DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204442

NDA APPROVAL

Titan Pharmaceuticals, Inc.
c/o Braeburn Pharmaceuticals
47 Hulfish Street, Suite 441
Princeton, NJ 08542

Attention: Frank E. Young, MD, PhD
EVP, Regulatory and Medical

Dear Dr. Young:

Please refer to your New Drug Application (NDA) dated October 27, 2012, received October 31, 2012, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for PROBUPHINE (buprenorphine hydrochloride) implant.

We acknowledge receipt of your amendment dated August 27, 2015, which constituted a complete response to our April 30, 2013, action letter, and of your major amendment dated February 11, 2016, which extended the goal date by three months.

This new drug application provides for the use of PROBUPHINE (buprenorphine hydrochloride) implant, for the maintenance treatment of opioid dependence in patients who have achieved and sustained prolonged clinical stability on low-to-moderate doses of a transmucosal buprenorphine-containing product (e.g., doses of no more than 8 mg per day of Subutex or Suboxone sublingual tablet equivalent or generic equivalent).

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

WAIVER OF HIGHLIGHTS SECTION

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert and Medication Guide). Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

We request that the labeling approved today be available on your website within 10 days of receipt of this letter.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and immediate container labels that are identical to the enclosed carton and immediate container labels submitted on February 5, 2016, and May 3, 2016 (implant kit label), as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)*. Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 204442**." Approval of this submission by FDA is not required before the labeling is used.

Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for this application because necessary studies are impossible or highly impracticable. The population of treatment-seeking, opioid dependent adolescents appropriate for maintenance therapy is too low for studies to be feasible. The prevalence of opioid addiction in younger children is not captured in surveys and is considered to

be very low. Moreover, clinical practice guidelines dictate that minors are not to be placed on maintenance treatment with opioid agonists unless they have failed detoxification treatment.

POSTMARKETING REQUIREMENTS UNDER 505(o)

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

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to:

- assess a signal of serious risks related to insertion, localization, and removal of PROBUPHINE (buprenorphine hydrochloride), including nerve injury, device migration, and other complications.
- assess a signal of a serious risk of QT prolongation associated with PROBUPHINE (buprenorphine hydrochloride).
- identify unexpected serious risks, including migration of implants and loss of expected pharmacologic effect (reduced bioavailability), associated with insertion of PROBUPHINE (buprenorphine hydrochloride) into previously implanted sites at which there is scarring or inflammation.
- identify unexpected serious risks associated with insertion of PROBUPHINE (buprenorphine hydrochloride) at alternate body sites or using alternative methods of insertion into additional locations on the arm.

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

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

3078-1 A prospective descriptive observational cohort study of insertion-, localization-, and removal-related serious adverse events and their sequelae associated with PROBUPHINE (buprenorphine hydrochloride) use.

The timetable you submitted on May 9, 2016, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	10/2016
Final Protocol Submission:	03/2017
Annual Interim Reports:	03/2018
	03/2019
	03/2020

Study Completion:	05/2021
Final Report Submission:	11/2021

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

1. Numbers of providers in the study, linked insertion-removal pairs, patients lost to follow-up
2. Patient characteristics: for example, age, sex, race/ethnicity, BMI, prior opioid maintenance therapy
3. Health care provider characteristics: for example, type of provider (e.g., surgeon), extent of prior experience with PROBUPHINE insertion/removal procedures (e.g., number performed), type of institution (e.g., outpatient)
4. Insertion characteristics: for example, site of PROBUPHINE insertion, insertion attempts, number of treatment cycles
5. Insertion/removal tools and techniques that differ from marketed tools and techniques
6. Insertion-related events, such as pain, bruising, scarring, bleeding, infection, nerve damage, altered strength/range of motion, disability
7. Localization- and removal-related events, such as:
    - Pain, bruising, scarring, bleeding, infection, nerve damage, altered strength/range of motion, disability
    - Reason for removal (other than completing full treatment cycle)
    - Implant protrusion, expulsion, palpability, damage or tampering (by patient)
    - Implant migration; if migration to distant site is identified, document location, sequelae, and intervention (e.g., surgical procedures to remove implants)
        - enumerate implant migrations greater than 2 cm
        - enumerate implant migrations less than 2 cm but of clinical consequence

- Implant fragmentation, and documentation of removal of any fragments identified, as well as any fragments left behind
- Imaging modalities, if any, used to locate implants (e.g., ultrasound, MRI) prior to removal
- Referral to surgical specialties to complete removal
- Non-localized implants/implants never removed

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess a signal of a serious risk of QT prolongation associated with PROBUPHINE (buprenorphine hydrochloride); to identify unexpected serious risks, including migration of implants and loss of expected pharmacologic effect (reduced bioavailability), associated with insertion of PROBUPHINE (buprenorphine hydrochloride) into previously implanted sites at which there is scarring or inflammation; and to identify unexpected serious risks associated with insertion of PROBUPHINE (buprenorphine hydrochloride) at alternate body sites or using alternative methods of insertion into additional locations on the arm.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

3078-2 Clinical trial to assess the risk of QT prolongation with subdermal PROBUPHINE (buprenorphine hydrochloride**)**.

The timetable you submitted on May 09, 2016, states that you will conduct this trial according to the following schedule:

Draft Protocol Submission:	11/2016
Final Protocol Submission:	05/2017
Trial Completion:	02/2019
Final Report Submission:	08/2019

3078-3 Clinical trial to evaluate the effect of scarring or inflammation related to a prior implant on the safety of re-implantation/reinsertion, the potential for migration of implants, and the bioavailability of PROBUPHINE (buprenorphine hydrochloride) when the drug is implanted in a previously used site.

The timetable you submitted on May 09, 2016, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	11/2016
Trial Completion:	02/2019
Final Report Submission:	08/2019

3078-4 Clinical trial to evaluate the safety, feasibility, and pharmacokinetics of PROBUPHINE (buprenorphine hydrochloride) implantation at alternate body sites. The trial should also evaluate the safety of other methods of inserting PROBUPHINE (buprenorphine hydrochloride) into additional locations on the arm.

The timetable you submitted on May 09, 2016, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	11/2016
Trial Completion:	02/2018
Final Report Submission:	08/2018

Submit the protocols to your IND 070852, with a cross-reference letter to this NDA. Submit all final reports to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **"Required Postmarketing Protocol Under 505(o)," "Required Postmarketing Final Report Under 505(o)," "Required Postmarketing Correspondence Under 505(o)."**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

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

In accordance with section 505-1 of FDCA, we have determined that a REMS is necessary for PROBUPHINE (buprenorphine hydrochloride) to ensure the benefits of the drug outweigh the risks of complications of migration, protrusion, expulsion, and nerve damage associated with the

insertion and removal of PROBUPHINE (buprenorphine hydrochloride); and the risks of accidental overdose, misuse, and abuse.

Your proposed REMS must also include the following:

Medication Guide: In accordance with section 505-1 of FDCA, as one element of a REMS, FDA may require the development of a Medication Guide as provided for under 21 CFR 208. Pursuant to 21 CFR 208, FDA has determined that PROBUPHINE (buprenorphine hydrochloride) poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of PROBUPHINE (buprenorphine hydrochloride). FDA has determined that PROBUPHINE (buprenorphine hydrochloride) is a product for which patient labeling could help prevent serious adverse effects, and that has serious risks (relative to benefits) of which patients should be made aware because information concerning the risks could affect patients' decisions to use, or continue to use PROBUPHINE (buprenorphine hydrochloride). Under section 505-1 of the FDCA, FDA has also determined that a Medication Guide is necessary to ensure the benefits of the drug outweigh the risks of complications of migration, protrusion, expulsion and nerve damage associated with the insertion and removal of PROBUPHINE (buprenorphine hydrochloride), and the risks of accidental overdose, misuse, and abuse.

Under 21 CFR 208, you are responsible for ensuring that the Medication Guide is available for distribution to patients who are dispensed PROBUPHINE (buprenorphine hydrochloride).

Elements to assure safe use: Pursuant to 505-1(f)(1), we have also determined that PROBUPHINE (buprenorphine hydrochloride) can be approved only if elements necessary to assure safe use are required as part of the REMS to mitigate the risk of complications of migration, protrusion, expulsion and nerve damage associated with the insertion and removal of PROBUPHINE (buprenorphine hydrochloride), and the risks of accidental overdose, misuse, and abuse listed in the labeling. In addition, we have determined that a Medication Guide and a communication plan are not sufficient to mitigate the serious risks. The elements to assure safe use will require prescribers and dispensers[1] to be specially certified, ensure PROBUPHINE (buprenorphine hydrochloride) is only inserted in healthcare settings in which a certified prescriber is practicing, and ensure patients are monitored for removal of PROBUPHINE (buprenorphine hydrochloride) to ensure PROBUPHINE (buprenorphine hydrochloride) is removed by healthcare providers who are certified to insert.

Your REMS includes the following elements to mitigate these risks:

- Healthcare providers have particular experience or training, or are specially certified
- Practitioners, or health care settings that dispense the drug are specially certified
- The drug is dispensed to patients only in certain health care settings
- Each patient using the drug is subject to certain monitoring

[1] For the purpose of this REMS, the term dispense refers to the insertion of PROBUPHINE.

Implementation System: The REMS must include an implementation system to monitor and evaluate the implementation of the elements to assure safe use (outlined above) that require practitioners who implant the drug be specially certified and the drug be implanted in patients only in certain health care settings.

Your proposed REMS, submitted on May 25, 2016, and appended to this letter, is approved. The REMS consists of a Medication Guide, elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS.

We remind you to submit the final version of the "PROBUPHINE REMS Program Surgical Procedures Recertification Video" to your NDA 90 days prior to implementation. The video must be consistent with "PROBUPHINE REMS Program PROBUPHINE Surgical Procedures Recertification" video transcript approved as part of the REMS.

The REMS assessment plan must include, but is not limited to, the following:

1. **REMS Program Outreach and Communication**
   a) Number of *PROBUPHINE REMS Prescriber Enrollment forms* sent to prescribers who attempt to order PROBUPHINE or inquire about certification

   b) Number and location of REMS training programs
      i. Number of healthcare providers (HCPs) certified as prescribers, inserters, or dually certified to both prescribe and insert at each training program

2. **REMS Program Utilization**
   a) Number of certified HCPs who prescribe
      i. Number of orders per certified prescriber
      ii. Degree, specialty, practice setting, and geographic location
      iii. Number of replacement kit orders shipped.
      iv. Number of times unused implants from replacement kits are returned per certified prescriber.
         1) Number of unused implants from each replacement kit returned.

   b) Number of certified HCPs who insert
      i. Degree, specialty, and geographic location
      ii. Number of certified inserters who are re-certified by method of certification (i.e. live training, video)
         1) If recertified by video, number of certified HCPs who insert who have operating privileges versus those successfully performing 10 or more procedures

   c) Number of dual-certified HCPs who prescribe and insert
      i. Number of orders per dual-certified prescriber
      ii. Degree, specialty, and geographic location
      iii. Number of replacement kit orders shipped and returned per dual-certified prescriber

iv. Number of dual-certified prescribers that are re-certified by method of certification (i.e. live training, video)
    1) If recertified by video, number of certified HCPs who insert who have operating privileges versus those successfully performing 10 or more procedures

3. REMS Program Infrastructure and Performance

a) Number of non-certified prescribers attempting to prescribe PROBUPHINE and corrective actions taken

b) Number of orders shipped to non-certified prescribers and corrective actions taken

c) Number of insertions/removals performed by a HCP not certified or dually certified to insert PROBUPHINE and corrective actions taken

d) Summary of results of audits of 10% (or 15, whichever is greater) of recertification forms for inserters (beginning at the 24-month assessment)

e) Summary of call center calls; include corrective actions taken for any non-compliance identified through the call center by stakeholder type

f) Number of certified prescribers, inserters, and dual-certified prescribers that have been decertified and a summary of the reasons for decertification

g) Assessment of the distribution and use of the Medication Guide in accordance with 21 CFR 208.24 and the PROBUPHINE REMS Program requirements

h) Report on failures to adhere to distribution requirements, and corrective actions taken to address noncompliance

4. Evaluation of knowledge

a) Healthcare Providers - Results of evaluation of healthcare providers' knowledge of the risk of complications of migration, protrusion, expulsion and nerve damage associated with the insertion and removal of PROBUPHINE, and the risks of accidental overdose, misuse, and abuse if an implant comes out or protrudes from the skin. Results should be stratified by certified prescriber, certified inserter, and dual-certified prescribers

b) Patients – Results of evaluation of patients' knowledge of the risk of complications of migration, protrusion, expulsion, and nerve damage and the risks of accidental overdose, misuse, and abuse if an implant comes out or protrudes from the skin.

5. Overall REMS evaluation

As required for assessments of an approved REMS under section 505-1(g)(3) the Applicant will include, with respect to each goal included in the strategy, an assessment of the extent to

which the approved strategy, including each element of the strategy, is meeting the goal or whether one or more such goals or such elements should be modified.

We remind you that in addition to the REMS assessments submitted according to the timetable in the approved REMS, you must include an adequate rationale to support a proposed REMS modification for the addition, modification, or removal of any goal or element of the REMS, as described in section 505-1(g)(4) of the FDCA.

We also remind you that you must submit a REMS assessment when you submit a supplemental application for a new indication for use as described in section 505-1(g)(2)(A). This assessment should include:

a) An evaluation of how the benefit-risk profile will or will not change with the new indication.

b) A determination of the implications of a change in the benefit-risk profile for the current REMS.

c) *If the new, proposed indication for use introduces unexpected risks*: A description of those risks and an evaluation of whether those risks can be appropriately managed with the currently approved REMS.

d) *If a REMS assessment was submitted in the 18 months prior to submission of the supplemental application for a new indication for use*: A statement about whether the REMS was meeting its goals at the time of the last assessment and if any modifications of the REMS have been proposed since that assessment.

e) *If a REMS assessment has not been submitted in the 18 months prior to submission of the supplemental application for a new indication for use:* Provision of as many of the currently listed assessment plan items as is feasible.

f) *If you propose a REMS modification based on a change in the benefit-risk profile or because of the new indication of use, submit an adequate rationale to support the modification, including*: Provision of the reason(s) why the proposed REMS modification is necessary, the potential effect on the serious risk(s) for which the REMS was required, on patient access to the drug, and/or on the burden on the health care delivery system; and other appropriate evidence or data to support the proposed change. Additionally, include any changes to the assessment plan necessary to assess the proposed modified REMS. *If you are not proposing a REMS modification*, provide a rationale for why the REMS does not need to be modified.

If the assessment instruments and methodology for your REMS assessments are not included in the REMS supporting document, or if you propose changes to the submitted assessment instruments or methodology, you should update the REMS supporting document to include specific assessment instrument and methodology information at least 90 days before the assessments will be conducted. Updates to the REMS supporting document may be included in a

new document that references previous REMS supporting document submission(s) for unchanged portions. Alternatively, updates may be made by modifying the complete previous REMS supporting document, with all changes marked and highlighted. Prominently identify the submission containing the assessment instruments and methodology with the following wording in bold capital letters at the top of the first page of the submission:

NDA 204442 REMS CORRESPONDENCE
(insert concise description of content in bold capital letters, e.g.,
UPDATE TO REMS SUPPORTING DOCUMENT - ASSESSMENT METHODOLOGY

An authorized generic drug under this NDA must have an approved REMS prior to marketing. Should you decide to market, sell, or distribute an authorized generic drug under this NDA, contact us to discuss what will be required in the authorized generic drug REMS submission.

We remind you that section 505-1(f)(8) of FDCA prohibits holders of an approved covered application with elements to assure safe use from using any element to block or delay approval of an application under section 505(b)(2) or (j). A violation of this provision in 505-1(f) could result in enforcement action.

Prominently identify any submission containing the REMS assessments or proposed modifications of the REMS with the following wording in bold capital letters at the top of the first page of the submission as appropriate:

NDA 204442 REMS ASSESSMENT

NEW SUPPLEMENT FOR NDA 204442/S-000
CHANGES BEING EFFECTED IN 30 DAYS
PROPOSED MINOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR NDA 204442/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED MAJOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR NDA 204442/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABEL CHANGES SUBMITTED IN SUPPLEMENT XXX

NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR NDA 204442/S-000 REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)

Should you choose to submit a REMS revision, prominently identify the submission containing the REMS revisions with the following wording in bold capital letters at the top of the first page of the submission:

REMS REVISION FOR NDA 204442

To facilitate review of your submission, we request that you submit your proposed modified REMS and other REMS-related materials in Microsoft Word format. If certain documents, such as enrollment forms, are only in PDF format, they may be submitted as such, but the preference is to include as many as possible in Word format.

If you do not submit electronically, please send 5 copies of REMS-related submissions.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert, Medication Guide, and patient PI (as applicable) to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

METHODS VALIDATION

We have not completed validation of the regulatory methods. However, we expect your continued cooperation to resolve any problems that may be identified.

EXPIRATION DATING

The drug product is granted an expiry dating of 36 months when stored at 20 to 25°C (68 to 77°F) with excursions permitted to15 to 30°C (59 to 86°F).

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Swati Patwardhan, Regulatory Project Manager, at (301) 796-4085.

Sincerely,

{See appended electronic signature page}

Rigoberto Roca, MD
Deputy Director
Division of Anesthesia, Analgesia,
and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosures:
Content of Labeling
Carton and Container Labeling
REMS

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

/s/

JUDITH A RACOOSIN on behalf of RIGOBERTO A ROCA
05/26/2016