CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022445Orig1s000

OTHER ACTION LETTERS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022445

COMPLETE RESPONSE

A.P. Pharma, Inc.
Attention: Michael A. Adam, Ph.D.
Senior Vice President, COO
123 Saginaw Drive
Redwood City, CA 94063

Dear Dr. Adam:

Please refer to your New Drug Application (NDA) dated May 16, 2009, received May 18, 2009, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Sustol (granisetron) injection, 10 mg/0.4 mL.

We acknowledge receipt of your amendments dated July 10, 2009; August 3, 2009; August 27, 2009; September 17, 2009; September 21, 2009; September 22, 2009; October 20, 2009; November 17, 2009; January 21, 2010; January 25, 2010; February 1, 2010; February 4, 2010; February 5, 2010; February 19, 2010; February 25, 2010; March 1, 2010; April 2, 2010; April 21, 2010; April 22, 2010; April 29, 2010; December 16, 2010; December 23, 2010; February 1, 2011; February 15, 2011; March 10, 2011; March 16, 2011; March 30, 2011; November 17, 2011; September 27, 2012; October 18, 2012; October 25, 2012; December 7, 2012; December 20, 2012; January 4, 2013; January 9, 2013; January 10, 2013; January 16, 2013; January 18, 2013; January 24, 2013; January 25, 2013; January 28, 2013; January 30, 2013; February 6, 2013; February 11, 2013; February 13, 2013; February 20, 2013; February 27, 2013; February 28, 2013; March 5, 2013; March 6, 2013; and March 14, 2013.

The September 27, 2012, submission constituted a complete response to our March 16, 2010, action letter.

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

FACILITY INSPECTIONS

1. During a recent inspection of the (b) (4) A.P. Pharma (Redwood City, CA), and (b) (4) manufacturing facilities for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

CONTAINER / CLOSURE SYSTEM

2. Your completed human factors validation study (XP-1179-045 Report) did not confirm that users could adequately administer Sustol with the proposed product design and its labeling, including instructions for use. Participants in the study reported difficulty pushing the plunger due to the viscosity of the product. We are concerned that, given the amount of force needed to administer this product, the instructions for use tested in the human factors study will result in administration errors. The instructions required that a health care professional use a single hand to both push the plunger and stabilize the syringe while administering the product. The force required to expel the viscous product from the syringe will make it difficult to maintain the injection in the correct tissue plane with use of a single hand.

   You have proposed revised instructions for use that include an alternative technique to administer the product. Therefore, you must conduct additional human factors validation testing to demonstrate that Sustol can be safely and effectively administered with the modified instructions for use. Please see the FDA correspondence dated March 26, 2013, containing our comments on your formative human factors testing and our recommendations on your proposed human factors validation study protocol.

CLINICAL

3. [redacted (b) (4)]. Sustol was [redacted (b) (4)] effective for prevention of both acute and delayed phase nausea and vomiting associated with moderately emetogenic chemotherapy (MEC). The proposed indication should be revised to reflect the populations that will benefit from Sustol in both the acute and delayed phase.

   To support this revision, provide the dataset and identify the variables used to determine if a patient was in the "HEC" or "MEC" stratum for randomization in trial C2006-01, the major efficacy trial submitted in this NDA. Please also provide the algorithm and/or program for this classification. Moreover, please reclassify the patients into "HEC" and "MEC" categories according to the recently modified ASCO 2011 Guideline, Anti-emetic: American Society of Clinical Oncology Clinical Practice Guideline Update, and provide the dataset with patient information, variables used for the classification, and the category index for both original and new classification.

PRODUCT QUALITY

4. Your proposed acceptance criteria for the *in vitro* drug release (IVR) test are not adequate. There is a high level of variability for the different lots, especially [redacted (b) (4)] the IVR profiles. Development of a new IVR method may be necessary to reduce the variability that is currently observed at different time points of the drug release profile of your product.

[redacted] (b) (4)

While we are aware of the complexity of the release of granisetron from this product, the acceptance criteria for the IVR test will be used as a major attribute to control the quality of your product. Therefore, generate new data using new IVR methodology (as appropriate) to set the acceptance criteria of your product. The proposed criteria should also include specification-ranges for the [redacted] (b) (4) release profile.

LABELING

We reserve comment on the proposed labeling until the application is otherwise adequate. If you revise labeling, your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm.

SAFETY UPDATE

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

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

   - Present new safety data from the studies/clinical trials for the proposed indication using the same format as the original NDA submission.
   - Present tabulations of the new safety data combined with the original NDA data.
   - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
   - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

6. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).

7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

8. Provide English translations of current approved foreign labeling not previously submitted.

ADDITIONAL COMMENTS

Although the following comments are not approvability issues at this time, we request that you address them in your resubmission.

1. The metabolic fate study (C2011-02) you submitted in this resubmission only accounted for approximately 1/3 of the polymer. The proposed dosage and administration instructions allow for administration of Sustol every 7 days. Although the major trial submitted to support this NDA, C2006-01, included patients who were exposed to up to 4 doses of Sustol, there was no control arm beyond the first cycle to allow for optimal interpretation of the safety data in this complex patient population with underlying malignancies. In addition, serum chemistries from patients who received subsequent doses of Sustol were not submitted for review in the NDA. For these reasons, we are considering whether a postmarketing, randomized, controlled safety trial that evaluates patients who receive Sustol doses as frequently as every 7 days over the course of a year will be a condition for future approval.

2. As discussed at the February 25, 2011 Type B meeting, a two-year carcinogenicity study in the rat and SHE cell assay will be performed as a postmarketing study. Provide your expected timeframe for submission of the final study report.

OTHER

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

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA Guidance for Industry, "Formal Meetings Between the FDA and Sponsors or Applicants," May 2009 at

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf.

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

If you have any questions, call Jagjit Grewal, Regulatory Project Manager, at (301) 796-0846.

Sincerely,

{See appended electronic signature page}

Donna Griebel, M.D.
Director
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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

/s/

DONNA J GRIEBEL
03/27/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022445 **COMPLETE RESPONSE**

A.P. Pharma, Inc.
Attention: John Barr, Ph.D.
Senior Vice President
Research and Development
123 Saginaw Drive
Redwood City, CA 94063

Dear Dr. Barr:

Please refer to your new drug application (NDA) dated May 14, 2009, received May 18, 2009, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Sustol (granisetron) Injection, 10 mg/0.4 mL.

We acknowledge receipt of your amendments dated June 29, 2009; July 30, 2009; August 25, 2009; September 15, 2009; September 21, 2009; September 22, 2009; October 19, 2009; November 17, 2009; January 12, 2010; January 22, 2010; January 25, 2010; January 29, 2010; and February 5, 2010.

We also acknowledge receipt of your amendments dated February 3, 2010; February 18, 2010; and February 25, 2010, which were not reviewed for this action. You may incorporate applicable sections of the amendments by specific reference as part of your response to the deficiencies cited in this letter.

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

FACILITY INSPECTIONS

1. During recent inspections of the (b) (4) A.P. Pharma, and (b) (4) manufacturing facilities for this application, our field investigator conveyed deficiencies to the representative of each facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

CONTAINER / CLOSURE SYSTEM

2. Transfer of drug from the [redacted] 1.25 mL [redacted] syringe through the [redacted] Luer Lock-to-Luer Lock into the [redacted] 1 mL Syringe Luer-Lock Tip Plastic syringe is an atypical process for subcutaneous product preparation and administration. The proposed two syringe design utilizing a luer lock connector and the [redacted] Needle is unacceptable because it may lead to wrong route of administration errors, drug overdose, and introduces added risk of microbial contamination during the preparation process. These risks arise from the following:

   a. The luer lock design of the pre-filled [redacted] 1.25 mL [redacted] syringe allows a needle to be attached directly to the syringe or the syringe to be attached directly to a needleless delivery system. This can lead to inadvertent intravenous administration (i.e., IV push or infusion) of granisetron injection. Administration directly from the [redacted] 1.25 mL [redacted] syringe can also lead to overdose due to overfill in the glass syringe.

   b. The [redacted] Needle provided in the product kit is larger than what is typically used for a subcutaneous injection (i.e. 1/2 inch to 5/8 inch long with a gauge of 25 to 30). Providing this size needle can lead to wrong route of administration errors, i.e. intramuscular injection.

   c. There is not a marking on the [redacted] 1.25 mL [redacted] syringe to indicate the fill volume. Without this marking, it is difficult to know the total fill volume in the syringe and to determine if tampering has occurred.

   d. No device usability studies were conducted for the entire system. Due to the potential error prone design of this product we request a Human Factors analysis. We recommend you provide the proposed protocol for review and comment prior to initiation of these studies.

   e. No justification is presented for why the product cannot be directly filled into a syringe that has an adequate tip bore diameter.

   To address this deficiency, you must change to a single syringe system or otherwise adequately address each of the above safety issues, such that each safety issue has been resolved.

3. Your terminal sterilization scheme presented in the January 29, 2010, amendment for the [redacted] syringe is not acceptable for the following reasons:

   a. We are requiring an alternative container/closure to the [redacted] 1.25 mL [redacted] syringe that allows for direct product administration. Terminal sterilization should be described for the alternate container-closure system. For the alternate system include both:
      i. Depyrogenation validation data.
      ii. Container-closure integrity validation.

b. You have not provided adequate information on the sterilization facility and sterilization process. To address this deficiency you must provide:

i. Clarification regarding whether the [redacted] facility in [redacted] will be used for commercial sterilization.

ii. A description of the facility and details on how filled syringes will be presented to the irradiation source for terminal sterilization.

iii. Terminal irradiation dose mapping studies conducted with full production loads at the commercial site.

c. The proposed gamma irradiation dose of [redacted] kGy is based on a [redacted] and does not allow for a margin of error in the estimate. To address this deficiency you must revise your estimate to one that is 2 orders of magnitude higher, i.e. [redacted] As per the ISO 11137-2 guideline, for a sterility assurance level of [redacted] this will require that the gamma irradiation dose be increased to [redacted] kGy.

4. Insufficient information was provided for pyrogen testing. To address this deficiency you must provide the most valid dilution and the routine dilution that will be used for APF530 endotoxin testing.

DEVICE CONSTITUENT PARTS

5. DMF [redacted] has been found deficient. The deficiencies have been communicated to the DMF holder.

6. The NDA lacks adequate information to assess the safety of the [redacted] Connector, Luer Lock-to-Luer Lock device to establish its safety and effectiveness as part of this combination product. To address this deficiency, you need to provide the following information:

a. A description of the materials and methods used for packaging the product to maintain the device sterility during shipping and delivery.

b. The sterilization test protocols, pass/fail criteria, and test results for this device.

c. Documentation that FDA recognized standards are utilized for the sterilization test protocols for this device.

d. The test protocol, the pass/fail criteria, and the test results to support that claim that the device is “non pyrogenic.”

7. The NDA lacks adequate information to assess the safety and effectiveness of the combined use of all device constituent parts.

   a. We are unable to locate the bench test results for the entire device system, which includes the [redacted] 1 mL Syringe Luer-Lock Tip Plastic syringe, the [redacted] Connector, Luer Lock-to-Luer Lock, and the [redacted] Needle. To address this deficiency, provide the bench testing protocols, pass/fail criteria and test results to demonstrate that all of the system devices meet the design requirements for the entire system. Test protocols should address product stiffness, resistance to breakage, resistance to corrosion, leak, injection force, and dose delivery accuracy.

   b. We are unable to locate the biocompatibility test for the [redacted] 1.25 mL [redacted] syringe and [redacted] Connector, Luer Lock-to-Luer Lock. To address this deficiency, provide the biocompatibility test protocols, pass/fail criteria, and the test results for [redacted] 1.25 mL [redacted] syringe and [redacted] Connector, Luer Lock-to-Luer Lock. We recommend the biocompatibility test follow the FDA recognized standard ISO 10993, or equivalent.

DRUG PRODUCT QUALITY

Drug Substance

8. DMF [redacted] has been found deficient. The deficiencies have been communicated to the DMF holder.

AP135: Novel Polymeric Excipient

9. The proposed [redacted] in the polymer structure has not been adequately demonstrated. To address this deficiency, you should provide a summary of critical experiments that lead to the proposed structure.

10. The specifications for the starting materials [redacted] lack impurity testing. Of particular concern is the absence of testing for [redacted]. To address this deficiency, you should update the corresponding specifications with impurity testing, especially with testing for [redacted].

11. The proposed specification for AP135 lacks limits for PDI or M_n, for low molecular weight impurities (monomers, dimers, and trimers should be quantitated separately), and for unreacted monomers (as requested in the end of phase 2 meeting). To address this deficiency, you should provide specifications for these impurities and unreacted monomers. These limits should be based on batches used in clinical trials.

12. The stability studies of AP135 lack monitoring for the M_n (PDI) and degradation impurities. To address this deficiency, you should revise the stability protocol to monitor any changes in M_n (or PDI) in addition to M_w, and degradation impurities.

13. The AP135 batches manufactured at [redacted] (b) (4) are significantly different in terms of M_n and PDI, as shown in the report DR-919-079. The effect of these differences on the systemic availability of the drug substance has not been established. To address this deficiency, you should demonstrate that the bioavailability of the products manufactured at these two sites is equivalent.

14. The proposed In-Vitro Release (IVR) methodology has not been validated for discriminating drug products using the polymer (AP135) with different M_w, M_n and PDI. To address this deficiency, you should provide validation that demonstrates that the method can discriminate among products with different M_w, M_n or PDI.

15. Gel Permeation Chromatography (GPC) method P-394, which is used to determine the amount of [redacted] (b) (4), has not been validated. To address this deficiency, you should provide validation data and revise the specification for [redacted] (b) (4) with acceptance criteria for [redacted] (b) (4)

Drug Product

16. We are requiring an alternative container/closure to the [redacted] (b) (4) 1.25 mL [redacted] (b) (4) syringe that allows for direct product administration. Terminal sterilization should be described for the alternate container/closure system. For the alternate system, you must provide the following CMC information:

    a. Full description of the revised manufacturing process and process controls, including the terminal gamma irradiation procedures.

    b. A revised master batch record.

    c. Information on the new container/closure system.

    d. Stability data on three batches of drug product that were manufactured at the commercial manufacturing sites, using the revised manufacturing process and packaged in the new container/closure system.

17. The NDA lacks quantitative data for individual polymer-related impurities (including monomers, dimers, and other degradation products) in batches that were used in pre-clinical, clinical and stability studies. To address this deficiency, these data from the pre-clinical, clinical, and stability studies must be submitted for review.

18. The NDA lacks sufficient acceptance criteria for the drug product specification, including the following:

    a. Limits for PDI or M_n with an acceptance range based on clinical batches.

b. All polymer-related impurities, including monomers and degradation products with acceptance criteria based on batches used in clinical trials.

c. Fill weight.

To address these deficiencies, acceptance criteria must be developed and submitted for review.

19. Your IVR specification proposing the following time points: [redacted] hours is not adequate. [redacted] To address this deficiency, you should revise the dissolution specification with the suggested time points. You are advised to take into consideration the Agency's IVIVC guidance recommendation to select the specification range at any given time point.

20. The NDA lacks stability data for the drug product manufactured with drug substance from [redacted]. These data should be submitted for review.

Labeling

21. Your proposed established name for the drug product, [redacted] is not acceptable. The established name for the drug substance and dosage form should be "(granisetron) injection, extended release."

CLINICAL/CLINICAL PHARMACOLOGY

22. Your justification for your request to waive the thorough QT study is not acceptable because APF530 has demonstrated a higher pattern of granisetron exposure than other granisetron formulations.

23. You have not adequately identified, characterized and quantified the specific breakdown products of [redacted] in humans and have not adequately addressed the safety implications in humans. To address this deficiency you should identify, characterize, and quantify specific breakdown products of [redacted] in the plasma, urine, and injection site in humans and the time course of their elimination using validated assay methods (non-radiometric). We recommend that you submit the protocol, including the validated assay methods, for the above study for review and evaluation prior to initiating the study.

CLINICAL/STATISTICAL

24. Your single clinical trial did not provide substantial evidence of efficacy of Sustol for your proposed indications for the following reasons:

    a. The Per Protocol analysis is important for evaluating and establishing non-inferiority. We cannot accurately characterize your Per Protocol analysis population because we have identified discrepancies in how you applied the protocol violation definitions. The protocol violation definitions are key for determining whether a patient should be included in the Per Protocol population. To address this deficiency, you will need to submit an electronic listing of all patients in the study identified by their Per Protocol or Intent-to-Treat status and provide justification for patient assignment to their respective groups. Per Protocol violations should be clearly explained.

    b. We cannot accurately characterize your Intent–to-Treat (ITT) and Per Protocol analysis populations because there is insufficient information to determine whether the exclusion of all of the data from Site 504 was valid. To address this deficiency, you will need to provide clear justification as to why the Site 504 patients should be excluded from the Per Protocol analysis.

    After correcting these analysis populations, including corrections defined in part a. and b. above, resubmit your primary efficacy analyses for the following populations: the full ITT population (all subjects randomized); the modified ITT population (all subjects randomized with at least one diary entry) and the Per-Protocol population. Your ITT and mITT analyses should assign treatment failure to patients with missing data (i.e. no imputation). Subjects from Site 504 should be included in the appropriate analysis populations. This resubmission of your primary analysis should also include the corrected analysis data sets, supporting data definition files, and SAS programs.

    c. Your submission lacks clear justification for your non-inferiority margin of 15%. Ideally, non-inferiority margin selection is based on historical studies with similar design demonstrating the effect size of your current active control. For further discussion of margin selection criteria, we refer you to the following draft guidance: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM202140.pdf. To address this deficiency, you will need to submit an evidence based justification for your selection of a 15% non-inferiority margin.

25. You have not provided sufficient information to describe the safety of Sustol because your administration site reaction data, as presented in the NDA, are inadequate to assess duration of these reactions and time to resolution of these reactions. You should provide the following additional information, by subject ID line listing, for administration site reactions: trial number, study drug and dose, emetogenic strata, type of administration site reaction (i.e. bruising, nodule, etc.), the date of onset of the adverse reaction, the date the adverse reaction resolved, the cycle when the adverse reaction occurred, information on whether the adverse reaction persisted into the subsequent cycle or cycles, and the time elapsed between injection and onset of the adverse reaction.

PATENT CERTIFICATION

In addition, we note that this application is not eligible for approval because the 45-day period described in section 505(c)(3)(C) of the Federal Food, Drug, and Cosmetic Act (the Act) has not yet expired. This prohibition reflects AP Pharma's failure to comply with the statutory requirements for the timing of sending notice of paragraph IV certification as set forth in section 505(b)(3)(B) of the Act.

LABELING

We reserve comment on the proposed labeling until the application is otherwise adequate. If you revise labeling, your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm.

SAFETY UPDATE

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

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

    - Present new safety data from the studies/clinical trials for the proposed indication using the same format as the original NDA submission.
    - Present tabulations of the new safety data combined with the original NDA data.
    - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
    - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

6. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).

7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

8. Provide English translations of current approved foreign labeling not previously submitted.

OTHER

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

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

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

If you have any questions call Todd Phillips, Regulatory Project Manager, at (301) 796-4857.

Sincerely,

{See appended electronic signature page}

Donna Griebel, M.D.
Director
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22445	ORIG-1	A. P. PHARMA, INC.	APF530

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

/s/

DONNA J GRIEBEL
03/16/2010