules can be ensured by palpation after the insertion has been completed. After placement of the sixth capsule, sterile gauze may be used to apply pressure to the insertion site to ensure hemostasis.

Removal:

Once all six capsules are located by palpation, a small amount of local anesthetic is applied to the original incision site. A 4-mm incision is made with the scalpel close to the ends of the capsules. Each capsule is pushed gently towards the incision. When the tip of a capsule is visible near the incision, it is grasped with mosquito forceps and retrieved.



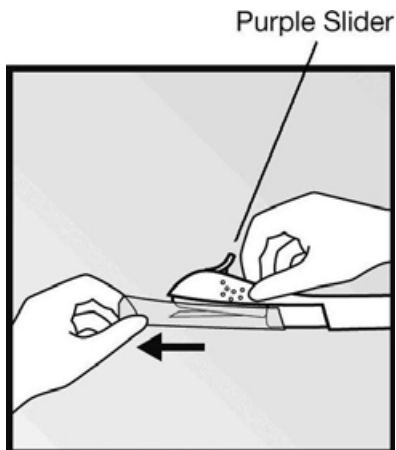
Should minor dissection be necessary to free up the capsules, a scalpel or forceps can be used to gently open the tissue sheath that has formed around the capsule. The capsule is removed from the incision with the second pair of forceps. Steri-strips are applied to the incision once the procedure is completed.

Nexplanon

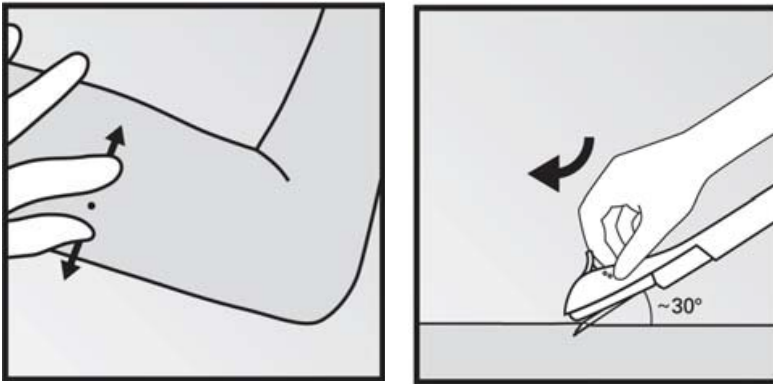
The insertion and removal procedures for Nexplanon are included for comparison with Norplant.

Insertion:

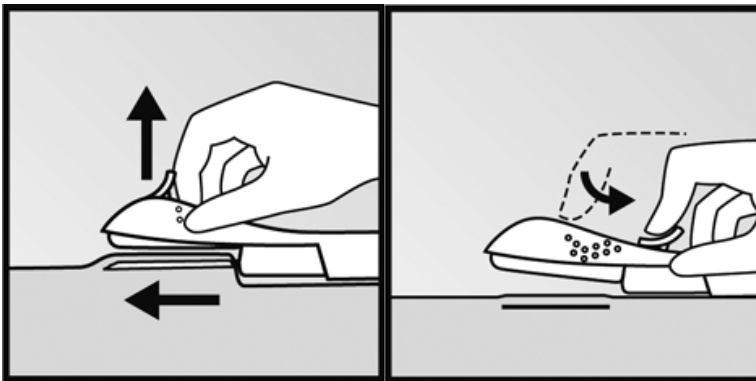
Insertion of Nexplanon is in the same area of the non-dominant arm as Norplant. This area is prepped with antiseptic solution and local anesthesia is applied. A sterile, disposable Nexplanon applicator, preloaded with the implant, is removed from its blister pack. The applicator is held above the needle and the transparent protection cap is removed by sliding it horizontally in the direction of the arrow away from the needle.



After stretching the skin with the free hand, the skin is punctured with the tip of the needle at a 30° angle.

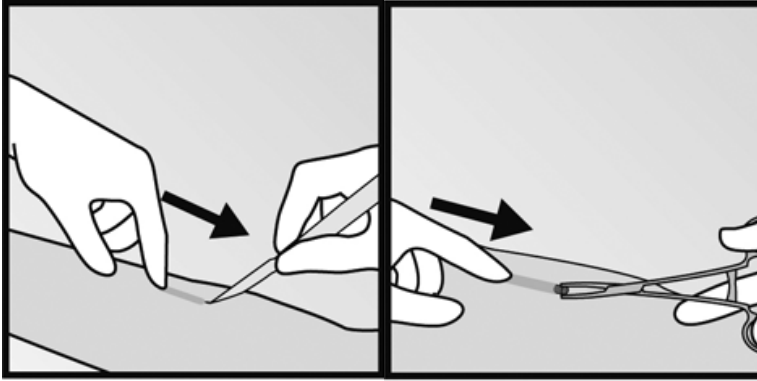


The applicator is then lowered to a horizontal position. With the skin tented by the tip of the needle, the needle is inserted to its full length. The purple slider is then unlocked and moved fully backward. The implant is now in its final subdermal position, and the needle is locked inside the body of the applicator. The applicator can now be removed.



Removal:

After applying antiseptic solution and local anesthesia, the implant is located by palpation. The proximal end of the implant is pushed down to stabilize it. Starting at the distal tip of the implant, a longitudinal, 2-mm incision is made towards the elbow. The implant is grasped with curved mosquito forceps and gently removed. Steri-strips are applied to the incision.



Insertion and Removal/Device Related Adverse Events

The Norplant label describes the nature and frequency of adverse events related to insertion and/or removals as follows:

- Removal difficulties affecting subjects (based on 849 removals): 6.2%
- Pain or itching near implant site (usually transient): 3.7%
- Infection at the implant site: 0.7%

With respect to literature, one comprehensive review article (Brache et al Contraception 2002)⁶ of adverse events from clinical trials for Norplant and other implantable progestins is summarized below:

- Removal complications occurred in up to 14.8% of users, mostly due to fibrous pericapsular sheath formation around the implant or due to implant breakage, deep placement or migration. In 0.8% of users, the procedure required a second incision or was not successful, i.e. not all the implanted rods could be removed.
- Removal complications in comparative studies between Norplant and Jadelle (two rods) were 6.9% for Jadelle and 14.8% for Norplant, respectively.
- Removal complications in comparative studies between Norplant and Implanon (single rod), were 0.2% for Implanon and 4.8% for Norplant, respectively.
- Infection rates with Norplant insertion in most studies were less than 0.5%, but two studies reported infection rates 1% or greater. Most infections occurred within the first two months (65%), but infections have been reported two years after insertion.
- For all implants, the rate of spontaneous expulsion was 0-0.6% in the absence of infection. When spontaneous expulsions occur, 35.7% occur within the first two months and 70% occur within first four months after insertion.
- Nerve damage was reported in 0.7-7.1% of users, including pain or numbness at the implant site or arm for any implant.
- In one study, US Norplant users were interviewed and 28% reported pain in the implant arm; pain was cited as the reason for implant removal in up to 2% of users.

⁶ Brache V, Faundes A, Alvarez F, Cochon L. Nonmenstrual adverse events during use of implantable contraceptives for women: data from clinical trials. Contraception 2002;65:63-74.

- Other insertion complications were reported in 0-1.7% of users, such as bleeding, hematoma, allergy to anesthetic or bandages, or dizziness.

Examples of reports that describe significant, Norplant device-related adverse events in the literature include several cases of ulnar neuropathy involving the musculocutaneous and antebrachial cutaneous nerves.^{7,8,9}

Compared to Norplant, the newer iterations of implants appear to be better tolerated. A meta-analysis of data from seven open-label, randomized studies in 1,378 women compared the ease of insertion and removal of the Implanon and Norplant implants and the frequency of associated complications. When done by trained providers, it was approximately four times quicker to insert and remove Implanon than Norplant (mean insertion times 1.1 vs. 4.3 min, respectively; mean removal times 2.6 vs. 10.2 min, respectively). Insertion complications were very rare with both Implanon (0.3%) and Norplant (0.0%). However, Implanon was associated with a significantly lower frequency of removal complications (0.2 vs. 4.8% with Norplant; $p < 0.001$).¹⁰

Finally, adverse event data for Norplant in the FDA Adverse Event Reporting System (FAERS)¹¹ were reviewed. This database was searched for all Norplant U.S. reports with the serious outcome disability received from 10 December 1990 (U.S. approval) until 06 February 2013. Forty-three cases of women reporting a disability related to the Norplant device were identified. The disabling event(s) reportedly occurred following device removal in 25 cases, insertion in 13 cases, and both insertion and removal in 2 cases. The remaining three cases had limited information. The cases generally reported paresthesia, dysesthesia or pain. Some users also reported decreased grip strength, restricted range of motion, or being unable to fully extend their arm. These reported events substantially limited one or more major life activities, such as caring for oneself, performing manual tasks, eating, and working. Where reported, the diagnoses included: ulnar nerve injury (11 cases), medial cutaneous nerve injury (5), “nerve damage” (3), injury to both the ulnar and medial cutaneous nerve (2).

⁷ Smith JM, Conwit RA, Blumenthal PD, Ulnar nerve injury associated with removal of Norplant implants, *Contraception*. 1998 Feb.;57(2):99-101

⁸ Hueston WJ, Locke KT, Norplant neuropathy: peripheral neurologic symptoms associated with subdermal contraceptive implants. *J Fam Pract*. 1995 Feb;40(2): 184-6

⁹ Marin R, McMillian D, Ulnar neuropathy associated with subdermal contraceptive implant, *South Med J*, 1998 Sep;91(9):875-8

¹⁰ Power J, French R, Cowan FM, Subdermal implantable contraceptives versus other forms of reversible contraceptives or other implants as effective methods for preventing pregnancy (Review), *The Cochrane Collaboration*, 2012

¹¹ FAERS is a database designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. FAERS data do have limitations (e.g., variable quality and quantity of information provided, cannot determine causality, voluntary reporting system, reporting biases). Additionally, FAERS cannot be used to calculate the incidence of an adverse event in the U.S. population. FDA implemented FAERS on September 10, 2012, and migrated all the data from the previous reporting system (AERS) to FAERS. Differences may exist when comparing case counts in AERS and FAERS. FDA validated and recoded product information as the AERS reports were migrated to FAERS. In addition, FDA implemented new search functionality based on the date FDA initially received the case to more accurately portray the follow up cases that have multiple receive dates.

In summary, contraceptive implants occasionally cannot be removed by palpation. In other cases implants were not implanted or were extruded because of faulty trocar placement. Other reports indicate that implants migrated to other parts of the body, including the chest and other locations in the arm. Implants also have been inserted into the vascular system and a case of migration to the pulmonary artery with Implanon was reported in FDA's FAERS database.

When the implants cannot be located by either visual inspection or palpation, additional imaging technologies such as ultrasound, high-resolution fluoroscopy with digital subtraction imaging, MRI, and compression film screen mammography have been used to locate the implants for removal.^{12,13,14,15} In the cases where imaging technology is necessary, dissection is often necessary to remove the implant. In other cases, general anesthesia was necessary to allow extensive dissection in the arm to remove an implant imbedded in fibrous tissue.¹⁶ Finally, Nexplanon can be located by X-ray. Neither Norplant nor Probughine can be located by X-ray methodology.

¹²Letterie GS, Garnaas M, Localization of "lost" Norplant capsules using compression film screen mammography, *Obstet Gynecol.* 1995 May;85(5 Pt 2):886-7

¹³ Silverstein MI, et. al., Fluoroscopically guided Norplant removal, *J Vasc Interv Radiol.* 2001 Feb; 12(2):253-5

¹⁴ Crist T, et. al. Difficulty finding and removing a Norplant capsule. *NC Med J.* 1994 Feb;55(2):76.

¹⁵ Thurmond AS, et. al., Localization of contraceptive implant capsules for removal. *Radiology*, 1994 Nov;193(2):580-1

¹⁶ Wechselberger G, et. al, Nerve injury caused by removal of an implantable hormonal contraceptive, *Am J Obstet Gynecol*, 2006 195, 323-6



Contraceptive Implants: Regulatory History and Lessons Learned

Barbara Wesley M.D., M.P.H.

Medical Officer

Division of Reproductive and Urologic Products



Overview Of Contraceptive Implants

- Features and History of Contraceptive Implants
- Procedures of Norplant and Nexplanon Implant Insertion and Removal
- Device-Related Adverse Events (AEs)



Overview Of Contraceptive Implants

- Features and History of Contraceptive Implants
- Procedures of Norplant and Nexplanon Implant Insertion and Removal
- Device-Related Adverse Events (AEs)



Key Features of Contraceptive Implants

- Contain a progestin which is released over 3 to 5 years
- Surgically implanted subdermally in the medial aspect of the upper, non-dominant arm
- Considered highly effective methods
- 4 iterations approved → improved tolerability



History of FDA Approved Contraceptive Implants

Product	# of capsules	Capsule Size	Marketing Status	Duration (years)
Norplant	6	34 mm x 2.4 mm	1990 to 2002	5
Jadelle	2	43 mm x 2.5 mm	1996; Never marketed in U.S.	3
Implanon	1	40 mm x 2.0 mm	2006 to 2011	3
Nexplanon*	1	40 mm x 2.0 mm	2011 to present	3

*The Nexplanon capsule is radio-opaque to enable easier detection by imaging modalities

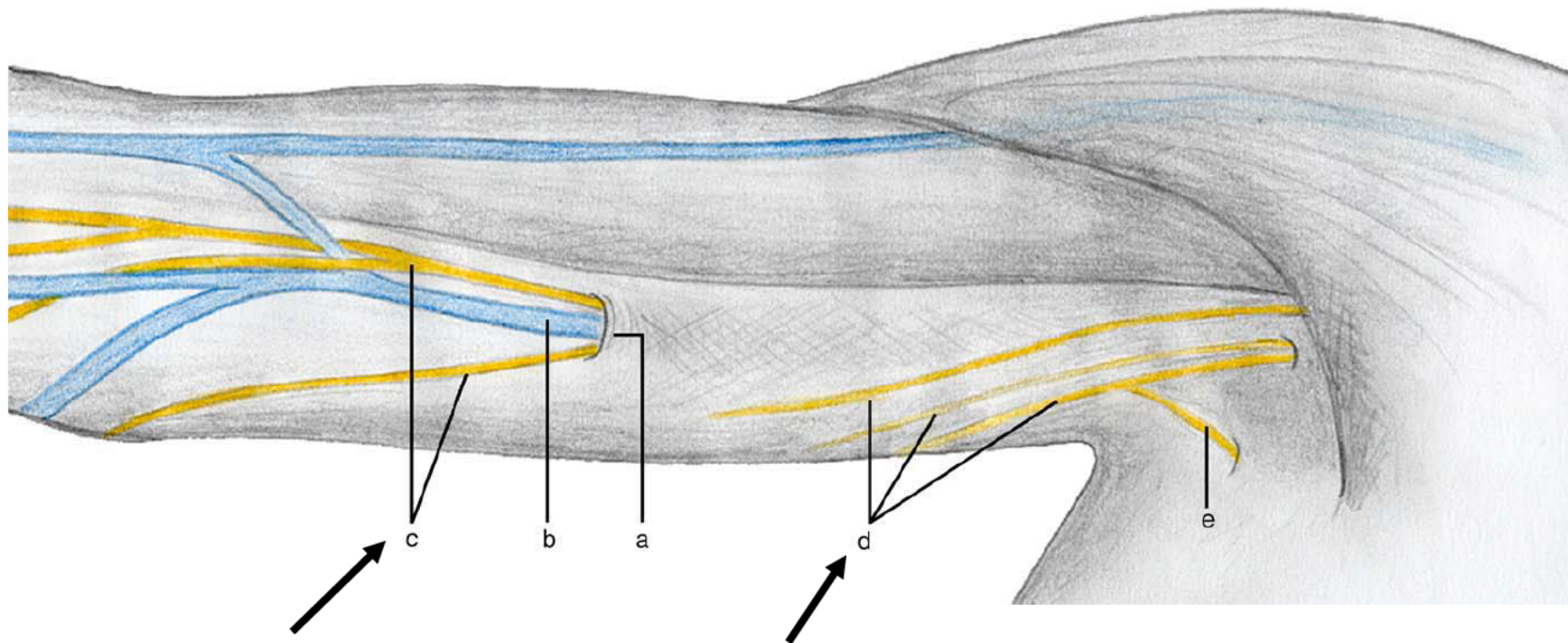
For comparison, the Probughine capsule is 26 mm x 2.5 mm in size



Overview Of Contraceptive Implants

- Features and History of contraceptive implants
- Procedures of Norplant and Nexplanon Implant Insertion and Removal
- Device-Related Adverse Events (AEs)

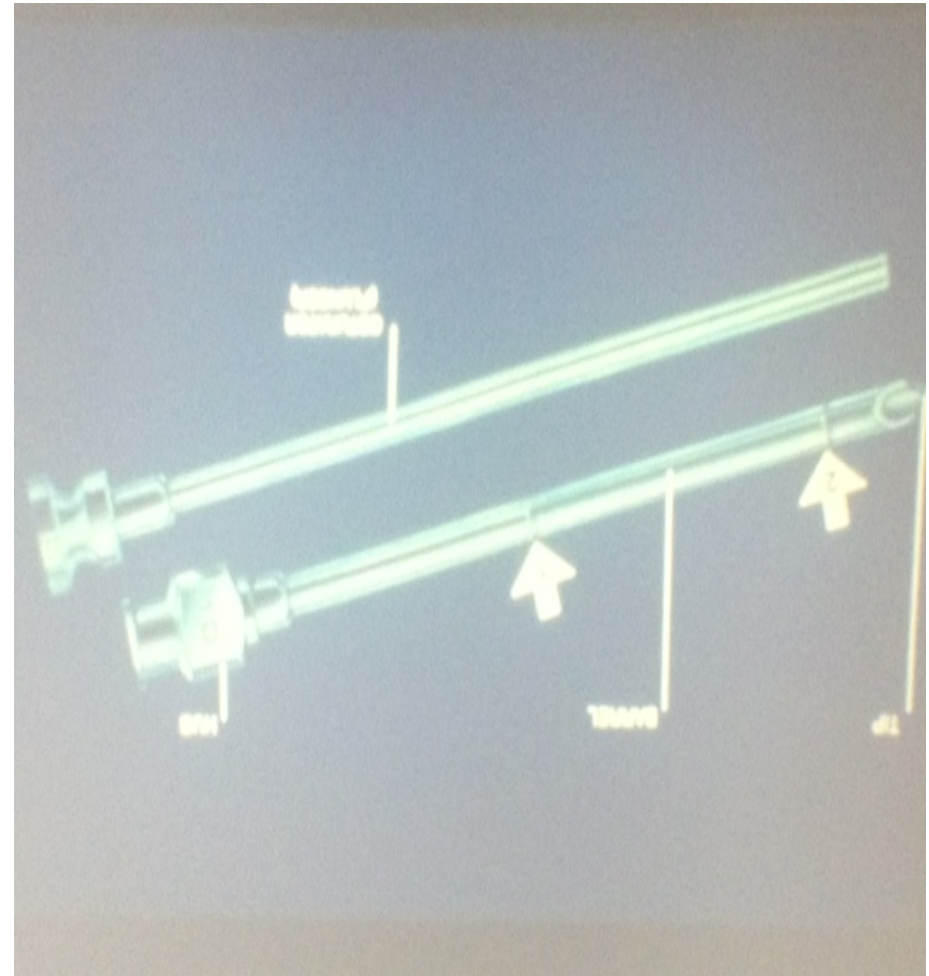
Anatomy of the Upper Arm



Source: Wechselberger 2006 Am J Obstet Gynecol



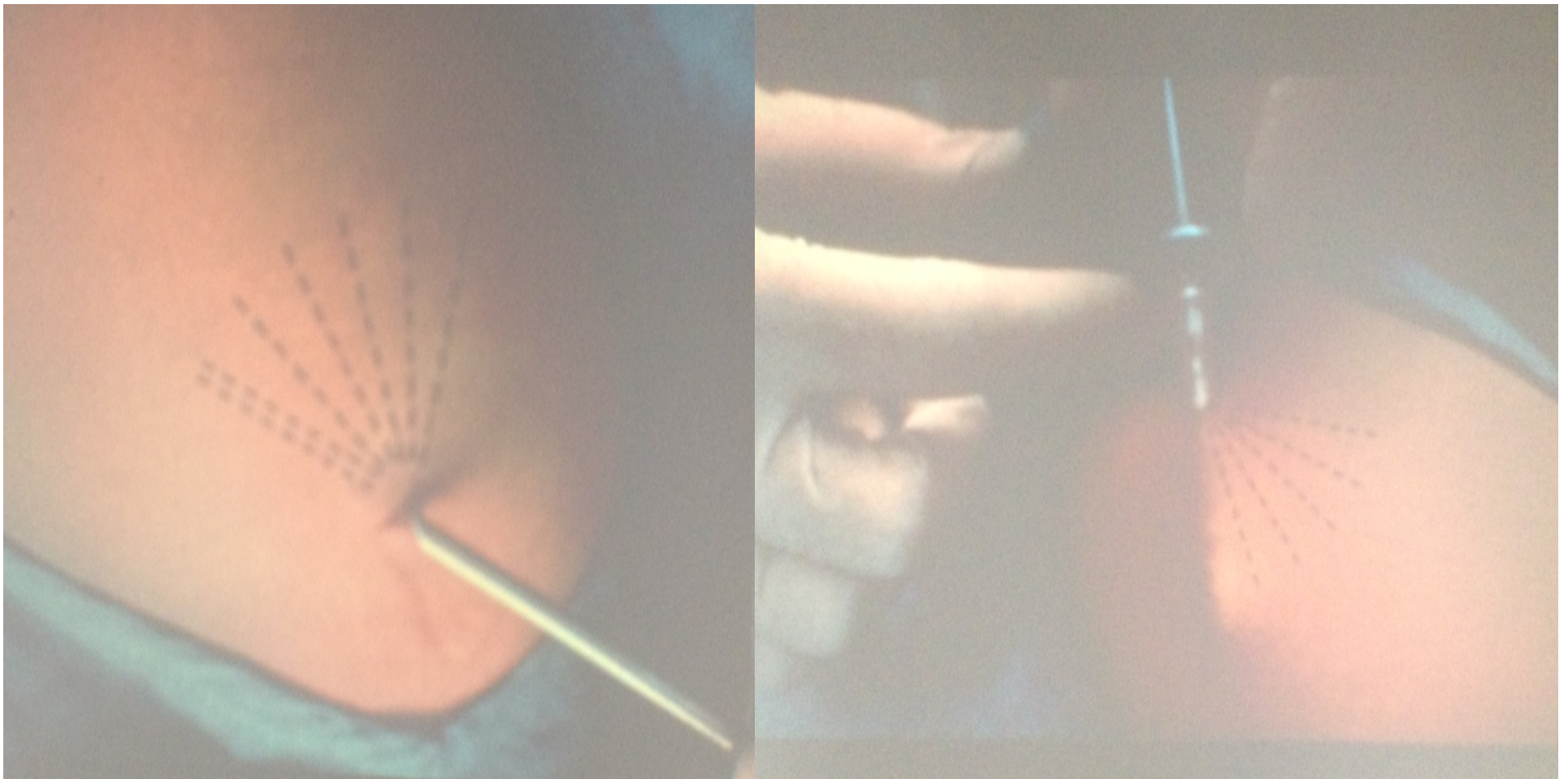
Norplant Insertion



Wyeth Postmarketing Training Materials for Norplant



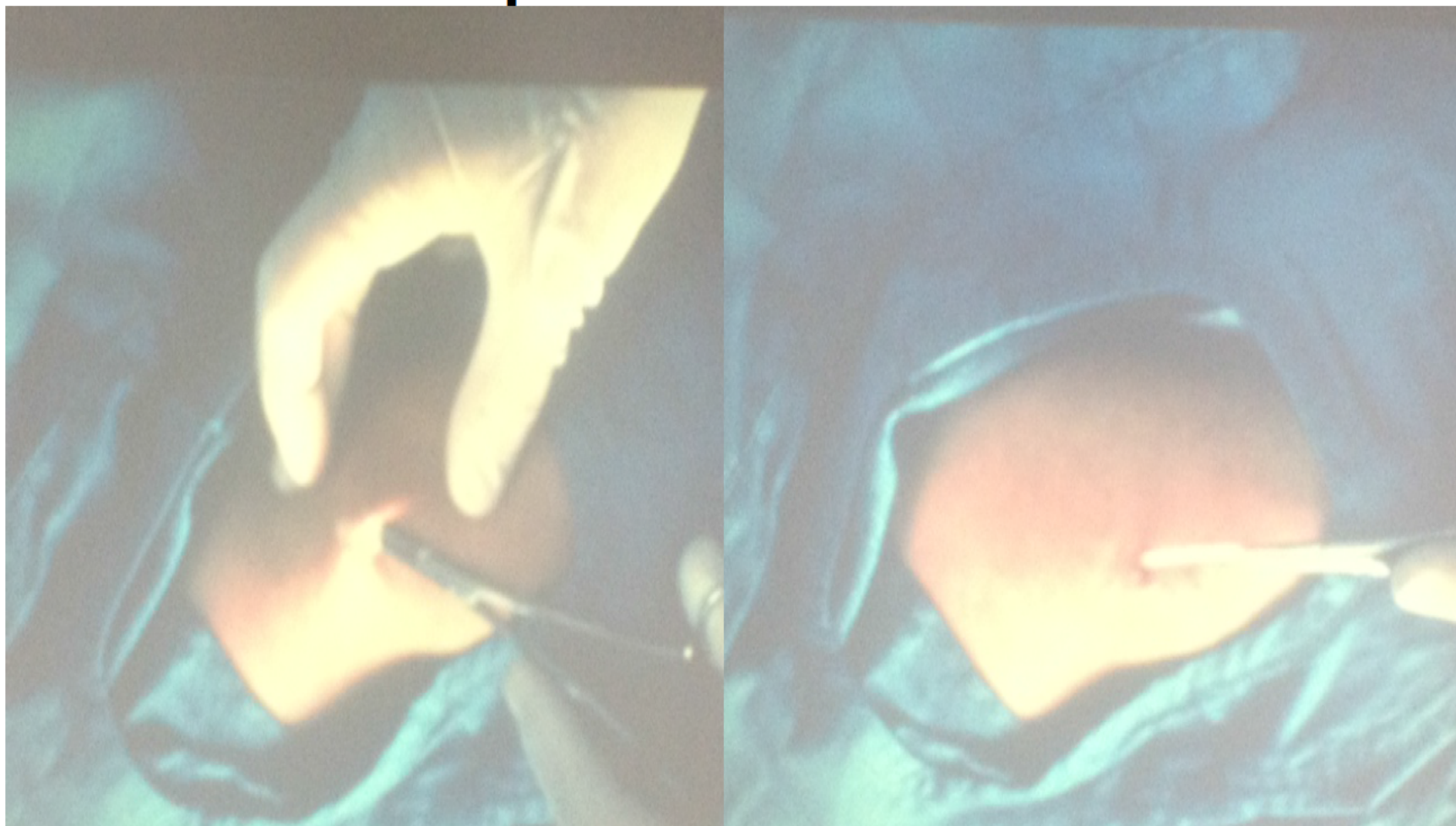
Norplant Insertion



Wyeth Postmarketing Training Materials for Norplant



Norplant Removal



Wyeth Postmarketing Training Materials for Norplant

Nexplanon

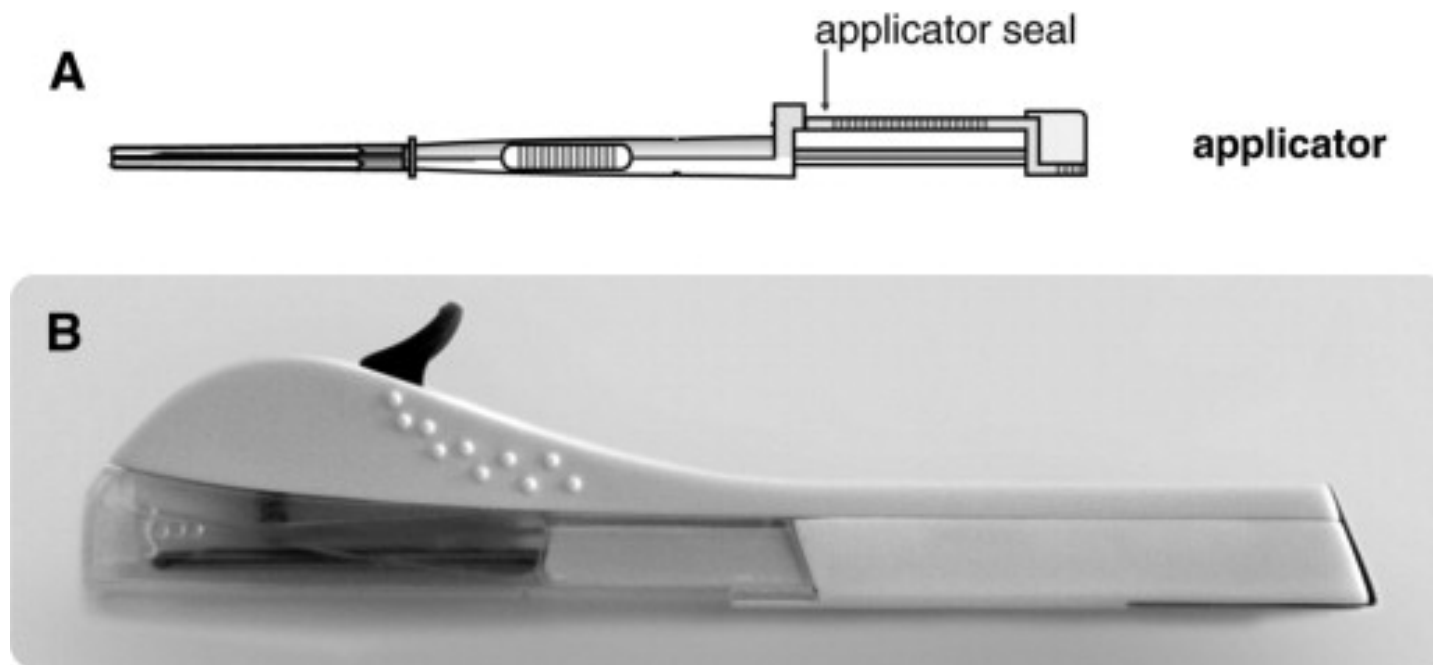
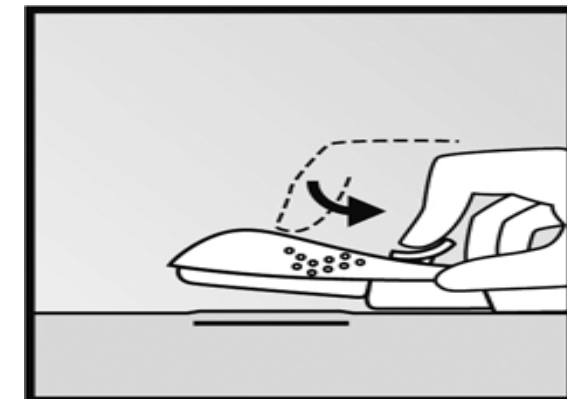
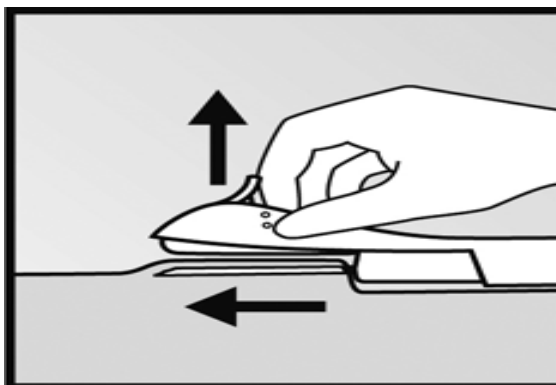
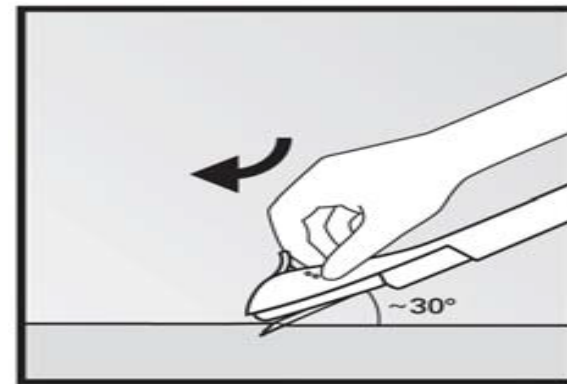
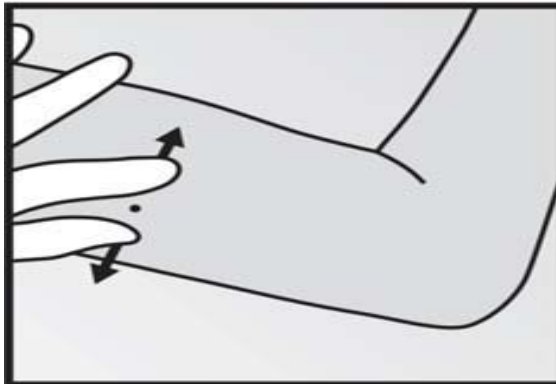


Image of the Implanon and Nexplanon applicator A, Implanon applicator and B, Nexplanon applicator. Implanon and Nexplanon; Merck & Co., Whitehouse Station, NJ. Source: Mommers 2012 Am J Obstet Gynecol

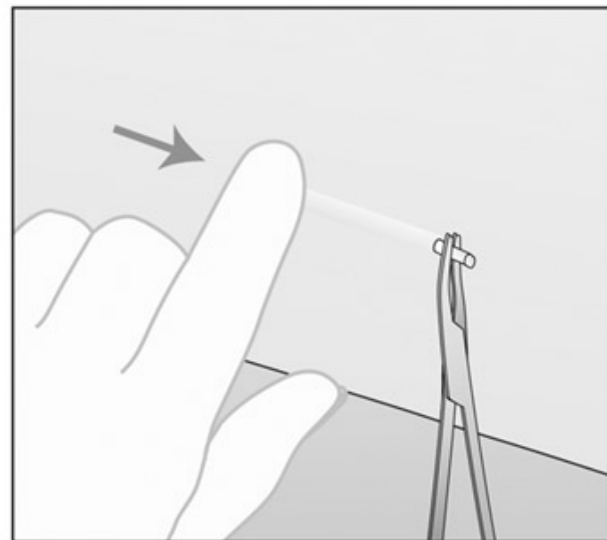
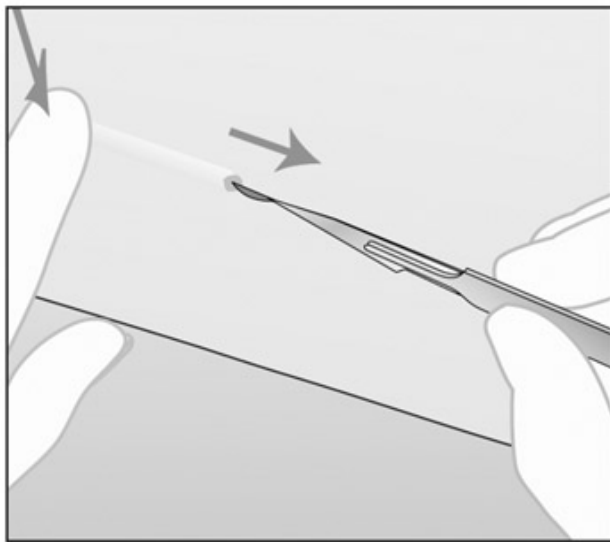
Nexplanon Insertion



Source: Merck website at
<http://www.medicines.org.uk/EMC/printfriendlydocument.aspx?documentid=23824>



Nexplanon Removal



Source: Nexplanon label



Overview Of Contraceptive Implants

- Features and History of Contraceptive Implants
- Procedures of Norplant and Nexplanon Implant Insertion and Removal
- **Device-Related (Norplant; Implanon) Adverse Events (AEs)**
 - Clinical Trial Database (Label)
 - Literature
 - Postmarketing Reports to FAERS



Norplant Device-Related AEs: Clinical Trials

- 849 removal procedures in development program:
 - Removal difficulties: 6.2%
 - Implant site pain/itching: 3.7%
 - Implant site infection: 0.7%



Jadelle Device-Related AEs: Clinical Trials

- > 1100 removal procedures in development program:
 - Removal complications or difficulties: 7.5%
- Procedural complications included deep placement, multiple or long incisions, bruising, displacement, pain, prolonged removal, incomplete removal requiring an additional visit or visits, broken implants, and fibrous pericapsular tissue.



Implanon/Nexplanon Device-Related AEs: Clinical Trials

- Implanon: 942 removal procedures
 - Implant site complications: 3.6%
 - Pain: 2.9%
 - Hematoma: 0.1%
 - Redness: 0.3%
 - Swelling 0.3%
- Nexplanon: 296 removal procedures
 - Removal difficulties: 5.4%, majority were related to development of fibrotic tissue around the capsule



All Device Insertion AEs: Literature review (Brache 2002)

- Insertion complications
 - Infection: 0.0% - 1.4%
 - Expulsion 0 - 0.6% (no infection)



All Device Removal AEs Literature review (Brache 2002)

- Removal Complications
 - Norplant: 4.8% to 14.8%;
 - 0.8% needed second incision or were unsuccessful at first removal attempt;
 - Jadelle: 6.9%
 - Implanon: 0.2%



Norplant vs. Implanon AEs

Cochrane Systematic Review (Power 2007)

Insertion times:

- Norplant 4.3 min
- Implanon 1.1 min

Removal times:

- Norplant 10.2 min
- Implanon 2.6 min

Removal Complications:

- Norplant 4.8%
- Implanon 0.2%



Norplant Device Complication Cases (FAERS)

- **Implant Migration:** to muscle (bicep), tendon, elbow, wrist, axilla, adipose tissue, on bone, near nerves (ulnar) and near veins leading to:
 - **Inability of providers to remove implant**
 - Implant never located or deemed too difficult to remove given proximity to vital structures
 - Up to 5 implants left in patients
 - **Lengthy removal procedures**
 - Several hours to remove
 - **Multiple removal attempts**
 - 2 or 3 attempts
 - patients not returning a second attempt
 - **Surgical removal with general anesthesia**
- **Implant Extrusion or Expulsion**



Norplant U.S. Disability Cases*

FAERS Results	# Cases (N)
Total U.S. Disability cases	43
Disability reportedly related to:	
Device Insertion	13
Device Removal	25
Both Insertion or Removal	2
Other/Unspecified	3

*Reports were excluded if the disability was due to the active ingredient and not due to device insertion or removal

Norplant U.S. Disability Cases

Reported diagnoses (N) included:

- Ulnar nerve injury (11)
- Medial cutaneous nerve injury (5)
- “Nerve damage” (3)
- Injury to both the ulnar and medial cutaneous nerve (2)



Lessons Learned

- Improper insertion technique (mostly deep insertion) is the most important factor leading to removal AEs
- Observation of unexpectedly high number of device-related AEs led to training (postmarketing) on Norplant insertion/removal procedures



Summary

- Adverse events related to contraceptive implants have been well documented with 23 years of U.S. experience.
- Although device-related AEs can be minimized with provider-experience with the drug-device system, risk of serious AEs related to insertion and removal cannot be entirely mitigated.
- The following risk mitigation strategies have led to improvement in implant design:
 - Drug delivery with only one capsule
 - Radio-opaque capsule for location in the event of migration
 - Capsule is preloaded in the applicator with needle, obviating the need for scalpel or trocar, thus enabling insertion with one hand only



Relevance to Probuphine

With Norplant as a predicate device, Probuphine may have a worse device-related AE profile due to:

- The need to replace the capsules every 6 months
- Potentially varied surgical experience of providers performing the procedures



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Backup Slides

Disability Case Example #1

- **FAERS case #:** 5319819
- **Age:** 26
- **Symptom Onset:** Norplant removal
- **Symptoms:** edema, induration & redness at removal site, 7 cm ecchymosis, left arm numbness and pain, inability to fully extend her arm, tingling at the removal site and difficult lifting objects.
- **Reported Disability:** unable to work as a hairstylist
- **Diagnostic test results:** not reported
- **Diagnosis:** injury to the left medial cutaneous nerve of her forearm



Disability Case Example #2

- **FAERS case #:** 4895446
- **Age:** 30
- **Symptom Onset:** Norplant insertion & removal
- **Symptoms:** numbness, pain, tingling of her 4th & 5th fingers and an “electric shock” sensation during prolonged insertion attempt. One year after removal, she had atrophy of the 1st dorsal interosseus and other interossei, atrophy of the ulnar aspect of the hand and the 4th & 5th fingers had mild flexion deformity, sensory loss, and markedly weak abduction and adduction.
- **Reported Disability:** unable to work as a seamstress
- **Diagnostic test results:** not reported
- **Diagnosis:** traumatic injury of the ulnar nerve at insertion



Disability Case Example #3

- **FAERS case #:** 3118192
- **Age:** 27
- **Symptom Onset:** Norplant removal
- **Symptoms:** 1 week after removal, pt required surgery for blood clot & remaining partial Norplant capsule in left arm. Still reporting pain radiating from shoulder to fingers with tingling & numbness in 2 fingers, loss of coordination, weak hand grip, and spasms.
- **Reported Disability:** unable to work as a hair stylist
- **Diagnostic test results:** EMG revealed mild, slow recent onset denervation and re-innervation changes along bilateral C3-C6 nerve roots and left C7-C8 nerve roots.
- **Diagnosis:** ulnar neuropathy. Arm pain and spasm due to cervical radiculopathy of multiple cervical nerve roots.



Imaging Technologies Used to Locate Implants

- Ultrasound – initial approach
- X-ray (primarily with Nexplanon)
- MRI
- Compression film screen mammography
- High resolution fluoroscopy with digital subtraction imaging
- Extensive dissection of the arm rarely necessary



Dislocation Case Example #1

- Norplant inserted for 3 years from 30 March 1992 to 20 April 1995. Norplant implants were removed with some difficulty as evidenced by unusually deep placement (difficult palpation), extensive scar tissue with one implant partially fixed to the bicep muscle at the most superior pole of the implant, and need for extension of incision which required seven 4-0 Prolene sutures for closure

Case # 3431147 version 1

Dislocation Case Example #2

- Norplant in place for eighteen months, experienced arm discomfort when one implant migrated causing a lump in arm. Five implants were successfully removed, however, the sixth implant had migrated to the antecubital fossa (adjacent to the antecubital vein) and required removal by a surgeon because of increased vascularity. Patient tolerated the procedure and there were no complications.

Case # 5359130 version 1



Dislocation Case Example #3

- Complaint of left arm pain and numbness including fingers following second set of Norplant implant inserted October 1991 in downward fan pattern below original incision; migration of implants occurred and 2 implants crossed or touched at one point; shallow insertion of third implant, physician expecting implant was touching ulnar nerve. Implants were removed and third set was inserted.

Case # 3008989 version 1

Dislocation Case Example #4

- Norplant system inserted in left arm approximately two years...had two unsuccessful removal procedures with a total of four implants retrieved...[and] the remaining two implants were close to the bone and patient to require surgery under general anesthesia [for removal]. Patient was referred to a surgeon by clinic physician.

Case # 5224754 version 1

36

Dislocation Case Examples #5,6

- Four implants removed on 11 June 1996 during 25-30 minute procedure; remaining 2 implants located via x-ray and were reported to be deep within the bicep muscle and to remain in place indefinitely. Case # 5552622 version 1
- Four implants were previously removed. X-ray examination of left arm located 5th implant in soft tissue and removed under intravenous sedation. Sixth implant visualized near axilla via X-ray but could not be palpated for removal. Patient referred to orthopedic surgeon.

Case # 5223794 version 1



Dislocation Case Example #7

- Therapy with Norplant system first set began January 1992 and ceased on 14 January 1999 [for 7 years] with second set or six implants inserted the same day. Two implants expelled on 17 January 1999 [3 days later]. The remaining implants from second set were removed 18 January 1999.

Case #3432327 version 1



Dislocation Case Example #8

- Patient experienced movement of implant close to surface of skin and appeared as if they might expel after nearly 2 years of Norplant system use. Patient to have Norplant system checked by physician.

Case # 3150359 version 1



FDA Adverse Event Reporting System (FAERS)

- Computerized database
- Spontaneous reports
- Contains human drug and therapeutic biologic reports
- > 7 million reports since 1969
- > 700K new reports in 2011





Strengths of FAERS

- Includes all U.S. marketed products
- Includes all uses
- Includes broad patient populations
- Simple, relatively inexpensive reporting system
- Especially good for events with a rare background rate
- Useful for events with short onset
- Detection of events not seen in trials (“signal generation”)
- Identification of trends, possible risk factors, populations, and other clinically significant emerging safety concerns



Limitations of FAERS

- Events with high background rates
- Worsening of pre-existing disease
- Issue is beyond the name of the drug
- Comparative incidence rates
- Comparing drugs in the same class
- Disease is reflected in the adverse event
- Looking for drug interactions
- Reporting Biases

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/s/

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MEMORANDUM
Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: March 27, 2013

To: Bob Rappaport, MD, Director
Division of Anesthesia, Analgesia, and Addiction Products
(DAAAP)

Through: Michael Klein, PhD, Director
Controlled Substance Staff

From: Stephen Sun, MD, Medical Officer
Controlled Substance Staff

Subject: **Topic:**
Abuse Potential Assessment of New Drug Application
Application:
NDA 204442 - Probuphine (buprenorphine) implant; 80 mg
buprenorphine per Probuphine implant; single treatment dose for 6-
month period is 4 (to 5) implants
Proposed Indication:
Treatment of Opioid Dependence
Sponsor:
Titan Pharmaceuticals

Materials reviewed: 1. Titan Pharmaceuticals. 1.11.4 Abuse Potential Assessment. NDA
204442 (Probuphine).
2. Titan Pharmaceuticals. Titan's Response to FDA's Clinical and
Controlled Substances Review Comments; Probuphine NDA 204442
60-Day Review Letter. Attachment A. Feb 1, 2013.

Table of Contents

I. SUMMARY	2
A. BACKGROUND:.....	2
B. CONCLUSIONS:	2
C. RECOMMENDATIONS TO DIVISION:	4
II. DISCUSSION	7
A. CHEMISTRY:	7
B. PHARMACOLOGY	8
C. CLINICAL PHARMACOLOGY.....	8

D.	CLINICAL STUDIES	8
E.	INTEGRATED ASSESSMENT.....	10

I. Summary

A. Background:

This memorandum is in response to a CSS consult dated November 2, 2012, for the Division of Analgesics, Anesthetics, and Addiction Products pertaining to NDA 204442 (previously IND 70852) for Probuphine (buprenorphine) subcutaneous implant under development by Titan Pharmaceuticals. In addition to requesting CSS participation in the internal meeting and industry meetings, the consult involves a review of the submitted new drug application.

Buprenorphine is presently marketed for the treatment of opioid dependence and chronic pain in various marketed forms such as sublingual tablets, injections, sublingual films, and transdermal patches. Sponsor proposes that the advantage of the implant formulation over currently marketed forms of buprenorphine is to increase treatment compliance, maintain long-term pharmacotherapy for indicated patients. (b) (4)

B. Conclusions:

1. Probuphine is a first-in-class buprenorphine implant formulation for the treatment of opioid dependence. The Sponsor proposes this application as a 505(b)(2) submission given the known history of buprenorphine; therefore, the preclinical and clinical abuse-related literature are referenced. Buprenorphine is a well-characterized, partial mu-opioid receptor agonist and kappa-opioid receptor antagonist that are found in currently marketed products for the treatment of opioid dependence and chronic pain. The active ingredient, buprenorphine, resides on an implant matrix consisting of ethylene vinyl acetate (EVA), an excipient found in previously marketed gynecologic products that use a similar implant technology.
2. The following are the abuse-related highlights of Probuphine:
 - a. Regulatory
 - (i) Sponsor proposes a labeling language similar to Suboxone.
 - (ii) Sponsor proposes the product as a DEA Schedule III controlled substance.
 - b. Non-clinical Studies
 - (i) Heat application study in dogs did not show evidence of accelerated drug release.

c. Clinical Pharmacology

- (i) Pharmacokinetic profiles show a consistent buprenorphine plasma level over its several weeks of implantation use.

d. Clinical Studies

- (i) (Abuse-related adverse events) Abuse-related adverse events in double-blinded and open-labeled studies are generally consistent with known buprenorphine adverse events. Unique events are primarily implant-site related events.
- (ii) (Residual drug following full-course dose) Sponsor indicated the presence of approximately 40% residual buprenorphine following the removal of the implant over a six-month period in clinical studies.
- (iii)(Dislodged implant) Two cases of accidental dislodgement of the implant were reported in earlier studies. Sponsor updated the training program and improved the implant product; latter studies did not experience such events.
- (iv) (Lost to follow-up) Sponsor indicated that 9.1% of implants in Probuphine and 7.6% of placebo implants did not have implants removed in the clinical studies. A few patients subsequently returned months after the study period while others were lost to incarceration or inpatient treatment. One subject was documented as unwilling to return for implant removal.

e. Integrated Assessment

- (i) Probuphine is the first DEA-scheduled drug implant. Due to the complexity involving the dispensing and distribution of scheduled drugs and the prescribing of buprenorphine for opioid dependence, the product will need to meet both the requirements of the Controlled Substances Act and the Drug Abuse Treatment Act. The Sponsor has previously provided information to both the DEA and SAMHSA to seek clarification for meeting their legal requirements and was reminded to meet directly with the respective agencies for updates.
- (ii) Sponsor proposed a Risk Evaluation and Mitigation Strategy (REMS) to minimize inappropriate implant placement using structured training and incorporate safeguards to minimize misuse, abuse, and diversion. As proposed, Sponsor's proposed REMS is a closed distribution system consisting of a central pharmacy that directly distributes the product to the healthcare professional following the verification of a valid prescription (patient does not have access to the implant until the procedure). At the time of this implant, the REMS will be further updated with the FDA's Division of Risk Management following recent dialogue with the DEA.

(iii) Sponsor proposes (b) (4) to document drug disposal and follow state and federal guidelines on controlled substance disposal as a method to minimize the risk of diversion.

3. An implantable buprenorphine for the management of opioid dependence would ideally optimize the compliance of buprenorphine daily dosing for a patient over a six-month period and provide patient convenience while keeping the controlled substance out of physical reach from misuse, abuse, and diversion by the patient, caregivers, and associates. While the volume of abusable doses and its accessibility when compared to the existing sublingual formulation (standard of care which equates to 180 to 360 oral doses over a 6-month period) are far less, the risks of overdose and death exist at a greater hazard per dose if fully extracted and used non-medically. The intent of the Sponsor's adequate REMS is to address the following risks:
 - a. (Pre-Implant) The risk of diversion exists if the product is not appropriately handled or accounted at the following locations: the distribution center, the centralized pharmacy, medical site for implantation.
 - b. (Implanted) The risk of misuse, abuse, and diversion if the product is not implanted correctly and subsequently dislodges or is intentionally removed from the implant site.
 - c. (Post-implant) The risk of diversion exists if the product is not appropriately discarded upon removal.

C. Recommendations to Division:

1. Overall, if the Sponsor's REMS is revised with a model of care that meets the requirements of both the CSA and DATA, the benefits for this Probuphine implant should outweigh the risks of misuse, abuse, and diversion. While the potential for non-medical use may still exist, the product's inaccessibility when implanted as indicated in this high-risk population of opioid-dependent patients seeking treatment would likely be a net positive benefit. No abuse-related, specific deficiencies are noted if the provisions for safe use are well-incorporated into the REMS.
2. As a first-in-class controlled substance implant, the Sponsor should ensure that the REMS and its model of care meet the legal and regulatory requirements specified by the CSA and DATA and should meet with DEA and SAMHSA directly to obtain any clarifications.
3. If the product is approved, any attempts of intentional removal of implants to access the buprenorphine for abuse should be reported as a 15-day postmarketing surveillance safety report as an important medical event. Any cases of early

removal, lost implants, and lost-to-follow up patients (who do not have implants removed) should be well-summarized and reported in the periodic safety reports.

4. Sponsor's proposal for maintaining this buprenorphine product as a DEA Schedule III status is acceptable. Using the existing, approved oral buprenorphine as a template label, the final product label should be customized for this implant formulation. If the product is approved, the abuse relevant sections of the label should incorporate the following text:

5 WARNINGS AND PRECAUTIONS

5.1 Abuse Potential

Buprenorphine is a DEA Schedule III opioid and can be abused in a manner similar to other opioids. Appropriate safeguards, including routine patient monitoring and assessment, should minimize the risks. Buprenorphine can be extracted from new and used implants for abuse; thus, strict accounting and handling of implants prior to insertion and after removal are required.

5.5 Unintentional Pediatric Exposure

While the risk from direct contact to caregivers and family members may be reduced by the subdermal location of the implant, risks associated with expulsion or extraction of the buprenorphine-containing implants remain. Buprenorphine can cause severe, possibly fatal, respiratory depression in children who are accidentally exposed to it. Immediate medical attention should be sought if there is the potential for direct contact to a dislodged or expelled implant.

5.6 Dependence

Buprenorphine is a partial agonist at the mu-opioid receptor and chronic administration produces dependence of the opioid type, characterized by withdrawal upon abrupt discontinuation or rapid taper. The withdrawal syndrome is milder than that seen with full agonists, and may be delayed in onset.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

PROBUPHINE contains buprenorphine, a Schedule III narcotic under the Controlled Substances Act. *Under the Drug Addiction Treatment Act (DATA) codified at 21 U.S.C. 823(g), prescription use of this product in the treatment of opioid dependence is limited to physicians who meet certain qualifying requirements, and who have notified the Secretary of Health and Human Services (HHS) of their intent to prescribe this product for the treatment of opioid dependence and have been assigned a unique identification number that must be included on every prescription.*

9.2 Abuse

Buprenorphine, like morphine and other opioids, has the potential for being abused and is subject to criminal diversion. This should be considered when prescribing and implanting PROBUPHINE in situations when the clinician is concerned about an increased risk of misuse, abuse, or diversion. Healthcare professionals should contact their state professional licensing board or state controlled substances authority for information on how to prevent and detect misuse, abuse, and diversion of this product.

PROBUPHINE is implanted under the skin in the upper arm by a trained healthcare provider. However, implants may be intentionally or unintentionally removed and buprenorphine can be released and extracted. A physical inspection of the patient's implant site should be performed during routine evaluation when possible to ensure proper placement. Used implants contain active buprenorphine and should be accounted for and disposed appropriately to prevent misuse, abuse, and diversion.

Some patients who are treated with Probuphine may need supplemental buprenorphine from time to time. Care should be taken in prescribing and monitoring patients' appropriate use of this medication. Patients who continue to misuse, abuse, or divert buprenorphine products or other opioids should be provided with or referred for more intensive and more structured substance abuse treatment.

Abuse of buprenorphine poses a risk of overdose (See 10. Overdose) and death. This risk is increased with the concomitant abuse of CNS depressants, including opioids, alcohol and other substances, especially benzodiazepines.

The physician may be able to more easily detect misuse, abuse, and diversion by maintaining records of medications prescribed including date, dose, quantity, and frequency of refills and renewal requests of medications prescribed.

Proper assessment of the patient, proper dispensing practices, periodic re-evaluation of therapy, and proper handling and storage of PROBUPHINE are appropriate measures that help to limit misuse, abuse, and diversion of opioid drugs.

9.3 Dependence

Buprenorphine is a partial agonist at the mu-opiate receptor and chronic administration produces physical dependence of the opioid type, characterized by moderate withdrawal signs and symptoms upon abrupt discontinuation or rapid taper. The withdrawal syndrome is typically milder than that seen with full agonists and may be delayed in onset [*see Warnings and Precautions (X.X)*].

A neonatal withdrawal syndrome has been reported in the infants of women treated with buprenorphine during pregnancy [*see Warnings and Precautions (X.X)*].

10 OVERDOSAGE

The manifestations of acute overdose include pinpoint pupils, sedation, hypotension, respiratory depression, and death. In the event of overdose, the respiratory and cardiac status of the patient should be monitored carefully.

In the case of overdose, the primary management should be the re-establishment of adequate ventilation with mechanical assistance of respiration with intravenous fluids and vasopressors, if required.

Naloxone may be of (limited) value for the management of buprenorphine overdose, as higher than normal doses, repeated administration, and continuous infusion may be necessary.

Removal of the Probuphine implant may be considered after stabilizing a patient from overdose.

II. Discussion

A. Chemistry:

1. Probuphine is a novel polymeric matrix of approved buprenorphine (BUP) with an ethylene vinyl acetate (EVA) excipient. The concept is based on the subcutaneous implantation (requiring a small skin incision and an implanting device) of 4 to 5 “extruded” rods of BUP/EVA to deliver continuous therapeutic dose levels of BUP over a 6-month single treatment period after an initial induction period of sublingual buprenorphine. Each implant stick is 26 mm in length and 2.5 mm in diameter with a weight of 112 mg and intended for placement on the inner aspect of the patient’s upper arm, approximately 2.5 to 3 mm underneath the skin’s surface, by a “course-certified” medical professional. Each Probuphine implant contains 80 mg of buprenorphine HCl and an inactive excipient of EVA that is intended to provide sustained release of drug for up to 6 months.
2. Buprenorphine is a well-characterized, partial mu-opioid receptor agonist and kappa-opioid receptor antagonist and is a DEA Schedule III controlled substance. As a 505(b)(2) application, Sponsor cites the reference listed drug (RLD) of approved buprenorphine as the basis for evaluation.
3. EVA is considered to be an inert excipient that is found in several existing marketed products including Implanon® (etonogestrel, NDA#21529, Organon USA) and Nexplanon® (etonogestrel, NDA#21529, Organon USA)¹.

¹ FDA. Orange Book – online at www.fda.gov. Accessed: 9/30/11.

4. As a surrogate for evaluating the effects of skin exposure, data from dissolution study indicates that an implant placed in 900 mL of purified water at 37°C for 4-hours shows that the amount of buprenorphine released ranges between 4.2 mg and 6.2 mg. In the absence of formal studies, brief exposure to the implants, e.g. several minutes, would result in less than 4.2 mg to 6.2 mg of drug exposure.
5. Sponsor provided information that in the event of intentional extraction, majority of buprenorphine may be released within 24 hours using methanol and at least 80% of buprenorphine will be released in purified water over 96 hours.

B. Pharmacology

1. No self-administration or discrimination studies were provided by the Sponsor. As a 505(b)(2), Sponsor uses the RLD as the basis for abuse-related evaluation.

C. Clinical Pharmacology

1. To better understand the risk severity of drug exposure after an implant was used for six months, Study TTP-400-02-01 showed that 40% of the 90 mg of buprenorphine dose (earlier formulation) in each implant remained while in Study PRO-805, 40% of the 80 mg buprenorphine remained.

D. Clinical Studies

1. No human abuse potential studies were provided by the Sponsor. As a 505(b)(2), Sponsor uses the RLD as the basis for abuse-related evaluation of buprenorphine.
2. Following a six-month dosing period, the product would be removed and another implant is placed in the contralateral arm. The sequence would be rotated every 6 months. However, Sponsor has only provided data for a two-implant cycle totaling 12-months.
3. Occurrence of abuse-related adverse events in the clinical studies included the following:
 - a. Adverse event profiles for drug abuse, dependence, and withdrawal in double-blind studies of Probuphine v. placebo vs. sublingual buprenorphine did not differentiate except for nausea (8.5% v. 4.6% v. 6.7%), depression (6.3% v. 4.6% v. 2.5%), fatigue (4.1% v. 1.8% v. 0.0%), somnolence (3.2% v. 0.0% v. 0.8%), and asthenia (2.3% v. 0.0% v. 0.8%). Adverse event profiles for open-label studies (PRO-807 and PRO-811) had similar rates. However, in all studies, investigators also had opportunities for rescue medications of sublingual buprenorphine.

- b. 33M (Subject (b) (6)) reported one AE of “euphoric mood” but was confounded with findings of concurrent drug abuse (6-mono-acetylmorphine, codeine, and morphine on urine toxicology).
- 4. Sponsor cites that “... no evidence of withdrawal or dependence was observed on the basis of AEs collected in the 14-to 39-day period following implant removal...” as collected all studies. According to the Sponsor, subjects may have self-medicated or clinicians were given authority to prescribe sublingual buprenorphine during their transition period to minimize withdrawal events.
- 5. Sponsor reports two overdose events and one case of accidental fatal overdose across the clinical studies of Probuphine but none were attributed to Probuphine during the development program, as described below:
 - a. (Subject (b) (6)) 26F assigned to placebo group overdosed on 50-500 mg Tylenol tablets and was discontinued from the study.
 - b. (Subject (b) (6)) 22M assigned to the Probuphine group overdosed on methadone after 18 weeks following insertion; subject recovered and the event was reported as serious but not related to the study drug.
 - c. (Subject 619-036) 29F assigned to SL buprenorphine group withdrew from the study but subsequently had an accidental, fatal overdose attributed to heroin 3 days after her study withdrawal.
- 6. No documented intentional attempts to remove the implant for the purpose of abuse were reported. However, 3 cases of spontaneous implant expulsion were documented due to poor implant technique.
 - a. (Study PRO-807) One subject returned to clinic 3.5 months after initial implant insertion with an implant reported expelled half-way on its own and removed 3 days prior to the clinic; at the visit, the clinic staff removed a second implant that was also partially expelled. Case was attributed to improper insertion technique.
 - b. (Study PRO-806) One subject had implants fall out at 2 different times with the first implant falling out due to infection and a second implant reported as discarded. Case was attributed to improper insertion technique.
 - c. As reported by the Sponsor, the instructions for proper insertion technique and implant insertion equipment were both improved; latter expulsion events were subsequently infrequent.

7. Overall, 36 subjects (9.1% of implants) in the Probuphine group and 9 subjects (7.6% of placebo implants) in the Placebo group did not have implants removed. The long-term effects of a non-removed implant should be reported as a subsequent post-marketing surveillance update. The following cases were reported by the Sponsor for products removed outside of the clinical schedule:
 - a. 3 Probuphine subjects and 1 placebo subject had implants removed several months after the study ended.
 - b. 3 subjects in the Probuphine and 2 subjects were unaccounted for due to incarceration or inpatient drug treatment programs.
 - c. 1 subject was identified as unwilling to return for implant removal.

E. Integrated Assessment

1. Postmarketing Experience - Review of Literature

- a. Probuphine is a first-in-class implant formulation of buprenorphine and the first controlled substance implant that requires a subsequent device removal procedure. There is no postmarketing experience.
- b. Sponsor provided an overview on the state of buprenorphine abuse based on published information from DEA's ARCOS and NFLIS, SAMHSA's DAWN and NSDUH, AAPCC's NPDS, proprietary databases RADARS, and other literature sources showing abuse of prescribed formulations (only oral). Notably, Sponsor cites 1,199 cases of accidental ingestion of buprenorphine in 2009, with 95% (1,126 cases) involving children under the age of 6.
- c. According to recent statistics, "The estimated number of emergency department visits in which buprenorphine was involved as either a direct cause or a contributing factor increased from 3,161 in 2005 to 30,135 in 2010, according to a recently released report from the Substance Abuse and Mental Health Services Administration (SAMHSA). More than half (52%) of these buprenorphine-related emergency department (ED) visits were for the nonmedical use of pharmaceuticals." (University of Maryland, 2013)²
- d. According to OSE's consult review, there were approximately 10.7 million dispensed prescriptions of oral buprenorphine-containing products for 1

² University of Maryland. Number of U.S. emergency department visits involving buprenorphine increases nearly ten-fold from 2005 to 2010. CESAR Fax. February 4, 2013. 22(5).

million patients during year 2012; an estimated 94% of patients were prescribed buprenorphine products intended for opioid dependence management. The top three specialties who prescribed oral buprenorphine were general practitioner/family medicine (26-32%), psychiatry (22 to 24%), and internal medicine (14 to 16%).³

2. Misuse, Abuse, and Diversion

- a. The proposed Probuphine formulation contains only buprenorphine, a DEA Schedule III substance. The formulation is proposed to minimize the risks of misuse, abuse by implanting the six-month buprenorphine product underneath the skin for patients with opioid drug dependence and thereby keeping it out of reach for nonmedical use. Due to its six-month duration or dosing period, the public health benefit is its large reduction in the volume of tablets/pill/doses that would otherwise be dosed and be potentially abused over the same time period. However, while the number of abuse opportunities is reduced (# of doses), the potency of buprenorphine in each Probuphine implant is greater and becomes a higher hazard per dose if abused and the active is extracted fully.
- b. To ensure that the implant is correctly inserted and product is handled appropriately to minimize misuse, abuse, and diversion, the Sponsor proposed a Risk Evaluation and Mitigation Strategy to address these two concerns and is currently being evaluated by the Division of Risk Management. As a DEA Schedule III buprenorphine product, the Sponsor will need to meet both the Controlled Substances Act and the Drug Addiction Treatment Act in their model of care. As of the date of this consult, the Sponsor had recently received feedback of their proposed model of care from the DEA and was deemed not acceptable. One of the primary concerns is the Sponsor's proposal (b) (4)
- c. The product is inserted as an implant in the subcutaneous space as performed by a "course-certified" prescriber. Following the procedure, the small "skin" incision is closed by adhesive tape provided by the Implanter that will be visible by the patient. The patient may only be able to palpate the 4-5 implants. As proposed by the Sponsor, when used as prescribed the implants will be removed after six months by a healthcare professional and disposed through guidelines recommended by the Centers for Disease Control on biowaste. The EVA implant is non-biodegradable.
- d. While not observed in the clinical studies, during the immediate, post-placement period, an abuser or diverter could conceivably, with physical

³ Mathew J. Buprenorphine (Subutex® tabs) and buprenorphine/naloxone (Suboxone® tablet and film). FDA / Office of Surveillance and Epidemiology. Drug Use Review Memorandum. February 19, 2012.

manipulation, intentionally remove the high-dose buprenorphine rods for non-medical use and diversion. Therefore, routine physical examination by a clinician of the implant site will be recommended in the proposed label.

- e. No formal extraction study was performed on the product itself given its proposed closed distribution system (handling only by qualified healthcare professionals). However, Sponsor indicated that in vitro release rate showed 90-95% of active is released within 4 to 5 days in water and 15 mg of buprenorphine can be washed off after 30 minutes using ethanol (buprenorphine is known to be soluble in ethanol). Since accidental pediatric exposure remains a concern particularly with the higher dose of buprenorphine that is in each rod, potential evaluation of the child by a medical professional will be recommended in the label if accidental exposure may have occurred.
- f. To assess the potential that temperature may affect the release (absorption) of active, Study PRO-NDR-1202 conducted in dogs showed that external heat applied ($40\pm 1^{\circ}\text{C}$) at the implant site had no impact before, during, and after the heat application on the pharmacokinetic profile.
- g. Following implant removal, residual buprenorphine after six months of use in Study TTP-400-02-01 showed 40% (36 to 37mg) of the 90 mg buprenorphine dose remained in each implant. In study PRO-805, using the final 80 mg formulation of buprenorphine, 40% of buprenorphine also remained following a six-month course.
- h. While the REMS and DATA requirements include the requirements for the prescribing physician, the “technical” healthcare professional (a surgeon or other equipped internist) should also be trained on the appropriate disposal of an explanted controlled substance. The removed “explant” must not be cleaned and returned to the patient; the healthcare professional should be similarly trained or follow disposal guidelines as described in the REMS given the risk of unintentional exposure and possibility for high-dose buprenorphine extraction for abuse and used implant diversion.
- i. In the event that the implant is dislodged or protruding from the wound site, appropriate handling instructions should be provided to minimize the risk of diversion.
- j. Appropriate documentation and accountability of four or five implants should be in place to minimize the risk of unintentional exposure and diversion, particularly if the prescriber, implanting physician and removal physician are different persons. To encourage proper drug accountability, Sponsor proposes

the use of a Probuphine Distribution Log to be kept by the prescriber (b) (4)
(b) (4) as part of the Sponsor's REMS.

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/s/

STEPHEN W SUN
03/27/2013

MICHAEL KLEIN
03/27/2013

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: January 31, 2013

SUBJECT: Evaluation of Response from NAMSA (North American Science Associates, Inc.) Regarding 2006 FDA Warning Letter Related to Study 01T-06823-00 "Chronic Toxicity Study of Buprenorphine Delivery System Implanted Subcutaneously for 10 Months in Dogs" submitted with IND 70,852 and NDA 204-442 by the sponsor, Titan Pharmaceuticals, Inc., South San Francisco, CA

FROM: Zhou Chen, M.D., Ph.D.
Pharmacologist, Good Laboratory Practice (GLP) Branch
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations (OSI)

THROUGH: Charles R. Bonapace, Pharm.D.
Acting Branch Chief, GLP Branch
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations (OSI)

William H. Taylor, Ph.D.
Director, Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations (OSI)

TO: Bob A. Rappaport, M.D.
Director
Division of Anesthesia, Analgesia and Addiction Products (DAAAP)

Summary: A GLP inspection was conducted at North American Science Associates, Inc. (NAMSA) in Northwood, Ohio from April 11, 2005 to May 9, 2005 following a request from the Division of Anesthesia, Critical Care, and Addiction Drug Products on February 1, 2005. At the close-out of the inspection, a 14-item Form FDA 483 was issued, which included seven observations relevant to CDER. In the CDER EIR review dated August 29, 2005, OSI (DSI at the time of the review) recommended that nonclinical study # 01T-06823-00 titled "Chronic Toxicity Study of Buprenorphine Delivery System Implanted Subcutaneously for 10 Months in Dogs" not be accepted for review. On May 11, 2006, DSI issued a Warning Letter to NAMSA, highlighting six GLP violations during the conduct of the 10-month dog toxicity study. On June 2, 2006, NAMSA submitted their response to the FDA Warning Letter with supporting materials. However, a DSI review of NAMSA's responses to Form FDA 483 and the Warning Letter was not performed at the time of receipt, possibly because of significant personnel changes, workload, and inadequate internal oversight.

This memo is an evaluation of the firm's May 18, 2005 response to Form FDA 483 and the June 2, 2006 response to the FDA Warning Letter.

Based on NAMSA's response to Form FDA 483 and the FDA Warning Letter, this reviewer recommends that the final study report be accepted for review. No conclusions linking the dose of buprenorphine to toxicological findings can be drawn for Groups A1 and A2 animals. However, data establishing the link between the dose of buprenorphine and toxicological findings in Groups B1 and B2 animals are adequate, and the association between plasma concentrations of buprenorphine and toxicological effects could also be evaluated based on the available data.

Review and evaluations:

Study 01T-06823-00 was initiated on July 9, 2001 and finalized on September 23, 2002. The evaluation of the deficiencies listed in the FDA Warning Letter and NAMSA's responses to Form FDA 483 and the 2006 Warning Letter follow.

Warning Letter Item 1: Your study director failed to assure that the protocol, including any changes, was followed, and that all experimental data were accurately recorded and verified. [21 CFR 58.33(a, b) and 21 CFR 58.130(a, e)]

The protocol required that each dog in test groups A1, A2, B1, and B2 be implanted with either 24 test article rods (delivering controlled-release buprenorphine) or 24 control rods. Study records fail to document the number of test article or control article rods implanted in each dog. In the May 18, 2005 response to Form FDA 483, the firm acknowledged that the implant procedure records do not document the number of control or test article rods actually implanted. However, study records also do not document the specific lot(s) of test article implanted in each animal and, consequently, characterization information for those lots cannot be linked to specific animals. Because the firm failed to document the number of rods inserted into, or identify the lot of test article administered to, each animal, the dose of buprenorphine delivered to the test animals cannot be assured per the protocol. Thus, no conclusions linking the administered dose of buprenorphine to toxicological findings can be drawn for Groups A1 and A2 animals. However, the association between the plasma concentrations of buprenorphine and toxicological effects could be evaluated based on the available data.

NAMSA's Response: The firm's management acknowledged that the test and control articles implanted for particular animals and times were not appropriately recorded. (b) (4)

[REDACTED]

[REDACTED] (b) (4)

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(b) (4)

Evaluation: The protocol specified the number of rods to be implanted, and the firm's response to the Warning Letter stated that the protocol was adhered to. However, the firm did not document the actual number of rods inserted in each animal to assure that the protocol was in fact followed. Study records also do not document the specific lot(s) of test article implanted in each animal and, consequently, characterization information for those lots cannot be linked to specific animals. Because the firm failed to document the number of rods inserted into, or identify the lot of test article administered to, each animal, the dose of buprenorphine delivered to the test animals cannot be assured per the protocol. Thus, no conclusions linking the administered dose of buprenorphine to toxicological findings can be drawn for Groups A1 and A2 animals.

(b) (4)

The (b) (4) records provide indirect documentation to support the number of rods implanted. However, the reviewer believes that

(b) (4) adequate documentation to support the number of rods actually implanted in Groups B1 and B2 animals. (b) (4)

(b) (4). Therefore, the lack of direct documentation to support the number of rods implanted in Groups A1 and A2 animals should not preclude the acceptance of the study report for review.

Warning Letter Item 2: The final report did not identify the test article by strength, purity, and other appropriate characteristics. [21 CFR 58.185(a)(4)]

The study records indicate that five lots (batches) of test article (13657-06, 13933-17, 13933-19, 13922-22, and 13657-44) were used during the study. However, the final report dated September 23, 2002 indicated, incorrectly, that only lot 13657-06 was used. In response to the Form FDA 483 inspectional findings, the study director amended the final report on May 18, 2005 to acknowledge that three additional lots (13933-17, 13933-19, and 13922-22) were used in the study. However, the amended study report still did mention use of lot 13657-44. Additionally, the final study report and the amended report failed to include the required characterization information (e.g., strength, purity) for any lot of the test article used.

NAMSA's Response:

(b) (4)

(b) (4)

Evaluation: The complete lot numbers for both control and test articles were provided. Test article characterization information, including purity and strength, was also provided. The firm

(b) (4)
(u) (4) lots of
test article had dosage and characterization data within the acceptable range.

Warning Letter Item 3: The final report for the study did not include a description of all circumstances that may have affected the quality or integrity of the data. [21 CFR 58.185(a)(9)]

The final study report failed to include the occurrence of elevated body temperatures experienced by some study animals and the potential implications for study data. The 6 month, 9 month, and termination physical examination records indicated that several study animals had elevated body temperatures ranging from 103.1 to 107.1°F (normal body temperature for beagle dogs is approximately 102°F). The elevated body temperatures could have resulted from exposure to the study drug, among other things, and may have affected the pharmacokinetics and pharmacodynamics of buprenorphine in the test animals and thus affected the quality of the study data. The examination records only state "AN" or "Appeared Normal." There is no documentation to indicate that the study director investigated either the cause or possible effects of the elevated body temperatures on the integrity of the study data.

NAMSA's Response:

(b) (4)

(b) (4)

Evaluation: The response is adequate. The reviewer agrees that based on the data seen in both control and test animals, the elevated temperatures did not appear to be treatment-related.

Warning Letter Item 4: You failed to retain reserve samples for each batch of test and control articles for studies more than 4 weeks long. [21 CFR 58.105(d)]

Specifically, the firm did not retain reserve samples for test article lots #13657-06, 13933-17, 13933-19, 13933-22, and 13657-44, and control article lot EVA #13657-22.

NAMSA's Response:

(b) (4)

(b) (4)

Evaluation: Samples of test and control articles used for the original implantation were not retained. Since the firm provided characterization data in the study report amendment for all lots of test and control articles used in the study, the deficiency of not retaining reserve samples of all lots of test and control articles does not impact the study data integrity and conclusions.

Warning Letter Item 5: Your study director did not have overall responsibility for the technical conduct of the study, as well as for interpretation, analysis, documentation, and reporting of results, and she was not the single point of study control. [21 CFR 58.33]

The approved protocol dated July 9, 2001, stated that animals designated for 9 month termination would be re-implanted with test article rods at 6 months or when levels of buprenorphine had dropped to 80% of the initial steady state values, whichever came first. The protocol also stated that re-implantation would be on the left side of the chest/back and that the original implants on the right side of the chest/back would be removed at the time of re-implantation. The sponsor changed the procedure on March 21, 2002 so that re-implantation would be based solely on the blood levels of buprenorphine and the original implants on the right side would remain in place. However, the study director never saw the pharmacokinetic data needed for her to determine whether blood levels met the criteria for re-implantation. She merely followed the sponsor's instructions to implant the rods based on pharmacokinetic data in the possession of the sponsor. For the study director to fulfill her responsibility as the single point of study control, she should have reviewed the actual pharmacokinetic data to determine when to implant the additional rods. The study director also failed to amend the protocol with these changes until August 15, 2002, five months after the re-implantations were performed.

NAMSA's Response:

(b) (4)

(b) (4)

(b) (4)

(b) (4)

Evaluation: The study director's responsibility was not addressed in the response. In this study, the study director relied on written instructions from the sponsor in proceeding with the re-implant procedure and did not represent the single point of study control. However, as the PK data submitted to the study director met the re-implantation criteria (buprenorphine

concentrations dropped to 80% of the initial steady state values), this observation does not impact the study data integrity and conclusions.

Warning Letter Item 6: The signed and dated reports of each of the individual scientists or other professionals involved in the study were not included in the final report. [21 CFR 58.33, 58.185 (a)(12)]

The final study report must include the signed and dated reports of each of the individual scientists or other professionals involved in the study. The final study report did not have a contributing scientist report containing the pharmacokinetic data and analyses, did not provide a rationale of why they were missing, and did not identify the scientist or other professionals involved in that portion of the study.

NAMSA's Response:

(b) (4)
(b) (4)

Evaluation: The firm's response is not adequate. The PK contributing scientist report is required to be included with the study report (b) (4) It is not acceptable to (b) (4) not include the contributing scientist report. However, this deficiency does not impact the study data integrity and conclusions.

Conclusions and Recommendations:

The firm's response to the Warning Letter was adequate for Warning Letter Items 2, 3, and 4. For Warning Letter Item 1, the response verified that the number of rods implanted in all animals was not appropriately documented and there was no direct evidence to support the number of rods implanted in Groups A1 and A2 animals. For Groups B1 and B2 animals, (b) (4) documented the number of rods implanted. (b) (4)

Indirect evidence, (b) (4) are not adequate to support the number of rods implanted in any of these animals.

The firm's response to Warning Letter Item 5 is inadequate because the study director's responsibility as a single point of study control was not addressed in the response. However, this deficiency did not impact the data integrity and study conclusions because the PK data submitted to the study director were consistent with the re-implantation criteria (buprenorphine concentrations dropped to 80% of the initial steady state values).

The firm's response to Warning Letter Item 6 is inadequate because the PK report was not included with the final study report. However, this deficiency does not impact the data integrity

and study conclusions because the interpretation of the PK report by the study director did not differ from the sponsor.

Based on the review of the firm's responses to Form FDA 483 and the Warning Letter, this reviewer recommends that the amended study report be accepted for review. Because the firm failed to appropriately document the number of rods implanted in each animal, the dose of buprenorphine delivered to the test animals cannot be assured per the protocol. No conclusions linking the dose of buprenorphine to toxicological findings can be drawn for Groups A1 and A2 animals. However, the association between plasma concentrations of buprenorphine and toxicological effects could be evaluated based on the available data.

cc:

OSI/DBEGLPC/Taylor/Bonapace/ChenZ/Matthews/CF

OND/DAAAP/Basham/Bond/Wasserman

Draft: Z. Chen 1/4/2013, 1/17/2013, 1/23/2013, 1/30/2013

Edits: C. Bonapace 1/11/2013, 1/18/2013; W. Taylor 1/15/2013, 1/30/2013

ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good Laboratory Practice

Compliance/Electronic Archive/GLPB/NAMSA, Northwood, Ohio/FY2013/Response Review

File: GLP0501

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/s/

ZHOU CHEN

01/31/2013

CHARLES R BONAPACE

01/31/2013

WILLIAM H TAYLOR

02/01/2013

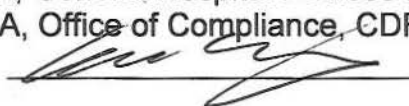
DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Center for Devices and Radiological Health
Office of Compliance, Division of Enforcement A
General Hospital Devices Branch

DATE: January 22, 2013

TO: Lisa Basham, Division of Anesthesia, Analgesia, and
Addiction Products, Office of Drug Evaluation II, Office of
New Drugs, Center for Drug Evaluation and Research
WO22, Room 3156

Cc: Office of Combination Products at combination@fda.gov

THRU: Carl Fischer, Ph.D., Chief, General Hospital Devices Branch,
Division of Enforcement A, Office of Compliance, CDRH,
WO-66, Room 3526  1/22/13

FROM: Latoya Oliver-Powell, General Hospital Devices Branch,
Division of Enforcement A, Office of Compliance, CDRH,
WO-66, Room 3552

SUBJECT: Inter-Center consult requested by CDER/OND for NDA
204442

CONSULT INSTRUCTIONS: DAAP requests CDRH/OC assistance with facility
inspections for the device component of this application.

Objective

The Office of Compliance at CDRH received a consult request from CDER/DAAP requesting CDRH/OC assistance with facility inspections for the device component associated with this application.

Product Description

The product is: Probuphine Applicator (buprenorphine subdermal implant)

The intended use is:

1. Intended to place Probuphine in the subdermal space of the body, by trained healthcare providers.
2. Implantable formulation developed for maintenance for opioid dependence.

Titan Pharmaceuticals provided their NDA submission, the sponsor indicates that it has produced a device that is substantially equivalent to predicate devices marketed and or/ cleared.

Consult Evaluation

CDRH Office of Compliance has reviewed the list of manufacturing and testing sites.

Manufacturing and assembly of the Applicator will take place at (b) (4) (FEI: (b) (4)). This facility had a medical device inspection (b) (4) and was classified Voluntary Action Indicated (VAI). Based on the classification and the date of the inspection, CDRH does not believe that an additional inspection is needed.

Sterility and Endotoxin release testing will be contracted out and take place at (b) (4) (FEI: (b) (4)). CDRH does not believe that other inspections are needed related to the applicable device manufacturing regulations.

(b) (4) will be contracted out and take place at (b) (4) (FEI: (b) (4)). CDRH does not believe that other inspections are needed related to the applicable device manufacturing regulations.

Secondary Packaging of Probuphine Kits and Warehousing will be contracted out and will take place at Sharp Corporation (FEI: 3004161147). CDRH does not believe that other inspections are needed related to the applicable device manufacturing regulations.

CDRH Recommendation

Upon review of the available documentation, CDRH is not recommending additional inspections related to compliance with medical device manufacturing regulations.



Latoya Oliver-Powell

Prepared/typed: LOliver-Powell: 01/18/2013, 1/22/2013
Reviewed: CFischer:
Revised:

cc:
WO66-3515 (DOE-A Firm File)
WO66-3515 (Division Chron File)
WO66-3552 (LOliver-Powell, Reviewer)

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/s/

LISA E BASHAM

01/22/2013

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MEMORANDUM
Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: December 18, 2012

To: Bob Rappaport, MD, Director
Division of Anesthesia, Analgesia, and Addiction Products
(DAAAP)

Through: Michael Klein, PhD, Director
Controlled Substance Staff

From: Stephen Sun, MD, Medical Officer
Controlled Substance Staff

Subject: **Topic:**
Request for Information: Abuse Potential Assessment of New Drug
Application
Application:
NDA 204442 - Probuphine (buprenorphine) implant; 80 mg
buprenorphine per Probuphine implant; single treatment dose for 6-
month period is 4 (to 5) implants
Proposed Indication:
Treatment of Opioid Dependence
Sponsor:
Titan Pharmaceuticals

Materials reviewed: Titan Pharmaceuticals. 1.11.4 Abuse Potential Assessment. NDA 204-442 (Probuphine).

I. Summary

A. Background:

This memorandum is in response to a CSS consult dated November 2, 2012, from the Division of Analgesics, Anesthetics, and Addiction Products, pertaining to NDA 204-442 (previously IND 70852) for Probuphine (buprenorphine) subcutaneous implant under development by Titan Pharmaceuticals. In addition to requesting CSS participation in the internal meeting and industry meetings, this document represents needed clarifications related to the NDA filing.

B. Conclusions:

1. There are no abuse-related filing issues.
2. Sponsor has submitted an Assessment of Abuse Potential for preliminary review that requires clarifications.

C. Recommendations (to be conveyed to the Sponsor):

1. You should provide scientific data, e.g. in vitro data, on the various tampering and extraction conditions of buprenorphine from the Probuphine implant to better understand the exposure risks associated with a buprenorphine implant that is unintentionally or intentionally handled directly by individuals before insertion or dislodged following placement.
2. You should explain in detail the process for prescribing, delivering, and handling the controlled substance from the central pharmacy to the implantation procedure site if the prescriber differs from the health professional that is actually placing the insert.
3. You should include appropriate warnings and education on the handling of the buprenorphine implant by appropriately trained and untrained individuals, including patients, since the risk of direct contact is possible and the persons who insert and remove the implant may be different. Additionally, the risk of a product being returned to the patient by a healthcare professional after removal should be mitigated.
4. You should explain how the healthcare professional, who may differ from the person who placed the implant, will know how many implants to remove (4 or 5 implants) so as to prevent the risk of un-removed implants resulting in the unintentional overdose for a subsequent dosing period in the contralateral arm.
5. You should provide the appropriate risk mitigation methods for the controllable “potential points of diversion” cited in the submitted abuse potential assessment.

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/s/

STEPHEN W SUN
12/18/2012

MICHAEL KLEIN
12/20/2012

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Drug Use Review

Date: February 19, 2012

Reviewer: Justin Mathew, Pharm.D.
Drug Use Data Analyst
Division of Epidemiology II

Team Leader: Hina Mehta, Pharm.D.
Drug Use Data Analysis Team Leader
Division of Epidemiology II

Deputy Director: Laura Governale, Pharm.D., MBA
Division of Epidemiology II
Office of Pharmacovigilance and Epidemiology
Office of Surveillance and Epidemiology

Drug Name(s): buprenorphine (Subutex[®] tabs) and buprenorphine/naloxone (Suboxone[®] tablet and film)

Application Type/Number: Multiple

Applicant/sponsor: Multiple

OSE RCM #: 2013-396

****This document contains proprietary drug use data obtained by FDA under contract. The drug use data/information in this document has been cleared for public release.****

CONTENTS

Executive Summary	3
1 Background.....	3
1.1 Introduction	3
1.2 Product Information	3
2 Methods and Material	4
2.1 Determining Settings Of Care	4
2.2 Data Sources Used	4
3 Results.....	4
3.1 Outpatient Dispensed Prescriptions for buprenorphine/naloxone and buprenorphine: Prescription volume	4
3.2 Number of Patients Who Received Dispensed Prescriptions for buprenrenorphine/naloxone and buprenorphine	5
3.3 Top 10 Prescribing Specialties	5
4 Discussion	6
5 Conclusions.....	6
APPENDIX 1: tables and figures.....	7
APPENDIX 2: Databases Description	9

EXECUTIVE SUMMARY

The Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) requested a review of the drug utilization patterns for oral buprenorphine and buprenorphine/naloxone for years 2003 through 2012, with a focus on year 2012.

Summary of findings:

U.S. Outpatient Retail Pharmacy Utilization Data, years 2003 through 2012:

- Approximately 10.7 million prescriptions from outpatient retail pharmacies were dispensed and approximately 1 million patients received a dispensed prescription for buprenorphine containing products during year 2012.
- The top prescriber specialties for the oral combination buprenorphine/naloxone products and single-ingredient buprenorphine products were General Practice/Family Medicine/Doctor of Osteopathy, Psychiatry, and Internal Medicine.
- A small proportion of prescriptions dispensed were written by physicians who may have training in surgical procedures.

1 BACKGROUND

1.1 INTRODUCTION

The Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) is currently reviewing NDA 204442 (Probuphine[®]), a new buprenorphine product which is surgically implanted to deliver doses for 6 months at a time. DAAAP would like to determine what proportion of the physicians currently providing buprenorphine treatment have a medical specialty that involves any type of surgical procedures, and could, therefore, easily learn to do the implantation and removal procedures. An Advisory Committee Meeting will be held on March 22, 2013, to discuss the safety and efficacy of this agent. In support of this, the Division of Epidemiology II (DEPI II) was requested to provide drug utilization data for buprenorphine tablets (Subutex[®]) and buprenorphine/naloxone tablets and films (Suboxone[®]) for years 2003 through 2012.

1.2 PRODUCT INFORMATION

Suboxone[®] (buprenorphine/naloxone) is indicated for the maintenance treatment of opioid dependence. It is partial agonist at the mu-opioid receptor and an antagonist at the kappa-opioid receptor.¹

Subutex[®] (buprenorphine) is indicated for the treatment of opioid dependence and is preferred for induction.² Subutex[®] was discontinued by the sponsor on September 16, 2011 therefore, it is currently only available as generic buprenorphine tablets.

Table 1. Summary of product information			
Product Name	Formulations/Strengths	Approval Date	NDA/ANDA

¹ http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/020733s007s008lbl.pdf

² http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/020732s006s007lbl.pdf

Suboxone [®] (buprenorphine and naloxone)	Tablet: 2-0.5mg; 8-2mg	October 8, 2002	020733
Subutex [®] (buprenorphine)	Tablet: 2mg; 8mg	October 8, 2002	020732
Buprenorphine	Tablet: 2mg; 8mg	October 8, 2009 May 7, 2010 September 24, 2010	078633 090360 090622
Suboxone [®] (buprenorphine and naloxone)	Film: 2-0.5mg; 8-2mg	August 30, 2010	022410

2 METHODS AND MATERIAL

2.1 DETERMINING SETTINGS OF CARE

The IMS Health, IMS National Sales Perspectives[™] (see Appendix 2 for full description) was used to determine the various retail and non-retail channels of distribution for oral buprenorphine and buprenorphine/naloxone. During year 2012, approximately 86% of bottles/cartons sold were of buprenorphine/naloxone while 14% were of buprenorphine. Approximately 92% of buprenorphine and 92% of buprenorphine /naloxone were distributed to outpatient retail pharmacies (including chain, independent and food stores).³ As a result, outpatient retail pharmacy utilization patterns were examined in this review. Inpatient and mail-order/specialty pharmacy settings data were not included in this analysis.

2.2 DATA SOURCES USED

Proprietary drug use databases were used to conduct this analysis (see Appendix 2 for full database description).

The IMS Health, Vector One[®]: National (VONA) was used to obtain the nationally estimated number of prescriptions dispensed for all oral brand and generic versions of buprenorphine (Subutex[®]) products as well as both sublingual tab and film formulations of buprenorphine/naloxone (Suboxone[®]) products for years 2003 through 2012. The IMS Health, VONA database was also used to obtain the nationally estimated number of prescriptions dispensed by prescriber specialty for years 2003 through 2012, cumulative. The IMS Health, Vector One[®]: Total Patient Tracker (TPT) was used to obtain the nationally estimated number of patients receiving dispensed prescriptions for all oral brand and generic buprenorphine (Subutex[®]) products as well as both sublingual tab and film formulations of buprenorphine/naloxone (Suboxone[®]) products for years 2003 through 2012.

3 RESULTS

3.1 OUTPATIENT DISPENSED PRESCRIPTIONS FOR BUPRENORPHINE/NALOXONE AND BUPRENORPHINE: PRESCRIPTION VOLUME

³ IMS Health, National Sales Perspectives[™] Data Extracted Feb 2013. File: NSPC molecule 2013-396 Buprenorphine Prescriber Specialty Use.xlsx

Table 1 in Appendix 1 shows the nationally estimated total number of dispensed prescriptions (TRxs) for oral buprenorphine and buprenorphine/naloxone products, stratified by formulation, from U.S. outpatient retail pharmacies. Overall, there has been an increase in the total number of dispensed prescriptions for oral buprenorphine-containing products from approximately 76,000 prescriptions dispensed during year 2003 to about 10.7 million prescriptions dispensed during year 2012. During the time period examined, the majority of prescriptions dispensed were for buprenorphine/naloxone (Suboxone®) products ranging from 84%-93% of all oral buprenorphine-containing products.

During year 2012, approximately 9.7 million buprenorphine/naloxone (Suboxone®) prescriptions (~91% of all oral buprenorphine-containing products) were dispensed of which, approximately 70% (6.8 million prescriptions) were of the film formulation and 30% (2.9 million prescriptions) were of the sublingual tablet formulation. During year 2012, of the 1 million buprenorphine (Subutex®) prescriptions dispensed (~10% of all oral buprenorphine-containing products) the majority (>99% or 1 million prescriptions) were the generic sublingual tabs.

3.2 NUMBER OF PATIENTS WHO RECEIVED DISPENSED PRESCRIPTIONS FOR BUPRENORPHINE/NALOXONE AND BUPRENORPHINE

Table 2 in Appendix 1 provides the nationally estimated number of patients who received a dispensed prescription for oral buprenorphine or buprenorphine/naloxone sublingual tablet/film products from U.S. outpatient retail pharmacies during years 2003 through 2012. The patient count data showed a similar pattern to the dispensed prescription data. Overall, there has been an increase in the total number of patients receiving dispensed prescriptions for oral buprenorphine-containing products from approximately 16,000 patients during year 2003 to about 1 million patients during year 2012. During the time period examined, the majority of patients received dispensed prescriptions for buprenorphine/naloxone (Suboxone®) products ranging from 86%-96% of all oral buprenorphine-containing products.

During year 2012, approximately 946,000 patients (94% of total patients) received a dispensed prescription for buprenorphine/naloxone (Suboxone®) of which, approximately 78% (739,000 patients) of the patients received the film formulation and 37% (353,000 patients) received the sublingual tablet formulation. During year 2012, of the 113,000 patients (11% of total patients) receiving a prescription for buprenorphine (Subutex®), the majority (>99% or 112,700 patients) received the generic tabs.

3.3 TOP 10 PRESCRIBING SPECIALTIES

Table 3 in Appendix 1 provides the nationally estimated number of outpatient retail dispensed prescriptions for buprenorphine and buprenorphine/naloxone oral products by the top 10 prescribing specialties during the cumulative time period from year 2003 through year 2012. There was a total of 39.6 million prescriptions dispensed during the time examined with oral formulations of buprenorphine/naloxone comprising approximately 91% (36.1 million prescriptions) and buprenorphine comprising of approximately 9% (3.5 million prescriptions) of the total prescriptions.

Among the buprenorphine/naloxone dispensed prescriptions, General Practice/Family Medicine/Doctor of Osteopathy was the top prescribing specialty with approximately 32% (11.4 million prescriptions) of total prescriptions dispensed during the cumulative time period examined. Psychiatry, Internal Medicine, and Unspecified specialties followed accounting for approximately 22% (8 million prescriptions), 16% (5.7 million prescriptions), and 9% (3.3 million prescriptions) of dispensed prescriptions for buprenorphine/naloxone oral products, respectively. Emergency Medicine and Anesthesiologists each accounted for approximately 3% of prescriptions dispensed.

For single-ingredient buprenorphine oral products, General Practice/Family Medicine/Doctor of Osteopathy was the top prescribing specialty with approximately 26% (923,000 prescriptions) of total prescriptions dispensed from year 2003 through 2012, cumulative. Psychiatry, Internal Medicine, and Unspecified specialties followed accounting for approximately 24% (847,000 prescriptions), 14% (478,000 prescriptions), and 10% (334,000 prescriptions) of dispensed prescriptions for buprenorphine oral products, respectively. Anesthesiologists, Emergency Medicine Physicians, and General Surgeons accounted for approximately 4%, 2% and 1% of prescriptions dispensed, respectively.

4 DISCUSSION

Our analysis indicates that the majority of use during the time examined has been for the combination buprenorphine/naloxone products. The number of prescriptions and patients receiving prescriptions has increased during the time examined. The top prescriber specialties for the oral combination buprenorphine/naloxone products and single-ingredient buprenorphine products were General Practice/Family Medicine/Doctor of Osteopathy, Psychiatry, and Internal Medicine. A small proportion of prescriptions dispensed were written by physicians who may have training in surgical procedures.

Findings from this review should be interpreted in the context of the known limitations of the databases used. Based on the IMS Health, IMS National Sales Perspectives™, sales distribution data indicated that the majority of buprenorphine/naloxone and buprenorphine was distributed to the outpatient retail pharmacy setting. These data do not provide a direct estimate of use but do provide a national estimate of units sold from the manufacturer into the various channels of distribution.

We focused our analysis on the outpatient retail pharmacy; therefore, these estimates may not apply to other settings of care in which these products are used (e.g. mail-order/specialty pharmacy). The estimates provided are national estimates, but no statistical tests were performed to determine statistical significant changes over time or between products. Therefore, all changes over time or between products should be considered approximate, and may be due to random error.

5 CONCLUSIONS

There were approximately 10.7 million dispensed prescriptions and 1 million patients who received a dispensed prescription for oral buprenorphine-containing products during year 2012. The majority of prescriptions (90% of all oral buprenorphine-containing products) dispensed and patients (94% of all oral buprenorphine-containing products) received buprenorphine/naloxone (Suboxone®) products. The film formulation of buprenorphine/naloxone (Suboxone®) is currently the most widely used. The top prescribing specialties for both the oral combination buprenorphine/naloxone and single-ingredient buprenorphine products was General Practice/Family Medicine/Doctor of Osteopathy, Psychiatry, and Internal Medicine. A small proportion of prescriptions dispensed were written by physicians who may have training in surgical procedures.

APPENDIX 1: TABLES AND FIGURES

TABLE 1.

Nationally estimated number of prescriptions for buprenorphine and buprenorphine/naloxone tablets/films dispensed through U.S. outpatient retail pharmacies, years 2003 through 2012																				
	2003		2004		2005		2006		2007		2008		2009		2010		2011		2012	
	TRxs	Share%	TRxs	Share%	TRxs	Share%	TRxs	Share%	TRxs	Share%	TRxs	Share%	TRxs	Share%	TRxs	Share%	TRxs	Share%	TRxs	Share%
Total Market	75,834	100.0%	284,095	100.0%	560,841	100.0%	1,040,584	100.0%	1,945,915	100.0%	3,544,510	100.0%	5,608,606	100.0%	7,079,884	100.0%	8,815,840	100.0%	10,677,960	100.0%
buprenorphine hcl/naloxone hcl	63,359	83.5%	239,123	84.2%	491,116	87.6%	918,170	88.2%	1,745,495	89.7%	3,255,187	91.8%	5,212,319	92.9%	6,498,365	91.8%	8,059,438	91.4%	9,655,649	90.4%
Suboxone	63,359	100.0%	239,123	100.0%	491,116	100.0%	918,170	100.0%	1,745,495	100.0%	3,255,187	100.0%	5,212,319	100.0%	6,498,365	100.0%	8,059,438	100.0%	9,655,649	100.0%
Film	--	--	--	--	--	--	--	--	--	--	--	--	--	--	437,512	6.7%	4,107,705	51.0%	6,791,666	70.3%
Subling/Buccal Tab	63,359	100.0%	239,123	100.0%	491,116	100.0%	918,170	100.0%	1,745,495	100.0%	3,255,187	100.0%	5,212,319	100.0%	6,060,853	93.3%	3,951,733	49.0%	2,863,984	29.7%
Buprenorphine	12,475	16.5%	44,972	15.8%	69,725	12.4%	122,414	11.8%	200,421	10.3%	289,323	8.2%	396,287	7.1%	581,520	8.2%	756,402	8.6%	1,022,310	9.6%
Buprenorphine generic tab	--	--	--	--	--	--	--	--	1	0.0%	3	0.0%	18,879	4.8%	361,611	62.2%	708,525	93.7%	1,021,274	99.9%
Subutex tab	12,475	100.0%	44,972	100.0%	69,725	100.0%	122,414	100.0%	200,419	100.0%	289,321	100.0%	377,408	95.2%	219,909	37.8%	47,877	6.3%	1,036	0.1%

Source: IMS Health, Vector One®: National (VONA). Data Extracted Feb 2013. File: VONA RX 2013-396 Buprenorphine Prescriber Specialty Use.xls

TABLE 2.

Nationally estimated number patients who received a dispensed prescription for buprenorphine and buprenorphine/naloxone tablets/films dispensed through U.S. outpatient retail pharmacies, years 2003 through 2012																				
	2003		2004		2005		2006		2007		2008		2009		2010		2011		2012	
	TRxs	Share%	TRxs	Share%	TRxs	Share%	TRxs	Share%	TRxs	Share%	TRxs	Share%	TRxs	Share%	TRxs	Share%	TRxs	Share%	TRxs	Share%
Total	15,643	100.0%	49,187	100.0%	90,387	100.0%	154,770	100.0%	293,709	100.0%	447,747	100.0%	640,613	100.0%	763,905	100.0%	902,887	100.0%	1,003,833	100.0%
Buprenorphine HCL/Naloxone HCL	13,423	85.8%	42,175	85.7%	79,887	88.4%	138,369	89.4%	267,357	91.0%	419,510	93.7%	607,292	94.8%	729,243	95.5%	861,427	95.4%	945,714	94.2%
Suboxone Film	--	--	--	--	--	--	--	--	--	--	--	--	--	--	141,850	19.5%	521,521	60.5%	739,103	78.2%
Suboxone Tabs	13,423	100.0%	42,175	100.0%	79,887	100.0%	138,369	100.0%	267,357	100.0%	419,510	100.0%	607,292	100.0%	694,700	95.3%	522,501	60.7%	352,384	37.3%
Buprenorphine HCL	3,445	22.0%	11,150	22.7%	16,331	18.1%	25,733	16.6%	41,426	14.1%	49,460	11.0%	57,621	9.0%	76,528	10.0%	89,886	10.0%	112,699	11.2%
Buprenorphine Tab	--	--	--	--	--	--	--	--	--	--	--	--	9,350	16.2%	52,840	69.0%	85,511	95.1%	112,584	99.9%
Subutex	3,445	100.0%	11,150	100.0%	16,331	100.0%	25,733	100.0%	41,426	100.0%	49,460	100.0%	54,516	94.6%	42,991	56.2%	9,148	10.2%	640	0.6%

*Due to the possibility of double counting patients who are receiving treatments over multiple periods in the study, unique patient counts may not be added across time periods.

Source: IMS Health, Vector One®: National Total Patient Tracker. Data Extracted Feb 2013. File: TPT Total 2013-396 Buprenorphine Prescriber Specialty Use.xls; TPT Buprenorphine Tab 2013-396 Buprenorphine Prescriber Specialty Use.xls; TPT Suboxone Film 2013-396 Buprenorphine Prescriber Specialty Use.xls; TPT Suboxone Tab 2013-396 Buprenorphine Prescriber Specialty Use.xls

TABLE 3.

**Nationally estimated number of prescriptions dispensed for oral buprenorphine and
buprenorphine/naloxone products by top 10 prescribing specialties, January 2003-December 2012**

	January 2003 - December 2012	
	TRxs	Share%
Total Market	39,634,085	100.0%
Buprenorphine hcl/Naloxone hcl	36,138,242	91.2%
General Practitioner/Family Medicine/Doctor of Osteopathy	11,397,012	31.5%
Psychiatry	7,955,079	22.0%
Internal Medicine	5,704,917	15.8%
Unspecified	3,298,730	9.1%
Other	1,638,234	4.5%
Emergency Medicine	1,102,619	3.1%
Anesthesiology	1,057,363	2.9%
Physical Medicine and Rehabilitation	763,531	2.1%
Obstetrics & Gynecology	458,800	1.3%
Neurology	368,449	1.0%
All Others	2,393,510	6.6%
Buprenorphine hydrochloride	3,495,809	8.8%
General Practitioner/Family Medicine/Doctor of Osteopathy	923,398	26.4%
Psychiatry	847,215	24.2%
Internal Medicine	477,866	13.7%
Unspecified	334,266	9.6%
Other	226,704	6.5%
Anesthesiology	146,434	4.2%
Emergency Medicine	98,305	2.8%
Physical Medicine and Rehabilitation	72,636	2.1%
Obstetrics & Gynecology	63,666	1.8%
General Surgery	43,432	1.2%
All Others	261,887	7.5%

Source: IMS Health, Vector One® National, extracted February 2012; File: 2013-396 Buprenorphine Prescriber Specialty Use.xls

APPENDIX 2: DATABASES DESCRIPTION

IMS Health, IMS National Sales Perspectives™: Retail and Non-Retail

The IMS Health, IMS National Sales Perspectives™ measures the volume of drug products, both prescription and over-the-counter, and selected diagnostic products moving from manufacturers into various outlets within the retail and non-retail markets. Volume is expressed in terms of sales dollars, eaches, extended units, and share of market. These data are based on national projections. Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings.

IMS Health, Vector One®: National (VONA)

The IMS, Vector One®: National (VONA) database measures retail dispensing of prescriptions or the frequency with which drugs move out of retail pharmacies into the hands of consumers via formal prescriptions. Information on the physician specialty, the patient's age and gender, and estimates for the numbers of patients that are continuing or new to therapy are available.

The Vector One® database integrates prescription activity from a sample received from payers, switches, and other software systems that may arbitrage prescriptions at various points in the sales cycle. Vector One® receives over 1.9 billion prescription claims per year, representing over 158 million unique patients. Since 2002 Vector One® has captured information on over 15 billion prescriptions representing over 356 million unique patients.

Prescriptions are captured from a sample from the universe of approximately 59,000 pharmacies throughout the U.S. There are over 800,000 physicians in the VECTOR One database, which supplies VONA, TPT, & DET. The pharmacies in the database account for most retail pharmacies and represent nearly half of retail prescriptions dispensed nationwide. IMS receives all prescriptions from approximately one-third of stores and a significant sample of prescriptions from many of the remaining stores.

IMS Health, Vector One®: Total Patient Tracker (TPT)

The IMS, Vector One®: Total Patient Tracker is a national-level projected audit designed to estimate the total number of unique patients across all drugs and therapeutic classes in the retail outpatient setting over time.

TPT derives its data from the Vector One® database which integrates prescription activity from a sample received from payers, switches, and other software systems that may arbitrage prescriptions at various points in the sales cycle. Vector One® receives over 1.9 billion prescription claims per year, representing over 158 million unique patients. Since 2002 Vector One® has captured information on over 15 billion prescriptions representing over 356 million unique patients.

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/s/

JUSTIN A MATHEW
02/19/2013

HINA S MEHTA
02/19/2013
Drug use data cleared

LAURA A GOVERNALE
02/19/2013