

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

204442Orig1s000

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204442

MEETING MINUTES

Titan Pharmaceuticals, Inc.
c/o: Braeburn Pharmaceuticals
47 Hulfish Street
Princeton, NJ 08542

Attention: Frank Young, M.D., Ph.D.
Executive Vice President, Braeburn Pharmaceuticals

Dear Dr. Young:

Please refer to Titan Pharmaceuticals Inc.'s New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Probuphine (buprenorphine hydrochloride implant) for subdermal use.

We also refer to the meeting between representatives of your firm and the FDA on November 19, 2013. The purpose of the meeting was to discuss the Sponsor's approach to responding to the Agency's April 30, 2013, Complete Response letter.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-1175.

Sincerely,

{See appended electronic signature page}

Lisa E. Basham, M.S.
Senior Regulatory Health Project Manager
Division of Anesthesia, Analgesia,
and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure:

Meeting Minutes

Attachments:

Meeting Preliminary Comments sent November 15, 2013

Graphs presented by Sponsor in November 19, 2013, meeting



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type C
Meeting Category: Post-Action
Meeting Date and Time: November 19, 2013; 3 PM
Meeting Location: 10903 New Hampshire Ave,
White Oak Building 22, Room 1421
Silver Spring, MD 20993
Application Number: NDA 204442
Product Name: Probuphine (buprenorphine hydrochloride implant) for subdermal
use
Indication: maintenance treatment of opioid dependence
Sponsor/Applicant Name: Titan Pharmaceuticals

FDA Attendees:

Curtis J. Rosebraugh, MD, MPH	Director, Office of Drug Evaluation II (ODE II), Office of New Drugs (OND)
Mary Parks, MD*	Deputy Director, ODEII, OND
Bob A. Rappaport, MD*	Director, Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Rigoberto Roca, MD	Deputy Division Director, DAAAP
Chandahas Sahajwalla, PhD	Director, Division of Clinical Pharmacology II (DCPII), Office of Clinical Pharmacology (OCP), Office of Translational Science (OTS)
Vikram Sinha, PhD	Director, Division of Pharmacometrics, OCP, OTS
Patricia Love, MD, MBA*	Deputy Director, Office of Combination Products (OCP)
Celia Winchell, MD	Clinical Team Leader, DAAAP
Janice Derr, PhD	Team Lead, Division of Biometrics II (DBII), Office of Biostatistics (OB), OTS
Adam Wasserman, PhD	Pharmacology/Toxicology Supervisor, DAAAP
Yun Xu, PhD	Team Leader, Clinical Pharmacology, DCPII, OCP, OTS
Rachel Skeete, MD, MHS	Clinical Reviewer, DAAAP
David Petullo, PhD	Statistics Reviewer, DBII, OB, OTS
Gary Bond, PhD*	Pharmacology/Toxicology Reviewer, DAAAP
David Lee, PhD	Clinical Pharmacology Reviewer, DCPII, OCP, OTS
Venkatesh Atul Bhattaram, PhD	Pharmacometrics Reviewer, Division of Pharmacometrics, OCP, OTS
Bindi Nikhar, MD*	Senior Clinical Advisor, OCP

LT Morgan Walker, PharmD, MBA*	Team Leader, Division of Medication Error Prevention and Analysis (DMEPA), Office of Medication Error Prevention and Risk Management (OMEPRM), Office of Surveillance and Epidemiology (OSE)
CDR Irene Z. Chan, PharmD, BCPS*	Team Leader, DMEPA, OMEPRM, OSE
Vicky Borders-Hemphill, PharmD*	Safety Evaluator, DMEPA, OMEPRM, OSE
Reema Mehta, PharmD, MPH	Team Leader, Division of Risk Management (DRISK), OMEPRM, OSE
Jason Bunting, PharmD*	Risk Management Analyst, DRISK, OMEPRM, OSE
Jamie Wilkins-Parker, PharmD	Risk Management Analyst, DRISK, OMEPRM, OSE
Mark Liberatore, PharmD*	Team Lead, Project Management, OSE
Lisa Skarupa, MSN *	Project Manager, OSE
Parinda Jani*	Chief, project Management Staff
Lisa Basham, MS *	Senior Regulatory Health Project Manager, DAAAP
Mary Lockett, MD	Medical Officer, DAAAP

SPONSOR ATTENDEES

Seth L. Harrison, MD	Executive Chairman, Braeburn Pharmaceuticals
Behshad Sheldon	President and Chief Operating Officer, Braeburn Pharmaceuticals
Frank E. Young, MD, PhD	Executive Vice President, Clinical and Regulatory Affairs, Braeburn Pharmaceuticals
(b) (4)	Counsel to Braeburn Pharmaceuticals, (b) (4)
Katherine L. Glassman-Beebe, PhD	Executive Vice President and Chief Development Officer, Titan Pharmaceuticals
Scott Henley, MBA	Vice President, Clinical Operations and Project Management, Titan Pharmaceuticals
(b) (4)	Clinical Consultant to Braeburn Pharmaceuticals, (b) (4)
(b) (4)	Biostatistical Consultant to Titan Pharmaceuticals, (b) (4)
(b) (4)	Pharmacometrics Consultant to Braeburn Pharmaceuticals, (b) (4)
(b) (4)	Clinical Pharmacology Consultant to Braeburn Pharmaceuticals, (b) (4)
(b) (4)	Human Factors Consultant to Braeburn Pharmaceuticals, (b) (4)
(b) (4)	(b) (4)
(b) (4)	Toxicology Consultant to Braeburn Pharmaceuticals, (b) (4)
(b) (4)	Clinical Pharmacology Consultant to Braeburn Pharmaceuticals, (b) (4)

(b) (4)	Human Factors Consultant to Braeburn Pharmaceuticals, (b) (4)
(b) (4)	(b) (4) Clinical & Clinical Pharmacology Consultant to Braeburn Pharmaceuticals, (b) (4)
(b) (4)	Clinical Consultant to Braeburn Pharmaceuticals, (b) (4)
(b) (4)	(b) (4) Human Factors Consultant to Braeburn Pharmaceuticals, (b) (4)
(b) (4)	(b) (4) Human Factors and Clinical Consultant to Braeburn Pharmaceuticals, (b) (4)
(b) (4)	(b) (4) Toxicology Consultant to Braeburn Pharmaceuticals, (b) (4)

**on the phone*

BACKGROUND

The drug product is Probuphine (buprenorphine hydrochloride implant), and the proposed indication is for the maintenance treatment of opioid dependence. The application is a 505(b)(2) application referencing the Agency's prior findings of safety and efficacy for Subutex (buprenorphine sublingual tablets), NDA 020732, and Suboxone (buprenorphine/naloxone combination tablets), NDA 020733. Probuphine is a rod-shaped implant designed to provide sustained delivery of a therapeutic level of buprenorphine (BPN), a partial agonist at the μ -opiate receptor, for up to six months when 4 to 5 rods are implanted subdermally.

The initial New Drug Application (NDA) was submitted by Titan Pharmaceuticals and received by the Agency on October 31, 2012. A Complete Response letter was issued on April 30, 2013. The deficiencies in the letter noted inadequate demonstration of clinical benefit and inadequate evaluation and validation of the insertion and removal surgical procedure. Additional comments recommended a study to evaluate the effect of scarring or inflammation at previously implanted sites on the re-implantation and bioavailability of Probuphine, a study of efficacy in patients with lower sublingual BPN requirements, and modification of the implant to include a radio-opaque marker to facilitate removal. A comment was also included on the inadequacy of the applicant's method for deriving, from the approved listed drug labeling, safety margins to be reflected in the labeling for Probuphine. The purpose of this meeting is to discuss the applicant's strategy for addressing the deficiencies and Agency comments in the Complete Response letter.

The meeting request was received on September 3, 2013, and the meeting package was received on October 10, 2013. Preliminary responses were sent to the applicant on November 15, 2013. The Sponsor responded via email on **November 18, 2013**, that they wish to focus discussion on

two proposals for moving forward. That submission was formally submitted to the NDA on November 19, 2013. The Sponsor did not need to discuss our specific responses to the questions. In addition, they included responses to our comments on the Human Factors protocol but, in the interest of time, they wished to handle interactions on that topic separate from this meeting. The face-to-face meeting occurred on **November 19, 2013**. On **November 24, 2013**, Braeburn emailed a high level summary (dated November 22, 2013) of the meeting and requested a follow-up teleconference (this submission was formally submitted on December 12, 2013). The Agency requested specific questions for discussion at the teleconference as there were no questions included in the request. Specific questions were emailed on **November 25, 2013**. The teleconference was held on **November 27, 2013**.

NOTE: The Sponsor's new proposals and discussion during the face-to-face meeting immediately follow this paragraph. The November 24, 2013, summary and November 25, 2013, follow-up questions for a subsequent teleconference follow, with minutes from the November 27, 2013, follow-up teleconference. The preliminary comments, sent November 15, 2013, are an attachment at the end of this document.

Titan/Braeburn's November 18, 2013, response to the Agency's November 15, 2013, preliminary responses

Note that Braeburn's submission also included responses to our comments on the Human Factors Study proposal. The Agency will address those comments/questions under separate cover.

The following text was sent to the Agency via email on November 13, 2013. Titan/Braeburn is proposing a two-pronged approach to addressing the Agency's concerns noted in the April 30, 2013, Complete Response letter and reiterated in the November 15, 2013, preliminary comments for this meeting.

[....]

We appreciate the thorough and well-considered preliminary comments you prepared in response to our Briefing Package. We also appreciate that you shared your comments with sufficient time for us to modify our proposed approach to the CRL. We now propose what we believe is a constructive path forward to obtain agreement leading to Probuphine approval. Our proposal contains two elements:

- (1) Limiting Probuphine's indication to the treatment of patients stabilized on sublingual buprenorphine at doses of 8 mg or less; and*
- (2) Committing to a one-year (post launch) patient registry that will generate "real world" data on drug use patterns, psychosocial functioning, and medical consequences in Probuphine-treated outpatients.*

We believe this approach can accomplish our shared goal of bringing to market treatments that address the epidemic of opioid dependence, and that reduce the misuse, abuse, and diversion of sublingual BPN.

Revised Objective for Tuesday Meeting

We seek FDA's concurrence with, and guidance regarding the proposed path to Probuphine approval based on (1) limiting the indication to patients stabilized on 8 mg or less and (2) a patient registry.

Revised Agenda for Tuesday Discussion

- 1. New proposed indication for patients stabilized on SL BPN 8 mg or less*
- 2. A patient registry*
- 3. Acceptability to FDA of proposed path to approval*

Public Health Benefits of Probuphine

We appreciate FDA's acknowledgement of the public health benefits that Probuphine can provide. An epidemic of opioid dependence has created substantial risk of overdose, death, disease, and poisoning related to illicit opioid use, including pediatric poisoning and death. Addressing the public challenge of opioid dependence and the risks of abuse has become a Federal policy priority, including for FDA.¹ Probuphine will provide patients and clinicians with the most diversion-proof, tamper-resistant, compliance-ensured and abuse-deterrent BPN formulation available.

Areas Not Requiring Discussion in Light of Current Proposal

Acceptance of FDA's Recommendations

We propose to accept all of FDA's guidance and recommendations regarding:

- Submitting a full protocol for a post-approval study of the impact of scarring and inflammation on bioavailability (FDA Response to Question 3);*
- Revising the proposed Human Factors study (FDA Response to Question 4), as specified in the attached document providing responses to each of FDA's comments;*
- Ensuring that only REMS-trained and certified providers perform the implantation procedure (FDA Response to Question 5);*

¹ FDA, Draft Guidance for Industry: Abuse-Deterrent Opioids - Evaluation and Labeling (Jan. 2013), available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM334743.pdf>.

- *Exploring the incorporation of a radio-opaque marker into a subsequent version of the implant (FDA Response to Question 6);*
- *Conducting a post-approval QT Prolongation study based on FDA guidance (FDA response to Question 7); and*
- *Revising our proposed toxicokinetic bridging study protocols (FDA Responses to Questions 8.1, 8.2, and 8.3), which has been completed.*

Safety of Probuphine

We maintain that the safety results from our two randomized, controlled clinical studies are adequate to support approval of Probuphine as a 505(b)(2) NDA. The March 21, 2013 Advisory Committee voted 12-2-1 regarding Probuphine's safety, and no critical deficiencies were identified. No significant safety concerns have been identified in the CRL, apart from the implantation/removal procedure. Consistent with our proposed Human Factors study and the patient registry, we submit for FDA's consideration that all concerns about the implantation/removal procedure can be adequately addressed. There appears to be agreement on Probuphine's safety profile.

Demonstration of Clinical Benefit

Several issues may be constructively resolved in light of our current proposal:

- (1) We disagree that the reductions of drug use observed in our studies do not represent significant clinical benefit in the population studied. Pre-specified primary and secondary endpoints, as well as the agency-specified composite endpoint, were met in two randomized, controlled clinical studies, with statistical significance. The effect sizes were large, and patients and doctors reported meaningful clinical benefit. The Advisory Committee voted 10-5 that "substantial evidence of effectiveness of Probuphine for the maintenance treatment of opioid dependence" was demonstrated despite concerns about lack of adequate information about dose. We note that the concerns about dose appeared to be related principally to determining the comparability of Probuphine to doses of SL BPN used in current clinical practice, rather than whether the dose was effective.*
- (2) We disagree about whether complete or near-complete opioid blockade must be achieved to ensure effective clinical outcomes when treating patients with BPN. Clinicians are effectively treating many patients with maintenance BPN doses of 8 mg or less,² which, according to FDA's evaluation of BPN concentrations and receptor*

² Apelt S.M., Scherbaum N., Golz J., Backmund M., Soyka M. (2013). Safety, effectiveness and tolerance of buprenorphine-naloxone in the treatment of opioid dependence: results from a nationwide non-interventional study in routine care. *Pharmacopsychiatry*, 46, 94-107; Meade C.S., Weiss R.D., Fitzmaurice G.M., Poole S.A., Subramaniam G.A., Patkar A.A., Connery H.S., Woody G.E. (2010). HIV risk behavior in treatment-seeking opioid-dependent youth: results from a NIDA clinical trials network multisite study. *J Acquir Immune Defic Syndr*, 55(1),

occupancy, means many patients are being effectively maintained at doses below the occupancy threshold at which FDA says is necessary to provide opioid blockade.

- (3) *We disagree that the potential to titrate SL BPN to “stave off withdrawal without blocking the effects of illicit opioids” or to take “vacations” from SL BPN precludes the clinical utility of Probuphine as an effective treatment option for some patients—particularly among patients stabilized on 8 mg or less.*

Path Forward

Revised Indication for Patients Stabilized on SL BPN 8 mg or Less

We agree that four Probuphine implants yield BPN concentrations very similar to those seen with 4 to 8 mg based on average exposure (e.g., mean AUC values) or concentration, and propose to work with FDA to revise Probuphine’s indication consistent with Probuphine’s BPN concentrations. We specifically ask the agency to accept a revised indication of Probuphine for the treatment of patients stabilized on sublingual buprenorphine at doses of 8 mg or less.

We propose that this indication is supported by:

- (1) Well-established safety and effectiveness of BPN in maintenance treatment of opioid dependence;*
- (2) Published literature clearly showing improvement in psychosocial functioning and physical and mental health with BPN treatment of opioid dependence³;*
- (3) Comparability of BPN plasma concentrations of 4 Probuphine implants and SL BPN doses of 4-8 mg;*
- (4) Safety and efficacy results of two randomized, well-controlled clinical trials that met all pre-specified endpoints, as well as an agency-specified composite endpoint, in a population of patients stabilized for as little as 3 days;*
- (5) The approved Suboxone label, which establishes an approved maintenance range of 4-24 mg SL BPN, the low end of which yields BPN concentrations comparable to the concentrations yielded by four Probuphine implants; and*

65-72; Mattick R., Kimber J., Breen C., Davoli M. (2008). Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence (Review). Cochrane Database of Systematic Reviews, Issue 2, Art. No.: CD002207.

³ Raisch D., Campbell H., Garnand D., Jones M., Sather M., Naik R., Ling W. (2011). Health-related quality of life changes associated with buprenorphine treatment for opioid dependence. *Qual Life Res*, 21, 1177-1183; Apelt S.M., Scherbaum N., Golz J., Backmund M., Soyka M. (2013). Safety, effectiveness and tolerance of buprenorphine-naloxone in the treatment of opioid dependence: results from a nationwide non-interventional study in routine care. *Pharmacopsychiatry*, 46, 94-107; Meade C.S., Weiss R.D., Fitzmaurice G.M., Poole S.A., Subramaniam G.A., Patkar A.A., Connery H.S., Woody G.E. (2010). HIV risk behavior in treatment-seeking opioid-dependent youth: results from a NIDA clinical trials network multisite study. *J Acquir Immune Defic Syndr*, 55(1), 65-72.

- (6) *Published literature regarding effective of use of maintenance doses of SL BPN 8 mg or less.*

This proposed indication and the supporting data and rationale for it are consistent with FDA's guidance for clinical effectiveness of human drugs⁴ and the regulatory standards for 505(b)(2) approval. FDA guidance indicates that "a single additional efficacy study should ordinarily be sufficient" even where "the pharmacokinetics of the new dose, regimen, or dosage form differ from the previous one." Two efficacy studies of Probuphine, each of which met all pre-specified endpoints, as well as an agency-specified composite endpoint, with statistical significance, provide sufficient evidence to support the approval of Probuphine for patients with lower buprenorphine dose requirements.

We acknowledge that four Probuphine implants do not yield BPN concentrations that are the same as those yielded by SL BPN 16 mg/day based on mean AUC values. However, comparability of four Probuphine implants to BPN concentrations within the approved maintenance dose range is consistent with our proposed indication at the low-end of the maintenance dose range. It is reasonable to expect that individuals stabilized at lower doses of SL BPN could be expected to have results superior to the mean opioid negative urines from PRO-805 and PRO-806.

Patient Registry

Although we propose that available data support approval of Probuphine for the proposed indication, we recognize that FDA seeks additional information that would more fully characterize the clinical benefits of Probuphine and advance the regulatory science of demonstrating effectiveness in addiction treatment. We therefore propose to work with FDA to develop a comprehensive patient registry during the first year of marketing. Such a system would offer significant benefits, including:

- (1) Full characterization of Probuphine's clinical benefits and practices in "real world" clinical practice;*
- (2) A method to "examin[e] drug use patterns and measures of psychosocial functioning and medical consequences in buprenorphine-treated outpatients" (FDA General Comments);*
- (3) A structured mechanism for gathering additional safety information that FDA may seek;*
- (4) A means to validate the effectiveness of training procedures for the safe and effective implantation and removal of Probuphine rods among certified clinicians; and*
- (5) Providing a framework for evaluating the effectiveness of, and compliance with, a final approved REMS.*

⁴ FDA, Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products (May 1998), p.8., available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm078749.pdf>.

We welcome an opportunity to collaborate with FDA in designing the specific elements that would be included in the patient registry. Likely elements to be discussed with FDA include:

- (1) Formal reporting obligations undertaken by both participating clinicians and the Sponsor;*
- (2) An advisory board to provide oversight on the roll-out;*
- (3) Criteria for the selection and training of participating clinicians consistent with the final REMS and results of the Human Factors study; and*
- (4) Data collection (e.g., SL BPN doses prior to treatment with Probuphine, quantitative urine screenings, evaluation of psychosocial functioning and medical consequences, use of supplemental SL BPN, desire to use drugs and self-reporting regarding use of illicit drugs).*

Conclusion

We propose the approach outlined in this letter is a constructive path forward that would enable the Agency to responsibly ameliorate the public health crisis of opiate dependence, “a deadly disease ... a serious, life-threatening disorder,”⁵ by allowing the most diversion-proof and tamper-resistant, BPN product yet developed to reach the market. There remains an intense need among clinicians and patients for additional treatment options, and Probuphine can satisfy a targeted portion of this need among individuals with lower SL BPN requirements. Our proposal also affords us the opportunity to work constructively with FDA to develop new data sets that will provide not only valuable information regarding Probuphine’s indicated population but also data that can advance the field of opioid dependence treatment generally.

DISCUSSION during November 19, 2013, Face-to-Face meeting:

The Agency began the discussion by emphasizing that we wish to work with the Sponsor to develop a reasonable path forward and that we do appreciate the potential of an implantable BPN product for improving compliance and reducing diversion, abuse, and accidental exposure. The Agency also stated that it may not be possible to come to an agreement on the contents of the new proposal during this meeting in light of having received the materials on the previous day. The Sponsor noted that a new management team has reviewed the past data, interactions with the Agency, and the literature, and they are committed to a path forward. They propose limiting the patient population to those who are stabilized on 8 mg or less of sublingual buprenorphine (SL

⁵ FDA, Meeting Transcript for the March 21, 2013 Meeting of the Psychopharmacologic Drugs Advisory Committee, p.366, available at <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PsychopharmacologicDrugsAdvisoryCommittee/UCM351452.pdf>.

BPN) and see this approach as consistent with the 505(b)(2) pathway. They went on to say that, although it is clear that there is an unmet medical need, very little investment has been made by industry in this field. The Sponsor conveyed their long-term commitment to addiction medicine.

The Sponsor noted that the safety and efficacy of BPN for opioid addiction is well established and that Suboxone labeling provides for a dose range of 4 – 24 mg for maintenance treatment of opioid addiction. They continued that the plasma level of BPN from 4-8 mg of Suboxone is comparable to that achieved with four implants of Probuphine. They feel that the safety and efficacy of Probuphine were established in two adequate and well-controlled trials in patients who were not stabilized on a BPN dose but who were, instead, in the early stages of recovery and, in turn, more difficult to treat. They feel that these data can be extrapolated to a stabilized population and that it is reasonable to surmise that more stable patients would do better.

The Agency agreed that patients stabilized on a lower dose of BPN might benefit from Probuphine but asked the sponsor's clinical consultant, (b)(4) for more information on the types of patients that he typically sees as a practicing doctor in addiction medicine, and whether there exists a population of well-stabilized patients maintained on lower doses of sublingual BPN. He responded that he runs a private practice where many patients have been stabilized on BPN for many years. He also runs a clinic for homeless IV drug users and treats patients in residential drug treatment. He submitted that, unlike other opioids, with buprenorphine, less is needed over time. He emphasized that a very high percentage of his private patients are stabilized on 8 mg BPN or less and he therefore feels that there is a real role for a drug like Probuphine in drug abuse treatment. He sees the long-acting and tamper-resistant features of Probuphine as very appealing in that patients will have improved compliance and would not have to carry around Suboxone, thus avoiding some of the stigma associated with being a recovering addict, and minimizing thefts. He noted that recovery is a long process and that when patients are stabilized on BPN they begin to make improvements in all aspects of their lives that are critical for long-term recovery.

The Agency thanked (b)(4) for his insights and conveyed that our residual area of discomfort is the lack of adequate and well-controlled efficacy data in this particular population. The scientific and regulatory requirements for the establishment of efficacy will be difficult to meet without adequate and well-controlled trial data attained directly in a stabilized population.

The Agency noted that the term "stabilized" was defined differently in the Probuphine clinical trials than in (b)(4) practice. In the clinical trials, "stabilized" meant that patients were on the same dose for 10-16 days. (b)(4) considers "stabilized" patients to be those that are clinically stable over a long period of time, including refraining from illicit drug use. The Agency asked whether patients new to treatment tend to need doses higher than 8 mg. (b)(4) (b)(4) responded that sometimes patients do, or some may only think they do because that is the mindset they are accustomed to, but he actually finds that patients need less over time. The Sponsor shared several graphs (attached) illustrating a pharmacometric analysis comparing patients stabilized on 8 mg or less of SL BPN to those with implants. They noted that the steady state exposure with SL BPN is comparable to that of Probuphine, with 8 mg SL BPN levels 30%

higher, and 4 mg levels 30% lower. They continued that the population PK model as shown on the slide indicates that Probuphine levels are generally bracketed between 4 mg and 8 mg SL BPN levels. It is this concept of bridging based on exposures as demonstrated in the pharmacometric analysis that the Sponsor proposes will support approval. The Agency noted that Suboxone was approved under these circumstances, as the clinical trials were performed with a different sublingual formulation that was not ultimately marketed. However, for this drug product, the data may not be adequate to support approval, because the differences are so great between the daily dosing of a sublingual product and the six-month dosing of the implant. It was noted that the Agency does not approve depot forms of neuroleptics based only upon PK, and the new treatment paradigm proposed for Probuphine is analogous to that for the depot neuroleptics. The Agency emphasized, however, that we are in agreement that this product at the proposed dose has the potential to be very useful for the right population. We are simply struggling with how to support its approval based solely on existing data, given the lack of data in support of the proposed revised indication or in this more circumscribed population. The Sponsor stated that an understanding of the exposure-response relationship for Probuphine that covers 4-8 mg should support making the bridge. However, it was noted that in behavioral disorders, a perfect exposure/response relationship would be difficult to demonstrate because there are many factors affecting response. The Sponsor is continuing to probe the data to see if they can extract exposure information for the 4 mg dose.

The Sponsor acknowledged the lack of data in the proposed population and explored whether there are sufficient data available to mitigate the risk of using a PK approach to support approval. They cited sources suggesting that many patients may be stabilized on lower doses. It was agreed that the dose necessary to relieve withdrawal is much lower than the dose necessary to blunt the effect of illicit opioids. The Sponsor plans to perform an exposure/response analysis pooling the Probuphine and SL BPN data, and evaluate exposure and outcome.

The Agency noted that, when we consider exposure concentration data, we also look at both C_{max} and the shape of the exposure curve. In the Probuphine group, using these parameters, the systemic exposure is less than that associated with 8mg SL BPN. The Sponsor will need to justify their focus on concentrations only, and their intent to disregard the commonly-used parameters, and will need to explain why the difference in shape does not impact efficacy.

The Agency noted that, while the labeling for the referenced product may state that the recommended dose of sublingual buprenorphine is in the range of 4 mg-24 mg/day, this was meant to convey the idea of individual titration and not that efficacy had been established at every point in that range. The efficacy database included two trials of sublingual solution, one that established efficacy of an 8 mg solution dose (approximately equivalent to a 12 mg tablet dose), and one dose-ranging study using various doses of solution that confirmed efficacy at 8 mg solution (12 mg tablet). One additional, short-term, controlled study used tablet doses of 16 mg/day. Therefore, there is not a strong foundation of evidence from adequate and well-controlled clinical trials to support the efficacy of plasma levels of buprenorphine that equate to tablet doses of 8 mg or lower. This represents a shortcoming of a strategy that proposes to rely on reference to the established efficacy of this lower dose, and the Sponsor was encouraged to

identify any sources of evidence from adequate and well-controlled trials supporting this dose that could be brought to bear to support an approval of their product.

The Agency emphasized that we must, in the end, be able to articulate in our reviews why we feel that the application meets the regulatory requirements for approval. We agree that the compliance aspect of Probuphine is very appealing, however, the label must be clear about what we know and what we do not know. We must have an explanation for what was observed in the first two studies and be able to explain that the results were either incorrect or can be corrected. We continue to be concerned that patients will require supplemental BPN. Although there was not a huge amount of SL BPN use in the studies, the physicians were blinded to the urine screen results, and unaware of the repeated submissions of opioid-positive urines. We feel that, in clinical practice, if physicians were aware that patients are submitting opioid-positive urine samples, those patients would be given supplemental BPN. If patients are still going to be provided with supplies of sublingual buprenorphine, the impact of Probuphine on diversion, abuse, and accidental exposure would be undermined.

The Sponsor stated that, in their resubmission, they will include discussion of what will happen in the real world as they move toward patients who are stable and committed. In labeling, they would recommend not providing supplemental BPN. The sponsor noted that supplemental sublingual buprenorphine use would be mitigated by the stabilized population, and they will recommend supervised administration.

The Agency expressed concern that the Sponsor is pursuing an indication that is not in the patient population studied and that we are not sure that we can get around that fact when trying to support approval. The Sponsor responded that there was a small number of the intended population represented in the PK study but they also feel that the intended population is less vulnerable than that studied and that it should be acceptable to down-extrapolate to an easier-to-treat population. The Agency was not aware that there was precedence for the downward extrapolation that was proposed. The Agency stated that this type of information on the population differences will be helpful but it will only be part of what we need. We asked the Sponsor whether it would be possible to obtain additional efficacy data at higher doses in the more vulnerable population that requires higher doses of BPN. The Sponsor stated that they would be willing to study that population further in Phase 4, and that they are not abandoning pursuit of an indication for Probuphine for new entrants to treatment.

The Agency stated that we are commonly faced with a situation where everything seems rational and logical and that a product should work but we do not have substantial evidence to support an approval action. Although intuitively, it seems that if the 8 mg tablets are effective for the stabilized population, which represents a population less difficult to treat than the studied population, then the stabilized patients are likely to benefit from an implant that provides similar exposure. However, outside of a clinical trial, it is difficult to make such conclusions. The Sponsor will have to help the review team find the substantial evidence needed to support approval. The Sponsor suggested running a small confirmatory study focusing on the revised population, along with the additional pharmacometric data. The Agency responded that those

data would be helpful. The Sponsor asked whether the study could be open-label. The Agency responded that data from a controlled trial are needed. It was agreed that a placebo-controlled design might be unpalatable, because removing stable and successful patients from a treatment that is helping them may be unacceptable to patients and their doctors. A double-dummy design comparing to sublingual buprenorphine is a possibility. The choice of endpoint will need to be determined, because it is understood that, typically, it would be necessary to show a difference in the number of patients relapsing, but clinicians are loath to see any of their stable patients relapse.

The Sponsor noted that if approval is not dependent on a complete trial they could be ready to resubmit in 6 months. However, if they must perform an adequate and controlled trial of double dummy design, it will take at least a year. The Agency stated that we do not want to end up in a situation where a lot of time was spent on approaches that will not ultimately meet the requirements needed to approve this product, so setting an unduly optimistic timeline in which only inconclusive data can be generated would not be the best course.

The Sponsor summarized that both the FDA and they are enthusiastic about the need for this product and that an acceptable path forward is desired by both parties. The primary issue now is how to obtain the data required to support the new proposed indication. There are certain pieces that may provide support: literature, PK bridging, downward extrapolation, and discussion of clinical presentation. The core piece is the type of additional data needed. The Sponsor will recommend a study that they can undertake as soon as possible. The Agency will make every attempt to provide timely input as needed.

Titan/Braeburn's November 22, 2013, meeting summary and request for follow-up teleconference (emailed November 24, 2013).

[...]

We very much appreciated the discussions at our meeting and are pleased that there is substantial agreement on the most suitable approval pathway for Probuphine indicated for maintenance treatment of individuals stabilized on SL BPN 8 mg/day or less. We are encouraged by the Division's strong commitment to work collaboratively with us toward an approval decision and labeling for the new indication.

Items Not Discussed

Prior to the Meeting, we indicated we had accepted all of the Division's recommendations regarding scarring/inflammation, Human Factors, REMS, a radio-opaque marker, QT prolongation, and toxicology (Questions 3-8). Accordingly, there was no discussion of these items at the Meeting. We note that it is our understanding the Division will review our response to the Agency's comments to the Human Factors testing proposal (submitted to the Probuphine NDA as SN 0026) separately and provide written feedback within 30 days. We would appreciate confirmation from the Division that there are no remaining elements of the CRL that we have yet

to address except for questions regarding clinical benefit (as discussed at the Meeting) and issues that are not yet timely because they are dependent on the Division reaching an approval decision (e.g., labeling, post-marketing safety update).

FDA Responses to Questions 1.1 to 1.7 and 2.1 to 2.9

We indicated in our November 18, 2013 letter that we would provide written responses to Questions 1.1 to 1.7 and 2.1 to 2.9 as necessary depending on the discussion at the Meeting. Based on the Meeting discussion and commitment to ongoing dialogue with the Division, we respectfully request confirmation that it is not necessary to respond to FDA's recommendations regarding Questions 1.1 to 1.7 and 2.1 to 2.9 at this time, except insofar as they relate to our current proposal and the Meeting discussion, as reviewed below.

Discussion at Type C Meeting

The Type C Meeting revealed significant areas of agreement. Key areas of agreement include:

- Shared enthusiasm for additional treatment options for opioid dependence. Drs. Rosebraugh, Rappaport, and Winchell indicated that the Division had "enthusiasm" for long-acting drug products like Probuphine that provide significant potential for reducing risks of diversion, abuse, and accidental exposure. Dr. Rappaport closed the meeting by indicating that it is "extremely important" to get products such as Probuphine approved.
- Alignment regarding proposed indication of patients stabilized on SL BPN 8 mg/day or less. Notwithstanding the fact that the Division had only a limited opportunity to review our new proposal prior to the meeting, the Division indicated that the role envisioned for Probuphine, i.e., patients who are stabilized on SL BPN 8 mg/day or less, was in alignment with FDA's view of the appropriate role for four Probuphine implants.
- Data and rationale to support new indication. The Division and Sponsor agreed that PRO-805 and PRO-806 studied patients induced on SL BPN 12-16 mg/day and thus do not provide direct data regarding use of Probuphine implants to treat individuals stabilized on SL BPN 8 mg/day or less prior to treatment with Probuphine. The Division and the Sponsor agreed with the importance of assembling sufficient evidence to support labeling for the proposed indication. The Sponsor indicated that it would prepare a more thorough rationale for the proposed indication for Division review.
- Value of pharmacokinetic bridging. The Division and Sponsor agreed that the plasma concentrations of four Probuphine implants are comparable to SL BPN 4 and 8 mg/day, as supported by population PK data shared by the Sponsor at the Meeting, and that comparability of plasma concentrations can help support the proposed indication.

- Downward extrapolation of clinical study results from PRO-805 and PRO-806. The Sponsor indicated that the populations studied in PRO-805 and PRO-806 were on average more unstable and more severely impaired than those for whom the treatment appears to work best, and thus more difficult to treat than the proposed indicated population of individuals stabilized on 8 mg/day or less. The Sponsor further indicated that the more unstable and substantially impaired population studied in two Phase 3 randomized, controlled trials enables a downward extrapolation, i.e., that Probuphine can be expected to be more effective in a more stabilized population. The Sponsor further indicated that Study TTP-400-02-01 evaluated six patients who were inducted on SL BPN 8 mg/day and subsequently treated with two Probuphine implants. The Division agreed that a “downward extrapolation” argument could be very helpful as evidence to support the proposed indication.
- Ongoing exploration of higher dose products. The Division inquired about the possibility of exploring the use of Probuphine in patients with higher SL BPN requirements. The Sponsor indicated that it was willing to study higher doses post-approval.
- Importance of “Expeditious” Path to Approval. ODE II Director Curtis Rosebraugh indicated that a determination should be made about the extent of additional data, if any, that is needed to support the proposed indication. He further indicated that a mutually feasible path should be developed and the most expeditious path to approval should be pursued. The Sponsor agreed with the need for a feasible and expeditious path to approval.
- Consideration of Proposals to Provide Additional Supporting Data. The Division indicated it would entertain proposals to provide additional data to support the proposed indication and an approval decision. The Sponsor committed to submitting a draft protocol synopsis for Division review.
- Willingness to collaborate. The Division and Sponsor agreed to work closely and iteratively to identify and develop the data and rationale needed to support the proposed indication. The Division Director indicated that he would provide expedited consideration of all requests for written or oral feedback from the Division.

Remaining Issues

There were no specific areas of disagreement identified during the meeting. With agreement on the suitability of the proposed indication and the intended population for treatment with Probuphine, the remaining critical issues are (1) developing appropriate labeling for the new indication and (2) submitting the data and rationale necessary to support the new indication.

Given the broad areas of agreement and commitment to ongoing dialogue, Braeburn respectfully requests an opportunity to have an informal follow-up teleconference with you and Dr. Celia

Winchell, along with any other clinical team personnel you deem appropriate. The purpose of the call would be to receive any guidance the Division may have about the data and rationale necessary to support the new indication and to discuss timelines for moving forward. Because we want to proceed as expeditiously as possible, we respectfully request an opportunity to speak briefly prior to the Thanksgiving holiday.

Titan/Braeburn's November 25, 2013, email containing specific questions for consideration during our November 27, 2013 teleconference.

Hi Lisa:

Thank you for the clarification. We concluded from last week's meeting that the Division is interested in entertaining proposals about ways to provide the evidence necessary for an approval based on the new proposed indication. We are working on a summary analysis of the evidentiary support for our proposed indication and evaluating study designs that might provide additional supportive information. We would like an opportunity to discuss possible approaches before submitting an actual protocol synopsis for review. As indicated in our November 18, 2013 letter and at our Type C meeting, we propose that an indication for individuals stabilized on SL BPN 8 mg/day or less is supported by 1) the safety and effectiveness of SL BPN in treatment of opioids dependence, 2) effective use of lower SL BPN doses (8 mg/day or less) for maintenance treatment of individuals stabilized on 8 mg ; 3) PK bridging between 4 Probuphine implants an SL BPN 4-8 mg/day, 3) downward extrapolation of efficacy results from our two randomized, controlled studies of individuals inducted on 12-16 mg/day who were, on average, not as well stabilized as individuals stabilized on 8 mg/day or less. We are currently analyzing our study results to determine whether it is possible to identify a subset of patients who were better stabilized than others to aid in this bridging even though PRO-805 and PRO-806 do not provide direct data regarding use of Probuphine to treat individuals stabilized on SL BPN 8 mg/day or less.

We are presently considering the feasibility of a transfer study in about 40 patients. Because we already have two well-controlled studies over a full six month period (and longer for patients who continued into PRO-807 and PRO-811), we propose to focus analysis on treatment results during the first two months of Probuphine treatment. Enrollment would be limited to patients on a stable dose of SL BPN of 8 mg/day or less for at least 1 month prior to enrollment. Patients would then continue on their pre-enrollment dose of SL BPN for an additional month before being switched to Probuphine for a six-month treatment cycle. If a protocol could be finalized by January 2014 and enrollment can be completed in two months, it may be possible to report 8-week Probuphine treatment (primary end point data) data by July or August 2014. Patients would be followed for the full six months with additional reports provided to FDA at the 16-week and 24-week treatment milestones.

At present, we anticipate resubmitting the NDA around March 2014 by which point we expect to have complete study reports available from the Human Factors study, nonclinical toxicology studies, and pharmacometric analysis. We propose that FDA accept the NDA resubmission for filing around March 2014 when all data and rationale will be submitted except for the results of additional clinical study data, and that FDA review 8-week clinical study data during the review cycle.

Question 1: Will FDA consider acceptance for filing of an NDA resubmission for the proposed indication of individuals stabilized on SL BPN 8 mg/day or less (e.g. in March 2014), supported by the complete results of a Human Factors study, nonclinical toxicology studies, pharmacometric analysis results, and a rationale for the proposed indication based on data from PRO-805, PRO-806, PRO-807, and PRO-811 as well as reference to Suboxone and published literature, with partial study results (e.g. 4-8 weeks for some or all Probuphine treatment subjects) to be submitted during the review cycle and full 24-week results submitted post-approval by the 120-day safety update?

Question 2: Has sufficient data and rationale been submitted to establish a PK bridge of four Probuphine implants to SL BPN 4-8 mg/day? If not, what is necessary to establish a sufficient PK bridge?

DISCUSSION during November 27, 2013, teleconference:

In response to the proposal above, the Agency stated that the study must be an adequate and well-controlled clinical trial in the population discussed (stabilized on 8 mg or less SL BPN) and must support labeling for the duration of treatment (6 months). In addition, all data must be submitted at the time of resubmission of the NDA. The Sponsor asked if there is any way around providing a complete dataset at the time of NDA resubmission. The Agency responded that there is no exception to that policy and that it applies to all applications, even those that qualify for priority review or propose a drug for an urgent medical need. PDUFA IV and V negotiations between the Agency and Pharma resulted in the development of the 21st Century Review Process. As there is not a minute to spare in the review timeline, the Agency cannot accept data for the review after NDA resubmission as it does not provide sufficient time for review.

The Sponsor responded that, given their current body of data and the fact that the population studied was a more fragile one than that proposed, they need to have a shorter than six-month study duration requirement. The Sponsor pointed out that they were trying to find a path forward that would get the needed data more efficiently, and noted that short of a two-year timeframe for resubmission, the study report would not be available for such a study. The Agency replied that this approach is up to the Sponsor and that, if they believe that will work, we will discuss it with them. The Agency, however, does not think this approach is feasible. The Sponsor went on to discuss other possibilities. They want to target patients who are stable and they have considered using historical data of stability and then a one-month, run-in phase on Suboxone to confirm stability prior to transfer to Probuphine. The Agency asked for clarification that the Sponsor is

proposing [REDACTED] (b) (4) The Sponsor responded affirmatively, [REDACTED] (b) (4) The Agency said that this approach would be very novel and would require a policy discussion. We continued that the Sponsor would have to provide an explanation [REDACTED] (b) (4)

[REDACTED] (b) (4)
The Sponsor stated [REDACTED] (b) (4)

The Agency stated that it is highly unlikely that this approach will be acceptable but that the Sponsor is welcome to submit a proposal for evaluation.

The Sponsor suggested [REDACTED] (b) (4)
[REDACTED] (b) (4) The Agency said that we cannot comment without a full proposal and protocol that can be reviewed by the clinical and statistical review teams. The Sponsor asked about submitting a case for approval via PK data only and filing the NDA with just that, while starting a study. The Agency responded that doing so would likely result in a Refuse-To-File situation. We have discussed this with management. That being said, if that comes to pass with the approaches the Sponsor chooses to take, the Sponsor can certainly file over protest.

POST MEETING NOTE: As this application was already filed and acted upon, Refuse To File is not applicable. In this case, the resubmission would be considered an incomplete response and, therefore, the review clock would not be started.

The Sponsor asked if the Agency feels that there are any conclusions that can be drawn from Studies 805 and 806 that will help them get an idea of the magnitude of data needed from an additional study. The Agency responded that we did feel that Studies 805 and 806 provided useful information about the level of buprenorphine that 4 implants of Probuphine delivered over time, and information that this dose didn't seem high enough to help most patients cease drug use. The Agency responded that the study likely need not be large and that the Sponsor should come up with development and design options for us to consider. The Sponsor asked whether it is safe to say that the Agency is confident that Probuphine will work in patients stable on 8 mg or less of BPN. The Agency responded that we are pretty sure that those are the people it should work for but we do not have the required body of evidence to make that conclusion. The available information, however, does lead us to anticipate that it would work in that population. The Agency continued that an adequate and well-controlled trial of adequate duration is necessary. The Sponsor may submit a different proposal but it is highly unlikely that anything less will be adequate. The study does not have to be large. The Agency understands the issues around cost and time, but regulatory standards cannot be compromised in this regard.

The Sponsor will submit a protocol for review in the near future.



**FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

PRELIMINARY MEETING COMMENTS

Meeting Type: Type C
Meeting Category: Post-Action
Meeting Date and Time: November 19, 2013; 3 PM
Meeting Location: 10903 New Hampshire Ave,
White Oak Building 22, Room 1421
Silver Spring, MD 20993
Application Number: NDA 204442
Product Name: Probuphine (buprenorphine hydrochloride implant) for subdermal
use
Indication: maintenance treatment of opioid dependence
Sponsor/Applicant Name: Titan Pharmaceuticals

Invited CDER Participants:

Curtis Rosebraugh, MD, MPH	Director, Office of Drug Evaluation II (ODEII), OND
Mary Parks, MD	Deputy Director, ODE II
Bob A. Rappaport, MD	Division Director, Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Rigoberto Roca, MD	Deputy Division Director, DAAAP
Celia Winchell, MD	Clinical Team Leader, DAAAP
Adam Wasserman, PhD	Pharmacology/Toxicology Supervisor, DAAAP
Yun Xu, PhD	Team Leader, Clinical Pharmacology, Division of Clinical Pharmacology II (DCPII), Office of Clinical Pharmacology (OCP), Office of Translational Science (OTS)
Rachel Skeete, MD, MHS	Clinical Reviewer, DAAAP
Gary Bond, PhD	Pharmacology/Toxicology Reviewer, DAAAP
David Lee, PhD	Clinical Pharmacology Reviewer, DCPII, OCP, OTS
Vikram Sinha, PhD	Director, Division of Pharmacometrics, OCP, OTS
Venkatesh Atul Bhattaram, PhD	Pharmacometrics Reviewer, Division of Pharmacometrics, OCP, OTS
Patricia Love, MD, MBA	Deputy Director, Office of Combination Products (OCP)
Bindi Nikhar, MD	Senior Clinical Advisor, OCP
Jamie Wilkins-Parker, PharmD	Team Leader, Division of Medication Error Prevention and Analysis (DMEPA), Office of Medication Error Prevention and Risk Management (OMEPRM), Office of Surveillance and Epidemiology (OSE)
Vicky Borders-Hemphill, PharmD	Safety Evaluator, DMEPA, OMEPRM, OSE

Reema Mehta, PharmD, MPH

Jason Bunting, PharmD
Jamie Wilkins-Parker, PharmD
Mark Liberatore, PharmD
Lisa Skarupa, MSN
Lisa Basham, MS

Team Leader, Division of Risk Management (DRISK),
OMEPRM, OSE
Risk Management Analyst, DRISK, OMEPRM, OSE
Risk Management Analyst, DRISK, OMEPRM, OSE
Team Lead, Project Management, OSE
Project Manager, OSE
Senior Regulatory Health Project Manager, DAAAP

SPONSOR ATTENDEES

Seth L. Harrison, MD
Behshad Sheldon

Frank E. Young, MD, PhD

(b) (4)
Katherine L. Glassman-Beebe, PhD

Scott Henley, MBA

(b) (4)

Executive Chairman, Braeburn Pharmaceuticals
President and Chief Operating Officer, Braeburn
Pharmaceuticals
Executive Vice President, Clinical and Regulatory
Affairs, Braeburn Pharmaceuticals
Counsel to Braeburn Pharmaceuticals, (b) (4)
Executive Vice President and Chief Development
Officer, Titan Pharmaceuticals
Vice President, Clinical Operations and Project
Management, Titan Pharmaceuticals
Clinical Consultant to Braeburn Pharmaceuticals,
(b) (4)
Biostatistical Consultant to Titan Pharmaceuticals,
(b) (4)
Pharmacometrics Consultant to Braeburn
Pharmaceuticals, (b) (4) a
Clinical Pharmacology Consultant to Braeburn
Pharmaceuticals, (b) (4)
Human Factors Consultant to Braeburn
Pharmaceuticals, (b) (4)
(b) (4)
Toxicology Consultant to Braeburn Pharmaceuticals,
(b) (4)
Clinical Pharmacology Consultant to Braeburn
Pharmaceuticals, (b) (4)
Human Factors Consultant to Braeburn
Pharmaceuticals, (b) (4)
(b) (4)
Clinical & Clinical Pharmacology Consultant to
Braeburn Pharmaceuticals, (b) (4)
Clinical Consultant to Braeburn Pharmaceuticals, (b) (4)
(b) (4)
Human Factors Consultant to Braeburn
Pharmaceuticals, (b) (4)
(b) (4)

(b) (4)

Human Factors and Clinical Consultant to Braeburn
Pharmaceuticals, (b) (4)

(b) (4)

(b) (4)
Toxicology Consultant to Braeburn Pharmaceuticals,
(b) (4)

Introduction:

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for November 19, 2013, between Titan Pharmaceuticals and the Division of Anesthesia, Analgesia, and Addiction Products. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. However, if these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the meeting (contact the regulatory project manager (RPM)). If you choose to cancel the meeting, this document will represent the official record of the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). It is important to remember that some meetings, particularly milestone meetings, can be valuable even if the pre-meeting communications are considered sufficient to answer the questions. Contact the RPM if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

BACKGROUND

The drug product is Probuphine (buprenorphine hydrochloride implant), and the proposed indication is for the maintenance treatment of opioid dependence. The application is a 505(b)(2) application referencing the Agency's prior findings of safety and efficacy for Subutex (buprenorphine sublingual tablets), NDA 020732, and Suboxone (buprenorphine/naloxone combination tablets), NDA 020733. Probuphine is a rod-shaped implant designed to provide sustained delivery of a therapeutic level of buprenorphine, a partial agonist at the μ -opiate receptor, for up to six months when 4 to 5 rods are implanted subdermally.

The initial New Drug Application (NDA) was submitted by Titan Pharmaceuticals and received by the Agency on October 31, 2012. A Complete Response letter was issued on April 30, 2013. The deficiencies in the letter noted inadequate demonstration of clinical benefit and inadequate evaluation and validation of the insertion and removal surgical procedure. Additional comments recommend a study to evaluate the effect of scarring or inflammation at previously implanted sites on the re-implantation and bioavailability of Probuphine, a study of efficacy in patients with lower sublingual buprenorphine requirements, and modification of the implant to include a radio-opaque marker to facilitate removal. A comment was also included on the inadequacy of the applicant's method for deriving, from the approved listed drug labeling, safety margins to be

reflected in the labeling for Probuphine. The purpose of this meeting is to discuss the applicant's strategy for addressing the deficiencies and Agency comments in the Complete Response letter.

The meeting request was received on September 3, 2013, and the meeting package was received on October 10, 2013. For ease of reference, the applicant's questions are reproduced below in italicized text. Our comments and responses are presented in bolded text.

DISCUSSION

General Comments:

On review of your briefing package for the Type C meeting, outlining your proposal for addressing the Complete Response letter, we find that most of the questions that you have posed are matters for review. However, we note that, on face, we have concerns that the direction that you have taken to address the complete response letter will not adequately address the issues identified during the first cycle review of the NDA.

In endeavoring to justify the clinical benefit associated with the patterns of drug-taking behavior observed during treatment with Probuphine, you have highlighted guidelines that indicate that abstinence is not the only measure of treatment response in opioid addiction, and you have relied on the guidance of a small number of clinical experts in addiction medicine who served on the 2-day panel to define other measures of success in opioid addiction treatment. We agree that abstinence is not the only measure of treatment response in opioid addiction. We also agree that patients may experience a relapsing and remitting course in their drug use, particularly when they leave treatment. However, neither of these points supports your contention (b) (4)

You have not provided evidence demonstrating that these surrogate measures of clinical benefit actually do correlate with some measure of clinical benefit to the patient, e.g., improvements in health or psychosocial functioning.

We are not persuaded (b) (4)

For example, the treatment guidelines provided by SAMHSA¹ provide a flow chart that includes dose increases when a patient continues to use illicit drugs; this would imply that ongoing drug use is not an expected, acceptable, and routine issue to be overlooked. They also advise that "Elimination of objective evidence of opioid use (negative toxicology) represents the key target sign for which to strive. The goal is to reduce self-reported cravings and self-reported use of illicit opioids." Furthermore, in the same guidelines clinicians are advised to consider referring a patient to a more intensive

¹ Clinical Guidelines for the Use of Buprenorphine in the Treatment of Opioid Addiction. Treatment Improvement Protocol (TIP) Series 40. DHHS Publication No. (SMA) 04-3939. Rockville, MD: Substance Abuse and Mental Health Services Administration, 2004.

treatment environment "...if toxicology tests are still not free of illicit drugs after 8 weeks." These expectations with regard to the clinical course with opioid substitution treatment also inform clinical trial designs in literature, which often incorporate either definitions of treatment success or criteria for protective transfer due to treatment failure, each involving an expectation that persistent illicit drug use will not occur in the successfully-treated patient. Because you propose to offer this product at a single dose for all patients, we believe that it should be a dose at which patients can achieve treatment success as it is more customarily measured.

Your submission did not address our request to provide evidence supporting the clinical benefit of the patterns of drug use observed in your studies. While we are aware of studies showing improvements in mortality, seroconversion, and crime in patients who participate in methadone maintenance programs notwithstanding ongoing drug use, we do not know how to extrapolate those findings to patients who are being treated under vastly different circumstances, potentially involving very little clinician contact or "treatment" other than the circulating buprenorphine plasma level, as will be possible for patients treated with Probuphine implants. Not all patients will be injection drug users, so arguments pertaining to avoidance of blood-borne illnesses may not be relevant to the patient population intended for marketing. If, however, there are available datasets examining drug use patterns and measures of psychosocial functioning and medical consequences in buprenorphine-treated outpatients longitudinally, these data may provide some helpful information to support choice of a pattern of drug use on-treatment that is a valid surrogate for clinical benefit.

You have also argued that the opioid-blocking properties of this partial agonist, buprenorphine, are questionable from the standpoint of pharmacodynamics, and that blockade is not a relevant goal of medication-assisted treatment of opioid dependence. We do not agree. We believe that it is well-accepted that cross-tolerance to other opioids, which results in attenuation or blockade of the subjective effects of illicit opioids, is a well-recognized mechanism of action of both methadone and buprenorphine treatment, and that both researchers and clinicians appreciate this concept, even if clinicians do not assess blockade when titrating doses during clinical care. We note that the SAMHSA treatment guidelines indicate that "One benefit worth achieving is a self-reported increase in opioid blockade such that self-administered illicit opioids induce little or no euphoria."

Patients are also well aware of the role of opioid blockade in buprenorphine treatment, and of its dose-dependent nature, as evidenced by discussions on internet message forums advising how to reduce the dose of buprenorphine so that "vacations" from treatment are not necessary in order to experience the effects of the opioid of choice. These patients are also well aware that at much lower levels, buprenorphine can stave off withdrawal without blocking the effects of illicit opioids.

We agree with you that studies in the literature do not support a consistent conclusion about the relationship between administered buprenorphine doses and blockade of clinically relevant doses of opioids of abuse. There is heterogeneity in the challenge doses used, the interpretation of the term "blockade" (to mean either any detectable attenuation

of agonist effect, or complete prevention of agonist effect), and in the doses, route, and timing of the buprenorphine administration, and some literature reviews are confounded by confusing more bioavailable sublingual solution doses with tablet doses, because some papers do not identify which formulation was used. Nevertheless, overall, we believe that the plasma level produced by four Probuphine implants is too low for opioid blockade, and that a dose-response does exist, such that a higher number of implants may be able to produce blockade. Studies which evaluate the relationship between opioid blockade and mu-receptor occupancy^{2,3} suggest that 85% receptor occupancy or better would be a reasonable target for full blockade, that the threshold for any blockade is between 50–60% occupancy, and that the shape of the curve relating plasma level to receptor occupancy is exponential. The point at which 50% of receptors are occupied appears to fall at approximately the 1 ng/mL plasma level, but any exposure below that level, even slight, is associated with much lower receptor occupancy. For this reason, the plasma levels associated with four Probuphine implants are likely to produce inadequate receptor occupancy to accomplish any attenuation of illicit opioid effects.

Lastly, you have noted that Probuphine offers passive compliance and that there are a number of adherence issues with sublingual (SL) buprenorphine such that the plasma exposure in patients who are prescribed 16 mg/day is not as high as the known plasma level associated with this dose. We agree that Probuphine offers a valuable opportunity to overcome adherence issues, and to deliver the expected plasma level that compliant patients would achieve. We note that the original studies supporting approval involved supervised administration, so the studied doses were actually delivered. (b) (4)

CLINICAL EFFICACY

Adequacy of Dose

Question 1.1: Does FDA agree that 4 Probuphine implants yields predictable BPN plasma concentrations within a range of 0.5 – 1.0 ng/mL with low intersubject and intra-subject variability?

FDA Response:
Yes, we agree.

Question 1.2: Does FDA agree that SL BPN has been found to yield plasma concentrations with high inter-subject and intra-subject variability and that patient non-adherence in

²Greenwald, M., Johanson, C., Moody, D., et al. (2003). Effects of buprenorphine maintenance dose on mu-opioid receptor availability, plasma concentrations, and antagonist blockade in heroin-dependent volunteers. *Neuropsychopharmacology* 28, 2000–2009.

³Greenwald, M., Johanson, C., Bueller, J., et al. (2007). Buprenorphine duration of action: Mu opioid receptor availability and pharmacokinetic and behavioral indices. *Biol Psychiatry* 61, 101–110.

clinical settings results in higher variability than observed in inpatient PK settings with observed administration of doses?

FDA Response:

Yes, we agree. However, if you plan to compare BPN concentrations from four Probuphine implants to the efficacious concentrations of Suboxone, you will need to use the dosing regimen approved by the Agency for Suboxone; therefore, patients' 'non-adherence' or 'non-compliance' cannot be counted into the overall assessment.

Question 1.3: Does FDA agree that 4 Probuphine implants yield therapeutic plasma concentrations within the therapeutic range of SL BPN 4-24 mg/day for maintenance treatment of opioid dependence?

FDA Response:

Because sublingual buprenorphine is titrated to effect, there is not a range which is considered "therapeutic" for all patients. Based on mean AUC values, it appears that four Probuphine implants will yield BPN concentrations closer to a SL dose between 4 to 8 mg.

Question 1.4: Does FDA agree that 4 Probuphine implants yield therapeutic plasma concentrations comparable to the trough levels observed following SL BPN 8 mg/day in inpatient PK studies with observed administration of SL BPN doses?

FDA Response:

We agree that the trough concentrations are comparable. However, when systemic exposures are compared, AUC and C_{max} values are also considered in addition to trough concentrations. There is no evidence that efficacy of BPN is only related to trough concentrations (i.e., regardless of C_{max} and AUC).

Question 1.5: Does FDA agree [REDACTED] (b) (4)

FDA Response:

No. [REDACTED] (b) (4)

Question 1.6: Does FDA agree

(b) (4)

?

FDA Response:

Although we agree that the titration-to-effect design did not provide support for the benefit of a fifth implant in those patients who met criteria for up-titration, we do not agree with your argument

(b) (4)

We further believe that had all patients received a higher dose at the outset (e.g., 6-8 implants), clear success may have been achieved in many patients. However, it is premature at this time to discuss the dosing regimen to be included in labeling.

Question 1.7: Does FDA agree that the results on dose presented in this submission coupled with a pharmacometric analysis would form the basis of a complete response to elements of the CRL related to dose?

FDA Response:

Please refer to Agency's concerns regarding adequacy of dose finding under General Comments. Additionally see our Responses to Questions 1.1 to 1.6. We have additional comments on the analysis if you plan to conduct a pharmacometric analysis:

1. The exposure-response analysis that you plan to conduct will use average concentrations of buprenorphine (BPN). You must provide an adequate rationale for us not to consider differences in the shape of concentration-time profile associated with sublingual BPN and Probuphine implants (e.g., C_{max} and AUC differences).
2. You plan to derive average concentration across visits in your analysis. The analysis should also link within-patient variability in concentrations to the clinical outcomes by visit.

Clinical Benefit of the Behavioral Changes Observed in the Probuphine Clinical Studies

Question 2.1: Given the nature of opioid addiction, the complex and nonlinear process of recovery, and contemporary understandings of the value of reductions in drug-abuse behavior, does FDA agree that reductions in drug use, retention in treatment, control of withdrawal symptoms, control of patient cravings, and clinical global impression are important measures of clinical benefit as well as total abstinence?

FDA Response:

Other measures of clinical benefit (directly measuring how patients feel or function) may be helpful in assessing the benefit of opioid addiction treatment. However, we have reservations about some of the measures proposed, as discussed below.

Question 2.2: Does FDA agree that the magnitude of decreases in drug taking behavior observed in PRO-805 and PRO-806, as part of the totality of the evidence, contribute to a demonstration of clinical benefit?

FDA Response:

Assessment of the extent to which the pattern of drug-taking behavior observed in the PRO-805 and PRO-806, as part of the totality of the evidence, contributes to a demonstration of clinical benefit is a matter for review. We recommend that various approaches to imputing missing data after drop-out be explored. We also note that the observed patterns of on-treatment drug use may or may not represent reductions from the patients' individual pre-treatment patterns, particularly in patients submitting a substantial number of positive urine samples. Also, as described above additional, evidence-based justification of the clinical benefit of the observed on-treatment use patterns is needed.

Question 2.3: Does FDA agree that the magnitude of improved retention-in-treatment outcomes demonstrated in PRO-805 and PRO-806, as part of the totality of the evidence, contribute to a demonstration of clinical benefit?

FDA Response:

This again is a matter for review. However, we note that the propensity of study subjects to remain in the study was influenced by a variety of factors, including the protocol-specified procedures for removing patients who took more than the threshold number of rescue doses. We observe that other protocols have included ongoing drug use as a criterion for "protective transfer" (removal from the study) and we note that this renders interpretation difficult. We also question whether retention-in-treatment as documented in the study has relevance as a predictor of clinical benefit. As discussed above, we do not believe that it would be appropriate to assume the benefits of retention in addiction treatment will accrue to Probuphine-treated patients after approval, because Probuphine requires no "treatment" contact after initial implantation, and you have identified a target population of "patients who have difficulty making frequent office visits (e.g., those in rural or remote areas, those with limited mobility, frequent travelers)."

Question 2.4: Does FDA agree that the levels of symptom control and craving abatement demonstrated in PRO-805 and PRO-806, as part of the totality of the evidence, contribute to a demonstration of clinical benefit?

FDA Response:

Assessment of the extent to which the levels of symptom control and craving abatement demonstrated in PRO-805 and PRO-806, as part of the totality of the evidence, contributes to a demonstration of clinical benefit is a matter for review. However, we note that the term “craving” may not be sufficiently well-defined to serve as a measure of patient benefit. The literature on “craving” in addiction suggests that the term “craving” is not a well-defined concept, having different meanings to different patients, as well as different meanings to clinicians as compared to patients.⁴ Moreover, “provoked craving” (also called “cue-induced craving”) that may occur later in treatment in patients who are not in withdrawal is seen as separate and distinct from craving for drug during acute withdrawal. Although some researchers have asserted that “craving” is predictive of relapse, and that drugs that treat “craving” would be expected to reduce illicit drug use, some of the literature suggests that this is not a clear relationship and is further confounded by the distinction between abstinence- or withdrawal-associated craving and provoked, or cue-induced craving. For this reason, we are not confident that the term “craving” is sufficiently well-defined to serve as a medical product claim. Moreover, a recent study of opioid-dependent patients treated with either methadone or buprenorphine found that craving did not predict relapse, suggesting that the effect of opioid dependence treatment is not mediated through control of craving.⁵ Your figures depicting the measures of withdrawal suggested that, in general, all groups had withdrawal scores in the “asymptomatic” range throughout, so differences may not be meaningful.

Question 2.5: Does FDA agree that the magnitude of improvement in CGI scores observed at end of treatment in PRO-805 and PRO-806, as part of the totality of the evidence, contribute to the demonstration of clinical benefit?

FDA Response:

Determination of the extent to which the magnitude of improvement in CGI scores observed at end of treatment in PRO-805 and PRO-806, as part of the totality of the evidence, contributes to a demonstration of clinical benefit is a matter for review. In general, clinical global impression scales and scores are not used to define treatment success, but rather they are secondary measures and used in a confirmatory fashion.

⁴ Kozlowski, L., and Wilkinson, D. (1987). Use and misuse of the concept of craving by alcohol, tobacco, and drug researchers. *British Journal of Addiction* 82, 31–36.

⁵ Nava, F., Caldiroli, E., Premi, S., and Lucchini, A. (2006). Relationship between plasma cortisol levels, withdrawal symptoms and craving in abstinent and treated heroin addicts. *Journal of Addictive Diseases* 25(2), 9–16.

As noted above, you have not provided evidence to support your expert-proposed responder definition [REDACTED] (b) (4)

Question 2.6: Does FDA agree that the results of the PRO-806 Suboxone arm may provide supportive evidence of clinical benefit?

FDA Response:

It is difficult to interpret the comparison to the open-label Suboxone arm as a comparison to “real-world” Suboxone efficacy for several reasons. First, patients volunteering for a clinical trial of a new, implantable formulation may, understandably, have been dismayed to be assigned to an open-label arm in which they received a medication already available—potentially, one they had already tried. For some patients, there were likely other less burdensome and less intrusive ways to receive treatment with sublingual buprenorphine tablets than participation in a clinical trial that required multiple weekly visits. Furthermore, the protocol permitted only doses between 12 and 16 mg/day. Patients could not have dose escalations above 16 mg, and if the dose was decreased at any point, it could not be increased again. Therefore, the dosing was not individualized or titrated to effect, as patients would experience in the normal course of clinical practice. (It is acknowledged that a clinical trial does, customarily, provide dosing flexibility less than “real-world” practice, but to the extent that we wish to know how Probuphine compares to “usual care,” this becomes a relevant issue.) We also note that in “real-world” practice physicians are not blind to the results of their patients’ toxicology screens and can titrate the medication to effect or refer patients to more structured treatment if necessary, which was not a feature of the treatment provided in the clinical trial.

Question 2.7: Does FDA agree that the Probuphine efficacy results accord with the levels of drug-use-behavior and retention-in-treatment improvements demonstrated for Suboxone, thereby providing supportive evidence of the clinical benefits associated with Probuphine treatment?

FDA Response:

Regarding the comparison to the open-label arm of PRO-806, we note that if, as the submission suggests, patients in the open-label Suboxone arm were frequently non-compliant with the prescribed medication, then the effect in the Probuphine arm would have been expected to be *better than* in the Suboxone arm. Comparisons to

CLINICAL SAFETY

Human Factors

Question 4: Does FDA agree that Braeburn's proposed Human Factors study protocol is adequately designed to address FDA's concerns?

FDA Response:

We agree 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.**
- 2. 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 how to locate inserted implants, etc.**
- 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.**
- 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 and experience. 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.

- 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.**
- 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.**
- 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.**
- 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.**
- 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 a 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 the original insertion site.**
 - d. Disinfect the insertion site.**

- e. Apply a sterile drape.
 - f. Anesthetize the insertion site (i.e., 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.
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.
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.
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 a 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.
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 the removal site with an alcohol prep pad.**
 - d. Mark locations of implants with a sterile marker.**
 - e. Unwrap the surgical tray and place the equipment in the sterile field on the Mayo stand.**
 - f. Put on sterile gloves.**
 - g. Dis-infect the insertion site.**
 - h. Apply a sterile drape.**
 - i. Make a 7-10 mm incision with the scalpel, parallel to the access of the arm, between the 2nd and third implants.**
 - j. Confirm that the 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 the incision site.**
- 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.**
- 15. For improved readability, consider making the following modification based on our review of the instructions for use in the insert labeling that were submitted to NDA 204442 in January, 2013.**
- 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.**
 - 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.**
 - 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.

- 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.
- 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.
- 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.
- 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)."
- 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.
- i. Consider revising 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.
- 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).
- 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).
 - 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.
 - 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.”
 - 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.”
 - 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.
 - 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).
 - 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.

- 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).
- 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.
- 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.
- 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).
- 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.
- 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)

- 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).
- 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.”
- 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.*”
- 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.
- 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.”
- 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.”

- 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.**
- ee. Consider adding to Figure 15 (for Probuphine implant dose increase: fifth implant insertion), 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.**
- ff. Consider combining Steps 6 (clean insertion site) and 7 (apply sterile drape) into one single step (for removal procedure).**
- 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.**
- 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.**

REMS

Question 5: Does FDA agree that a closed distribution system that includes the use of a single distributor network can provide [REDACTED] (b) (4)

[REDACTED]?

FDA Response:

A critical objective of the proposed risk mitigation strategy is to ensure that only REMS-trained and certified providers perform the implantation and removal procedures for Probuphine due to the risk of complications associated with the procedures. Therefore, if you would like to include the aforementioned distribution system in the proposed REMS that is submitted after your response to the Complete Response Letter, the proposal must include a mechanism to ensure that only a REMS-trained and certified provider would perform the implantation procedure.

As mentioned, we will continue discussion of your proposed REMS after your response to the Complete Response Letter has been submitted.

Consideration of a Radio-Opaque Marker

Question 6: Does FDA agree that the decision to modify the implant formulation to include a radio-opaque marker can be guided by the results of the planned post-approval scarring/inflammation study?

FDA Response:

We recommend that you begin to explore how a radio-opaque marker can be incorporated into the implant without waiting for the results of the post-approval study.

QT Prolongation

Question 7: Can FDA confirm that the post-marketing obligations specified in the CRL regarding QT prolongation may be addressed in a post-approval submission, and that FDA's data and information needs on this matter will be provided by FDA in the context of an approval letter?

FDA Response:

Yes, we confirm that a clinical trial to assess the risk of QT prolongation with subdermal buprenorphine, i.e., a thorough QT (tQT) trial, may be conducted post-approval.

NONCLINICAL

Note: The following nonclinical responses were sent in our October 11, 2013, advice letter.

Question 8.1: Does the Agency concur with Braeburn's proposal to provide toxicokinetic data derived from SC administration of BPN for 14 days in gravid rats and rabbits to support animal to human exposure margin calculations in the Pregnancy section of the Probuphine product label?

FDA Response:

For Developmental Toxicity, SC doses of 0.1, 1, & 5 mg/kg/day in rats and 5 mg/kg/day in rabbits as you propose and as listed in the reference NDA label are acceptable. It is assumed you mean that the toxicokinetic samples will be taken on the first day of dosing (Day 6 of gestation) and then 14 days later (Day 20 of gestation). If so, this is acceptable. In order to account for potentially extended elimination half-lives of buprenorphine, additional time points should be considered for sampling, particularly after the last dose.

Question 8.2: Does the Agency concur with Braeburn's proposal [REDACTED] (b) (4) [REDACTED]?

FDA Response:

No. [REDACTED] (b) (4)

In order to provide a more meaningful description of labeled studies, conduct bridging studies targeting dietary doses of 0.6, 5.5, and 56 mg/kg/day in rats and 100 mg/kg/day in mice as listed in the reference NDA label. The duration of daily dosing and toxicokinetic sampling should be appropriate so as to adequately define steady state for daily dosing with a long enough sampling time, most notably after the last dose.

For the Impairment of Fertility section of the label, you will need to provide bridging TK data for the SC dose of 5 mg/kg/day in rats as described in the reference NDA label. The duration of daily dosing and toxicokinetic sampling should be appropriate so as to adequately define steady state with a long enough sampling time, most notably after the last dose.

Question 8.3: Since toxicity was observed in the DART study with rats following SC administration, (the clinically relevant route of administration), the inclusion of data for other routes of administration (IV, IM, PO) does not further inform the prescribing physician to the potential risks of Probuphine for reproductive and developmental toxicity. Braeburn therefore proposes to remove from the label the description of these other routes of administration (IV, IM, PO). Does FDA agree?

FDA Response:

If the exposure data obtained in the SC bridging TK study would provide for a safety margin for human exposure to be expressed in the label, the inclusion of nonclinical findings from the other exposure routes is unnecessary. However, if the SC dosing data indicates that exposure does not adequately cover human exposure then study findings utilizing non-SC routes may be of greater relevance and must be included and addressed in the label.

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
11/15/2013

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
12/10/2012



IND 070852

MEETING MINUTES

Titan Pharmaceuticals
400 Oyster Point Blvd
Suite 505
South San Francisco, CA 94080

Attention: Sunil Bhonsle
President

Dear Mr. Bhonsle:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for buprenorphine hydrochloride/ethylene vinyl acetate (Probuphine).

We also refer to the meeting between representatives of your firm and the FDA on October 25, 2011. The purpose of the meeting was to discuss your proposed NDA submission.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-1245.

Sincerely,

{See appended electronic signature page}

Matthew W. Sullivan, M.S.
Senior Regulatory Project Manager
Division of Anesthesia, Analgesia, and
Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

SPONSOR MEETING MINUTES

MEETING DATE: October 25, 2011
TIME: 11:00 am to 12 noon
LOCATION: FDA White Oak Campus
Silver Spring, MD
APPLICATION: IND 070852
PRODUCT: Buprenorphine hydrochloride/ethylene vinyl acetate
(Probuphine)
INDICATIONS: Treatment of opioid dependence
SPONSOR: Titan Pharmaceuticals, Inc
TYPE OF MEETING: Type B (pre-NDA)
MEETING CHAIR: Celia Winchell, M.D., Clinical Team Leader, Division of
Anesthesia, Analgesia, and Addiction Products (DAAAP)
MEETING RECORDER: Matthew Sullivan, M.S., Senior Regulatory Project
Manager, DAAAP

FDA Attendees	Title
Bob A. Rappaport, M.D.	Director, Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Rigoberto Roca, M.D.	Deputy Division Director, DAAAP
Celia Winchell, M.D.	Clinical Team Leader, DAAAP
Rachel Skeete, M.D.	Clinical Reviewer, DAAAP
Ramesh Raghavachari, Ph.D.	CMC Lead, Office of New Drug Quality Assessment (ONDQA)
Yun Xu, Ph.D.	Clinical Pharmacology Team Leader, Division of Clinical Pharmacology II (DCP II)
David Lee, Ph.D.	Clinical Pharmacology Reviewer, DCP II
Adam Wasserman, Ph.D.	Pharmacology/Toxicology Supervisor, DAAAP
Gary Bond, Ph.D.	Pharmacology/Toxicology Reviewer, DAAAP
Stephen Sun, M.D.	Clinical Reviewer, Controlled Substances Staff (CSS)
Dionne Price, Ph.D.	Statistical Team Leader, Division of Biostatistics II (DB II)
Jon Norton, Ph.D.	Statistical Reviewer, DB II
Denise Baugh, PharmD, BCPS	Safety Evaluator, Office of Surveillance and Epidemiology (OSE), Division of Medication Error and Prevention (DMEPA)
Lubna Merchant	Safety Evaluator, OSE/DMEPA
Jean Mulinde, M.D.	Medical Officer, Office of Scientific Investigations
Denise Miller	Microbiologist, Office of Pharmaceutical Sciences, New Drug Microbiology Staff
Matthew Sullivan, M.S.	Regulatory Project Manager, DAAAP

Titan Attendees	Title
Sunil Bhonsle, MBA	President
Marc Rubin, MD	Executive Chairman
Katherine L. Beebe, PhD	Executive Vice President and Chief Development Officer
Scott Henley, MBA	Executive Director, Clinical Operations and Project Management
Mike Beier	Senior Vice President, Operations
Raj Patel	Vice President, Process and Manufacturing Development
Sunil Sreedharan	Vice President, Technology and Product Development
(b) (4)	(b) (4) Probuphine Investigator (consultant)
(b) (4)	(b) (4) Scientific Affairs (statistical consultant)
(b) (4)	regulatory affairs consultant
(b) (4)	REMS consultant

Opening Discussion: Following introductions, the discussion focused on the Sponsor's questions that were included in the September 12, 2011, meeting package. Written comments were sent to the Sponsor on October 21, 2011, and are shown in bold text. The Sponsor provided brief responses on October 24, 2011, which are shown below in bold italic text. The Sponsor's questions are shown below in italic text, and the discussion is shown in normal text.

Question 1 *The overall Probuphine clinical development plan and trial results are acceptable to support the submission and registration of a New Drug Application via the 505(b)(2) mechanism for the indication of the treatment of opioid dependence following induction with 12-16 mg/day of SL BPN for repeat six-month treatments? Does the Division concur?*

Division Response:

The overall clinical development plan and trial results appear acceptable to support submission of an NDA via the 505(b)(2) pathway. The current safety database has fewer exposures than typically required; however, it may be possible that a safety database of approximately 86 patients treated for one year could provide an adequate basis for identification of important safety events. Note that in the event that an unexpected safety signal is identified, additional safety information may be required. Furthermore, results for the combined urine toxicology/self-report analysis for PRO-805 were not submitted with your meeting package. The combined urine toxicology/self-report analyses must be included with your NDA submission and will serve as the key analyses for efficacy assessment. Additionally, as you are pursuing an indication for Probuphine for repeat six-month treatments, the primary endpoint must be assessed over a six-month period, that is, Weeks 1–24 for both Phase 3 trials¹.

¹ We acknowledge that the protocol-specified primary analysis for the first of your clinical trials incorporated only the first four months of treatment, and that weeks 17-24 were analyzed as a secondary endpoint. However, we remind you that this was permitted because you had not yet established that the implant would be effective for a full six months, and wished to retain the option to conclude that the trial supported implantation for four months. However, because you are now

Discussion:

There was no discussion beyond the Division's initial written response.

Question 2 *There are no additional integrated analyses of the clinical data that the Division considers to be necessary to support the NDA? Does the Division concur?*

Division Response:

The proposed ISE and ISS format and content appear to be adequate. For the ISS, safety data from the two open-label re-treatment studies should also be summarized based on the assigned treatment in the controlled phase. In addition to summaries of AEs, the ISS should also summarize lab values, vital signs, and other routine safety assessments made during the studies. Include analyses of information derived from controlled clinical trials, analyses of information derived from open-label extension studies, and analyses considering all data. Separate sections addressing specific buprenorphine safety issues should be included, analyzing all available data pertinent to the issues of CNS and respiratory depression, opioid withdrawal syndrome, implant site reactions, hepatic injury, allergic reactions, abuse potential, and orthostatic effects. Shift tables categorizing liver function tests, i.e., AST, ALT, total bilirubin, should be included and the tables should display baseline and post-baseline categories of "normal," "elevated," or ">3 x ULN," and extreme categories (e.g., "> 5 x elevated" and "> 10 x elevated"). The clinical trial database should be examined for Hy's Law cases. (Refer to the Guidance for Industry *Drug-Induced Liver Injury: Premarketing Clinical Evaluation* available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf>). Any available data on implantation related to provider and patient characteristics should be included. These data should also be provided for re-implantation.

The ISE should also provide results for the primary analyses of the primary endpoint when a grace period that allows for patients to engage in treatment is incorporated into the analysis. For the primary endpoint, both urine toxicology and self-report should be used to adjudicate treatment response. Datasets should contain all information on self-reported illicit drug use and urine toxicology results. Any available data on subjects' experience with withdrawal should be included. Any available information on patient experience following discontinuation of therapy should also be included.

Refer to the attachment below for additional guidance on assembling the ISS and ISE.

Titan October 24, 2011, comments:

Please clarify what is being requested by the above statement: "The ISE should also provide results for the primary analyses of the primary endpoint when a grace period that allows for patients to engage in treatment is incorporated into the analysis."

proposing a six-month dosing interval, the relevant analyses are those which document that the drug is effective throughout the proposed interval.

Discussion:

The Sponsor asked the Division to provide additional details regarding the grace period cited in the initial response. The Division replied that it would like to see the cumulative distribution of treatment response analyzed allowing for an initial period of time to further engage patients in treatment (a “grace period” during which positive urine toxicology results and self-report are not counted in the assessment of response). If patients are still using illicit drugs early in treatment, but become abstinent as they are more engaged in the treatment process, this analysis may give a different picture of treatment response, and could also point to the need to encourage additional support early in treatment. The Sponsor should explore grace periods of varying lengths and submit these analyses with the NDA submission.

The Sponsor stated their understanding of this request.

Question 3 The dosing regimen as presented in the overall trial results is sufficient to support the proposed indication for Probuphine, specifically for the treatment of opioid dependence following induction with SL BPN? Does the Division concur?

Division Response:

The dosing regimen as presented in the overall trial results appears sufficient. However, we note that as part of the clinical development program, only a minimum effective dose was identified, while no higher doses were explored. During the review, the effectiveness of Probuphine at the proposed dose will be assessed in the context of the overall risk-benefit determination. i.e., whether the level of effectiveness at the dose evaluated sufficiently outweighs the potential risks associated with your drug product.

Discussion:

There was no discussion beyond the Division’s initial written response.

Question 4 The bioavailability data comparing SL BPN to Probuphine as presented in the Briefing Document is adequate to support a 505(b)(2) NDA? Does the Division concur?

Division Response:

We agree the relative bioavailability study presented in the meeting package, comparing your product Probuphine to the reference product Suboxone, is adequate to support the NDA filing. Whether it will support the approval of the NDA will be determined after review of the data.

Discussion:

There was no discussion beyond the Division’s initial written response.

Question 5 Does the Division concur that given the extent of clinical experience with BPN to date in treating opioid dependence and the Probuphine clinical study results, Titan may rely on FDA’s prior findings for the Reference Listed Drug

(RLD), BPN, and that the following special studies are not required for Probuphine:

- a. Hepatic and Renal Studies*
- b. Drug-Drug Interactions Studies*
- c. Thorough QT (tQT) evaluation? And, if the Division determines that a tQT assessment is required for Probuphine, does it concur that such a study can be conducted as a post-marketing study?*

Division Response:

Based on the preliminary results presented in the meeting package, that the systemic exposure of your product Probuphine is lower than the reference product Suboxone, no additional hepatic impairment study, renal impairment study, or drug-drug interaction study will be required. A thorough QT study will not be required for NDA filing; however, you may need to submit a thorough QT data as a post-marketing requirement.

Discussion:

There was no discussion beyond the Division's initial written response.

Question 6 Titan may conduct [REDACTED] (b) (4) as a post-marketing study? Does the Division concur?

Division Response:

We are unable to ascertain from the study synopsis provided in the meeting package whether the proposed study will answer all the questions the study intends to address.

Titan October 24, 2011, comments:

This study was under consideration as a potential post-marketing study. Please describe the usual process for the Agency to communicate with Titan regarding any requirements for post-marketing study(-ies) and when is the appropriate time to have this discussion?

Discussion:

The Division stated that there are generally three situations when a Post-Marketing Requirement may be triggered:

- 1) Additional data are needed, but it's acceptable to wait until after approval of the application,
- 2) A safety issue arises (or safety issues arise) during review of the application, but is (are) not a barrier to approval, or
- 3) Anytime after approval if the need arises to address a safety issue that emerges.

In the first scenario, occasionally it is known already, before the application is submitted, that additional information will be required in the future, but it has been determined that the data would not

be required for initial approval. The nature of such studies should be discussed and the study should be planned for initiation as soon as possible.

The Division noted that studies which are required to address safety issues that arise during the review of the NDA will be discussed with the Sponsor during the review process, and the action letter will include a description of the required studies.

With regard to study (b) (4) the Division stated that the purpose of the study was not clear and, therefore, the Division could not provide specific feedback. The Sponsor stated that they understood the comment from the Division and would revise the protocol for inclusion with the NDA submission.

Question 7 Given the known safety profile of BPN, together with the limited use of this medication in adolescent patients, does the Division concur that a Pediatric Deferral for subjects (b) (4) years of age and a waiver for subjects (b) (4) years of age are appropriate?

Division Response:

A pediatric deferral and waiver for the two age groups that you have defined appear appropriate. In the Pediatric Plan for the NDA, you will be required to provide data to support both the waiver and the deferral requests. During the NDA review, the Pediatric Plan will be presented to the Pediatric Review Committee (PeRC) who will make a determination about the appropriateness of the deferral and/or waiver. Refer to the attachment below.

Discussion:

There was no discussion beyond the Division's initial written response.

Regulatory/Product Development Questions:

Question 8 Does the Division concur that a Fast Track development designation or a Priority Review is acceptable?

Division Response:

Fast track designation generally is requested early in the drug development process (i.e., at the time of IND submission). Although benefits associated with fast track designation may occur throughout the drug development process, as a practical matter, requests should ordinarily occur no later than your pre-NDA meeting with the Agency, as many of the benefits of fast track designation will no longer be applicable after that time. Please refer to the Guidance for Industry: *Fast Track Development Programs – Designation, Development, and Application Review* (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079736.pdf>).

A determination regarding Priority Review of an NDA will be made at the time of filing the NDA. Please note, an IND does not need to be designated fast track in order to receive priority review status.

Titan Response:

We understand that the priority review will be determined at a later point. Do you take into consideration the public health problem with currently available formulations and the potential advantage that this formulation provides? Is there anything that Titan might provide to facilitate this being a priority review?

Discussion:

The Division stated that a priority review based upon a claim of improved efficacy would need to be supported by actual comparative data from head-to-head studies, and could not be inferred based upon assumed improved efficacy due solely to increased compliance. The Division further stated that other improvements over existing products, however, could be used to support a priority review request, and that the Division would likely look favorably upon such a request.

The Sponsor should submit a request for priority review that explicates the ways in which Probuphine represents an improvement over existing products; for example, that the product addresses known safety issues of existing products, such as the potential for abuse and diversion or accidental pediatric exposure.

Question 9 Does the Division concur that the proposed elements of the Prescribing Information (PI) are generally acceptable?

Division Response:

Yes, the proposed elements of the Prescribing Information (PI) are generally acceptable. However, the PI will be examined in greater detail during the NDA review to determine the acceptability of the full contents of the PI. We note that you have asserted previously that there are two possible implantation sites on each arm. The PI, however, does not reflect these four possible sites, and it is our understanding that clinical trials to date have used only one implant site per arm. The directions for use provided in the proposed labeling do not provide directions for identifying two sites on each arm. If you intend that an implant site is to be used every 18 months, the PI will need to reflect the ability to rotate implant sites (returning to a previously-implanted site) and you will need to provide justification for the ability to rotate sites. As we have noted previously, information on the effect of scarring or inflammation at previously-used sites on the bioavailability of the implants should be developed to establish whether rotation of sites beyond four implantations is possible.

Furthermore, the PI should include information on the following:

- **Environmental conditions, if any, that may impact the drug release rate of the implant (e.g., heat, compression, trauma, intentional skin manipulation)**

- **Instructions for acute pain management and anesthesia management for patients with implants**
- **Additional dispensing details, namely, whether both the 4-implant kit and the additional dose implant kit each contain an applicator and whether the 4-implant kit and the additional dose implant kit are dispensed simultaneously. If dispensed simultaneously, instructions for storage of the additional dose implant kit until it is implanted or disposal if it is not implanted need to be provided.**

Refer to the attachment below for additional details of the content and format requirements for prescription drug labeling as per the Physician Labeling Rule.

Titan Response:

As indicated in prior communications, Titan plans to study the re-implantation of the implants at previously utilized sites as part of a post-marketing study. Information on the effect of scarring or inflammation at previously-used sites on the bioavailability of Probuphine will be collected as part of post-marketing assessments. Available nonclinical information does not reveal any adverse effects on drug release from breakage of implants that could be caused by trauma, compression or skin manipulation. Due to the matrix formulation of the drug product, there is no possibility of drug dumping. Titan is planning to conduct in vitro studies to evaluate the effect of heat on release of the active substance and this will be submitted with the NDA. Does the Agency have any further guidance?

Discussion:

The Sponsor reiterated that they intend to study implantation of Probuphine into previously-implanted sites, and the effect (b) (4) on the pharmacokinetics of Probuphine as a Post-Marketing Requirement. The Division stated that this was acceptable, but that the study should be initiated as soon as possible so that data could be submitted and reviewed and included in approved labeling by the time the first patient was ready for their fifth implantation. (b) (4)

The Division also observed that the studies did not appear to have been conducted using four possible implantation sites (two per arm), and that the directions for use provided instructions for locating only one possible implantation site per arm. Therefore, additional information justifying the feasibility of using two implantation sites per arm should be submitted to support the proposed rotation procedure, and the possibility that the data on implantation into previously-implanted sites might be needed sooner rather than later should be considered.

The NDA submission should also include any data about the re-use of previously-implanted sites from other products or other sources of information, and make the case that the submission of the data on re-use of implantation sites can be safely deferred until after NDA approval.

Question 10 Does the Division concur that the proposed elements of the Risk Evaluation and Mitigation Strategy (REMS) are generally acceptable?

DRISK Response:

We note that your proposed REMS for Probuphine includes a Medication Guide, Communication Plan, and Elements to Assure Safe Use (ETASU). Specifically, the ETASU include physician training and certification, as well as controlled distribution from a specialty pharmacy to the prescriber (or implanting clinician). We also note that this proposal is more extensive than the approved REMS for other currently marketed buprenorphine products and addresses risks specific to this product (i.e., risks associated with the surgical procedure).

To determine whether your proposed REMS is acceptable, a complete review of the proposed REMS in conjunction with the full clinical review (once the NDA is submitted) will be necessary, since additional information regarding risks and safe product use may emerge during the review of your NDA.

If you plan to submit a REMS with the original NDA submission, please submit all planned materials (e.g., proposed communication and education materials, enrollment forms, prescriber and patient agreements) identified within the plan that will be necessary to implement your proposal. To facilitate review of this submission, we have the following high-level comments on the proposed REMS submitted as part of this meeting package. These comments should be considered as general advice only and cannot be considered final until a complete REMS review has been performed.

- Education or communication provided as part of a REMS should emphasize the safety messages important for the safe use of the product.
- Product marketing materials generally are not appropriate to educate about product risks.
- We refer you to the Suboxone sublingual film REMS for how the components of DATA 2000 are incorporated in the approved REMS.

We remind you that a proposed REMS will not be approved as a REMS unless and until the FDA determines that it is required to ensure that the benefits of the drug outweigh the risks and that it meets the FDAAA criteria.

Titan Response:

Based on your comments that the information provided may be more extensive than necessary, in addition to the PI and medication guide, what additional elements for safe use would Division wish to be included?

Discussion:

The Division clarified that the proposal was perhaps not more extensive than necessary, and noted that the REMS components necessary for Probuphine would likely be substantially different than for currently marketed buprenorphine products because the risks to be mitigated are different. For example, the risks to be mitigated with Probuphine largely revolve around proper training for the

surgical implantation and removal procedure. The Division also stated that the proposed REMS should not address training elements that are already addressed in the Drug Abuse Treatment Act of 2000 (DATA 2000), but could include training elements specific to the implantation and removal procedure.

Question 11 Does the Division concur that the overall plan for the structure and contents of the Probuphine NDA to be submitted as an electronic CTD is acceptable?

Division Response:

The overall plan for the structure and contents of the planned eCTD are acceptable.

Refer also to the Guidance for Industry: *Providing Regulatory Submissions in Electronic Format — Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* for additional details, available at:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

We note that you plan to submit CDISC-compliant tabulation and analysis files. Our recommendations for implementation of the CDISC standards can be found in the CDER Common Data Standards Issues Document:

<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM254113.pdf>.

Discussion:

There was no discussion beyond the Division's initial written response.

Chemistry, Manufacturing and Controls Questions:

Question 12 Regarding Probuphine Implants (Probuphine), does the Division concur that:
a. The plan to source and control the raw materials utilized in the manufacture of Probuphine, including the proposal to demonstrate comparability for a new BPN supplier(s) as described in the briefing document, is acceptable to support the registration of Probuphine?

Division Response:

The proposed qualification plan appears to be acceptable. Provide complete data to bridge the quality of the drug substance used in clinical trials with that of the proposed source(s).

Discussion:

There was no discussion beyond the Division's initial written response.

b. The information to be provided in the NDA for BPN and ethylene vinyl acetate (EVA) as described in the briefing document is acceptable?

Division Response:

Based on the limited information provided in this package, the proposed information for buprenorphine appears to be acceptable.

The proposed information for the Ethyl Vinyl acetate is inadequate. You are expected to include complete physical and chemical characterization data for this polymeric material, (b) (4) and other ingredients used in the manufacturing process. We recommend that you set appropriate specifications and provide analytical data for the amount (b) (4) in the drug product.

Titan Response:

- Extensive physicochemical and biological testing have been conducted on the polymer

- (b) (4) the EVA manufacturing process were not separately characterized, although the majority of the extractables and leachables in the EVA have been identified. Additional analytical work is planned to complete the characterization of the extractables and leachables in the EVA.

- Extensive toxicology testing was conducted on this EVA

- (b) (4) has not been detected in the EVA in testing completed to date. There are (b) (4) used in the manufacture of Probuphine. Titan plans to include a specification (b) (4) in the final product.

Does the Agency have any additional comments?

Discussion:

The Sponsor stated that they are working hard to provide all the necessary data to support the safety of ethyl vinyl acetate. The Division responded that a DMF reference would be helpful, but if that wasn't available, all components (b) (4) should be fully characterized.

Additionally, inclusion of leachable and extractable data in the application is necessary. The Sponsor stated that a DMF will not be available for the product, but that they will provide the data requested, including data collected under physiologic conditions as well as using approaches described in the published Product Quality Research Institute guidelines on safety qualification of leachables and extractables.

- c. *The Probuphine manufacturing process and controls information to be provided in the NDA submission, including the validation plan, are generally acceptable?*

Division Response:

The manufacturing process and controls information provided appears acceptable, but final determination will be made during the NDA review. However, we do not review or

approve process validation approaches, protocols, or specific batches used in process validation studies. The Agency requires that drug manufacturers validate their manufacturing processes [21 CFR 211.100(a) and 211.110(a)] but does not prescribe how that is to be accomplished as it will depend on multiple factors, some of which are specific to the complexity of the product and process. It is your responsibility to conduct all studies necessary to assure your commercial manufacturing process is capable of consistently delivering quality product. Process validation is evaluated during on-site inspections.

Please find more information in the Guidance for Industry, *Process Validation: General Principles and Practices* (January 2011).

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070336.pdf>

Discussion:

There was no discussion beyond the Division's initial written response.

- d. *The proposed specifications for BPN, EVA and Probuphine, including those for assessing degradation, impurity, microbial and sterility, are generally acceptable to support the submission of the Probuphine NDA?*

Division Response:

The specifications for Probuphine appear to be appropriate from a microbiology perspective. Consider establishing a microbial limits specification for the (b) (4) EVA rather than report results as currently listed in Table 29 of the meeting package. Validation (b) (4) and the release specifications for the applicator should be included in the NDA application.

In addition to the proposed specifications for Probuphine degradants, data and specifications on leachables should be included after their characterization and safety assessment.

Titan Comment:

The EVA and Probuphine extracts containing all the leachables have undergone extensive safety testing. The physicochemical characterization of the EVA extract is ongoing and, if possible, the Probuphine extract will be similarly characterized and the specifications will be modified as appropriate. If levels of leachables are below quantification limits, placebo implants (b) (4) % EVA) will be analyzed. Does the Agency have any further guidance?

Discussion:

The Division stated that the Sponsor should define the limits of detection, and provide supportive details based upon the technique utilized.

- e. *The plan to provide data from the six ongoing cGMP lot stability studies as well as at least 3 months of stability data from the three registration lots at the time of NDA submission, with additional stability data to be submitted during the review process at the intervals described in Section 10.3.2.3, is acceptable and will support an initial expiration dating of at least (b) (4) months? Additionally, that the expiry period (b) (4) [REDACTED] ?*

Division Response:

Your expiry dating period depends upon the stability data provided in your proposed NDA submission. We recommend you follow ICH Q1E and provide a minimum of 12 months data for 18 month expiry dating. The expiry dating period (b) (4) [REDACTED] however, you should provide adequate data to support the 'in-use stability' of the implants. Provide results of in-use stability data (e.g., assay, impurities, drug content etc.) for the drug product under the physiological conditions (temperature and pH).

Titan Comment:

By way of reference, the Titan stability program includes a 6-month evaluation of product maintained at 40°C. As a practical measure of the physiological temperature conditions, is this sufficient to support in-use stability of the Probuphine implants?

Discussion:

The Division stated that all products require accelerated stability data, but that this product would also require physiologic stability data since it is intended for implantation. The Division also noted that there did not appear to be any mass balance data submitted, and that such data (for both ethyl vinyl acetate as well as buprenorphine) would be useful to have during NDA review. The Sponsor inquired as to the specifics of the physiologic testing conditions, to which the Division responded that they should submit a proposal to the IND and the Division would provide comments as necessary.

- f. *An environmental monitoring assessment waiver is appropriate?*

Division Response:

To claim categorical exclusion you should provide adequate justification to show that the EEC is below 1 ppb.

Discussion:

There was no discussion beyond the Division's initial written response.

- Question 13** *Regarding the Probuphine Disposable Applicator (Applicator), Titan proposes to incorporate this information as part of Module 3 by providing two 3.2 P sections. Does the Division concur that Titan's overall plan to supply the Applicator specifically for use with Probuphine, and to submit supporting*

information for the Applicator as part of the Probuphine NDA (within Module 3 - Quality) is acceptable?

Division Response:

Your overall plan to supply the applicator specifically for use with the Probuphine appears to be acceptable. The applicator device will be reviewed by the CDRH and additional comments from CDRH may be forthcoming and will be included in the meeting minutes if not earlier.

Titan Comment:

We look forward to obtaining the CDRH's comments. Titan requests the opportunity to seek guidance from CDRH should further clarification be necessary.

Discussion:

The Division stated that it will remain the primary point of contact for all issues related to this application unless it instructs the Sponsor differently.

Question 14 Regarding the Commercial Product Cartons, does the Division concur that the plan to provide the product packaging and distribution as described in Sections 10.3.4 and 10.1.6 respectively in the briefing document is acceptable to support the commercial use of Probuphine?

Division Response:

The overall plan for primary and secondary packaging seems reasonable.

Discussion:

There was no discussion beyond the Division's initial written response.

Nonclinical Question:

Question 15 Titan has conducted all the required nonclinical pharmacokinetics, safety, toxicology and biocompatibility studies on the Probuphine drug product as submitted with IND 70,852. As described in the Briefing Document, Titan plans to rely on data from its sponsored studies and published data for the nonclinical safety and toxicity studies to be provided in the Probuphine NDA. Titan also plans to reference the Division's prior reviews of nonclinical data for the respective RLD NDAs for any additional data that are relevant to BPN (e.g., reproductive toxicity, carcinogenicity, CYP induction, etc). Does the Division concur that the nonclinical information planned for inclusion in the Probuphine NDA is acceptable to support marketing approval of Probuphine under the 505(b)(2) process?

Division Response:

Nonclinical data from Titan-sponsored studies are acceptable for inclusion in the Probuphine NDA to support marketing approval of Probuphine under the 505(b)(2) process. Nonclinical data described in the approved product labels will also support marketing approval pending submission of appropriate pharmacokinetic bridging data. However, as noted to you in the meeting minutes of February 15, 2005, not all studies reported in the literature are supported by data that exists within the public domain. Most studies in the literature are supported by proprietary data. Also, note that nonclinical data contained in the Summary Basis of Approval, even though available in the published literature, are not available for use in the submission unless you have ownership of the data or a right of reference from the data owner.

Prior to preparation of your NDA submission, refer to nonclinical comments contained in Attachment 1 as well as those sent to you previously. Of particular importance are those relating to label bridging data (#3), genotoxic impurities (#6), and evaluation of extractables/leachables in the drug product (#8).

Titan Comment:

Provided below is a tabulation of sources for toxicological and other available nonclinical safety data, including the information as presented in the Briefing Document. This is specific for EVA, BPN and Probuphine. Titan wishes to obtain the Division's guidance as to the suitability of this information.

Table: Proposed Data Sources to Support the Probuphine NDA

<i>Product Tested</i>	<i>Test</i>	<i>Source</i>	<i>Status</i>
<i>Probuphine (extract)</i>	<i>Acute toxicity</i>	<i>Titan nonclinical study</i>	<i>Completed</i>
<i>Probuphine</i>	<i>Chronic toxicity</i>	<i>Titan nonclinical study</i>	<i>Completed</i>
<i>Probuphine (extract)</i>	<i>Genotoxicity</i>	<i>Titan nonclinical study</i>	<i>Completed</i>
<i>Probuphine, Suboxone</i>	<i>Pharmacokinetic bridging data</i>	<i>Titan PRO-810 clinical study</i>	<i>Completed</i>
<i>EVA</i>	<i>Chronic toxicity</i>	<i>Titan nonclinical study</i>	<i>Completed</i>
<i>EVA (extract)</i>	<i>Genotoxicity – chromosomal aberration</i>	<i>Titan nonclinical study</i>	<i>Completed</i>
<i>EVA (extract)</i>	<i>Extractables and leachables</i>	<i>Titan analytical study</i>	<i>To be submitted</i>
<i>EVA</i>	<i>Toxicity</i>	<i>Published literature</i>	<i>To be referenced</i>
<i>Subutex/Suboxone</i>	<i>Carcinogenicity</i>	<i>Product Insert</i>	<i>To be referenced</i>
<i>Subutex/Suboxone</i>	<i>Reproductive toxicity</i>	<i>Product Insert</i>	<i>To be referenced</i>
<i>Subutex/Suboxone</i>	<i>ADME</i>	<i>Product Insert</i>	<i>To be referenced</i>
<i>Subutex/Suboxone</i>	<i>Buprenorphine toxicity</i>	<i>Product Insert, published literature</i>	<i>To be referenced</i>

Discussion:

The Division stated that the information presented in the table appears adequate to support the NDA submission. However, the Division noted that (b) (4)

(b) (4) presents difficulties and the current preliminary nonclinical sections of the proposed label are not entirely appropriate. The Probuphine (b) (4) are not appropriate for section 13.1 of the label *Carcinogenesis, Mutagenesis, Impairment of Fertility*. Instead, the 505(b)(2) reference drug product label data for mutagenicity is appropriate for section 13.1.

The Division noted that the studies described in the reference label utilize several routes of administration and do not contain information which will allow safety margins to be calculated based on plasma exposure. Ideally a bridging toxicokinetic study would be conducted by the sponsor to allow the findings in the reference label to be related to the clinical exposure attained with Probuphine. The Sponsor was told that if a mg/m^2 approach was used instead, the amount of buprenorphine released from the present maximum recommended human dose of 5 implantable Probuphine devices should be used for computations. The sponsor will need to provide justification for the proposed safety margins whether they are based on a mg/m^2 body surface area basis or on blood levels, since the referenced product described studies which utilized different routes of administration.

General Discussion:

1. The Division stated that an Advisory Committee meeting may be necessary prior to approval of the NDA. This is because the approach to evaluate the clinical effect is novel in this setting, and input from the Committee on whether the treatment effect is meaningful would likely be important.
2. The Division encouraged the Sponsor to speak with both NIDA and DEA regarding their product, and to engage in a discussion regarding how the requirements of DATA 2000 would apply to this product. For example, what should happen when the physician implanting the Probuphine rods is not DATA-waived?

Action Items:

1. The Sponsor will perform and submit a number of exploratory analyses which allow for a "grace period" early in treatment. In addition to these analyses, data for the full six months of treatment will be submitted as well.
2. The Sponsor will provide a rationale and data supporting their assertion that Probuphine is an improvement over currently marketed products for the treatment of opioid dependence, to support the request for priority review.
3. Data supporting the safety of the ethyl vinyl acetate compound will be submitted with the NDA. These data will specifically include results of extractables and leachables under multiple conditions, including physiologic conditions.
4. The Sponsor will endeavor to perform a mass balance study for both ethyl vinyl acetate and buprenorphine.

Additional Comments

Biopharmaceutics

1. Determination of the in vitro release rate characteristics of your proposed product is necessary as a measure of its quality control. You need to provide short-term drug release testing information at time of NDA filing. The proposed drug release methodology and release rate acceptance criteria needs to be supported by the following information:
 - (a) Release rate method report including the complete release rate profile data (individual, mean, SD, profiles) collected during the development and validation of the proposed method
 - (b) Complete release rate profile data (raw data and mean values) from the clinical and primary stability batches supporting the selection of the release rate acceptance criteria (i.e., specification-sampling time point and specification value); the proposed sampling point should include at least three time points for analysis, at the initial, mid-point, and end of the test period
 - (c) Conduct testing and provide data to demonstrate the discriminating capability of the selected release rate method.

Controlled Substance Staff

2. Include in the submitted NDA all nonclinical and clinical abuse-related data that allows for the thorough evaluation of abuse potential of the product including buprenorphine and any active metabolites, as summarized in the format as described in our draft Guidance *Assessment of Abuse Potential of Drugs* (Jan 2010).
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf>
3. Submit a proposal for scheduling of your product in an appropriate schedule of the Controlled Substances Act (CSA). As noted in your briefing materials, buprenorphine is a Schedule III substance but the risks of misuse, abuse, addiction, and overdose may be unique to the formulation.
4. Document and compile adverse events related to misuse, abuse, addiction, dependence, withdrawal, and overdose in all clinical studies. Drug accountability and study withdrawal should be evaluated for potentially inappropriate reasons of misuse, abuse, and diversion. See the draft Guidance on *Assessment of Abuse Potential of Drugs* for recommended abuse-related adverse events in clinical studies.
5. In the post-marketing planning, any attempts of intentional removal of implants to access the active buprenorphine substance for misuse or abuse should be reported as a 15-day safety report as an important medical event. Any cases of early removal and respective investigation on reason for removal should be summarized and reported.
6. Provide information on any evaluation of the residual drug content following the removal of the implant during any period.
7. Provide information on the management of unused buprenorphine implants that is in the care of the healthcare professional to minimize misuse and abuse.

Attachment 1

Nonclinical Comments

1. Include a detailed discussion of the nonclinical information in the published literature in your NDA submission and specifically address how the information within the published domain impacts the safety assessment of your drug product. Include this discussion in Module 2 of the submission. Include copies of all referenced citations in the NDA submission in Module 4. Journal articles that are not in English must be translated into English.
2. We recommend that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the October 1999 Draft Guidance for Industry "Applications Covered by Section 505(b)(2)" available at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions challenging the Agency's interpretation of this statutory provision (see Dockets 2001P-0323, 2002P-0447, and 2003P-0408 (available at <http://www.fda.gov/ohrms/dockets/dailys/03/oct03/102303/02p-0447-pdn0001-voll.pdf>)).

Note that you may only rely on the Agency's finding of safety and/or effectiveness as it is reflected in the approved labeling for the listed drug(s). You may not reference data in the Summary Basis of Approval or other FDA reviews obtained via the Freedom of Information Act or publically posted on the CDER website to support any aspect of your development program or proposed labeling of your drug product. Reviews are summary data only and do not represent the Agency's previous finding of safety and effectiveness.

If you intend to submit a 505(b)(2) application that relies for approval on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). Establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified. If you intend to rely on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature is scientifically appropriate.

3. The nonclinical information in your proposed drug product label must include relevant exposure margins with adequate justification for how these margins were obtained. If you intend to rely upon the Agency's previous finding of safety for an approved product, the exposure margins provided in the referenced label must be updated to reflect exposures from your product. If the referenced studies employ a different route of administration or lack adequate information to allow scientifically justified extrapolation to your product, you will need to conduct additional pharmacokinetic studies in animals in order to adequately bridge your product to the referenced product label. This bridging data should be submitted with the NDA.

4. New excipients in your drug must be adequately qualified for safety. Studies must be submitted to the IND in accordance as per the following guidance document: Guidance for Industry: Nonclinical Studies for Safety Evaluation of Pharmaceutical Excipients (May 2005) which is available on the CDER web page at the following <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

As noted in the document cited above, “the phrase *new excipients* means any ingredients that are intentionally added to therapeutic and diagnostic products but which: (1) we believe are not intended to exert therapeutic effects at the intended dosage (although they may act to improve product delivery, e.g., enhancing absorption or controlling release of the drug substance); and (2) are not fully qualified by existing safety data with respect to the currently **proposed level of exposure, duration of exposure, or route of administration.**” (emphasis added).

5. Any impurity or degradation product that exceeds ICH qualification thresholds must be adequately qualified for safety as described in ICHQ3A(R2) and ICHQ3B(R2) guidances at the time of NDA submission.

Adequate qualification would include:

- a. Minimal genetic toxicology screen (two *in vitro* genetic toxicology studies; e.g., one point mutation assay and one chromosome aberration assay) with the isolated impurity, tested up to the limit dose for the assay.
 - b. Repeat dose toxicology of appropriate duration to support the proposed indication.
6. Genotoxic, carcinogenic or impurities that contain a structural alert for genotoxicity must be either reduced to NMT 1.5 mcg/day in the drug substance and drug product or adequate safety qualification must be provided. For an impurity with a structural alert for mutagenicity, adequate safety qualification requires a negative *in vitro* bacterial reverse mutation assay (Ames assay) ideally with the isolated impurity, tested up to the appropriate top concentration of the assay as outlined in ICHS2A guidance document titled “Guidance on Specific Aspects of Regulatory Genotoxicity Tests for Pharmaceuticals.” Should the Ames assay produce positive or equivocal results, the impurity specification must be set at NMT 1.5 mcg/day, or otherwise justified. Justification for a positive or equivocal Ames assay may require an assessment for carcinogenic potential in either a standard 2-year rodent bioassay or in an appropriate transgenic mouse model.
 7. In Module 2 of your NDA (2.6.6.8 Toxicology Written Summary/Other Toxicity), include a table listing the drug substance and drug product impurity specifications, the maximum daily exposure to these impurities based on the maximum daily dose of the product, and how these levels compare to ICHQ3A and Q3B qualification thresholds along with a determination if the impurity contains a structural alert for mutagenicity. Any proposed specification that exceeds the qualification threshold should be adequately justified for safety from a toxicological perspective.

8. The NDA submission must contain information on potential leachables and extractables from the drug container closure system and/or drug product formulation as outlined in the FDA Guidance for Industry titled "Container Closure Systems for Packaging Human Drugs and Biologics." The evaluation of extractables and leachables must include specific assessments for residual monomers, solvents, polymerizers, etc. Based on identified leachables provide a toxicological evaluation to determine the safe level of exposure via the label-specified route of administration. The approach for toxicological evaluation of the safety of leachables must be based on good scientific principles and take into account the specific container closure system or patch, drug product formulation, dosage form, route of administration, and dose regimen (chronic or short-term dosing). As many residual monomers are known genotoxic agents, your safety assessment must take into account the potential that these impurities may either be known or suspected highly reactive and/or genotoxic compounds. The safety assessment should be specifically discussed in module 2.6.6.8 (Toxicology Written Summary/Other Toxicity) of the NDA submission. For additional guidance on extractables and leachables testing, consult the FDA Guidance documents "Container Closure Systems for Packaging Human Drugs and Biologics." Additional methodology and considerations have also been described in the PQRI leachables/extractables recommendations to the FDA, which can be found at http://www.pqri.org/pdfs/LE_Recommendations_to_FDA_09-29-06.pdf.
9. Failure to submit adequate impurity qualification, justification for the safety of new excipient use, or an extractable leachable safety assessment at the time of NDA submission can result in a Refusal-to-File or other adverse action.

Chemistry, Manufacturing and Control (CMC) Comments

1. Include a well documented Pharmaceutical Development Report as per the ICH-Q8 guideline and highlight how critical quality attributes and critical process parameters are identified and controlled.
2. Include at least 12 months of real time data and 6 months of accelerated data in the NDA. Alternatively, submit an appropriate amount of satisfactory stability data to cover the proposed expiry dating.
3. Provide a list of all manufacturing and testing facilities and their complete addresses in alphabetical order, and a statement about their cGMP status. For all sites, provide a name contact and address with telephone number and facsimile number at the site. Clearly specify the responsibilities (e.g., manufacturer, packager, release tester, stability tester etc.) of each facility, the site CFN numbers and designate which sites are intended to be primary or alternate sites. Note that facilities with unacceptable cGMP compliance may risk approvability of the NDA
4. Ensure that all of the above facilities are ready for inspection by the day the application is submitted, and include a statement confirming to this in the NDA cover letter.
5. Provide summary stability data on a parameter-by-parameter basis (instead of only on a batch to batch basis), and in addition, provide graphical plots of critical parameters and trending

parameters. The graphical plots should indicate the proposed acceptance criteria, and they should include both mean and individual data points.

The Abuse Potential section of the NDA is submitted in the eCTD as follows:

Module 1: Administrative Information and Prescribing Information

1.11.4 Multiple Module Information Amendment

This section should contain:

- A summary, interpretation and discussion of abuse potential data provided in the NDA.
- A link to a table of contents that provides additional links to all studies (non-clinical and clinical) and references related to the assessment of abuse potential.
- A proposal and rationale for placement, or not, of a drug into a particular Schedule of the CSA.

Module 2: Summaries

2.4 Nonclinical Overview

This section should include a brief statement outlining the non-clinical studies performed to assess abuse potential.

2.5 Clinical Overview

This section should include a brief statement outlining the clinical studies performed to assess abuse potential.

Module 3: Quality

3.2.P.1 Description and Composition of the Drug Product

This section should describe any additional studies performed to examine the extraction of the drug substance under various conditions (solvents, pH, or mechanical manipulation).

3.2.P.2 Description and Composition of the Drug Product

This section should describe the development of any components of the drug product that were included to address accidental or intentional misuse.

Module 4: Nonclinical Study Reports

4.2.1 Pharmacology

4.2.1.1 Primary Pharmacodynamics

These sections should contain study reports (*in vitro* and *in vivo*) describing the binding profile of the parent drug and all active metabolites.

4.2.3.7.4 Dependence

This section should include:

- A complete discussion of the non-clinical data related to abuse potential.
- Complete study reports of all preclinical abuse potential studies.

Module 5: Clinical Study Reports

5.3.5.4 Other Study Reports

This section should contain complete study reports of all clinical abuse potential studies.

5.3.6.1 Reports of Postmarketing Experience

This section should include information to all postmarketing experience with abuse, misuse, overdose, and diversion related to this product

General Clinical Comments

The NDA will be reviewed utilizing the CDER Clinical Review Template. Details of the template may be found in the Manual of Policies and Procedures (MAPP 6010.3R).

To facilitate the review, we request you provide analyses, where applicable, that will address the items in the template, including:

1. Section 2.6 Other Relevant Background Information - Important regulatory actions in other countries or important information contained in foreign labeling.
2. Section 4.4 – Clinical Pharmacology- Special dosing considerations for patients with renal insufficiency, patients with hepatic insufficiency, pregnant patients, and patients who are nursing.
3. Section 7.5.1 Dose Dependency for Adverse Events
4. Section 7.5.2 Time Dependency for Adverse Events
5. Section 7.5.3 Drug-Demographic Interactions
6. Section 7.5.4 Drug-Disease Interactions
7. Section 7.5.5 Drug-Drug Interactions
8. Section 7.6.4 – Overdose, Drug Abuse Potential, Withdrawal and Rebound

Sites for Inspection

To assist the clinical reviewer in selecting sites for inspection, include a table in the NDA that has the following columns for each of the completed Phase 3 clinical trials:

1. Site number
2. Principle investigator
3. Location: City State, Country
4. Number of subjects screened
5. Number of subjects randomized
6. Number of subjects treated who prematurely discontinued (or other characteristic of interest that might be helpful in choosing sites

7. Number of protocol violations (Major, minor, definition)

Pediatric Plan

You must submit a pediatric plan with the NDA submission regarding studies in pediatric patients to be conducted to fulfill the requirements of the Pediatric Research Equity Act (PREA). The plan must include the studies to be conducted; a timeline for the studies that states for each study, the date of final protocol submission, date of study start, date of study completion, and date of final study report to be submitted to the Agency; requests for waivers and deferrals with justifications; and, where possible, protocol synopses of the proposed studies.

Common PLR Labeling Errors

Highlights:

1. Type size for all labeling information, headings, and subheadings must be a minimum of 8 points, except for trade labeling. This also applies to Contents and the FPI. [See 21 CFR 201.57(d)(6) and Implementation Guidance]
2. The Highlights must be limited in length to one-half page, in 8 point type, two-column format. [See 21 CFR 201.57(d)(8)]
3. The highlights limitation statement must read as follows: These highlights do not include all the information needed to use [insert name of drug product] safely and effectively. See full prescribing information for [insert name of drug product]. [See 21 CFR 201.57(a)(1)]
4. The drug name must be followed by the drug's dosage form, route of administration, and controlled substance symbol. [See 21 CFR 201.57(a)(2)]
5. The boxed warning is not to exceed a length of 20 lines, requires a heading, must be contained within a box and bolded, and must have the verbatim statement "See full prescribing information for complete boxed warning." Refer to <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm> for fictitious examples of labeling in the new format (e.g., Imdicon and Fantom) and 21 CFR 201.57(a)(4).
6. Recent major changes apply to only 5 sections (Boxed Warning; Indications and Usage; Dosage and Administration; Contraindications; Warnings and Precautions)
7. For recent major changes, the corresponding new or modified text in the Full Prescribing Information (FPI) must be marked with a vertical line ("margin mark") on the left edge. [See 21 CFR 201.57(d)(9) and Implementation Guidance].

8. The new rule [21 CFR 201.57(a)(6)] requires that if a product is a member of an established pharmacologic class, the following statement must appear under the Indications and Usage heading in the Highlights:

“(Drug/Biologic Product) is a (name of class) indicated for (indication(s)).”
9. Propose an established pharmacologic class that is scientifically valid AND clinically meaningful to practitioners or a rationale for why pharmacologic class should be omitted from the Highlights.
10. Refer to 21 CFR 201.57 (a)(11) regarding what information to include under the Adverse Reactions heading in Highlights. Remember to list the criteria used to determine inclusion (e.g., incidence rate).
11. A general customer service email address or a general link to a company website cannot be used to meet the requirement to have adverse reactions reporting contact information in Highlights. It would not provide a structured format for reporting. [See 21 CFR 201.57 (a)(11)]
12. Do not include the pregnancy category (e.g., A, B, C, D, X) in Highlights. [See comment #34 Preamble]
13. The Patient Counseling Information statement must appear in Highlights and must read See 17 for PATIENT COUNSELING INFORMATION. [See 21 CFR 201.57(a)(14)]
14. A revision date (i.e., Revised: month/year) must appear at the end of Highlights. [See 21 CFR 201.57(a)(15)]. For a new NDA, BLA, or supplement, the revision date should be left blank at the time of submission and will be edited to the month/year of application or supplement approval.
15. A horizontal line must separate the Highlights, Contents, and FPI. [See 21 CFR 201.57(d)(2)]

Contents (Table of Contents):

16. The headings and subheadings used in the Contents must match the headings and subheadings used in the FPI. [See 21 CFR 201.57(b)]
17. The Contents section headings must be in bold type. The Contents subsection headings must be indented and not bolded. [See 21 CFR 201.57(d)(10)]
18. Create subsection headings that identify the content. Avoid using the word General, Other, or Miscellaneous for a subsection heading.
19. Only section and subsection headings should appear in Contents. Headings within a subsection must not be included in the Contents.

20. When a subsection is omitted, the numbering does not change.
21. [See 21 CFR 201.56(d)(1)] For example, under Use in Specific Populations, subsection 8.2 (Labor and Delivery) is omitted. It must read as follows:

8.1 Pregnancy
8.3 Nursing Mothers (not 8.2)
8.4 Pediatric Use (not 8.3)
8.5 Geriatric Use (not 8.4)

22. When a section or subsection is omitted from the FPI, the section or subsection must also be omitted from the Contents. The heading “Full Prescribing Information: Contents” must be followed by an asterisk and the following statement must appear at the end of the Contents:

“*Sections or subsections omitted from the Full Prescribing Information are not listed.”

Full Prescribing Information (FPI):

23. Only section and subsection headings should be numbered. Do not number headings within a subsection (e.g., 12.2.1 Central Nervous System). Use headings without numbering (e.g., Central Nervous System).
24. Other than the required bolding [See 21 CFR 201.57(d)(1), (d)(5), and (d)(10)], use bold print sparingly. Use another method for emphasis such as italics or underline. Refer to <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm>
25. Do not refer to adverse reactions as “adverse events.” Refer to the “Guidance for Industry: Adverse Reactions Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format,” available at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.
26. The preferred presentation of cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. For example, [*see Use in Specific Populations (8.4)*] not *See Pediatric Use (8.4)*. The cross-reference should be in brackets. Because cross-references are embedded in the text in the FPI, the use of italics to achieve emphasis is encouraged. Do not use all capital letters or bold print. [See Implementation Guidance]
27. Include only references that are important to the prescriber. [See 21 CFR 201.57(c)(16)]

28. Patient Counseling Information must follow after How Supplied/Storage and Handling section. [See 21 CFR 201.56(d)(1)] This section must not be written for the patient but rather for the prescriber so that important information is conveyed to the patient to use the drug safely and effectively. [See 21 CFR 201.57 (c)(18)].
29. The Patient Counseling Information section must reference any FDA-approved patient labeling or Medication Guide. [See 21 CFR 201.57(c)(18)] The reference [See FDA-Approved Patient Labeling] or [See Medication Guide] should appear at the beginning of the Patient Counseling Information section to give it more prominence.
30. Since SPL Release 4 validation does not permit the inclusion of the Medication Guide as a subsection, the Medication Guide or Patient Package Insert should not be a subsection under the Patient Counseling Information section. Include at the end of the Patient Counseling Information section without numbering as a subsection.
31. The manufacturer information (See 21 CFR 201.1 for drugs and 21 CFR 610 – Subpart G for biologics) should be located after the Patient Counseling Information section, at the end of the labeling.
32. Company website addresses are not permitted in labeling (except for a web address that is solely dedicated to reporting adverse reactions). Delete company website addresses from package insert labeling. The same applies to PPI and MG.
33. If the “Rx only” statement appears at the end of the labeling, delete it. This statement is not required for package insert labeling, only container labels and carton labeling. [See Guidance for Industry: Implementation of Section 126 of the Food and Drug Administration Modernization Act of 1997 – Elimination of Certain Labeling Requirements]. The same applies to PPI and MG.
34. Refer to <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm> for fictitious examples of labeling in the new format.
35. Refer to the Institute of Safe Medication Practices’ website (<http://www.ismp.org/Tools/abbreviationslist.pdf>) for a list of error-prone abbreviations, symbols, and dose designations.

SPL Submission:

Structured product labeling (SPL) must be submitted representing the content of your proposed labeling. By regulation [21 CFR 314.50(l), 314.94(d), and 601.14(b); Guidance for Industry: Providing Regulatory Submissions in Electronic Format — Content of Labeling (April 2005): <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm> .], you are required to submit to FDA prescribing and product information (i.e., the package insert) in SPL format. FDA will work closely with applicants during the review cycle to

correct all SPL deficiencies before approval. Please email spl@fda.hhs.gov for individual assistance.

Integrated Summary of Effectiveness

Please refer to the Guidance for Industry Integrated Summary of Effectiveness located at the following web page

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079803.pdf>

Please refer to **Guidance for Industry - Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document**

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM136174.pdf>

Dataset Comments

1. Provide an integrated safety (adverse event) dataset for all Phase 2 and 3 trials. If the studies are of different design or duration, discuss with the division which studies are most appropriate for integration.

The integrated safety dataset that must include the following fields/variables:

- a. A unique patient identifier
 - b. Study/protocol number
 - c. Patient's treatment assignment
 - d. Demographic characteristics, including gender, chronological age (not date of birth), and race
 - e. Dosing at time of adverse event
 - f. Dosing prior to event (if different)
 - g. Duration of event (or start and stop dates)
 - h. Days on study drug at time of event
 - i. Outcome of event (e.g., ongoing, resolved, led to discontinuation)
 - j. Flag indicating whether or not the event occurred within 30 days of discontinuation of active treatment (either due to premature study drug discontinuation or protocol-specified end of active treatment due to end of study or crossover to placebo).
 - k. Marker for serious adverse events
 - l. Verbatim term
-
2. The adverse event dataset must include the following MedDRA variables: lower level term (LLT), preferred term (PT), high level term (HLT), high level group term (HLGT), and system

organ class (SOC) variables. This dataset must also include the verbatim term taken from the case report form.

3. See the attached mock adverse event data set that provides an example of how the MedDRA variables should appear in the data set. Note that this example only pertains to how the MedDRA variables must appear and does not address other content that is usually contained in the adverse event data set.
4. In the adverse event data set, provide a variable that gives the numeric MedDRA code for each lower level term.
5. The preferred approach for dealing with the issue of different MedDRA versions is to have one single version for the entire NDA. If this is not an option, then, at a minimum, it is important that a single version of MedDRA is used for the ISS data and ISS analysis. If the version that is to be used for the ISS is different than versions that were used for individual study data or study reports, it is important to provide a table that lists all events whose preferred term or hierarchy mapping changed when the data was converted from one MedDRA version to another. This will be very helpful for understanding discrepancies that may appear when comparing individual study reports/data with the ISS study report/data.
6. Provide a detailed description for how verbatim terms were coded to lower level terms according to the ICH MedDRA Term Selection: Points to Consider document. For example, were symptoms coded to syndromes or were individual symptoms coded separately.
7. Perform the following SMQ's on the ISS adverse event data and include the results in your ISS report: 1. Severe cutaneous adverse reactions SMQ and 2. Possible drug related hepatic disorders – comprehensive search SMQ. Also, provide any additional SMQ that may be useful based on your assessment of the safety database. Be sure the version of the SMQ that is used corresponds to the same version of MedDRA used for the ISS adverse event data.
8. The spelling and capitalization of MedDRA terms must match the way the terms are presented in the MedDRA dictionary. For example, do not provide MedDRA terms in all upper case letters.
9. For the concomitant medication dataset, you must use the standard nomenclature and spellings from the WHO Drug dictionary and include the numeric code in addition to the ATC code/decode.
10. For the laboratory data, be sure to provide normal ranges, reference ranges, and units as well as a variable that indicates whether the lab result was from the local lab or central lab. Also, the variable for the laboratory result must be in numeric format.
11. Perform adverse event rate analyses at all levels of MedDRA hierarchy (except for LLT) and also broken down by serious versus non-serious.
12. Across all datasets, the same coding must be used for common variables, e.g. "PBO" for the placebo group. Datasets must not incorporate different designations for the same variable, e.g.

"PBO" in one dataset, and "0 mg" or "Placebo," in another datasets. If the coding cannot be reconciled, another column using a common terminology for that variable must be included in the datasets.

13. All datasets must contain the following variables/fields (in the same format and coding):
 - a. Each subject must have one unique ID across the entire NDA
 - b. Study number
 - c. Treatment assignment
 - d. Demographic characteristics (age, race, gender, etc.)
14. A comprehensive listing of patients with potentially clinically significant laboratory or vital sign abnormalities must be provided. A listing must be provided of patients reporting adverse events involving abnormalities of laboratory values or vital signs, either in the "investigations" SOC or in an SOC pertaining to the specific abnormality. For example, all AEs coded as "hyperglycemia" (SOC metabolic) and "low blood glucose" (SOC investigations) should be tabulated. The NDA analyses of the frequency of abnormalities across treatment groups is not sufficient without ready identification of the specific patients with such abnormalities. Analyses of laboratory values must include assessments of changes from baseline to worst value, not simply the last value.
15. Provide CRFs for all patients with serious adverse events, in addition to deaths and discontinuations due to adverse events.
16. For patients listed as discontinued to due "investigator decision," "sponsor request," "withdrew consent," or "other," the verbatim reason for discontinuation (as written in the CRF) should be reviewed to ensure that patients did not dropout because of drug-related reasons (lack of efficacy or adverse effects). If discrepancies are found between listed and verbatim reasons for dropout, the appropriate reason for discontinuation should be listed and patient disposition should be re-tabulated.
17. With reference to the table on the following page, note that the HLGT and HLT level terms are from the primary MedDRA mapping only. There is no need to provide HLT or HLGT terms for any secondary mappings. This mock table is intended to address content regarding MedDRA, and not necessarily other data.

Unique Subject Identifier (USUBJID)	Sequence Number (AESEQ)	Study Site Identifier (SITEID)	Unique Subject Identifier	Coding Dictionary Information	Reported Term for AE (Verbatim)	Lower Level Term MedDRA Code	Lower Level Term (LLT)	Preferred Term High Level Term (HLT)	High Level Group Term (HLGT)	System Organ Class (SOC)	Secondary System Organ Class 2 (SOC2)	Secondary System Organ Class 3 (SOC3)	Secondary System Organ Class 4 (SOC4)
01-701-1015	1	701	1015	MedDRA version 8.0	redness around application site	10003058	Application site redness	Application site redness	Administration site reactions	General disorders and administration site conditions	Skin and subcutaneous tissue disorders		

CDER Data Standards Reference Guide/Checklist

The following resources are intended to assist submitters in the preparation and submission of standardized study data to CDER.

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>.

Attachment 2

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct the inspections (Item I and II).

The dataset that is requested as per Item III below, is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of site level datasets will facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 2, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

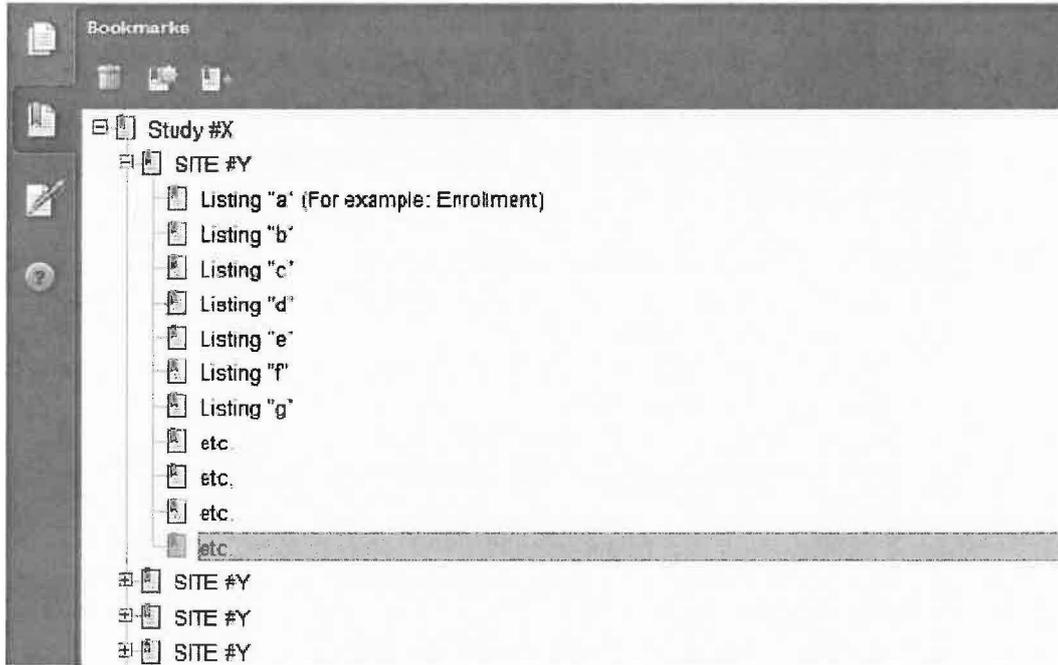
I. Request for general study related information and specific Clinical Investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

1. Please include the following information in a tabular format in the original NDA for each of the completed Phase 3 clinical trials:
 - a. Site number
 - b. Principal investigator
 - c. Site Location: Address (e.g. Street, City, State, Country) and contact information (i.e., phone, fax, email)
 - d. Current Location of Principal Investigator (if no longer at Site): Address (e.g. Street, City, State, Country) and contact information (i.e., phone, fax, email)
2. Please include the following information in a tabular format by site in the original NDA for each of the completed Phase 3 clinical trials:
 - a. Number of subjects screened for each site by site
 - b. Number of subjects randomized for each site by site
 - c. Number of subjects treated who prematurely discontinued for each site by site
3. Please include the following information in a tabular format in the NDA for each of the completed Phase 3 clinical trials:
 - a. Location of Trial Master File [actual physical site(s) where documents are maintained and would be available for inspection]
 - b. Name, address and contact information of all CROs used in the conduct of the clinical trials
 - c. The location (actual physical site where documents are maintained and would be available for inspection) for all source data generated by the CROs with respect to their roles and responsibilities in conduct of respective studies
 - d. The location (actual physical site where documents are maintained and would be available for inspection) of sponsor/monitor files (e.g. monitoring master files, drug accountability files, SAE files, etc.)

4. For each pivotal trial provide a sample annotated Case Report Form (if items are provided elsewhere in submission, please describe location or provide a link to requested information).
5. For each pivotal trial provide original protocol and all amendments (if items are provided elsewhere in submission, please describe location or provide a link to requested information).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data (“line”) listings. For each site provide line listings for:
 - a. Listing for each subject/number screened and reason for subjects who did not meet eligibility requirements
 - b. Subject listing for treatment assignment (randomization)
 - c. Subject listing of drop-outs and subjects that discontinued with date and reason
 - d. Evaluable subjects/ non-evaluable subjects and reason not evaluable
 - e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
 - f. By subject listing, of AEs, SAEs, deaths and dates
 - g. By subject listing of protocol violations and/or deviations reported in the NDA, description of the deviation/violation
 - h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
 - i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
 - j. By subject listing, of laboratory tests performed for safety monitoring
2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Electronic submission of site level datasets will facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. Please refer to Attachment 1, "Summary Level Clinical Site Data for Data Integrity Review and Inspection Planning in NDA and BLA Submissions" for further information. We request that you provide a dataset, as outlined, which includes requested data for each pivotal study submitted in your application.

Attachment 1

1 Summary Level Clinical Site Data for Data Integrity Review and Inspection Planning in NDA and BLA Submissions

1.1 Introduction

The purpose of this pilot for electronic submission of a single new clinical site dataset is to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process in support of the evaluation of data integrity.

1.2 Description of the Summary level clinical site dataset

The summary level clinical site data are intended (1) to clearly identify individual clinical investigator sites within an application or supplement, (2) to specifically reference the studies to which those clinical sites are associated, and (3) to present the characteristics and outcomes of the study at the site level.

For each study used to support efficacy, data should be submitted by clinical site and treatment arm for the population used in the primary analysis to support efficacy. As a result, a single clinical site may contain multiple records depending on the number of studies and treatment arms supported by that clinical site.

The site-level efficacy results will be used to support site selection to facilitate the evaluation of the application. To this end, for each study used to support efficacy, the summary level clinical site dataset submission should include site-specific efficacy results by treatment arm and the submission of site-specific effect sizes.

The following paragraphs provide additional details on the format and structure of the efficacy related data elements.

Site-Specific Efficacy Results

For each study and investigator site, the variables associated with efficacy and their variable names are:

- Treatment Efficacy Result (TRTEFFR) – the efficacy result for each primary endpoint, by treatment arm (see below for a description of endpoint types and a discussion on how to report this result)
- Treatment Efficacy Result Standard Deviation (TRTEFFS) – the standard deviation of the efficacy result (treatEffR) for each primary endpoint, by treatment arm
- Site-specific Efficacy Effect Size (SITEEFFE) – the effect size should be the same representation as reported for the primary efficacy analysis
- Site-specific Efficacy Effect Size Standard Deviation (SITEEFFS) – the standard deviation of the site-specific efficacy effect size (SITEEFFE)

- Endpoint (endpoint) – a plain text label that describes the primary endpoint as described in the Define file data dictionary included with each application.
- Treatment Arm (ARM) – a plain text label for the treatment arm that is used in the Clinical Study Report.

In addition, for studies whose primary endpoint is a time-to-event endpoint, include the following data element:

- Censored Observations (CENSOR) –the number of censored observations for the given site and treatment.

If a study does not contain a time-to-event endpoint, record this data element as a missing value.

To accommodate the variety of endpoint types that can be used in analyses please reference the below endpoint type definitions when tabulating the site-specific efficacy result variable by treatment arm, “TRTEFFR.”

- Discrete Endpoints – endpoints consisting of efficacy observations that can take on a discrete number of values (e.g., binary, categorical). Summarize discrete endpoints by an event frequency (i.e., number of events), proportion of events, or similar method at the site for the given treatment.
- Continuous Endpoints – endpoints consisting of efficacy observations that can take on an infinite number of values. Summarize continuous endpoints by the mean of the observations at the site for the given treatment.
- Time-to-Event Endpoints – endpoints where the time to occurrence of an event is the primary efficacy measurement. Summarize time-to-event endpoints by two data elements: the number of events that occurred (TRTEFFR) and the number of censored observations (CENSOR).
- Other – if the primary efficacy endpoint cannot be summarized in terms of the previous guidelines, a single or multiple values with precisely defined variable interpretations should be submitted as part of the dataset.

In all cases, the endpoint description provided in the “endpoint” plain text label should be expressed clearly to interpret the value provided in the (TRTEFFR) variable.

The site efficacy effect size (SITEEFFE) should be summarized in terms of the primary efficacy analysis (e.g., difference of means, odds ratio) and should be defined identically for all records in the dataset regardless of treatment.

The Define file for the dataset is presented in Exhibit 1: *Table 1 Clinical Site Data Elements Summary Listing (DE)*. A sample data submission for the variables identified in Exhibit 1 is provided in Exhibit 2. The summary level clinical site data can be submitted in SAS transport file format (*.xpt).

Exhibit 1: Table 1 Clinical Site Data Elements Summary Listing (DE)

Variable Index	Variable Name	Variable Label	Type	Controlled Terms or Format	Notes or Description	Sample Value
1	STUDY	Study Number	Char	String	Study or trial identification number.	ABC-123
2	STUDYTL	Study Title	Char	String	Title of the study as listed in the clinical study report (limit 200 characters)	Double blind, randomized placebo controlled clinical study on the influence of drug X on indication Y
3	DOMAIN	Domain Abbreviation	Char	String	Two-character identification for the domain most relevant to the observation. The Domain abbreviation is also used as a prefix for the variables to ensure uniqueness when datasets are merged.	DE
4	SPONNO	Sponsor Number	Num	Integer	Total number of sponsors throughout the study. If there was a change in the sponsor while the study was ongoing, enter an integer indicating the total number of sponsors. If there was no change in the sponsor while the study was ongoing, enter "1".	1
5	SPONNAME	Sponsor Name	Char	String	Full name of the sponsor organization conducting the study at the time of study completion, as defined in 21 CFR 312.3(a).	DrugCo, Inc.
6	IND	IND Number	Num	6 digit identifier	Investigational New Drug (IND) application number. If study not performed under IND, enter -1.	010010
7	UNDERIND	Under IND	Char	String	Value should equal "Y" if study at the site was conducted under an IND and "N" if study was not conducted under an IND (i.e., 21 CFR 312.120 studies).	Y
8	NDA	NDA Number	Num	6 digit identifier	FDA new drug application (NDA) number, if available/applicable. If not applicable, enter -1.	021212
9	BLA	BLA Number	Num	6 digit identifier	FDA identification number for biologics license application, if available/applicable. If not applicable, enter -1.	123456
10	SUPPNUM	Supplement Number	Num	Integer	Serial number for supplemental application, if applicable. If not applicable, enter -1.	4
11	SITEID	Site ID	Char	String	Investigator site identification number assigned by the sponsor.	50
12	ARM	Treatment Arm	Char	String	Plain text label for the treatment arm as referenced in the clinical study report (limit 200 characters).	Active (e.g., 25mg), Comparator drug product name (e.g., Drug x), or Placebo
13	ENROLL	Number of Subjects Enrolled	Num	Integer	Total number of subjects enrolled at a given site by treatment arm.	20
14	SCREEN	Number of Subjects Screened	Num	Integer	Total number of subjects screened at a given site.	100

Variable Index	Variable Name	Variable Label	Type	Controlled Terms or Format	Notes or Description	Sample Value
15	DISCONT	Number of Subject Discontinuations	Num	Integer	Number of subjects discontinuing from the study after being enrolled at a site by treatment arm as defined in the clinical study report.	5
16	ENDPOINT	Endpoint	Char	String	Plain text label used to describe the primary endpoint as described in the Define file included with each application (limit 200 characters).	Average increase in blood pressure
17	ENDPTYPE	Endpoint Type	Char	String	Variable type of the primary endpoint (i.e., continuous, discrete, time to event, or other).	Continuous
18	TRTEFFR	Treatment Efficacy Result	Num	Floating Point	Efficacy result for each primary endpoint by treatment arm at a given site.	0, 0.25, 1, 100
19	TRTEFFS	Treatment Efficacy Result Standard Deviation	Num	Floating Point	Standard deviation of the efficacy result (TRTEFFR) for each primary endpoint by treatment arm at a given site.	0.065
20	SITEEFFE	Site-Specific Efficacy Effect Size	Num	Floating Point	Site effect size with the same representation as reported for the primary efficacy analysis.	0, 0.25, 1, 100
21	SITEEFFS	Site-Specific Efficacy Effect Size Standard Deviation	Num	Floating Point	Standard deviation of the site-specific efficacy effect size (SITEEFFE).	0.065
22	CENSOR	Censored Observations	Num	Integer	Number of censored observations at a given site by treatment arm. If not applicable, enter -1.	5
23	NSAE	Number of Non-Serious Adverse Events	Num	Integer	Total number of non-serious adverse events at a given site by treatment arm. This value should include multiple events per subject and all event types (i.e., <u>not limited to</u> only those that are deemed related to study drug or treatment emergent events).	10
24	SAE	Number of Serious Adverse Events	Num	Integer	Total number of serious adverse events excluding deaths at a given site by treatment arm. This value should include multiple events per subject.	5
25	DEATH	Number of Deaths	Num	Integer	Total number of deaths at a given site by treatment arm.	1
26	PROTVIOL	Number of Protocol Violations	Num	Integer	Number of protocol violations at a given site by treatment arm as defined in the clinical study report. This value should include multiple violations per subject and all violation type (i.e., not limited to only significant deviations).	20
27	FINLMAX	Maximum Financial Disclosure Amount	Num	Floating Point	Maximum financial disclosure amount (\$USD) by any single investigator by site. Under the applicable regulations (21 CFR Parts 54, 312, 314, 320, 330, 601, 807, 812, 814, and 860). If unable to obtain the information required to the corresponding statements, enter -1.	20000.00
28	FINLDISC	Financial Disclosure Amount	Num	Floating Point	Total financial disclosure amount (\$USD) by site calculated as the sum of disclosures for the principal investigator and all sub-investigators to include all required parties. Under the applicable regulations (21 CFR Parts 54, 312, 314, 320, 330, 601, 807, 812, 814, and 860). If unable to obtain the information required to the corresponding statements, enter -1.	25000.00

Variable Index	Variable Name	Variable Label	Type	Controlled Terms or Format	Notes or Description	Sample Value
29	LASTNAME	Investigator Last Name	Char	String	Last name of the investigator as it appears on the FDA 1572.	Doe
30	FRSTNAME	Investigator First Name	Char	String	First name of the investigator as it appears on the FDA 1572.	John
31	INITIAL	Investigator Middle Initial	Char	String	Middle initial of the investigator, if any, as it appears on the FDA 1572.	M
32	PHONE	Investigator Phone Number	Char	String	Phone number of the primary investigator. Include country code for non-US numbers.	44-555-555-5555
33	FAX	Investigator Fax Number	Char	String	Fax number of the primary investigator. Include country code for non-US numbers.	44-555-555-5555
34	EMAIL	Investigator Email Address	Char	String	Email address of the primary investigator.	john.doe@mail.com
35	COUNTRY	Country	Char	ISO 3166-1-alpha-2	2 letter ISO 3166 country code in which the site is located.	US
36	STATE	State	Char	String	Unabbreviated state or province in which the site is located. If not applicable, enter NA.	Maryland
37	CITY	City	Char	String	Unabbreviated city, county, or village in which the site is located.	Silver Spring
38	POSTAL	Postal Code	Char	String	Postal code in which site is located. If not applicable, enter NA.	20850
39	STREET	Street Address	Char	String	Street address and office number at which the site is located.	1 Main St, Suite 100

The following is a fictional example of a data set for a placebo-controlled trial. Four international sites enrolled a total of 205 subjects who were randomized in a 1:1 ratio to active or placebo. The primary endpoint was the percent of responders. The site-specific efficacy effect size (SITEEFFE) is the difference between the active and the placebo treatment efficacy result. Note that since there were two treatment arms, each site contains 2 rows in the following example data set and a total of 8 rows for the entire data set.

Exhibit 2: Example for Clinical Site Data Elements Summary Listing (Table 1)

STUDY	STUDYTL	DOMAIN	SPONNO	SPONNAME	IND	UNDERIND	NDA	BLA	SUPPNUM	SITEID	ARM	ENROLL	SCREEN	DISCONT
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	001	Active	26	61	3
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	001	Placebo	25	61	4
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	002	Active	23	54	2
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	002	Placebo	25	54	4
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	003	Active	27	62	3
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	003	Placebo	26	62	5
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	004	Active	26	60	2
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	004	Placebo	27	60	1

ENDPOINT	ENDTYPE	TRTEFFR	TRTEFFS	SITEEFFE	SITEEFFS	CENSOR	NSAE	SAE	DEATH	PROTVIOL	FINLMAX	FINLISC	LASTNAME	FRSTNAME
Percent Responders	Binary	0.48	0.0096	0.34	0.0198	-1	0	2	0	1	-1	-1	Doe	John
Percent Responders	Binary	0.14	0.0049	0.34	0.0198	-1	2	2	0	1	-1	-1	Doe	John
Percent Responders	Binary	0.48	0.0108	0.33	0.0204	-1	3	2	1	0	45000.00	45000.00	Washington	George
Percent Responders	Binary	0.14	0.0049	0.33	0.0204	-1	0	2	0	3	20000.00	45000.00	Washington	George
Percent Responders	Binary	0.54	0.0092	0.35	0.0210	-1	2	2	0	1	15000.00	25000.00	Jefferson	Thomas
Percent Responders	Binary	0.19	0.0059	0.35	0.0210	-1	3	6	0	0	22000.00	25000.00	Jefferson	Thomas
Percent Responders	Binary	0.46	0.0095	0.34	0.0161	-1	4	1	0	0	0.00	0.00	Lincoln	Abraham
Percent Responders	Binary	0.12	0.0038	0.34	0.0161	-1	1	2	0	1	0.00	0.00	Lincoln	Abraham

INITIAL	PHONE	FAX	EMAIL	COUNTRY	STATE	CITY	POSTAL	STREET
M	555-123-4567	555-123-4560	John@mail.com	RU	Moscow	Moscow	103009	Kremlin Road 1
M	555-123-4567	555-123-4560	John@mail.com	RU	Moscow	Moscow	103009	Kremlin Road 1
	020-3456-7891	020-3456-7890	george@mail.com	GB	Westminster	London	SW1A 2	10 Downing St
	020-3456-7891	020-3456-7890	george@mail.com	GB	Westminster	London	SW1A 2	10 Downing St
	01-89-12-34-56	01-89-12-34-51	tom@mail.com	FR	N/A	Paris	75002	1, Rue Road
	01-89-12-34-56	01-89-12-34-51	tom@mail.com	FR	N/A	Paris	75002	1, Rue Road
	555-987-6543	555-987-6540	abe@mail.com	US	Maryland	Rockville	20852	1 Rockville Pk.
	555-987-6543	555-987-6540	abe@mail.com	US	Maryland	Rockville	20852	1 Rockville Pk.

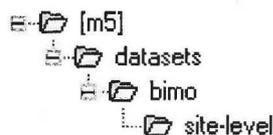
Attachment 2

Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named “BIMO [list study ID, followed by brief description of file being submitted].” In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be “bimo.” Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be “clinsite.xpt.”

DSI Pre-NDA Request Item ¹	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:



C. It is recommended, but not required, that a Reviewer’s Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be “BIMO Reviewer Guide.” The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

¹ Please see the OSI Pre-NDA Request document for a full description of requested data files

IND 070852

Page 44

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1

(<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf>)

FDA eCTD web page

(<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm>)

For general help with eCTD submissions: ESUB@fda.hhs.gov

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

/s/

MATTHEW W SULLIVAN
11/22/2011



IND 070852

MEETING MINUTES

Titan Pharmaceuticals
400 Oyster Point Blvd
Suite 505
South San Francisco, CA 94080

Attention: Sunil Bhonsle
President

Dear Mr. Bhonsle:

Please refer to your Investigational New Drug Application (IND) submitted December 20, 2004, received December 21, 2004, under section 505(i) of the Federal Food, Drug, and Cosmetic Act for buprenorphine hydrochloride/ethylene vinyl acetate (Probuphine).

We also refer to the teleconference between representatives of your firm and the FDA on May 6, 2011. The purpose of the meeting was to clarify the comments from our March 28, 2011, advice letter.

A copy of the official minutes of the teleconference is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-1245.

Sincerely,

{See appended electronic signature page}

Matthew W. Sullivan, MS
Senior Regulatory Project Manager
Division of Anesthesia, Analgesia, and
Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE:
Meeting Minutes

SPONSOR MEETING MINUTES

MEETING DATE: May 6, 2011
TIME: 1:30 pm to 2:30 pm
LOCATION: Teleconference
APPLICATION: IND 070852
PRODUCTS: buprenorphine hydrochloride/ethylene vinyl acetate (Probuphine)
INDICATIONS: Treatment of opioid dependence
SPONSOR: Titan Pharmaceuticals
TYPE OF MEETING: Type C
MEETING CHAIR: Celia Winchell, MD, Clinical Team Leader, Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
MEETING RECORDER: Matthew Sullivan, MS, Senior Regulatory Project Manager, DAAAP

FDA Attendees	Title
Bob A. Rappaport, MD	Director, Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Rigoberto Roca, MD	Deputy Director, DAAAP
Celia Winchell, MD	Clinical Team Leader, DAAAP
Rachel Skeete, MD	Medical Officer, DAAAP
Tom Permutt, PhD	Director, Division of Biometrics II (DBII)
Dionne Price, PhD	Statistical Team Leader, DBII
Jon Norton, PhD	Statistical Reviewer, DBII
Matthew Sullivan, MS	Regulatory Project Manager, DAAAP

Titan Pharmaceuticals	Title
Sunil Bhonsle, MBA	President
Katherine L. Beebe, PhD	Senior Vice President, Clinical Development and Medical Affairs
Scott Henley, MBA	Executive Director, Clinical Operations and Project Management
Marc Rubin	Executive Chairman
(b) (4)	Statistical consultant, (b) (4) Scientific Affairs
(b) (4)	Regulatory affairs consultant
(b) (4)	Director, (b) (4)

BACKGROUND

On March 28, 2011, the Division issued an advice letter concerning Study PRO-806, entitled "*A Randomized, Placebo and Active-Controlled, Multi-Center Study of Probuphine in Patients with Opioid Dependence.*" On April 12, 2011, the Sponsor submitted a meeting request to discuss certain issues raised in the March 28, 2011, letter. The Division granted the meeting request, and agreed to discuss the issues during the May 6, 2011, teleconference.

The questions from the April 12, 2011 meeting request are shown below in italics and the meeting discussion is shown in normal text.

DISCUSSION

Question 1: Please clarify the Division's comment that the use of the cumulative distribution function of negative urines of the treatment groups for the Probuphine development program as the primary endpoint is a concern. Specifically, what are the questions referred to in the comment: ". . . raises serious questions about the appropriateness of the endpoint. . . ." and what is the rationale?

Discussion:

The Sponsor stated that the goal of the Probuphine development program was to demonstrate a six month reduction in illicit opioid use, and that frequent urine toxicology assessment of at least thrice weekly was the "gold standard" for demonstrating such a reduction. The Sponsor additionally noted that they planned to use a cumulative distribution function of negative urines compared between the treatment arms to support this reduction.

The Division stated that it had previously agreed that urine toxicology assessments alone would be adequate to demonstrate a reduction in illicit opioid use. However, the preliminary study report for Study PRO-805 indicated that a greater proportion of buprenorphine-treated patients self-reported illicit drug use compared to patients treated with placebo, even though the buprenorphine-treated patients were more likely to have negative urine tests. This raised a concern that the urine toxicology results were not capturing drug use adequately, and that self-report needed to be incorporated into the assessment as well. The Division noted that it is unclear if the reported drugs were opioids or not, but that patients who self-report opioid use should be adjudicated as using opioids, even if their drug test results are negative.

Question 2: Please clarify what new information is being requested in the following comment: ". . . we are trying to get the most accurate picture of the clinical response of the patients by using all of the available sources of information. Any patient who reports using illicit drugs should be adjudicated as using illicit drugs during that time period. . . ."

Discussion:

The Sponsor stated that the frequency of collection of urine samples was thrice weekly, but that the collection of self-reported drug use was only every two weeks. The Division responded that, even though urine samples and drug use were collected at different intervals, the Sponsor should develop a method for incorporating both of these data elements, but that “abstinence from opioid drugs” should only be assigned for patients who have both a negative urine toxicology result and no self-reported opioid use. The Sponsor stated that they were already working on a re-analysis of the data from Study PRO-805 to address this concern. The Sponsor additionally noted that they will propose an alternate Statistical Analysis Plan to address this concern for Study PRO-806, and it will be submitted for Agency review.

General Discussion:

The Division stated their concern that the dose of buprenorphine provided by the Probuphine implants may be too low to fully block the endogenous effects of opioids. The dose does appear high enough, however, to block the effects of opioid withdrawal. This may result in a situation where a patient treated with Probuphine would not experience the unpleasant symptoms of opioid withdrawal, but the enjoyable opioids effects would not be blocked. The Sponsor stated their understanding of this concern.

Action items:

1. The Sponsor will perform a re-analysis of the data collected from Study PRO-805 incorporating urine toxicology assessments as well as self-reported opioid use to more accurately determine abstinence from illicit opioids.
2. The Sponsor will submit for review to the Agency a revised Statistical Analysis Plan (SAP) for Study PRO-806. This SAP should incorporate the concept described for PRO-805, namely taking all available information into account when determining if a patient was or was not abstinent from illicit opioids.

Post-Meeting Note: The Division will not be able to agree to any SAP for Study PRO-806 that is submitted after the data have been unblinded.

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

/s/

MATTHEW W SULLIVAN
06/02/2011



IND 70,852

Titan Pharmaceuticals
400 Oyster Point Blvd
Suite 505
South San Francisco, CA 94080

Attention: Patricia C. Hirano, MPH
Associate Director, Regulatory Affairs

Please refer to your Investigational New Drug Application (IND) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Probuphine (buprenorphine hydrochloride/ethylene vinyl acetate).

We also refer to the meeting between representatives of your firm and FDA on August 5, 2005. The purpose of this guidance meeting was to discuss the special protocol assessment letter dated June 23, 2005.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 827-7430.

Sincerely,

{See appended electronic signature page}

Sara E. Stradley, MS
Regulatory Project Manager
Division of Anesthesia, Analgesia and
Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

Industry Meeting Minutes

Date/Time: August 5, 2005

Location: teleconference

Application: IND 70,852

Sponsor: Titan Pharmaceuticals

Drug: Probuphine

Indication: maintenance treatment of opioid dependent patients who have undergone induction and stabilization with buprenorphine sublingual tablets



Type of Meeting: guidance on special protocol assessment letter

Meeting Chair: Celia Winchell, MD, Team Leader, Addiction Drug Products
 Division of Anesthesia, Analgesia and Rheumatology Products

Minutes Recorder: Sara Stradley, MS, Regulatory Project Manager

Titan Pharmaceuticals	Title
Anish Bhatnagar, MD	VP, Clinical Development
(b) (4)	Clinical Development Consultant
(b) (4)	Biostatistical Consultant
Lauren Constantini, PhD	Director, Product Development
Patricia Hirano	Assoc. Director, Regulatory Affairs
Rayasam (Ray) Prasad	Senior VP, Regulatory Affairs, Compliance and Quality Assurance
(b) (4)	Clinical Development Consultant
FDA	Title
Rigoberto Roca, MD	Deputy Division Director
Celia Winchell, MD	Team Leader, Addiction Drug Products
Howard Josefberg, MD	Medical Officer
Thomas J. Permutt, PhD	Team Leader, Statistics
Sara Stradley, MS	Regulatory Project Manager

Meeting Objective: The purpose of this guidance meeting was to discuss the special protocol assessment letter dated June 23, 2005, specifically items 1, 4, 5 and 6.

General Discussion: Following introductions, the discussion focused on the Sponsor's request for clarification included in the July 21, 2005 meeting package. Items 1, 4, 5 and 6 from the June 23, 2005 letter are listed below in italics. Discussion is presented in normal text.

Comments from June 23, 2005 letter

1. *Although the overall design (randomized, double-blind, parallel-group, dose controlled) is appropriate, as proposed, a single trial would not be sufficient to support an NDA. First, the proposed sample size will not generate the exposure necessary to establish the safety profile of the product. Second, as noted at the recent meeting with the Division on February 15, 2005, additional dose-finding, exploring both minimally effective and optimal doses, should be incorporated in the development plan. Adequate pharmacokinetic characterization of your product is also expected. Finally, the Agency has typically required just one pivotal study to support a depot reformulation of an approved drug when the drug is studied for use as a follow-on product in patients known to be responsive to, and stabilized on, the conventional formulation. If you choose to study probuphine in patients previously stabilized on sublingual buprenorphine, a single pivotal study would be sufficient. If you study probuphine as initial therapy (i.e., as the only treatment, or for use after a very brief period of induction on sublingual buprenorphine), replication of your efficacy findings in a second study would be needed.*

4. *The proposal [REDACTED] (b) (4) is a departure from the customary approach to collecting samples thrice weekly. That schedule was developed in order to achieve a balance between capturing all episodes of illicit drug use, and avoiding false-positive "carryover" results. Justify your choice [REDACTED] (b) (4) and explain how this will provide sufficient sensitivity to monitor the participants' clinical status.*

5. *You have asked about your proposal [REDACTED] (b) (4)*
[REDACTED]
Our recommendation is that [REDACTED] (b) (4)
[REDACTED] *study population should be chosen based on your anticipated indication. See below for a more complete discussion.*

6. *We wish to reiterate and amplify comments made at our recent meeting concerning your responder definition.*

[REDACTED] (b) (4)

[Redacted] (b) (4)

In contrast, you propose

[Redacted] (b) (4)

You also propose

[Redacted] (b) (4)

Finally, we reiterate that it is inappropriate

[Redacted] (b) (4)

It is likely that you will need to obtain information on the expected rate of opioid negative urines in the population you wish to study by surveying clinical practitioners who are using sublingual buprenorphine in a similar population, and monitoring their patients with urine toxicology screens on a similar schedule to the one proposed.

Discussion

The Sponsor proposed to define a stabilized patient based on three parameters: duration of buprenorphine sublingual treatment, subjective assessment and objective assessments. The Division stated that the proposed pre-study treatment duration of at least three months is acceptable. The subjective assessments of Clinical Opiate Withdrawal Scale (COWS) and a self-reported measure of craving appear to be acceptable. (b) (4)

Current treatment standards promulgated by institutions such as the Substance Abuse and Mental Health Services Administration (b) (4) these guidelines instruct that if a patient continues to have positive urine, then a different therapy should be explored.

The Sponsor stated that there is (b) (4)
It is not clear what is meant by this (b) (4)

The Sponsor also stated (b) (4)

It was noted by the Division (b) (4)

The Sponsor's intent is to develop Probuphine for "maintenance treatment of opioid dependent patients who have undergone induction and stabilization with buprenorphine sublingual tablets."

The Division advised the Sponsor to survey physicians in Australia and France to obtain specific details about their clinical experience with the product, which has been marketed in these countries longer than in the U.S. The Sponsor replied that they have been in contact with clinicians who are using buprenorphine in a similar patient population and will continue to have dialogue with them.

The Division stated that the Sponsor should only be enrolling patients who have already stopped using opioids (e.g., stable patients). The Sponsor stated that their definition of a responder (b) (4)

The Division questioned the Sponsor's definition of a stable patient (b) (4)

[REDACTED] (b) (4)

The Sponsor stated [REDACTED] (b) (4)

[REDACTED] (b) (4)

The Division emphasized that, in choosing the inclusion and exclusion criteria for a clinical trial, it is not always possible to include every possible outlier or exception to the definitions. The trial should enroll subjects who are sufficiently stable, as evidenced by lack of illicit drug use, that a difference could be detected between a dose which is capable of maintaining subjects at that level of stability and one that is not. This is the essential task for the clinical trial, and choosing a too-liberal entry criterion will make it very difficult for the study to detect a difference among treatments.

The Division also noted that the Sponsor's choice to study stabilized patients was based on their desire to perform only a single pivotal efficacy study; the Division had previously advised that only one study would be necessary if the Probuphine product was envisioned as a maintenance product to which stable patients could be switched after initial treatment with sublingual buprenorphine.

The Division expressed concern that the Sponsor is attempting to address every regulatory issue in a single trial. [REDACTED] (b) (4)

It is not possible for the Division to agree to the adequacy of the Probuphine program since the Division has never seen the protocol or the study report for Study TTP-400-02-01. The adequacy of the database can be revisited once additional data has been obtained. The Sponsor stated that they plan to capture efficacy in their pivotal study, PRO 805, and safety from Studies PRO 805 and 806. A comparative bioavailability study is also being planned. The Sponsor expects to have approximately 500 patients exposed for 6 months and approximately 100 patients exposed for one year. The Division emphasized that the Sponsor should adequately evaluate the entire dose range before initiating their pivotal trials.

The Division stated that the current protocol is still not acceptable for agreement under the special protocol assessment (SPA). The Division reiterated that the Sponsor is not ready for a special protocol agreement and advised them to submit the protocol to the Division for comment and not as a SPA.

ACTION ITEMS

The Sponsor should adequately evaluate the entire dose range before initiating their pivotal trials.

The Sponsor should submit a revised protocol to the Division for comment.

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

/s/

Sara Stradley
8/30/2005 08:36:15 AM



IND 70,852

Titan Pharmaceuticals
400 Oyster Point Blvd
Suite 505
South San Francisco, CA 94080

Attention: Patricia C. Hirano, MPH
Associate Director, Regulatory Affairs

Please refer to the meeting between representatives of your firm and FDA on February 15, 2005. The purpose of this guidance meeting was to discuss the clinical development plans for Probuphine (buprenorphine hydrochloride and ethylene vinyl acetate copolymer). The slides for the meeting were sent to you on February 10, 2005.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 827-7430.

Sincerely,

{See appended electronic signature page}

Sara E. Stradley, MS
Regulatory Project Manager
Division of Anesthetic, Critical Care,
and Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

Industry Meeting Minutes

Date/Time: February 15, 2005

Location: Chesapeake Conference Room

Application: IND 70,852

Sponsor: Titan Pharmaceuticals

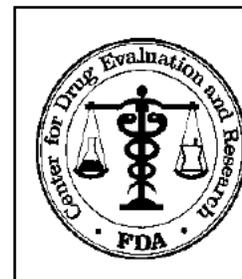
Drug: Probuphine

Indication: treatment of opioid dependence

Type of Meeting: guidance

Meeting Chair: Celia Winchell, MD, Team Leader, Drug Addiction Products

Minutes Recorder: Sara Stradley, MS, Regulatory Project Manager



Titan Pharmaceuticals	Title
Michael Beier	Operations
Anish Bhatnagar, MD	Clinical Development
Lauren Constantini, PhD	Product development
Patricia Hirano	Regulatory Affairs
Rayasam (Ray) Prasad	Regulatory Affairs, Compliance and Quality Assurance
(b) (4)	Biostatistical Consultant
FDA	Title
Bob A. Rappaport, MD	Division Director
Rigoberto Roca, MD	Deputy Division Director
Celia Winchell, MD	Team Leader, Addiction Drug Products
Howard Josefberg, MD	Medical Officer
Ravi Harapanhalli, PhD	Team Leader, Chemistry
Suzanne Thornton-Jones, PhD	Pharmacology/Toxicology Reviewer
Sue Chih Lee, PhD	Biopharmacology Reviewer
Thomas J. Permutt, PhD	Team Leader, Statistics
Mwango Kashoki, MD, MPH	Medical Reviewer
Joan Buenconsejo, PhD	Statistical Reviewer
Sara Stradley, MS	Regulatory Project Manager

Meeting Objective(s): The purpose of this guidance meeting was to discuss the clinical development plans for Probuphine (buprenorphine hydrochloride and ethylene vinyl acetate copolymer).

General Discussion: Following introductions, the discussion focused on the Sponsor's questions that were included in the January 12, 2005 meeting package. The slides for the meeting were sent to the Sponsor on February 10, 2005. The Sponsor's questions and Agency's responses are presented below in italicized text. Discussion is presented in normal text.

CMC COMMENTS

We refer to the following comments stated in the February 3, 2005 advice letter

- 1. A single lot of (b) (4) EVA polymer (b) (4) has been preclinically qualified and the purity profile has been reported. Since there is no DMF on file with the current vendor of EVA, a vendor with current DMF file should be selected before the current stock of EVA depletes. Refer to www.fda.gov/cder/dmf for the list of EVA DMF holders.*
- 2. Establish a two-sided acceptance criterion for the in vitro drug release test throughout the duration of drug release period.*
- 3. Establish a validated microbial sterilization process before the commencement of Phase 3 studies.*
- 4. For the NDA, provide data supporting the safety of the impurities and degradation products that exceed ICH thresholds.*

Discussion

The Sponsor requested clarification on statement #2. The Sponsor was concerned about the broad range of their current *in vitro* drug release test. The Division stated that the Sponsor did not need a vigorous acceptance criterion at this stage in their development, but by the end of Phase 2 this should be established. The Division stated that the Sponsor should perform a multi-point profile for the two-sided acceptance criterion. The Division advised that, depending on the method and when steady state is reached, more than 5 time points may be needed.

The Division stated that drug batches used for the pivotal studies should have two-sided acceptance criterion. The Sponsor agreed to establish a two-sided acceptance criterion.

Additional CMC Comment

If the synthetic process of buprenorphine from thebaine changes, then the drug substance should be carefully monitored for impurities and by-products that may contain structural alerts for mutagenicity,
(b) (4)

Discussion

No additional clarification was requested and there was no additional discussion beyond the information provided in the slide.

PRECLINICAL QUESTIONS

Q1. Do the reviewers concur that the non-clinical studies completed to date to support the marketing authorization for Subutex, Suboxone and Buprenex, together with the data from the Titan-conducted non-clinical studies with Probuphine, adequately characterized the non-clinical safety profile of Probuphine and that no further toxicology studies are required to support an NDA approval for Probuphine.

FDA RESPONSE

No additional non-clinical studies for Probuphine are required at this time.

Discussion

No additional clarification was requested and there was no additional discussion beyond the information provided in the slide.

Preclinical Comments: 505(b)(2) Applications

- *The following reference is available on the CDER website: October 1999 DRAFT Guidance for Industry: Applications Covered by Section 505(b)(2)*
- *For a 505(b)(2) application you must include the following:*
 - a) *Clearly identify those portions of the application that rely on information you do not own or to which you do not have a right of reference.*
 - b) *A 505(b)(2) application that relies upon the Agency's previous finding of safety or efficacy for a listed drug must specifically identify any and all listed drugs by established name, proprietary name, dosage form, strength, route of administration, name of the listed drug's sponsor and the application number.*
 - c) *A 505(b)(2) application relying upon literature must clearly identify the listed drug(s) on which the studies were conducted (if any).*
 - d) *For a 505(b)(2) application you must provide a patent certification or statement as required under section 505(b)(2) of the Act with respect to any relevant patents that claim the listed drug and that claim any other drugs on which the investigations relied on by the applicant for approval of the application were conducted, or that claim a use for the listed or other drug (21 CFR 314.54(a)(1)(vi)). (Listed in the Orange Book)*
 - *Patent certification should specify the exact patent number(s), and the exact name of the listed drug or other drug even if all relevant patents have expired.*
 - *You must also submit a Bioavailability/Bioequivalence (BA/BE) study comparing the proposed product to the listed drug (if any).*

- e) *Before submitting the NDA, you are strongly encouraged to submit a plan to the Division specifically identifying the types of bridging studies that will be conducted. You should also identify those components of its application for which it expects to rely on FDA's finding of safety and effectiveness of a previously approved drug product. The Division will critique the plan and provide guidance.*
- f) *If the only literature that you submit is within the public domain and/or you have right of reference to the studies and the data required to support them, you may be able to submit a 505(b)(1) application.*
- g) *If portions of your application rely upon studies that you do not have right of reference to or are not within the public domain, you must submit a 505(b)(2) application. Please note that not all studies reported in the literature are supported by data that exists within the public domain. Most studies in the literature are supported by proprietary data.*

Discussion

The Sponsor asked for clarification on the requirement for a Bioavailability/Bioequivalence (BA/BE) study comparing the proposed product to the listed drug (if any), because they do not anticipate bioequivalence to the reference listed product. The Divisions stated that a comparative bioavailability study is required in order to put into context the information on the other product. In the completed Phase 1 trial, PK samples for the sublingual formulation were collected at 2 fixed time points. The Division stated that this was inadequate and that full PK profile during a dosing interval should be determined for the sublingual formulation. This could be done in the proposed Phase 2 trial, where recruited patients will be on stable sublingual doses. In the same subjects, PK samples for the implant should also be collected to determine comparative C_{max} and steady state AUC.

The Division reiterated that all of the 505(b)(2) points listed are from the October 1999 DRAFT Guidance for Industry: Applications Covered by Section 505(b)(2).

Q2. Similarly, do the Reviewers agree that the use of the ethylene vinyl acetate copolymer (EVA), a component in Probuphine which has been used as an excipient in other marketed products, requires no additional toxicology studies?

FDA RESPONSE

- *No additional non-clinical studies are required at this time for EVA.*
- *Adequate toxicology data for EVA via the subcutaneous route of administration needs to be submitted for the NDA. The data should include local and systemic toxicological assessments.*
- *Toxicology information on leachables and extractables from the EVA needs to be submitted for the NDA.*

Discussion

The Sponsor requested clarification on the second bullet. The Division stated that this bullet is a reminder for the Sponsor to submit adequate toxicology data for EVA. Sufficient information regarding the toxicity of EVA is required and the information can come from the Sponsor's own non-clinical studies or other sources.

CLINICAL QUESTIONS

Q1. Do the Reviewers agree that the proposed Clinical Development Plan for Probuphine will support an NDA for the proposed indication?

FDA RESPONSE

No. The following issues have been identified and are discussed in detail in the following slides.

- Proposed dosing*
- Proposed Phase 3 trial design*
- Lack of long-term evaluation (after 6 months)*
- Overall patient exposure planned (safety database)*
- Number of studies proposed to support comparative claim*

Proposed Clinical Development Plan

Dosing

(b) (4)

- *At least one dose-finding study should be conducted*
 - Pharmacokinetics, not necessarily dose-response*
- *Adequate dosing may facilitate demonstration of efficacy*

Safety Database (Pre-Approval Patient Exposure)

- *The proposed patient exposure would not be adequate. We recommend exposure of*
 - approximately 500 patients treated for ≥ 6 months*
 - approximately 100 patients treated for \geq one year*
- *Data on long-term use including confirmation of interdose interval, rotation of sites, acceptable interval before repeat use of a site, effect of returning to previous implantation site*
- *Additional evaluation in 'special populations' (renal or hepatic impairment) could be required depending upon initial safety findings and anticipated product labeling*

Discussion

(b) (4)

The Division

(b) (4)

advised the Sponsor to explore higher Probuphine doses

(b) (4)

The discussion then focused on the anticipated patient exposure. The Sponsor questioned if the 500 patient exposures expected by the Division would all need to be from controlled/blinded studies.

(b) (4)

The Division stated that data from controlled trials would be preferable, but that this could be an acceptable approach. These 500 patients should have been treated with the “to-be-marketed” product. The majority should have received highest product doses proposed for marketing. Unbalanced randomization was identified as an acceptable method of increasing enrollment in the higher-dose arm(s).

(b) (4)

The Division also stated that it was important for the Sponsor to examine the long-term use (i.e., more than one year) of Probuphine since many patients are likely to continue buprenorphine maintenance for years. Repeat implantation at the same site should be evaluated, to demonstrate safety, as well as to characterize possible effects (of scarring) on buprenorphine absorption.

Q2. For the proposed pivotal trial, we would appreciate advice regarding study design, and choice of comparator and primary endpoint.

FDA RESPONSE

Trial Design Issues

- *Study must be blinded.*
- *Ancillary treatments (e.g. psychosocial treatments, criteria for use of rescue) must be standardized across study sites.*
- *Inclusion criteria should stipulate a specific range of duration of prior buprenorphine treatment. The protocol should not recruit a mixture of patients in the very earliest stages of stabilization and patients who have been on buprenorphine for years and have achieved substantial rehabilitation/stability.*
 - *If Probuphine is intended for use after a brief period of induction with Subutex/Suboxone, then only these patients should be included.*
 - *If Probuphine is intended for use in fully “stabilized” patients, then inclusion should be based on some measure of clinical stability, (b) (4)*
- *Conditions for an adequate non-inferiority trial are not present (no consensus on appropriate outcome measure, expected response, etc.)*
- *Appropriate designs include*
 - *Superiority to sublingual buprenorphine*
 - » *would require replication if comparative claim is sought*
 - » *if comparative claim is sought, approved doses of Subutex/Suboxone must be used*
- *Dose-ranging (several Probuphine arms of different doses)*
- *Please refer to the following Guidance documents:*

CDER Guidance for Industry (main page)

<http://www.fda.gov/cder/guidance/index.htm>

Providing Clinical Evidence of Effectiveness for Human

<http://www.fda.gov/cder/guidance/1397fnl.htm>

E10: Choice of Control Group and Related Issues

<http://www.fda.gov/cder/guidance/4155fnl.htm>

Comparator

- *Sublingual buprenorphine may be used as a comparator, but*
 - *To support a comparative claim, a dose of known efficacy must be tested and two studies would be needed*
- *The approved product is labeled for administration ‘as a single daily dose in the range of 12 to 16 mg/day’*

- *To establish superiority without making a comparative claim, a lower dose may be used if the dose can be justified*
- *Blinding may require double-dummy design*
- *Note that a comparative study is not required if no comparative claim is sought, and that a dose-controlled study of varying doses of Probuphine should be considered as an alternative to an active controlled study vs. sublingual buprenorphine*

Endpoint

- *There is some discrepancy/lack of clarity regarding your proposed primary endpoint*
 - *The protocol submitted with the IND states that the primary efficacy endpoint will test the following null hypothesis:* [REDACTED] (b) (4)
 - *The meeting package indicates that* [REDACTED] (b) (4)
- *We recommend an analysis which compares the distribution of % negative urines (how many subjects with 100%, how many with 90% or better, how many with 80% or better, etc.),* [REDACTED] (b) (4)
 - *The frequency of urine toxicology testing should be justified. Previous studies have used thrice-weekly sampling*
 - *A plan for imputation of missing data should be pre-specified*

Discussion

The Division stated that a blinded, controlled study would be necessary. The Sponsor indicated that a two-arm study was envisioned, and the Division encouraged them to explore additional doses, suggesting that Phase 2 studies to identify the range of effective doses would be desirable.

In discussing the approach to the blinded, dose-controlled design, the Sponsor inquired whether the Division had any objection to the use of placebo implants for the purpose of blinding. Subjects assigned to the low-dose arm, if qualifying per protocol for a supplemental implant, would receive a placebo implant to maintain the blind. As this would expose the subjects to a minor surgical procedure without benefit, the Sponsor was concerned about ethical objections. The Division agreed that this was the best approach, scientifically, but could not state whether IRBs might raise concerns about the procedure.

In reference to the Division's comment that psychosocial treatments should be standardized across treatment groups, the Sponsor questioned the feasibility of standardizing ancillary treatments across five different countries. The Division pointed out that, as planned, the Sponsor's trial would provide patients with different counseling regimens, based upon the treatment administered. The Division also stated that cross culturally standardized psychosocial treatments are available and are commonly used in clinical trials. The Sponsor

should assess the impact of the differences in the standard of care in the foreign sites. The Sponsor stated that they will try to enforce the protocol so that there is consistency.

The Division stated that, if such standardization were not possible, psychosocial treatment may need to be limited since it would be considered an active treatment, capable of affecting study outcome(s). The Sponsor agreed.

In terms of the planned patient population, the Sponsor indicated that they planned to enroll

(b) (4)

It was pointed out that the inclusion criteria stipulated (b) (4)

(b) (4) The Division expressed concern (b) (4)

(b) (4) It was recommended that level of stability, (b) (4) might be a preferable way of defining the patient population, so that clinicians would understand which patients had been shown to benefit from Probuphine (e.g., only stabilized patients, if this were the case). Approaches to defining clinical stability (e.g. negative urine toxicology screens) were discussed.

The Sponsor stated that they planned (b) (4)

(b) (4) The Division stated that (b) (4) could be an acceptable approach, but could not really comment further until the actual protocol and statistical analysis plan had been submitted.

The Sponsor's proposed primary endpoint was discussed next. The Division stated that the individual, within-subject measures of efficacy are preferred to the (b) (4) proposed by the sponsor. The Sponsor stated that they would (b) (4) look at individual patients. The Division reminded the Sponsor that, in defining success definitions for the purposes of analysis, it will be important to consider the population studied and the method of ascertaining clinical response. For example, prior studies reporting the frequency of "clean" urine samples have employed thrice-weekly testing; if (b) (4) testing is planned, assumptions should not be based on prior findings. Furthermore, data collected in new entrants to treatment should not be used to define success for a population of previously stabilized patients; the success definition should not be so liberal as to define a clinical deterioration from baseline as a success. One possible way of illustrating results across a range of success definitions was discussed, and the Division provided the Sponsor with a graph based on existing data showing how the data could be displayed (see Attachment 1-Dr. Winchell's Cumulative Response Graph).

The Sponsor inquired whether a single pivotal study of probuphine using a dose-control design would suffice for demonstration of efficacy. The Division explained that this was the approach for depot formulations of other chronically-used psychotropics, such as neuroleptics. In these cases, the drug is intended for use in patients previously stabilized on the oral formulation. Therefore, depending on the population studied and the labeling

language sought, it is theoretically possible to support an efficacy claim for Probuphine with a single, dose controlled study. No claim regarding relative efficacy of the different formulations would be possible.

It was noted, however, that although not required, comparison to sublingual would be desirable clinically.

Other Clinical Comments

- *The pilot study was to include [REDACTED] (b) (4), and was also amended [REDACTED] (b) (4) [REDACTED] [REDACTED] – Please clarify why “accrual into the study was placed on hold” prior to conduct of these portions of the study.*
- *Probuphine termination (end of treatment) should be addressed in each protocol (e.g. will subjects be tapered, discontinued without follow-up treatment, converted back to sublingual? How will taper be accomplished?)*

Discussion

The Sponsor explained that CMC concerns necessitated discontinuation of the pilot study.

[REDACTED] (b) (4)
[REDACTED]

The Sponsor stated that that no adverse events were attributable to this CMC problem, and consider the study results to be valid.

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS COMMENTS

1. *In Study TTP-400-02-01, only two plasma samples were collected while the patients were on sublingual tablets. Conduct an additional PK study so that the relative AUC (implant vs. sublingual tablets) can be determined. This PK study may be performed as part of the proposed clinical trial.*
2. *Indicate how dosage adjustment may be made in special populations (e.g. hepatic impairment patients) and provide the rationale. Additional clinical studies in special populations may be required to provide this information.*
3. *The issue of drug-drug interactions should be addressed in terms of proper dosing and actions to be taken if undesirable interactions occur.*
4. *Pharmacokinetics in obese patients vs. lean patients should be characterized.*

Discussion

Currently, PK profiles for the implant were determined for up to 4 implants. The Division stated that, if patients are to receive more than 4 implants, full PK profile for the higher dose will need to be determined.

ABUSE LIABILITY ASSESSMENT COMMENTS

Regarding the Product:

- *The amount of residual buprenorphine in the implants after removal from patients should be determined.*
- *A plan to properly dispose of used implants should be developed to ensure the complete destruction of any residual buprenorphine.*
- *The extractability of buprenorphine from unused Probuphine for parenteral abuse should be studied.*
- *The feasibility of the removal of implanted Probuphine by non-professionals, and extraction of buprenorphine from used Probuphine implants for abuse/diversion should be addressed.*

Discussion

The Sponsor questioned if a guidance regarding abuse liability was available. The Division stated that no guidance document was available, however the following slide was presented.

Under 21 CFR § 314.50 (d) (5) (vii), an NDA is required to contain a separate Abuse Potential Section that includes:

- 1) A proposal for scheduling and all scientific data that forms the basis of the proposal
- 2) An Abuse Potential Assessment:
 - Chemistry (including chemical similarity to other drugs with known abuse potential)
 - Pharmacology (clinical and pre-clinical)
 - Pharmacokinetics and Pharmacodynamics
 - Integrated Summaries of Safety and Efficacy
 -
- 3) Information related to overdose, diversion, misuse of drug

The Sponsor was advised to prepare a plan for their abuse liability assessment and request a formal meeting to discuss the plan. The Division will consult the plan to the Controlled Substance Staff for comment.

The Division also advised the Sponsor to prepare a Risk Management Plan and suggested they review the Risk Management Plans for Actiq, Palladone, and Subutex/Suboxone. The entire risk management plan should be submitted with the NDA.

REGULATORY QUESTIONS

We wish to seek the Reviewer's advice regarding potential registration strategies for Probuphine including:

- a) *Submission of a new drug application (NDA) under section 505(b)(2) of the Federal Food Drug and Cosmetic Act*
- *Submission under 505(b)(2) would be appropriate; refer to advice provided by the Pharmacology/Toxicology team above.*
 - *A 505(b)(2) application citing the Subutex or Suboxone NDAs cannot be approved while these drugs are protected by exclusivity of any type.*
- b) *Implications of orphan drug exclusivity of Subutex*
- *The Orphan Drug Exclusivity of Subutex would preclude approval of an NDA for another buprenorphine product for opioid dependence until the exclusivity has expired.*
- c) *Potential orphan drug designation for Probuphine*
- *This is still under internal discussion.*

Discussion

The Division stated that Probuphine will not be granted orphan drug designation because the law has changed since buprenorphine was designated. The economic argument for Subutex and Suboxone was based on limited distribution because it could only be prescribed in methadone clinics and the number of clinics was limited by law. Since that is no longer the case, it would be very difficult for them to demonstrate that they would be unable to recover development costs in seven years, plus the number of addicts is significantly over 200,000.

OVERALL DISCUSSION

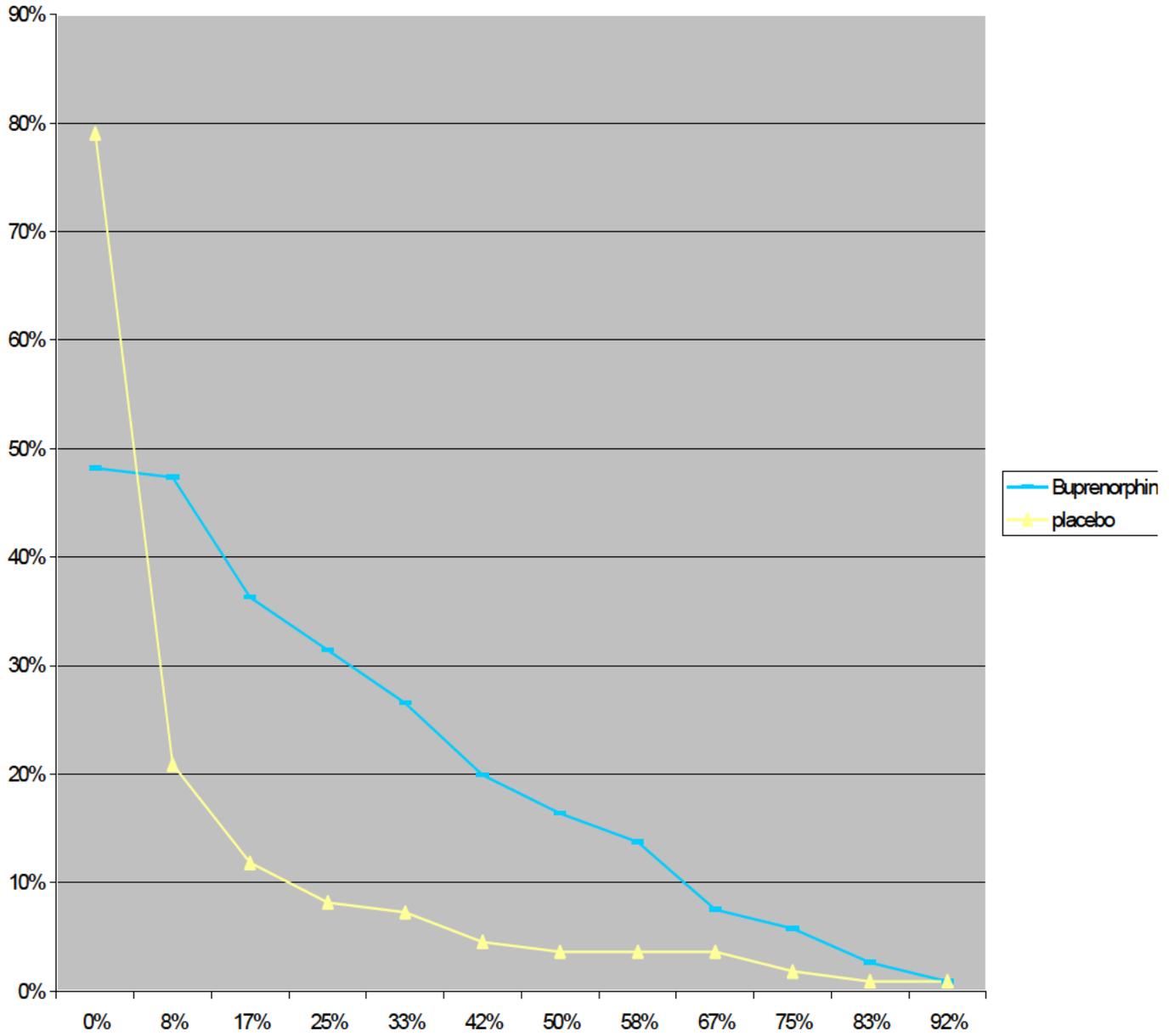
The Sponsor asked if they could send their protocol as a Special Protocol Assessment (SPA). The Division stated that Special Protocol Assessments were normally limited to Phase 3 studies, and reminded the Sponsor that, although the Sponsor seems to feel ready for Phase 3, further dose finding is desirable. The Division also noted that comments on the protocols can be provided without an SPA.

ACTION ITEMS

No specific action items were identified.

ATTACHMENT 1

Dr. Winchell's Cumulative Response Graph



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

/s/

Sara Stradley
3/11/05 02:23:29 PM