

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

022445Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22445

MEETING MINUTES

AP Pharma Inc.
Attention: Michael A. Adam, Ph.D.
123 Saginaw Dr.
Redwood City, CA 94063

Dear Dr. Adam:

Please refer to your New Drug Application (NDA), submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for granisetron extended release Injection.

We also refer to the telecon between representatives of your firm and the FDA on December 5, 2013. The purpose of the meeting was to address CMC issues on the consolidation of the manufacture supply chain sites, product presentation, and revised *in vitro* release method.

A copy of the official minutes of the telecon 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) 796-1765.

Sincerely,

{See appended electronic signature page}

Rebecca McKnight
Regulatory Health Project Manager
Division of New Drug Quality Assessment III
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type C
Meeting Category: Chemistry - Other
Meeting Date and Time: December 5, 2013, 11am – 12pm
Meeting Location: T-con
Application Number: 22445
Product Name: granisetron extended release Injection
Sponsor/Applicant Name: AP Pharma
Meeting Chair: Marie Kowblansky, Ph.D
Meeting Recorder: Rebecca McKnight

FDA ATTENDEES

Marie Kowblansky, Ph.D., CMC Lead, ONDQA
Tapash Ghosh, Ph.D., Biopharmaceutics Team Lead, ONDQA
Zhengfang Ge, Ph.D., CMC Reviewer, ONDQA
John Duan, Ph.D., Biopharmaceutics Reviewer, ONDQA
Rebecca McKnight, Project Manager, ONDQA

SPONSOR ATTENDEES

Michael Adam, Ph.D., A.P. Pharma, Regulatory Affairs
(b) (4) Device Engineer Consultant
Laura Lerner, Ph.D., A.P. Pharma, Pharmaceutical Development
Paul Marshall, A.P. Pharma, Manufacturing
Thomas Ottoboni, Ph.D., A.P. Pharma, Pharmaceutical Development
(b) (4), Device Regulatory
Barry Quart, Pharm. D., A.P. Pharma, Chief Executive Officer
Trisha Shimada, A.P. Pharma, Project Manager

1.0 BACKGROUND

AP135

A. Considering the scale up of AP135 and feedback provided in SN0036, A.P. Pharma intends to provide lot release data for 3 batches of (b) (4) AP135 manufactured at the (b) (4) site and for 1 batch of APF530 drug product containing AP135 manufactured at (b) (4). For these batches, we will provide 3 months of long term and accelerated stability data (at least 3 time points including the initial time point).

FDA Response:

Your proposal to submit release and stability data for three batches of AP135 manufactured at the (b) (4) site and for one batch of product containing AP135 manufactured at (b) (4) is acceptable. However, since you will be also be manufacturing your bulk at a new site (Lifecore), you will need to submit a bioequivalence study for product manufactured at Lifecore using AP135 from the (b) (4) site. Please see our response for question APF530.

Please note that the above proposal for stability studies is not in agreement with the stability program described in Table 3 (page 7) of your briefing package, where you indicate that you will only be providing three months of long term stability data for one batch of AP135 manufactured at (b) (4). The stability program proposed in Table 3 is insufficient to support the proposed manufacturing site change.

A.P. Pharma Response:

For the addition of the (b) (4) site, we propose to follow the criteria previously discussed in EOR Meeting Background Document NDA submission 0029 and Meeting Minutes dated 03/28/2011, and NDA Information Request letter dated 11/14/2012, that is as follows.

- AP135 manufactured at (b) (4) uses the same process for manufacture of AP135 as at (b) (4) at (b) (4) scale.
- AP135 (b) (4) Batch release data on 3 validation batches compared to the batch release data on the 3 (b) (4) validation batches at (b) (4)
- Proton and carbon-13 NMR data comparison and analysis of the 3 validation lots made at (b) (4) and comparison/equivalence to (b) (4) lots.
- GPC comparison of the (b) (4) validation lots to (b) (4) validation lots vs. specifications (note the specifications are based on the Phase 3 clinical and registration lots).
- Hydrolysis/HPLC analysis of the AP135 (b) (4) validation lots and the (b) (4) lots.
- AP135 (b) (4) 3 validation batches ICH stability with t=0,1,3 months data at submission.
- One AP135 (b) (4) validation batch converted to APF530 (at the (b) (4) scale) ; Batch release data comparing product made using AP135 made at (b) (4) to product made using AP135 made at (b) (4) and comparison to Phase 3 clinical material, specifically IVR, GPC, and NMR characterization.

- APF530, one batch (b) (4) scale), made from (b) (4) AP135 ICH stability with t=0,1,3 months data at submission.

Meeting Discussion:

Regarding the qualification of the (b) (4) site, FDA agreed that AP should follow the guidance previously given by FDA; qualification will only require the submission of CMC data. Bioequivalence studies for polymer from (b) (4) and (b) (4) will not be required. However, IVR profile comparisons will be needed. AP Pharma will not need to manufacture the Lifecore batch with polymer from (b) (4)

APF530

A. Considering the modifications to the manufacturing/supply chain, qualification of second prefilled syringe vendor and location of QC testing, is 1 month of stability at the time of resubmission, with 3 months of stability provided as an update on the three (b) (4) APF530 Registration lots at the time of resubmission acceptable?

FDA Response:

Yes, one month of stability data at the time of resubmission will be acceptable, provided the updated data are received no later than 60 days after resubmission. Please note that these stability studies should be conducted on batches that have been subjected to all your proposed manufacturing site changes (i.e., all new manufacturing sites for the drug product, including new sterilization sites).

Also, since the proposed site change is classified as Level 3 per SUPAC MR guidance, a bioequivalence study between the products manufactured at the newly proposed site and the clinical manufacturing site will be needed.

A.P. Pharma Response:

For the addition of the BDP manufacture at Lifecore, we propose to manufacture 3 registration batches and characterize them by proton and carbon-13 NMR, GPC and IVR comparing the data to the Phase 3 clinical lots and previous registration batches to show equivalent product is produced. This will also include stability study assessment.

Meeting Discussion:

The qualification of BDP manufacture at Lifecore will need to incorporate a bioequivalence assessment between material manufactured at Lifecore and at (b) (4). Approaches other than bioequivalence may be proposed for review. The question of what the source of the reference batch should be was discussed. Since the original clinical batches are not available, the current stability registration batches manufactured at (b) (4) should be appropriate for this purpose. AP Pharma will submit a proposal identifying the (b) (4) material that will be used. The reference lot for the clinical manufacturing site may be a registration lot made at (b) (4) or another representative lot manufactured at (b) (4)

CONTAINER /CLOSURE SYSTEM

Container Closure System

- A. Does the Agency have any comments on the plan for incorporating the (b) (4) glass syringe and (b) (4) tip cap as suppliers?

FDA Response:

Your proposed plan to qualify a second vendor for the syringe and tip cap by submitting leachables data and 3 months of stability data at the time of resubmission for one batch of product packaged in the new syringe with new cap (and to continue the stability study for two years) is acceptable.

A.P. Pharma Response:

To clarify, A.P. Pharma was planning on submitting with compatibility data on the (b) (4) syringe and tip cap and leachables development data with the commitment to monitor the leachables on one of the registration stability batches. Is this acceptable?

Meeting Discussion:

The general approach described in the briefing package for assessing the container closure is acceptable.

- B. Does the Agency concur with the proposed primary container closure leachables study on one Registration lot?

FDA Response:

Your proposal to study leachables on one registration batch is acceptable.

Sustol Syringe Warmer

- A. Does the Agency agree with the warmer precedent use, and that the warmer and pre-filled syringe is a combination product with mutually conforming labeling?
- B. Does the Agency agree with the proposed product configuration, using the syringe warmer before administration, for reducing the force necessary to deliver the formulation?
- C. Does the Agency agree or have comments on the development plan, Validation & Verification and Use Testing for the new product presentation?

FDA Response:

These issues were addressed at the Type B meeting held on Oct 30, 2013.

PRODUCT QUALITY

- A. Does the Agency agree that the (b) (4) IVR method adequately controls variability and will be acceptable to set drug product acceptance criteria?

FDA Response:

Based on the limited information provided, the (b) (4) IVR method seems reasonable if properly justified and validated. However, the final determination of the adequacy will be made when the complete data are submitted.

- B. Does the Agency agree that a (b) (4) IVR profile is acceptable?

FDA Response:

In general, a (b) (4) IVR is acceptable. However, the last time point should be selected at the point where the mean of the tested units just passes 80%. You should select the last time point according to this principle. Based on the limited information provided (Figure 16), the (b) (4)-hour time point seems more appropriate.

- C. Does the Agency agree with the proposed cross-over plan?

FDA Response:

We agree that sufficient lots and stability time points should be tested by both the old and the new methods. Your plan seems adequate.

Additional Meeting Discussion:

Since additional clinical studies will be submitted to the IND, FDA agrees that it will be acceptable to reference pertinent CMC information that has already been submitted to the NDA.

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/s/

MARIE KOWBLANSKY
12/23/2013



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22445

MEETING MINUTES

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

Dear Dr. Adam:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Sustol (b) (4) granisetron) Injection, extended-release.

We also refer to the meeting between representatives of your firm and the FDA on October 30, 2013. The purpose of the meeting was to discuss your plans to address the Container/Closure System and Clinical issues indicated in the Complete Response Letter dated March, 27, 2013.

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) 796-0260.

Sincerely,

{See appended electronic signature page}

Mary Chung, Pharm.D.
Regulatory Project Manager
Division of Gastroenterology and Inborn Errors
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: End of Review

Meeting Date and Time: October 30, 2013; 9:00 AM to 10:00 AM
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1315
Silver Spring, Maryland 20903

Application Number: NDA 22445
Product Name: Sustol (granisetron extended release) injection
Indication:

- Prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy
- Prevention of acute nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy

Sponsor/Applicant Name: A.P. Pharma

Meeting Chair: Ruyi He, M.D.
Meeting Recorder: Mary Chung, Pharm.D.

FDA ATTENDEES

Division of Gastroenterology and Inborn Errors Products

Donna Griebel, M.D.	Director
Joyce Korvick, M.D.	Deputy Director for Safety
Ruyi He, M.D.	Medical Team Lead
Sushanta Chakder, Ph.D.	Pharmacology Team Lead
Brian Strongin, R.Ph., M.B.A.	Chief, Project Management Staff
Mary Chung, Pharm.D.	Regulatory Project Manager

Office of Clinical Pharmacology

Sandhya Apparaju, Ph.D.	Clinical Pharmacology Reviewer
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Office of New Drug Quality Assessment/ Division of New Drug Quality Assessment II

Zhengfang Ge, Ph.D.	Chemistry Reviewer
Tapash Ghosh, Ph.D.	Biopharmaceutics Team Lead

Division of Biometrics III

Freda Cooner, Ph.D. Statistical Reviewer

Office of Surveillance and Epidemiology/ Division of Medication Error Prevention Analysis

Lubna Merchant, Pharm.D. Team Lead
Lisa Khosla, Pharm.D. Reviewer
Monica Calderon Reviewer

CDRH/ODE/DAGID/General Hospital Devices Branch

Jacqueline Ryan, M.D. Combination Products Team Lead

CDRH/OSMP/Office of Combination Products

Bindi Nikhar Senior Clinical Advisor (Acting)
Patricia Love Medical Reviewer

SPONSOR ATTENDEES

Barry D. Quart, Pharm. D.	Chief Executive Officer
Michael Adam, Ph.D.	Regulatory Affairs
Mark Stephen Gelder, M.D.	Chief Medical Officer
(b) (4)	Biostatistician, (b) (4)
Thomas Bert Ottoboni	Ph.D., Pharmaceutical Development
Trisha Ann Shimada	Project Management
(b) (4)	Consultant, Regulatory Affairs
(b) (4)	Consultant Device Engineering

1.0 BACKGROUND

A.P. Pharma requested a Type B, End of Review meeting to discuss their path forward for addressing their Complete Response (CR) to NDA 22445 Sustol (granisetron extended release injection) dated March 27, 2013. The application was issued a CR letter for deficiencies relating to facility inspections, container/closure system, clinical and CMC concerns. During this Type B meeting the applicant will discuss their plans for addressing the container/closure system and clinical deficiencies. The facilities inspections and CMC concerns will be discussed in a separate Type C CMC meeting.

The proposed product Sustol (granisetron extended release injection), is a new dosage form of granisetron, a 5HT3 inhibitor antiemetic that has been marketed in intravenous and oral formulations, and as a transdermal patch. Sustol is a new polymeric formulation of granisetron intended for subcutaneous injection. Its proposed indications are prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy, and prevention of acute nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy.

2.0 DISCUSSION

2.1 CONTAINER /CLOSURE SYSTEM

Question 1

Does the Agency agree with the warmer precedent use, and that the warmer and pre-filled syringe is a combination product with mutually conforming labeling?

FDA Response to Question 1

Based on available information, we agree that the warmer and prefilled syringe appear to be a combination product. Further, the warmer is proposed as part of product to ensure safety and effectiveness of the combination. The appropriate labeling will be determined during the review. Based on the October 8, 2013 meeting page 9 the warmer will be provided as a device constituent part of the combination and particularly as part of the co-package. It is not a standalone class-1 exempt device. Instead it would be reviewed under the NDA. See additional agency response to Questions 3 and 9.

Question 2

Does the Agency agree with the proposed product configuration, using the syringe warmer before administration, for reducing the force necessary to deliver the formulation?

FDA Response to Question 2

It appears from your normative data that the 95 percentile for three point grip among women is 65 N and the lowest peak and average grip forces expected would be 58N and 42N respectively. Heating the syringe to 37°C prior to injection appears to reduce expulsion forces below 20N which is acceptable. However, your usability study will be critical in determining if the combination product with the syringe warmer results in safe drug administration.

Question 3

Does the Agency agree or have comments on the development plan, Validation & Verification and Use Testing for the new product presentation?

FDA Response to Question 3

Validation plan and Verification test plan

Demonstration of the safety and effectiveness of the combination product in part depends upon the acceptability of the performance testing to assure that the syringe warmer meets the design specifications indicated in Tables 7 and 8. These data should be submitted to the NDA. Also see response to Question 9.

Use Testing for new product presentation

1. You did not submit a revised validation protocol to reflect the new product design configuration which includes the syringe warmer pouch. The validation protocol should be revised to assess critical steps and user tasks associated with use of the warmer pouch and understanding of the instructions related to use of the warmer pouch (i.e. bring kit to room temperature, flex metal disc to activate warmer pouch, etc.). In addition, the protocol should also include user-related risk analysis describing the potential negative consequences of use errors and task failures related to use of the warmer pouch. Please submit your revised protocol for evaluation.
2. In addition, we have the following recommendations to the IFU that could help clarify the instructions for using the warmer pouch:
 - Add images to the Steps 1 and 2 of the new section “Before you inject Sustol” to help users follow instructions.
 - Under “Before you inject Sustol” section, clarify the estimated amount of time needed to ensure that Sustol and the warming pouch are at room temperature before activating the warming pouch.
 - Ensure that recommendations regarding the IFU in the General Advice letter dated March 26, 2013 are incorporated in the final IFU that will be used in the Human Factors Usability study.

Discussion

A.P. Pharma will submit a revised HF validation protocol and associated IFU, incorporating the comments by the Agency, within a month. The protocol will include tracked changes denoting modifications for easy identification and will address the critical task associated with the use of the warmer. A.P. Pharma requests expedited review to aid in initiating the study in a timely fashion. FDA stated they will make their best efforts to review the protocol expeditiously, however, will have to balance with competing priorities.

Question 4

Does the Agency have any comments on the plan for incorporating the use of a syringe warmer into the Human Factors validation study?

FDA Response to Question 4

Please refer to response to Question 3.

2.2. CLINICAL

Question 5

Does the Agency agree with the Phase 3 C2006 data MEC and HEC reclassification by the modified ASCO2011 definitions?

FDA Response to Question 5

Your reclassification description according to ASCO 2011 definitions for MEC and HEC appears to be acceptable.

Question 6

Does the Agency agree with the Phase 3 C2006 data MEC and HEC dataset package for both the Hesketh algorithm emetogenic classification and the ASCO 2011 emetogenic classification?

FDA Response to Question 6

It seems acceptable at this time. However, its adequacy will be a review issue.

Question 7

Based on the Phase 3 reclassification by the ASCO 2011 definitions, does the FDA agree with the proposed label indication?

FDA Response to Question 7

The final label indication will be determined after analyses of the efficacy data.

Discussion

(b) (4)

(b) (4)

(b) (4)

Question 8

Does the Agency agree with the drug combination in the control arm and the doses proposed in the Phase 3 Clinical Study Protocol?

FDA Response to Question 8

Your proposed drug combination in the control arm and the doses proposed in the Phase 3 protocol appear acceptable.

Question 9

Does the Agency agree that this Phase 3 Clinical Study supports demonstration of superiority/activity of APF530 for the prevention of CINV in the delayed phase for patients receiving HEC?

FDA Response to Question 9

You will have to demonstrate statistical significance and clinically meaningful benefit. A determination will be made after evaluation of your trial data that includes both efficacy and safety. The protocol design appears adequate; however, we request that you incorporate the to-be-marketed final finished combination product into this clinical trial. This will necessitate that you complete the human factor validation study prior to initiation of the phase 3 clinical trial.

In addition, to address safety issues mentioned in the CR letter with repeat dosing, we recommend that your protocol plan for continuing treatment with repeat cycles focusing on safety data i.e., laboratory, injection site reaction, and refusal to receive repeat dosing.

Discussion

Sponsor stated they will take FDA's suggestion under consideration for incorporating repeat cycles in the proposed study but stated this change may be prohibitive in terms of cost and

duration of the study. FDA stated their request for repeat cycles is primarily a safety concern. Additionally FDA stated they recommend at least 4 cycles and stated a control arm in the repeat cycle phase is helpful to distinguish between treatment and underlying conditions.

Sponsor stated they plan on using a syringe and warmer that is made by the commercial process and representative of the commercial product with the IFU, evaluated and demonstrated to be successful in an HF formative study; however, packaged in the clinical trial configuration. FDA stated this would be acceptable. FDA stated that it generally recommends completion of the validation prior to the clinical study in case there are changes to the product configuration or container closure system. If there are any changes to these aspects post validation study, then the sponsor agrees to repeat the validation study with modifications and provide the rationale of how these changes do not affect the results of the clinical efficacy trial.

Question 10

Does the Agency have any comments or considerations on the proposed Phase 3 Clinical Study Protocol?

FDA Response to Question 10

We recommend using the key stratification factor of cisplatin-based regimens only for the randomization, and a Cochran-Mantel-Haenszel (CMH) test stratified by that variable as the primary analysis for the primary and secondary efficacy endpoints. Your proposed Fisher's exact test can be a supportive analysis. You should also specify sensitivity analyses in your protocol to investigate the impact of missing data on the study results.

2.3 SAFETY UPDATE

Question 11

Does the Agency require any additional safety analysis or update prior to resubmission?

FDA Response to Question 11

Please refer to the safety update requirements list in the CR letter dated March 27, 2013.

Discussion

Sponsor stated they will have no additional clinical or nonclinical safety data at the time of resubmission, and do not plan to provide a safety update or revised ISS. FDA stated that all requirements including the safety update section of the CR letter should be addressed in the resubmission. In addition, interim safety data for the ongoing clinical trial should be submitted with a 120 day safety update.

2.4 METABOLIC FATE

Question 12

Does the Agency agree with the proposed metabolic FATE analysis plan?

FDA Response to Question 12

If you've identified improved assay methodologies, it is reasonable to conduct re-analyses of samples from study C2011-02 provided adequate stability of the stored samples, but we will not require you to do so. The primary issue in the additional clinical comment # 1 in the CR letter pertains to the lack of safety information beyond the first cycle in the clinical trials. This may still need to be addressed via clinical data. Please refer to response to Question 9.

A near complete recovery of polymer dose and the time course of such recovery would certainly be informative in understanding accumulation potential following multiple weekly injections of Sustol. However, it is possible that the incomplete recovery in study c2011-02 could have been due to inadequate sampling duration (10 days). In addition, your exploratory analyses suggested propionic acid to be a significant breakdown product (theoretical quantitative estimate similar to TEG and PE). However this metabolite wasn't identified in your clinical study due to lack of analytical sensitivity. Your plan for assay improvements and re-analyses do not seem to address propionic acid assay. Therefore, re-analysis may not still account for total recovery.

Discussion

Sponsor stated the preliminary results from the reanalysis of the C20011-02 samples indicate the samples were stable and recovery of the polymer components was substantially improved. Sponsor stated they will continue to work on improved understanding of metabolic pathways.

Sponsor requested FDA confirm that the potential need for additional clinical safety data with repeat cycles is still considered a potential post-approval commitment. FDA confirmed this.

2.5 CARCINOGENICITY (Nonclinical)

Question 13

Does the Agency have any comments on our proposed timeline for executing the rat carcinogenicity and SHE cell assay?

FDA Response to Question 13

Your proposed timeline for the rat carcinogenicity study and SHE cell assay appears to be acceptable.

BIOPHARMACEUTICS ADDITIONAL COMMENTS

We understand that the IVR method will be discussed in a separate meeting. The following comments are to help prepare for the meeting based on the brief description you currently provided.

- 1. Explain how the new IVR method addresses the variability problem compared to the old method. Submit detailed description and supportive data.**
- 2. Provide variability ranges for the new method compared to the old method.**
- 3. Provide data to support the time point selections for the acceptance criteria of the new method. Based on the data shown in Figure 15, selection of a time earlier than (b) (4) hours as the last time point may be more appropriate.**

DEVICE CONSTITUENT PART ADDITIONAL COMMENTS

For the new glass syringes and design changes, we recommend that you consider the principles in the agency draft guidance “Glass Syringes for Delivering Drug and Biological Products: Technical Information to Supplement International Organization for Standardization (ISO) Standard 11040-4,” accessible at <http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM346181.pdf>

You will need to submit your design verification data for the (b) (4) glass syringe as well as a letter of authorization to review the drug master file for the syringe to the NDA.

MANUFACTURING PROCESS ADDITIONAL COMMENTS

We remind you that any changes to your combination product remain subject to 21 CFR Part 4 - Current Good Manufacturing Practice Requirements for Combination Products accessible at: <https://www.federalregister.gov/articles/2013/01/22/2013-01068/current-good-manufacturing-practice-requirements-for-combination-products>.

3.0 ATTACHMENTS AND HANDOUTS

There were no attachments or handouts for the meeting minutes.

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

/s/

MARY H CHUNG
11/27/2013



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22445

MEETING PRELIMINARY COMMENTS

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

Dear Dr. Adam:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Sustol (b)(4) granisetron) Injection, extended-release.

We also refer to your August 9, 2013, correspondence requesting a meeting to discuss your plans to address the Container/Closure System and Clinical issues indicated in the Complete Response Letter dated March, 27, 2013.

Our preliminary responses to your meeting questions are enclosed.

You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

If you have any questions, call me at (301) 796-0260.

Sincerely,

{See appended electronic signature page}

Mary Chung, Pharm.D.
Regulatory Project Manager
Division of Gastroenterology and Inborn Errors
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURE:
Preliminary Meeting Comments



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

PRELIMINARY MEETING COMMENTS

Meeting Type: Type B
Meeting Category: End of Review

Meeting Date and Time: October 30, 2013; 9:00 AM to 10:00 AM
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1315
Silver Spring, Maryland 20903 .

Application Number: NDA 22445
Product Name: Sustol (granisetron extended release I.V.)
Indication:

- Prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy
- Prevention of acute nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy

Sponsor/Applicant Name: A.P. Pharma

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for October 30, 2013; 9:00 AM to 10:00 AM, 10903 New Hampshire Avenue White Oak Building 22, Conference Room: 1315 Silver Spring, Maryland 20903 between A.P. Pharma and the Division of Gastroenterology and Inborn Errors 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.

1.0 BACKGROUND

A.P. Pharma requested a Type B, End of Review meeting to discuss their path forward for addressing their Complete Response (CR) to NDA 22445 Sustol (granisetron extended release I.V.) dated March 27, 2013. The application was issued a CR letter for deficiencies relating to facility inspections, container/closure system, clinical and CMC concerns. During this Type B meeting the applicant will discuss their plans for addressing the container/closure system and clinical deficiencies. The facilities inspections and CMC concerns will be discussed in a separate Type C CMC meeting.

The proposed product, Sustol (granisetron extended release I.V.), is a new dosage form of granisetron, a 5HT3 inhibitor antiemetic that has been marketed in intravenous and oral formulations, and as a transdermal patch. Sustol is a new polymeric formulation of granisetron intended for subcutaneous injection. Its proposed indications are prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy, and prevention of acute nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy.

2.0 DISCUSSION

2.1 CONTAINER /CLOSURE SYSTEM

Question 1

Does the Agency agree with the warmer precedent use, and that the warmer and pre-filled syringe is a combination product with mutually conforming labeling?

FDA Response to Question 1

Based on available information, we agree that the warmer and prefilled syringe appear to be a combination product. Further, the warmer is proposed as part of product to ensure safety and effectiveness of the combination. The appropriate labeling will be determined during the review. Based on the October 8, 2013 meeting page 9 the warmer will be provided as a device constituent part of the combination and particularly as part of the co-package. It is not a standalone class-1 exempt device. Instead it would be reviewed under the NDA. See additional agency response to Questions 3 and 9.

Question 2

Does the Agency agree with the proposed product configuration, using the syringe warmer before administration, for reducing the force necessary to deliver the formulation?

FDA Response to Question 2

It appears from your normative data that the 95 percentile for three point grip among women is 65 N and the lowest peak and average grip forces expected would be 58N and 42N respectively. Heating the syringe to 37°C prior to injection appears to reduce expulsion

forces below 20N which is acceptable. However, your usability study will be critical in determining if the combination product with the syringe warmer results in safe drug administration.

Question 3

Does the Agency agree or have comments on the development plan, Validation & Verification and Use Testing for the new product presentation?

FDA Response to Question 3

Validation plan and Verification test plan

Demonstration of the safety and effectiveness of the combination product in part depends upon the acceptability of the performance testing to assure that the syringe warmer meets the design specifications indicated in Tables 7 and 8. These data should be submitted to the NDA. Also see response to Question 9.

Use Testing for new product presentation

1. You did not submit a revised validation protocol to reflect the new product design configuration which includes the syringe warmer pouch. The validation protocol should be revised to assess critical steps and user tasks associated with use of the warmer pouch and understanding of the instructions related to use of the warmer pouch (i.e. bring kit to room temperature, flex metal disc to activate warmer pouch, etc.). In addition, the protocol should also include user-related risk analysis describing the potential negative consequences of use errors and task failures related to use of the warmer pouch. Please submit your revised protocol for evaluation.
2. In addition, we have the following recommendations to the IFU that could help clarify the instructions for using the warmer pouch:
 - Add images to the Steps 1 and 2 of the new section “Before you inject Sustol” to help users follow instructions.
 - Under “Before you inject Sustol” section, clarify the estimated amount of time needed to ensure that Sustol and the warming pouch are at room temperature before activating the warming pouch.
 - Ensure that recommendations regarding the IFU in the General Advice letter dated March 26, 2013 are incorporated in the final IFU that will be used in the Human Factors Usability study.

Question 4

Does the Agency have any comments on the plan for incorporating the use of a syringe warmer into the Human Factors validation study?

FDA Response to Question 4

Please refer to response to Question 3.

2.2. CLINICAL

Question 5

Does the Agency agree with the Phase 3 C2006 data MEC and HEC reclassification by the modified ASCO2011 definitions?

FDA Response to Question 5

Your reclassification description according to ASCO 2011 definitions for MEC and HEC appears to be acceptable.

Question 6

Does the Agency agree with the Phase 3 C2006 data MEC and HEC dataset package for both the Hesketh algorithm emetogenic classification and the ASCO 2011 emetogenic classification?

FDA Response to Question 6

It seems acceptable at this time. However, its adequacy will be a review issue.

Question 7

Based on the Phase 3 reclassification by the ASCO 2011 definitions, does the FDA agree with the proposed label indication?

FDA Response to Question 7

The final label indication will be determined after analyses of the efficacy data.

Question 8

Does the Agency agree with the drug combination in the control arm and the doses proposed in the Phase 3 Clinical Study Protocol?

FDA Response to Question 8

Your proposed drug combination in the control arm and the doses proposed in the Phase 3 protocol appear acceptable.

Question 9

Does the Agency agree that this Phase 3 Clinical Study supports demonstration of superiority/activity of APF530 for the prevention of CINV in the delayed phase for patients receiving HEC?

FDA Response to Question 9

You will have to demonstrate statistical significance and clinically meaningful benefit. A determination will be made after evaluation of your trial data that includes both efficacy and safety. The protocol design appears adequate; however, we request that you incorporate the to-be-marketed final finished combination product into this clinical trial. This will necessitate that you complete the human factor validation study prior to initiation of the phase 3 clinical trial.

In addition, to address safety issues mentioned in the CR letter with repeat dosing, we recommend that your protocol plan for continuing treatment with repeat cycles focusing on safety data i.e., laboratory, injection site reaction, and refusal to receive repeat dosing.

Question 10

Does the Agency have any comments or considerations on the proposed Phase 3 Clinical Study Protocol?

FDA Response to Question 10

We recommend using the key stratification factor of cisplatin-based regimens only for the randomization, and a Cochran-Mantel-Haenszel (CMH) test stratified by that variable as the primary analysis for the primary and secondary efficacy endpoints. Your proposed Fisher's exact test can be a supportive analysis. You should also specify sensitivity analyses in your protocol to investigate the impact of missing data on the study results.

2.3 SAFETY UPDATE

Question 11

Does the Agency require any additional safety analysis or update prior to resubmission?

FDA Response to Question 11

Please refer to the safety update requirements list in the CR letter dated March 27, 2013.

2.4 METABOLIC FATE

Question 12

Does the Agency agree with the proposed metabolic FATE analysis plan?

FDA Response to Question 12

If you've identified improved assay methodologies, it is reasonable to conduct re-analyses of samples from study C2011-02 provided adequate stability of the stored samples, but we will not require you to do so. The primary issue in the additional clinical comment # 1 in the CR letter pertains to the lack of safety information beyond the first cycle in the clinical trials. This may still need to be addressed via clinical data. Please refer to response to Question 9.

A near complete recovery of polymer dose and the time course of such recovery would certainly be informative in understanding accumulation potential following multiple weekly injections of Sustol. However, it is possible that the incomplete recovery in study c2011-02 could have been due to inadequate sampling duration (10 days). In addition, your exploratory analyses suggested propionic acid to be a significant breakdown product (theoretical quantitative estimate similar to TEG and PE). However this metabolite wasn't identified in your clinical study due to lack of analytical sensitivity. Your plan for assay improvements and re-analyses do not seem to address propionic acid assay. Therefore, re-analysis may not still account for total recovery.

2.5 CARCINOGENICITY (Nonclinical)

Question 13

Does the Agency have any comments on our proposed timeline for executing the rat carcinogenicity and SHE cell assay?

FDA Response to Question 13

Your proposed timeline for the rat carcinogenicity study and SHE cell assay appears to be acceptable.

BIOPHARMACEUTICS ADDITIONAL COMMENTS

We understand that the IVR method will be discussed in a separate meeting. The following comments are to help prepare for the meeting based on the brief description you currently provided.

1. Explain how the new IVR method addresses the variability problem compared to the old method. Submit detailed description and supportive data.
2. Provide variability ranges for the new method compared to the old method.

3. Provide data to support the time point selections for the acceptance criteria of the new method. Based on the data shown in Figure 15, selection of a time earlier than (b) (4) hours as the last time point may be more appropriate.

DEVICE CONSTITUENT PART ADDITIONAL COMMENTS

For the new glass syringes and design changes, we recommend that you consider the principles in the agency draft guidance “*Glass Syringes for Delivering Drug and Biological Products: Technical Information to Supplement International Organization for Standardization (ISO) Standard 11040-4*,” accessible at <http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM346181.pdf>

You will need to submit your design verification data for the (b) (4) glass syringe as well as a letter of authorization to review the drug master file for the syringe to the NDA.

MANUFACTURING PROCESS ADDITIONAL COMMENTS

We remind you that any changes to your combination product remain subject to 21 CFR Part 4 - Current Good Manufacturing Practice Requirements for Combination Products accessible at: <https://www.federalregister.gov/articles/2013/01/22/2013-01068/current-good-manufacturing-practice-requirements-for-combination-products>.

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

/s/

MARY H CHUNG
10/28/2013



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022445

MEETING MINUTES

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) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Sustol (granisetron) injection, extended-release, 10 mg.

We also refer to the meeting between representatives of your firm and the FDA on March 31, 2011. The purpose of the meeting was to discuss your plans for addressing the drug product quality, facility inspection, and container/closure system deficiencies outlined in our March 16, 2010 Complete Response letter.

A copy of the official minutes of the meeting 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) 796-0846.

Sincerely,

{See appended electronic signature page}

Jagjit Grewal, M.P.H.
Senior Regulatory Health Project Manager
Division of Gastroenterology and Inborn
Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure: Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type C
Meeting Category: End of Review Meeting

Meeting Date and Time: March 31, 2011; 11:30AM–12:30PM EST
Meeting Location: 10903 New Hampshire Avenue
White Oak Building #22, Conference Room #1309
Silver Spring, Maryland 20903

Application Number: NDA 022445
Product Name: Sustol (granisetron) injection, extended-release
Indication: 1) Moderately emetogenic cancer chemotherapy - prevention of acute and delayed nausea and vomiting associated with initial and repeat courses
2) Highly emetogenic cancer chemotherapy - prevention of acute nausea and vomiting associated with initial and repeat courses

Sponsor/Applicant Name: A.P. Pharma, Inc.

Meeting Chair: Marie Kowblansky, Ph.D.
Meeting Recorder: Jagjit Grewal, M.P.H.

FDA ATTENDEESDivision of Gastroenterology Products

Andrew E. Mulberg, M.D. Deputy Director
Ruyi He, M.D. Medical Team Leader
Karyn Berry, M.D. Medical Reviewer
Sushanta Chakder, Ph.D. Pharmacology Team Leader
Tamal Chakraborti, Ph.D. Pharmacology Reviewer
Jagjit Grewal, M.P.H. Senior Regulatory Health Project Manager

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Office of Compliance/ Division of Manufacturing and Product Quality

Francis Godwin

Compliance Officer

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Regulatory Affairs

John Barr, Ph.D.

Sr. VP, Research & Development

Devang Shah, Ph.D.

Polymer Chemist

Trisha Shimada

Project Manager

Stephen Minick

Process Development

John Whelan

Acting Chief Executive Officer

1.0 BACKGROUND

Reference is made to NDA 022445 Sustol (granisetron) Injection, dated May 14, 2009, and the FDA Complete Response letter, dated March 16, 2010. A.P. Pharma, Inc. submitted a type C End of Review meeting request, dated December 23, 2010, to discuss their plans for addressing the drug product quality, facility inspection, container/closure system, and labeling deficiencies outlined in the Complete Response letter. FDA granted A.P. Pharma's meeting request in the letter dated January 17, 2011. Paper desk copies of A.P. Pharma's background package were received on March 3, 2011. A.P. Pharma's electronic submission of the same background package was received on March 30, 2011. FDA preliminary comments were sent to the sponsor on March 28, 2011. On March 30, 2011, A.P. Pharma provided responses to the FDA preliminary comments for discussion at the meeting. It is noted that a separate type B, End of Review meeting was held on February 25, 2011 to discuss the device constituent parts, clinical, clinical pharmacology, statistical, and labeling deficiencies outlined in the Complete Response correspondence.

As described in the meeting background package, A.P. Pharma changed the container closure system for the drug product to a single syringe design consisting of a single, pre-filled, (b) (4) 1 mL (b) (4) glass syringe and an 18 gauge 5/8-inch thin wall needle. The product manufacturing process is revised to perform terminal sterilization using gamma irradiation (b) (4). The sponsor's proposed a gamma irradiation dose range of (b) (4). The sponsor conducted a feasibility study of the revised process demonstrating the sterility of the product, equivalence in performance, and stability. The product specifications and stability proposal were included in the background package for comment.

A.P. Pharma noted that the PAI issues at each manufacturing facility have either been addressed or are being addressed with the field offices.

The sponsor updated the structure elucidation/characterization of AP135 to include analysis by NMR spectroscopy and results of the hydrolytic degradation. The specifications for raw materials and the AP135 polymer were also updated. A.P. Pharma presented the analytical comparison of the AP135 manufacturers.

2.0 DISCUSSION

The format of these minutes provides for A.P. Pharma's questions in regular typeface, followed by the FDA's March 28, 2011 responses in **bolded** print. A.P. Pharma's March 30, 2011 replies to FDA's preliminary responses are presented in *italic* print. The March 31, 2011 meeting discussion is presented in *italic and bolded* print.

2.1 FACILITY INSPECTIONS

Question 1: What is the timing for resolution of the inspections? Is there any impact on the resubmission timeline?

FDA Response:

For the three sites identified in the complete response, each was found unacceptable during the review cycle. For further information, you should contact each site to determine if these deficiencies have been resolved. The sites can contact their local district office for more information regarding the current status of the deficiencies as it relates to the application. Note, resubmission of the application will lead to re-evaluation of the sites, which may include facility inspections.

2.2 DRUG PRODUCT PRESENTATION: CONTAINER/CLOSURE SYSTEM

Question 1: Does the FDA agree the proposed single syringe system addresses the FDA concerns with the previous two syringe system?

FDA Response:

We reviewed your usability data comparing a two-syringe kit to a single-syringe kit and concur with the results showing participants preferred the single-syringe kit. However, additional concerns with the single syringe system still need to be addressed (see response to Questions 2 and 3). Please see the FDA comments and meeting discussion regarding the (b) (4) syringe from the End of Review meeting held on February 25, 2011.

Since you plan to use a product overfill in the syringe, representing a range of (b) (4) mg of granisetron, you will need to provide data to demonstrate consistent delivery of 10 (b) (4) mg of granisetron with each injection.

Question 2: Does the FDA concur that markings on the syringe are not necessary?

FDA Response:

No, we believe that markings are necessary on the syringe. Data provided in the usability studies by the Applicant showed that a participant commented that there were no markings on the syringe and they could not verify that the correct amount of drug was present in the syringe to deliver the dose. A fill volume marking will also help users detect whether product tampering has occurred.

A.P. Pharma Response 3/30/11: Please clarify the fill line on the syringe is to ensure the minimum amount of product is available after the syringe needle is attached and the product is prepared for administration.

Meeting Discussion:

FDA clarified that the fill line is to ensure that there hasn't been any product loss or tampering with the product. The fill line should reflect the labeled amount of product in the syringe.

Question 3: Does the FDA agree the proposed single syringe system does not require additional device testing?

FDA Response:

Please see the FDA comments and meeting discussion regarding the (b) (4) syringe from the End of Review meeting held on February 25, 2011.

(b) (4)

(b) (4)

Based on the results of this study, and the deficiencies noted above, the Applicant should consider alternative product design improvements in addition to further human factors testing. We recommend you provide the proposed protocol for review and comment prior to initiation of these studies.

A.P. Pharma Response 3/30/11: A.P. Pharma plans to incorporate the comments on the formative human factors testing made by the FDA in our future human factors test. We will submit this protocol for FDA review and comment. Does the FDA have any comments on improvements to consider on the alternate product design?

Meeting Discussion:

A.P. Pharma will submit the protocol for future human factors study for review and comment by the Agency prior to implementation.

To clarify, labeling should not be relied upon to prevent identified failures.

Question 4: Does the FDA agree the packaging component materials for the primary container closure system for the old and new product presentation are equivalent?

FDA Response:

Yes, we agree that the materials used for the old and new primary container/closures are equivalent.

2.3 REVISION OF THE MANUFACTURING PROCESS TO USE TERMINAL STERILIZATION

Question 1: Does the FDA agree with the terminal sterilization dose of (b) (4) ?

FDA Response:

The proposed terminal sterilization dose range is acceptable from a microbiology quality perspective provided that, as stipulated in the meeting package, bioburden testing is conducted for every product lot prior to sterilization, and the average bioburden is determined to be within the (b) (4) .

2.4 CHARACTERIZATION OF NOVEL EXCIPIENT AP135

Question 1: Does the FDA agree that the additional analysis of AP135 adequately characterizes the repeating units?

FDA Response:

Yes, your combination of hydrolysis/HPLC and NMR experiments is sufficient to characterize AP135 and establish the ratio of repeat units in the polymer structure.

Question 2: Does the FDA agree with the revisions proposed for the [REDACTED] (b) (4)
[REDACTED] raw material specifications?

FDA Response:

Yes, your revised specifications for synthesis starting materials, which now include impurity testing, are acceptable.

Question 3: Does the FDA agree with the revisions proposed for the AP135 specifications?

FDA Response:

No, we do not agree.

(b) (4),
(b) (4)

This is data provided in the original NDA submission, showing a clear difference in product from the two facilities (the “General” procedure was used):

(b) (4)

Therefore please do not include the (b) (4) method in the specification.

The acceptance criteria for Mw, Mn, and PDI are unusually broad and need to be narrowed to reflect the values that represent materials used in clinical trials.

A.P. Pharma Response 3/30/11: A. P. Pharma will implement the general GPC method for testing AP135 and drop the (b) (4) method from the regulatory specifications. The general GPC test specification limits will be set based on the (b) (4) % prediction intervals around the 7 lots used in clinical trials.

Meeting Discussion:

FDA finds this acceptable but the specification based on the (b) (4) % prediction limit will need to be further evaluated. A specification based on the (b) (4) % prediction limit may be too liberal.

Question 4: Does the FDA have comments on the characterization and specifications for the LMW region?

FDA Response:

While your approach to limiting the low molecular weight impurities is interesting, as we emphasized in our Complete Response correspondence, we are particularly interested in testing for individual low molecular weight substances such as (b) (4) and suggest that you use standard techniques such as GC or HPLC for this purpose.

A.P. Pharma Response 3/30/11: A. P. Pharma will continue to limit the %LMW in the AP135 specifications. In addition, we will investigate testing for (b) (4) in AP135.

Meeting Discussion:

FDA finds the proposal to be acceptable. In investigating the (b) (4) the sponsor should evaluate any other low molecular weight impurities that may be present.

Question 5: Does the FDA agree with the demonstration of equivalence of AP135 made at both (b) (4) manufacturing sites?

FDA Response:

No, we do not agree. Please see our comments under item 3, above. We have the following additional questions regarding the data in the NDA and in the briefing package with respect to this issue:

- Data for a total of 84 batches, including 50 batches manufactured at (b) (4) and 34 batches at (b) (4), were submitted in the original NDA. However, only 50 batches, including 20 batches manufactured at (b) (4) and 30 batches manufactured at (b) (4) have been submitted as reintegrated data in the meeting package. Please explain why 34 batches of data were excluded in the current reanalyzed data set
- You will need to explain how the integration methods differ for the original and current data.
- Also explain why you only provided in-vitro drug release comparison profile data from selected 27 batches synthesized at (b) (4) and from 7 batches synthesized at (b) (4) instead of the total batches synthesized at each site.
- We remind you that you have not provided the information showing that the proposed In-Vitro Release (IVR) methodology can discriminate products using polymeric excipient (AF135) with different Mw, Mn and PDI. In the absence of such data a bioequivalence study will be needed unless there is a predictive and accepted in-vitro in-vivo correlation.

A.P. Pharma Response 3/30/11: In response to the comments made above. Regarding the 34 batches of AP135 excluded from the reanalysis data set, only batches that had both general and (b) (4) data from (b) (4) (b) (4) were included. This led to inclusion of only 20 batches from (b) (4) (b) (4). Engineering batches made at (b) (4) were also excluded from the reanalysis. This was also reflected in the reanalysis number.

Regarding the integration data, the revision of the method of analysis will be included in the resubmission.

Regarding the batches of AP135 reflected in the in vitro release comparison of APF530, the data presented is for the lots of AP135 converted to APF530. This was a subset of all of the lots of AP135 prepared.

Based on the response to question 3, A. P. Pharma will set the specifications for AP135 based on the data for the 7 lots used in Phase 2 and 3 clinical trials. Future lots of AP135 made at (b) (4) will meet these specifications. Does this negate the requirement for a bioequivalence study?

Meeting Discussion:

A.P. Pharma will compare the old and new integration procedures and will analyze all the original batches by both procedures pointing out which of these batches were used in phase 2 and 3 clinical trials. A.P. Pharma will analyze the lots that went into phase 3 and compare to those that were used in phase 2 and 3 for purposes of setting specifications.

In light of the commitment to match the commercial specifications to the specifications of the clinical lots for all future lots of AP135, a BE study is not necessary.

2.5 DRUG PRODUCT

Question 1: Does the FDA agree with the proposed revisions to the APF530 specifications?

FDA Response:

No, we do not agree. We have the following recommendations:

- You will need to include specific testing (such as GC or HPLC) to quantify the individual specified and unspecified degradation products that may be formed in the product. (Your determination of this in aggregate as LMW is not sufficient)

A.P. Pharma Response 3/30/11: A.P. Pharma will continue to determine the %LMW in APF530. In addition, we will investigate monitoring (b) (4) in APF530. Is this approach acceptable?

Meeting Discussion:

FDA finds the approach acceptable.

- We have the same comment regarding the addition of a (b) (4) method as we did for AP135.

A.P. Pharma Response 3/30/11: A. P. Pharma will change the specifications for APF530 to use only the general GPC method.

Meeting Discussion:

FDA finds the approach acceptable.

- Regarding the specifications for the in-vitro release of granisetron, we do not agree with the specification ranges proposed for the (b) (4) hours time points based on individual data.

A.P. Pharma Response 3/30/11: A. P. Pharma requests clarification on the FDA response. Is the concern on the range of the specifications proposed or on proposing the specification based on the individual data?

Meeting Discussion:

It was agreed that the IVR method is stability indicating. In general, show that the method is discriminating a product manufactured outside of the normal range (plus or minus (b) (4) % variation around the critical quality attributes and manufacturing variables). A.P. Pharma will evaluate such variations as part of the resubmission.

FDA clarified that the specification range should be set based on the mean data for each clinical lot.

The sponsor will explain the sampling replicate numbers for the IVR method. Also, FDA suggested that a (b) (4) hours specification time point be explored in lieu of (b) (4) hours specification sampling time points.

- Additionally, for your proposed IVR testing methodology, we have concerns with the (b) (4) approach being used to generate the in vitro drug release values for the specification-time points. Also, please note that the in vitro drug release values should be reported as the percentage of label claim, instead of reporting them as the percentage of drug normalized by the weight of the tested sample.

A.P. Pharma Response 3/30/11: A. P. Pharma asks for clarification on the concerns the FDA has with the (b) (4) approach.

Regarding reporting the in vitro release values, A. P. Pharma will change to reporting them as % label claim.

Meeting Discussion:

FDA clarified their preference that the samples be taken at the specific specification time points.

Question 2: Does the FDA agree the switch from (b) (4) to irradiation (b) (4) produces product of equivalent quality?

FDA Response:

From a microbiology quality perspective, the proposal to switch from (b) (4) to terminal sterilization increases the assurance of microbiology quality and adequately addresses deficiency 3a in the Complete Response letter.

Question 3: Does the FDA agree with resubmission with an update to the ongoing registration stability studies, the stability data on the terminal sterilization feasibility lots, plus batch analysis data on 3 registration batches made by the terminal sterilization process with the commitment to perform stability studies on these lots according to the current stability protocol (ICH) and submit the data to the NDA in the annual reports?

FDA Response:

We agree that you should submit updated data for the ongoing stability studies, but in the NDA resubmission, you will also need to submit at least 3 months of real time and accelerated stability data for drug product batches manufactured by the terminal sterilization process and packaged in the new container/closure at the commercial manufacturing facilities.

A.P. Pharma Response 3/30/11: A. P. Pharma requests a discussion of submitting the NDA resubmission with T=0 data on three drug product batches manufactured by the terminal sterilization process in the new container/closure at the manufacturing sites with submission of the 3 month accelerated and real time data during the NDA resubmission review.

Meeting Discussion:

Upon initial review, the sponsor's approach is acceptable. The sponsor should submit the data no later than 2.5 to 3 months after NDA resubmission. If the information is received more than 3 months after the NDA resubmission, it will not be reviewed.

2.6 LABELING

Question 1: Does the Agency have any comments on our proposed labels or nomenclature?

FDA Response:

Please see the FDA responses regarding labeling from the February 25, 2011 End of Review meeting. Additional label and labeling comments will be provided during the review cycle.

3.0 ISSUES REQUIRING FURTHER DISCUSSION

None

4.0 ACTION ITEMS

1. A.P. Pharma will submit their human factors study protocol for review and comment by the Agency prior to implementation.
2. A.P. Pharma will compare the old and new integration procedures and will analyze all the original batches by both procedures pointing out which of these batches were used in phase 2 and 3 clinical trials.
3. A.P. Pharma will analyze the lots that went into phase 3 and compare to those that were used in phase 2 and 3 for purposes of setting specifications.
4. A.P. may submit the 3 month accelerated and real time stability data no later than 2.5 to 3 months after the NDA resubmission.

5.0 ATTACHMENTS AND HANDOUTS

None

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/s/

JAGJIT S GREWAL
04/30/2011



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022445

MEETING MINUTES

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) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Sustol (granisetron) injection, extended-release, 10 mg.

We also refer to the meeting between representatives of your firm and the FDA on February 25, 2011. The purpose of the meeting was to discuss your plans for addressing the clinical, clinical pharmacology, statistical, and product presentation deficiencies outlined in our Complete Response letter dated March 16, 2010.

A copy of the official minutes of the meeting 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) 796-0846.

Sincerely,

{See appended electronic signature page}

Jagjit Grewal, M.P.H.
Regulatory Project Manager
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure: Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: End of Review meeting

Meeting Date and Time: February 25, 2011; 9:00-10:00 AM EST
Meeting Location: 10903 New Hampshire Avenue
White Oak Building #22, Conference Room #1309
Silver Spring, Maryland 20903

Application Number: NDA 022445
Product Name: Sustol (granisetron) injection, extended-release
Indication: 1) Moderately emetogenic cancer chemotherapy - prevention of acute and delayed nausea and vomiting associated with initial and repeat courses
2) Highly emetogenic cancer chemotherapy - prevention of acute nausea and vomiting associated with initial and repeat courses

Sponsor/Applicant Name: A.P. Pharma, Inc.

Meeting Chair: Ruyi He, M.D.
Meeting Recorder: Jagjit Grewal, M.P.H.

FDA ATTENDEESDivision of Gastroenterology Products

Donna Griebel, M.D.	Director
Ruyi He, M.D.	Medical Team Leader
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Tamal Chakraborti, Ph.D.	Pharmacology Reviewer
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Jagjit Grewal, M.P.H.	Senior Regulatory Health Project Manager

Office of Clinical Pharmacology

Sandhya Apparaju, Ph.D.	Reviewer
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Office of Pharmaceutical Science/ New Drug Microbiology Staff

Steven Fong, Ph.D., M.S.	Quality Microbiologist
--------------------------	------------------------

Division of Biometrics III

Mike Welch, Ph.D.	Deputy Director
Freda Cooner, Ph.D.	Reviewer

Office of Surveillance and Epidemiology/ Division of Medication Errors Prevention & Analysis

Walter Fava	Safety Evaluator
-------------	------------------

Center for Devices and Radiological Health/ Division of Anesthesiology, General Hospital,
Infection Control, and Dental Devices

Weihong Gu, Ph.D.

Reviewer

SPONSOR ATTENDEES

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Michael Adam, Ph.D.

Regulatory Affairs

John Barr, Ph.D.

Sr. VP, Research & Development

Trisha Shimada

Project Manager

John Whelan

Acting Chief Executive Officer

(b) (4)

VP, Chief Scientific Officer, Nonclinical Consultant

Clinical Consultant

Chief Scientific Officer, Cardiac Consultant

President, Statistics Consultant

1.0 BACKGROUND

Reference is made to NDA 022445 Sustol (granisetron) Injection, dated May 14, 2009, and the FDA Complete Response letter, dated March 16, 2010. A.P. Pharma, Inc. submitted a type B End of Review meeting request, dated December 16, 2010, to discuss their plans for addressing the container/closure system, device constituent parts, clinical, clinical pharmacology, statistical, and labeling deficiencies outlined in the Complete Response letter. FDA granted A.P. Pharma's meeting request in the letter dated January 6, 2011. A.P. Pharma's background package was received on February 2, 2011. FDA preliminary comments were sent to the sponsor on February 23, 2011. On February 24, 2011, A.P. Pharma provided responses to the FDA preliminary comments for discussion at the meeting.

As described in the meeting background package, A.P. Pharma changed the container closure system for the drug product to a single syringe design consisting of a single, pre-filled, (b) (4) 1 mL (b) (4) glass syringe and an 18 gauge 5/8-inch thin wall needle. The background package included references to human factors testing performed by the sponsor, but the study reports were not included. The sponsor subsequently submitted the human factors study reports on February 15, 2011 per FDA request.

To address the FDA concerns regarding granisetron exposure patterns, A.P. Pharma submitted a QT study protocol to IND 068213 dated December 23, 2010. The sponsor also presented the characterization of the hydrolytic breakdown pathway of (b) (4) and quantitation of the end products based on *in vitro* studies, *in vivo* animal studies, and literature. Additionally, safety

profiles of the end products were qualified in the nonclinical studies and supported by the clinical trials.

To address the statistical deficiencies, A.P. Pharma included an analysis of the ITT population and re-analyzed the mITT and PP populations. All analyses were performed with and without the inclusion of subjects from site 504. A Per Protocol population listing and violation criteria were presented. The sponsor noted that re-analyses of each of the three efficacy populations demonstrated non-inferiority of 500 mg APF530 to Aloxi, (b) (4). Furthermore, justification for the 15% non-inferiority margin was provided, which was based on the Aloxi registration studies and literature evidence.

Finally, the background package contained a revised subject ID line listing for administration site reactions across all studies to include data requested by FDA in the Complete Response letter.

2.0 DISCUSSION

The format of these minutes provides for A.P. Pharma's questions in regular typeface, followed by the FDA's February 23, 2011 responses in **bolded** print. A.P. Pharma's February 24, 2011 replies to FDA's preliminary responses are presented in *italic* print. The February 25, 2011 meeting discussion is presented in *italic and bolded* print.

Introductory FDA Comments:

Please be advised that our responses listed below are based on review of your meeting background package dated February 1, 2011. Our responses may be revised per review of additional materials you plan to submit for the type C meeting scheduled for March 31, 2011.

CONTAINER / CLOSURE SYSTEM

1. Does the FDA agree the proposed single syringe system addresses the FDA concerns with the previous two syringe system?

FDA Response:

In order to provide adequate responses to your container/closure system questions 1, 2, and 3, we will need to review the human factors study reports submitted on February 15, 2011. Therefore, we defer our responses to these questions until the type C end of review meeting scheduled for March 31, 2011.

2. Does the FDA agree that markings on the syringe are not necessary?

FDA Response:

See our response to question 1.

3. Does the FDA agree further Human Factors testing is not necessary?

FDA Response:

See our response to question 1.

4. Does the FDA agree that the Device Constituent Parts section of the Complete Response Letter (questions 6 and 7) are no longer relevant with the changes proposed for the new product presentation container-closure system?

FDA Response:

No, we do not agree. The proposed container closure system for the drug product is a single syringe design consisting of a single, pre-filled, (b) (4) 1 mL (b) (4) glass syringe and an 18 gauge 5/8-inch thin wall needle. You have indicated that the 18 gauge 5/8-inch needle was cleared by the Agency under 510(k) submission (b) (4). We have confirmed that this 510(k) has indeed been cleared by CDRH.

However, the (b) (4) 1 mL (b) (4) glass syringe that you have proposed to deliver the drug product has not been cleared through the medical device 510(k) regulatory pathway. Therefore, we still request the information described in points 6 and 7 of the Complete Response Letter dated March 16, 2010.

Please note there is a glass syringe in your proposed container closure system. In the performance bench testing, please provide the test data to demonstrate the safety of the luer lock (i.e., luer lock breakage) syringe component. It is noteworthy that the Agency recognizes the following standards that impact your glass, pre-filled syringe:

- ISO 11040-4, Prefilled syringes - Par 4: Glass barrels for injectables
- ISO 594-1, Connical fittings with a 6% (Luer) taper for syringes, needles and certain other medical equipment - Par 1: General Requirements
- ISO 594-2, Connical, Connical fittings with a 6% (Luer) taper for syringes, needles and certain other medical equipment - Par 2: Lock Fittings

The Agency refers to the recommendations within these standards when assessing the safety and effectiveness of glass barrel syringes.

A.P. Pharma Response 2/24/11: If the (b) (4) DMF deficiencies for the 1mL (b) (4) luer-lock syringe are addressed then are the requirements in the Complete Response Letter dated 3/16/10, points 6 and 7 met?

Meeting Discussion:

FDA preferred that the information from the Complete Response letter points 6 and 7 for the glass syringe be addressed as part of the NDA resubmission. A 510(k) application would not necessarily be needed if the information can be provided with the resubmission.

Alternatively, (b) (4) can submit the necessary information to the DMF.

LABELING

1. Does the FDA have any comments on our proposed labels or nomenclature?

FDA Response:

For the drug product name, the strength should not appear between the trade name and the established name. Instead it should be moved to the end of the name, i.e. SUSTOLTM (granisetron) injection, extended release 10 mg.

For the immediate container label:

- The established name should be in parentheses.
- The font size for the established name and dosage form should be the same and should be at least 50% of the proprietary name
- A bar code should be included

Additional comments on your proposed labeling may be issued pending final review of your resubmission.

CLINICAL / CLINICAL PHARMACOLOGY

1. Does the FDA agree with the proposed QT study design?

FDA Response:

Please see our comments dated February 15, 2011 regarding your thorough QT trial protocol.

In addition, administration site reactions should be included as a component of your proposed adverse reaction monitoring plan for the tQT trial. You should provide the following information, by subject ID line listing, for administration site reactions: trial number, study drug and dose, type of administration site reaction (i.e. bruising, nodule, etc.), the date of onset of the adverse reaction, the date the adverse reaction resolved, and the time elapsed between injection and onset of the adverse reaction.

2. Does the FDA agree the QT study can be done as an NDA post-approval commitment?

FDA Response:

No, we do not agree. The proposed tQT trial should be completed prior to the NDA resubmission. The systemic exposure potential of granisetron from Sustol is greater and more variable compared to the formulations approved to date. Understanding the QT prolongation potential is important in assessing risk-benefit of this new formulation for the proposed indication.

3. Does the FDA agree the characterization and safety of the breakdown pathway and products of (b) (4) are adequately addressed without the suggested clinical trial?

FDA Response:

No, we do not agree. (b) (4)

Therefore, we recommend that you conduct a clinical study to adequately characterize the metabolites and degradants in plasma and urine. You may consider consolidating these objectives with your planned tQT trial. However, you will need to justify that the tQT trial results will not be negatively impacted by these additional assessments.

A.P. Pharma Response 2/24/11: AP Pharma has only been able to identify aqueous or enzymatic hydrolysis via in vitro and in vivo data as the means of biodegradation of the (b) (4) to the ultimate end products. It is our understanding of the response that the Agency is requesting that the final biodegradation products be characterized in the urine and plasma of humans. Does this satisfy the Agency's request?

Meeting Discussion:

FDA is interested in the fate of polymer in humans, in vivo, which could theoretically be different than what was seen in animals. A.P. Pharma will specifically assess the urine and plasma for the known hydrolytic end products, with emphasis on TEG and PE looking for any other related metabolites. A.P. Pharma will assess any analytical issues that may impact the determination of specific metabolites and address these in the NDA resubmission. FDA will review the adequacy of the clinical assessment plan when the protocol is submitted.

CLINICAL / STATISTICAL

1. Does the FDA agree with the revised listings proposed for the Per Protocol, ITT, and m-ITT?

FDA Response:

We acknowledge receipt of your listings and they appear to be adequate on preliminary review. However, the final determination will be a review issue.

2. Does the FDA agree that the data from site 504 should be excluded from the primary analysis?

FDA Response:

While we agree that it appears appropriate to perform the analyses with and without this site, the issues identified raise questions regarding the adequacy of site monitoring

during conduct of the clinical trial. We will consider the need for additional DSI inspection during the next review cycle. You will need to submit your site monitoring plan with the NDA resubmission.

3. Does the FDA agree the evidence presented justifies the selection of the 15% non-inferiority margin?

FDA Response:

Based on preliminary review, your justification appears to be adequate. However, a final determination will be made during the review process.

4. Are the administration site reaction data presentations provided in a manner adequate to allow the FDA to evaluate the safety of APF530?

FDA Response:

Based on preliminary review, your data presentations appear to be adequate. However, a final determination will be made during the review process. In addition, we request that you submit summary analyses of the duration data by drug dose, cycle, and duration of adverse events. For example, we are interested in duration of adverse reactions across trials in the 10 mg versus 5 mg dose, and by cycle.

You also need to provide additional clarification of your legend, specifically how "C" and "D" were determined.

A.P. Pharma Response 2/24/11: Based on your response, our understanding is the Agency is requesting one table per cycle that displays means and standard deviations of the duration for each of the preferred terms that constitute subcutaneous Administration Site Reactions for the 5mg and 10mg dosage groups. Do you want to test for differences between the 2 dosage groups and if so, is a Wilcoxon Rank Sum (Mann-Whitney) test adequate? Does this response satisfy the Agency's request?

Meeting Discussion:

FDA requested one table per cycle that displays means, standard deviations, mins and max, and percentiles of the duration for each of the preferred terms that constitute subcutaneous Administration Site Reactions for the 5mg and 10mg dosage groups. No test statistics are required. Specifically, the sponsor should provide information to describe the distribution.

Additional FDA Comments:

1. The Division recommends 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/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079345.pdf> . 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://inside.fda.gov:9003/downloads/CDER/OfficeofNewDrugs/ImmediateOffice/ucm027521.pdf>) .

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). You should 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.

2. We remind you of the Pediatric Research Equity Act (PREA) of 2007 which requires all applications for a new active ingredient, new dosage form, new indication, new route of administration, or new dosing regimen to contain an assessment of the safety and effectiveness of the drug for the claimed indications in all relevant pediatric subpopulations unless this requirement is waived, deferred, or exempt (i.e., orphan designation letter issued). Therefore, in order to fulfill the PREA requirements, you should formulate a pediatric clinical development plan that incorporates all pediatric age ranges. You should also provide a timeline for completion of the planned pediatric trials. If you are planning to request a waiver for certain indications or age groups, you should provide a justification.

A.P. Pharma Response 2/24/11: Both the 505(b)(2) application reference and the PREA – pediatric clinical development plan were addressed in the NDA. Does the Agency have concerns or additional requests regarding these?

Meeting Discussion:

FDA has not yet reviewed the sponsor’s pediatric plan, and requested that the sponsor resubmit the pediatric plan with their NDA resubmission. The sponsor’s rationale for selection of deferral and waiver age ranges must also be included with the NDA resubmission.

At this time, FDA does not have any specific concerns regarding the 505(b)(2) application reference.

Additional Meeting Discussion:

The 2 year carcinogenicity study in the rat and SHE cell assay will be performed as a postmarketing study per previous agreement.

3.0 ISSUES REQUIRING FURTHER DISCUSSION

1. FDA will provide responses to the container/closure system questions #1-3 with the preliminary responses for the End of Review type C meeting scheduled for March 31, 2011.

4.0 ACTION ITEMS

1. A.P. Pharma may submit their response to the Complete Response letter points 6 and 7 with the NDA resubmission. Alternatively, the information may be submitted by (b) (4) to the DMF.
2. A.P. Pharma will assess the urine and plasma for the known hydrolytic end products, with emphasis on TEG and PE looking for any other related metabolites. A.P. Pharma will assess any analytical issues that may impact the determination of specific metabolites and address these in the NDA resubmission.
3. FDA will review the adequacy of the clinical assessment plan when the protocol is submitted.
4. A.P. Pharma will resubmit their pediatric plan and provide rationale for any waiver or deferral requests with the NDA resubmission.

5.0 ATTACHMENTS AND HANDOUTS

None

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

/s/

JAGJIT S GREWAL
03/25/2011



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND #68,213

A.P. Pharma
123 Saginaw Drive
Redwood City, CA 94063

Attention: John Barr
Vice President
Research and Development

Dear Dr. Barr:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for APF530 granisetron, (b) (4)

We also refer to the meeting between representatives of your firm and the FDA on December 13, 2006. The purpose of this meeting was to discuss and obtain consultation on your preclinical and clinical development to support a 505(b)(2) application. Specifically, we discussed the following objectives: 1) request for waiver of segment I and II reproductive toxicity studies for APF530, 2) request for waiver of carcinogenicity studies for APF530, and 3) request for waiver of a through clinical QT/QTc study with APF530.

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) 796-0980.

Sincerely,

{See appended electronic signature page}

Giuseppe Randazzo
Regulatory Project Manager
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure



FOOD AND DRUG ADMINISTRATION

Meeting Date and Time: December 13, 2006

Meeting Type: C – Face-to-Face

Meeting Category: Pre-NDA

Meeting Location: FDA/CDER
White Oak Building #22
10903 New Hampshire Ave.
Silver Spring, MD 20993

Application Number: I 68,213

Product Name: APF530 granisetron, (b) (4)

Received Briefing Package November 13, 2006

Sponsor Name: A.P. Pharma

Meeting Requestor: John Barr

Meeting Chair: Dr. Hugo Gallo-Torres

Meeting Recorder: Ryan Barraco for Giuseppe Randazzo

Meeting Attendees:

FDA Attendees:

Hugo Gallo-Torres, M.D., Ph.D., P.N.S., Division of Gastroenterology Products (DGP)
Gastrointestinal Medical Team Leader

Nancy Snow, D.O., Medical Reviewer (DGP)

Sue-Chih Lee, Ph.D., Clinical Biopharm Reviewer

Jasti Choudary, B.V. Sc., Ph.D., Supervisory Pharmacologist (DGP)

Tamal Chakraborti, Ph.D., Pharmacologist Reviewer (DGP)

Stella Grosser, Ph.D., Statistical Team Leader

Shari Targum, M.D., Medical Officer, Division of Cardiovascular and Renal Products

Don Hare, Pharm.D., Special Assistant, Office of Generic Drugs (OGD)

Ryan Barraco, Regulatory Project Manager (DGP)

External Attendees

John Barr, Ph.D.

Jelmer Miedema, Ph.D.

Devang Shah, Ph.D.

Kemon Papacosta

Trisha Ledda

(b) (4)

VP R&D, AP Pharma

Sr. Director, Scientific and Technical Affairs

Director, Technology Development

Manager, Process Development

Project Manager

Consultant, Toxicology

Consultant, Regulatory Counsel

Sr. Director, Compliance

1.0 BACKGROUND

AP Pharma formally requested a face-to-face type C meeting to address the preclinical and clinical program for IND 68,213. We received the meeting request on September 27, 2006. AP Pharma has intentions of pursuing a 505(b)(2) application for APF530, Granisetron, (b) (4) for Chemotherapy Induced Nausea and Vomiting (CINV).

Granisetron is a potent and selective 5-HT₃ receptor antagonist which has been approved for the prevention of CINV over a period of 24 hours (Kytril®, Roche Laboratories). The sponsor intends to use their novel formulation to deliver the drug over longer periods of time and reduce the incidence of both acute and delayed CINV and to pursue corresponding indications.

The proprietary polymer, AP135, which is used in this novel formulation, is a triethylene glycol based poly(ortho ester) or TEG-POE. This is a polymer class which undergoes controlled hydrolysis in the presence of water. The TEG-POE polymer (AP135) and methoxy polyethylene glycol (MPEG) (b) (4)

(b) (4) The formulation of granisetron (b) (4) is referred to as APF530.

AP Pharma has conducted nonclinical studies up to 90 days in rats and dogs, Segment II teratology studies in rats and rabbits, pharmacokinetic studies in rats and dogs, and an ICH recommended battery of genotoxicity studies with APF530 and/or (b) (4). In addition, AP Pharma has completed clinical trials through Phase 2 with the product and there was no unexpected toxicity. A Phase 3 clinical trial is currently ongoing.

The overall objective of the meeting is to seek our concurrence on the preclinical and clinical development programs for APF530 that will support a 505(b)(2) application. Specific objectives of the meeting include obtaining responses on the following:

- Request for a waiver of Segment I and III reproductive toxicity studies for APF530.
- Request for a waiver of carcinogenicity studies for APF530.
- Request for a waiver of a thorough clinical QT/QTc study with APF530

2.0 DISCUSSION

PRECLINICAL QUESTIONS

Question 1:

AP Pharma has conducted repeat dose studies in the rat and dog with APF530 in which daily injections were administered subcutaneously for up to 90 days. There was no evidence of preneoplastic lesions or mitogenic effects in the studies. AP Pharma has completed a standard battery of *in vitro* and *in vivo* genotoxicity studies with (b) (4) and APF530. The studies indicated that both (b) (4) and APF530 were nongenotoxic. APF530 will be administered short term and will not exceed the duration of dosing that would warrant conduct of carcinogenicity studies. Based on the intended patient population, the duration and frequency of exposure, the negative genotoxicity for (b) (4) and APF530, and the absence of systemic effects (i.e. preneoplastic findings) with APF530 and (b) (4) AP Pharma is requesting a waiver for carcinogenicity studies.

Does the Agency concur that a waiver of the carcinogenicity studies is appropriate?

Response for 12/13/06 meeting: No, we do not concur. As mentioned in the meeting minutes dated August 23, 2005 (Meeting dated August 4, 2005) and Division letter dated November 4, 2005, a carcinogenicity waiver will be considered after examining the outcome of 90-day subcutaneous toxicity studies in rats and dogs. In 90-day subcutaneous toxicity study in rats, there were treatment-related increased incidences and severity of hyperplasia of several lymph nodes and bone marrow. In addition, treatment-related increased incidences of splenic hematopoiesis were also seen in APF530 and (b) (4) treated animals. Sponsor's proposal for the waiver of the carcinogenicity studies is not acceptable based on the following considerations:

- Treatment-related increased incidences and severity of hyperplasia of several lymph nodes and bone marrow including treatment-related increased incidences of splenic hematopoiesis in the 90-day subcutaneous toxicity study in rats
- Potential for continuous or intermittent use of APF530 for 6 months or greater or over the life of the patient
- (b) (4) caused increased chromosomal aberrations in the CHO cells both in the absence and presence of metabolic activation
- (b) (4) has not been used in any approved formulation and no information is available regarding the carcinogenic potential of this vehicle used in APF530

Summary of Discussion held at meeting on 12/13/2006:

We are in agreement that the carcinogenicity studies with two species may begin around the time of NDA submission.

Question 2:

AP Pharma has conducted repeat dose toxicity studies in rats and dogs and Segment II reproductive toxicity studies in rats and rabbits. There were no effects on reproductive organs when APF530 and (b) (4) were administered daily by SC injection for up to 90 days. There were no maternal or embryofetal effects associated with SC administration of (b) (4) during the Segment II reproductive toxicity studies. Granisetron has been evaluated in the recommended ICH battery of reproductive toxicology studies (S5A: Guideline for Industry; Detection of Toxicity to Reproduction for Medicinal Products and S5B: Guideline for Industry; Detection of Toxicity to Reproduction for Medicinal Products: Addendum on Toxicity to Male Fertility). There were no results that indicated any potential for granisetron to adversely impact fertility or fetal development. AP Pharma believes that the nonclinical studies for APF530 and granisetron, the well-established understanding of the reproductive risk associated with the majority of cytotoxic chemotherapeutic agents used in the intended patient population, as well as the intended usage of APF530, support a scientifically based request for waiver of the Segment I and III studies.

Does the Agency concur?

Response for 12/13/06 meeting: No, we do not concur. As mentioned in the meeting minutes dated August 23, 2005 (Meeting dated August 4, 2005), there is no information available regarding the effects of (b) (4) on fertility and early embryonic development (Segment I) and on pre and postnatal development (Segment III), the sponsor's proposal to waive the Segment I and III reproductive toxicity studies in rats is not acceptable. The sponsor needs to conduct Segment I and III studies in rats with (b) (4) as recommended in the Agency Guidance "Guidance for Industry, Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients, May 2005."

CLINICAL QUESTIONS

Question 3.

In vitro nonclinical studies have demonstrated that granisetron has a potential to block cardiac Na channels, but not the potassium channels, at high concentrations. There was no indication of granisetron-induced QT/QT_c prolongation in the *in vivo* nonclinical studies. The absence of a potential for granisetron to prolong QT/QT_c interval duration is supported by the extensive pre and postmarketing surveillance for the drug. AP Pharma has not conducted an *in vitro* HERG channel assay or cardiovascular safety pharmacology study with APF530. The C_{max}, however, achieved for granisetron following administration of APF530 will be lower than that observed following administration of the approved intravenous formulation of granisetron. Furthermore, there was no evidence of cardiac liability based on ECG evaluation in the nonclinical toxicology studies in dogs, including a 90-day repeat dose toxicology study in which APF530 was administered daily. AP Pharma has evaluated cardiovascular safety in completed clinical trials and is assessing CV safety in ongoing clinical trials with APF530. Based on the absence of QT/QT_c interval prolongation in the extensive nonclinical and clinical data for granisetron and APF530 and the assessment of cardiovascular safety in the ongoing Phase 3 clinical trial with APF530, AP Pharma believes that a thorough QT/QT_c trial is not indicated.

Does the Division concur that a waiver of the thorough QT/QT_c trial is appropriate?

Response for 12/13/06 meeting: Your product is an extended-release formulation designed to achieve therapeutic effect over a longer period of time following subcutaneous injection. Specifically, the plasma concentrations are to maintain at a sufficient level for up to 96 hours to control both the acute and delayed nausea and vomiting associated with chemotherapy.

Your rationale for a waiver of a thorough QT study for your granisetron formulation is based on nonclinical and clinical arguments. The rationale that is related to clinical pharmacology is that your proposed product has lower C_{max} values compared to the approved granisetron (Kytril) I.V. injection. Regarding this, we have the following comments and questions:

1. From the data you provided, the product at the intended dose levels will result in mean C_{max} values of 4.17 ± 2.17 ng/mL and 10.6 ± 7.91 ng/mL for the 5 mg and 10 mg doses, respectively, in healthy subjects (Table 1). However, the information for Kytril I.V. injection as provided in Table 1 appears to be in error. Please clarify whether the dose for Kytril I.V. matches the corresponding PK information and provide the comparative PK profiles.
2. The PK parameters are more variable for the proposed product compared to Kytril I.V. When comparing the exposure for the two products, the variability should also be taken into consideration.
3. It is noted that clearance in cancer patients is quite different from that observed in young healthy subjects. It is expected that C_{max} in cancer patients will deviate more from that in healthy young subjects for the proposed product compared to Kytril I.V. because of the sustained release nature of the proposed product. The information in cancer patients in your Table 2 does not support your claim that the product at the proposed doses (Table 2) has a lower C_{max} compared to Kytril I.V. at the therapeutic dose of 10 mg/kg. (Note: Table 3 has PK parameters of granisetron for Kytril I.V. at 40 mg/kg.) Please explain how the comparative information in healthy young subjects (Table 1) can be meaningfully inferred to cancer patients.
4. You may want to consider how to dose patients for those who receive more than one dose of chemotherapy (e.g., chemotherapy every other day for a total of 3 chemotherapy doses in a week).
5. How does a single dose of a 1 mg I.V. Granisetron compare with your formulation?

Summary of Discussion held at meeting on 12/13/2006:

A.P. Pharma will submit a waiver request, along with supportive waiver request information, of the thorough QT/QT_c study and we will review the request. Additionally, the sponsor should submit the C2006-01 protocol for review.

REGULATORY QUESTIONS

Question 4.

On 19 May 2006 the FDA sent the following response in follow up to our Phase 3 Protocol Submission: 68,213 - 014 under Conclusions and Recommendations:

3. Historically, two successful well controlled trials are required to support approval of any new indication. The proposed single study appears to be adequately powered to demonstrate efficacy in both moderately and highly emetogenic chemotherapy regimens. This large single study may be adequate to support approval of a new indication; however, the results will need to be clinically as well as statistically "robust".

Can you further clarify what you mean by "robust" clinical and statistical results?

Response for 12/13/06 meeting: At this time it is difficult to quantitatively define the word "robust" for your proposed single study. However, we refer you to "*Guidance for Industry, Providing Clinical Evidence of Effectiveness for Human Drug and Biological Product, May 1998.*"

3.0 ISSUES REQUIRING FURTHER DISCUSSION

N/A

4.0 ACTION ITEMS

Please read dialogue above in the **DISCUSSION** section.

5.0 ATTACHMENTS AND HANDOUTS

N/A

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

/s/

Hugo Gallo Torres
1/10/2007 07:26:01 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 68,213

A.P. Pharma

(b) (4)

Dear (b) (4)

Please refer to your Investigational New Drug Application (IND) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for APF530 Granisetron (b) (4)

We also refer to the End-of-Phase 2 meeting between representatives of your firm and the FDA on December 13, 2005. The purpose of the meeting was to discuss your pre-clinical and clinical program.

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)-796-0991.

Sincerely,

{See appended electronic signature page}

Betsy Scroggs, Pharm.D.
Regulatory Health Project Manager
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF MEETING MINUTES

Meeting Date: December 13, 2005
Time: 11:00 AM to 12:00 PM
Location: CDER White Oak # 1309 Conference Room
Application: IND 68,213
Type of Meeting: Type B Meeting
Meeting Chair: Dr. Hugo Gallo-Torres, GI Team II Clinical Team Leader
Meeting Recorder: Dr. Betsy Scroggs, Regulatory Health Project Manager

FDA Attendees, Titles, and Office/Division:

Division of Gastroenterology Drug Products

Brian E. Harvey, M.D., Ph.D.	Division Director
Joyce Korvick,, M.D., M.P.H.,	Deputy Division Director
Gary Della'Zanna, D.O., M.Sc.	Medical Officer
Hugo Gallo-Torres, M.D., Ph.D., P.N.S.	Clinical Team Leader, GI Team II
Jasti Choudary, Ph.D., B.V.Sc.	Supervisory Pharmacologist
Tamal Chakraborti, Ph.D.	Pharmacology Reviewer
Betsy Scroggs, Pharm.D.	Regulatory Health Project Manager

Division of Pharmaceutical Evaluation II

Edward Bashaw, Ph.D.	Clinical Pharmacology Team Leader
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Office of Generic Drug Products

Donald Hare, R.Ph.	Special Assistant to Office Director
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External Constituent Attendees for AP Pharma

John Barr, Ph.D.

A.P. Pharma, Vice President, Research & Development

Patrick DeVillier, MS

A.P. Pharma, Director of Compliance

(b) (4) Vice President, Clinical Regulatory Affairs

Vice President, Chief Scientific Officer

(b) (4)

Pharmacokineticist

Regulatory Counsel

(b) (4) Senior Statistician

Background: On October 14, 2005, the firm submitted a Meeting Request and on November 14, 2005, a subsequent background package which contained specific questions to be addressed. The purpose of today's meeting is to discuss our responses to the sponsor's questions.

Discussion Points (bullet format): Following introductions, the firm's questions from the background package were addressed. The format of these minutes provide for the firm's questions in regular print, followed by the Agency's responses in bolded print.

CLINICAL QUESTIONS

1. In the August 4, 2005 meeting with the Agency, it was requested that we include patients on highly emetogenic chemotherapy in the protocol. (b) (4)

[REDACTED] (b) (4)

Response:

Your approach is not acceptable.

[REDACTED] (b) (4)

2. In the August 4, 2005 meeting with the Agency, it was recommended that our protocols include a standardized dose of steroids as a background. (b) (4)

[REDACTED]

Does this adequately address the Agency's request?

Response:

Your approach is not acceptable.



Ref: Background Package Page 213 of 245

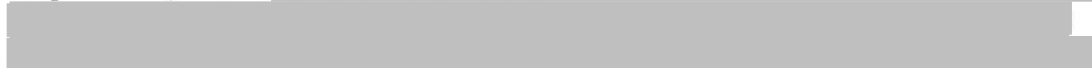
In clinical practice there are “Standard of Care” regimens that are widely accepted and published in the medical literature for the prevention of acute and delayed nausea and vomiting associated with moderately and highly emetogenic chemotherapy. You should submit current literature documenting that the proposed steroid dose is considered a “standard of care.”

The protocol should standardize the formulation of steroid used (i.e. oral *or* intravenous); allowing for both could make the analysis difficult to interpret. Additionally, we recommend defining a specific dose of steroid, not a range of dose. Using the proposed dosing schedule could result in some patients in the moderately emetogenic treatment arm to receive (b) (4) This would also make the efficacy analysis difficult to interpret.

3. The current clinical plan with two pivotal studies would provide a total of approximately 1300 patients exposed to APF530. This is slightly less than the 1500 patient exposures recommended by ICH E1A for Extent of Population Exposure for drugs intended for long term treatment of non-life-threatening conditions. Does the Agency agree that since granisetron is a well characterized substance and because the product is meant for short term, intermittent exposure, that 1300 exposures will adequately address the spirit of this guidance?

Response:

As previously stated, (b) (4)



4. In the August 4, 2005 meeting with the Agency, it was requested that we further elaborate on the statistical plan for testing non-inferiority of APF530 in the acute phase and superiority of APF530 in the delayed phase. Additional detail has been provided in the study outlines. Is the

proposed statistical approach acceptable to the Agency? Does the Agency have any additional comments or requests regarding the statistical approach?

Response:

- a. Please justify your rationale for selecting a 15% non-inferiority margin.
- b. Your plan for testing adjusts for two primary endpoints. The adjustment for multiplicity should also take into account the multiple doses of APF530 (250 mg and 500 mg) that are being compared to AloxiTM.

December 13, 2005 meeting comment: Using a similar approach as was done in the palonosetron application may be acceptable.

5. For quality-of-life measures, the FLIE has been validated for use at time points out to 5 days after administration of chemotherapy. We propose to use the FLIE at day 5 in order to capture quality-of-life in the acute plus delayed phases. We hope to include the FLIE results in the package insert.

- a. Does the Agency agree that day 5 is a reasonable time point?

Response:

Yes, day 5 is a reasonable time point to capture quality-of-life in the acute plus delayed phases.

- b. A portion of each pivotal trial may be conducted in a country which uses a language for which the FLIE has not previously been validated. Will this preclude consideration of including the FLIE data in the package insert?

Response:

The validity of translations of the FLIE can be studied using data from these protocols. If significant differences in the measurement properties of the new translations are observed in the data, efficacy analyses omitting these translations may still be used to support language in labeling as long as the results are convincing.

6. Regarding the evaluation of APF530 in pediatric subjects, (b) (4)

A.P.

Pharma plans to request a deferral for pediatric studies. Does the Agency agree that a deferral request would be reasonable and that pediatric studies could be deferred until after APF530 has been approved for marketing?

Response:

Yes, a deferral for pediatric studies may be acceptable. However, your New Drug Application must include a pediatric development plan and a timeline for completion of these studies.

PRECLINICAL QUESTION

7. Based on the intended patient population, the duration and frequency of exposure, and the absence of systemic effects with APF530 and the vehicle, (b) (4) A.P. Pharma will be requesting a waiver for carcinogenicity studies. With the exception of the ongoing 90-day repeat dose studies as well as biodisposition and reproductive toxicity studies, A.P. Pharma does not plan at this time to conduct any additional nonclinical studies to support an NDA for APF530 for the treatment of chemotherapy induced nausea and vomiting. Does the Agency concur that the studies in the proposed nonclinical package (See Table 6) are adequate to support a 505(b)(2) NDA for APF530?

Response:

As previously mentioned in the meeting minutes dated August 23, 2005 and November 4, 2005, a carcinogenicity waiver will be considered after examining the outcome of 90-day subcutaneous toxicity studies in rats and dogs. The planned studies outlined in Table 6 on page 17 of the background package are adequate to support a 505(b)(2) NDA for APF530.

Additional OCPB Comments:

- **For an NDA submission under 505(b)(2), you need to provide a link to the currently approved drug product. Therefore, you should perform a pharmacokinetic (PK) comparability study between your APF530 granisetron (b) (4) and an innovator's, e.g., granisetron product, in order to provide the link for PK data.**

December 13, 2005 Meeting note: A PK bridging study was submitted on August 29, 2005 and needs to be evaluated for adequacy of the link to granisetron.

- **The shape of the plasma profile obtained from your Phase I PK study (conducted in the United Kingdom and submitted with your original IND submission for IND 68,213) is different from that obtained from your Phase II study C2005-01.**

Please clarify if the same APF530 formulation was used in both Phase I and Phase II studies. We recommend that you use the to-be-marketed APF530 (b) (4) in your Phase III clinical trials and your definitive PK studies.

- **From your Phase II study C2005-01, your reported PK data showed dose-proportionality characteristics amongst the 250 mg, 500 mg, and 750 mg doses (pages 12-13 of 245), yet your preliminary efficacy data showed that the 250 mg dose is more efficacious than the 500 mg dose and the 500 mg dose is more efficacious than the 750 mg dose (pages 13-14 of 245). Considering that you propose to use the 250 and the 500 mg doses for the Phase III trials (pages 211 and 225 of 245), please provide the basis for your belief that the 250 mg dose is the minimum effective dose.**

Minutes Preparer: Dr. Betsy Scroggs

Chair Concurrence: Dr. Hugo Gallo-Torres

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

/s/

Betsy Scroggs
1/10/2006 06:37:48 PM



IND 68, 213

A.P. Pharma

(b) (4)

Dear (b) (4)

We refer to your October 14, 2005 correspondence, received October 17, 2005 requesting a Chemistry, Manufacturing, and Controls (CMC) End-of-Phase 2 (EOP2) meeting (Type B) to discuss your CMC drug development plans for APF530.

We also refer to our December 14, 2005 email containing our responses to the questions submitted in your November 21, 2005 meeting background package and your December 16, 2005 email confirming that you accepted our responses and that a meeting would not be necessary.

Our December 14, 2005 attached responses to your questions serve as the official CMC EOP2 meeting minutes of the planned and canceled meeting. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, you may call me at (301) 796-0991.

Sincerely,

{See appended electronic signature page}

Betsy Scroggs, Pharm.D.
Regulatory Health Project Manager
Division of Gastrointestinal and Coagulation Drug
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

IND 68,213 APF530

CMC EOP2 Meeting Minutes

List of specific questions

Drug Substance

8.1.1 Proposed synthetic starting materials

Does the Agency agree with the compounds designated as starting materials?

Response: *Your approach to justifying the designated starting materials is acceptable. However, a final decision on the acceptability of these materials will be made after you have submitted specifications for these materials, their batch analysis data, and a commitment to submit a supplement when there are any manufacturing changes for the starting material or changes of the supplier.*

8.1.2 Manufacturing plans

Does the Agency agree with the proposed approach for qualifying a second manufacturer of the drug substance?

Response: *Yes, your proposed approach is acceptable. You will also need to do polymorph screening for material from both manufacturers.*

8.1.3 Tests and Specifications

Does the Agency agree with the proposed tests and specifications for the drug substance?

Response: *Your proposed specifications appear generally acceptable, but we recommend that residual solvent limits be based on manufacturing history.*

8.1.4 Stability Plan

Does the Agency agree with the drug substance stability plan is satisfactory to support NDA submission?

Response: *Yes.*

Drug Product

8.2.1 Excipient control

Does the Agency agree with the plan for controlling the quality of excipients?

Response: *The specifications for AP135 should include limits for low molecular weight impurities and unreacted monomers. We also recommend that (b) (4) limits be based on manufacturing history. AP135 will be fully evaluated when (b) (4) submits the DMF for this material (we assume that the material from (b) (4) will be pharmaceutical grade).*

You note that in some batches of (b) (4) exceed the limits allowed in the NF monograph due to your handling and storage procedures. You will need to identify what variables are responsible for the increased levels of (b) (4) and if this would also be observed in the fully formulated product.

You will need to justify why it is necessary to (b) (4).

(b) (4) Does irradiation cause degradation of AP135 or MPEG (b) (4) in the formulation?

8.2.2 Manufacturing process

Does the Agency agree with the proposal for (b) (4)?

Response: *Your proposal is generally acceptable as long as it can be verified with data (see Guidance for Industry for the Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products) that the final drug product meets in-process and release specifications. The drug product would be safer and less risk would be introduced from (b) (4) operations if irradiation was performed after filling. Consider terminal sterilization by irradiation for this drug product.*

Container closure integrity validation for both (b) (4) and final product (1 mL glass syringe) will need to be performed to demonstrate the integrity of the microbiological barrier of the container closure system.

8.2.3 Tests and specifications

Does the Agency agree with the proposed specifications and tests for the drug product?

Response: *Regarding the weight average molecular weight for AP135 that is part of the specification, you will need to justify why the range has changed from (b) (4), which was specified for the unformulated excipient, to (b) (4) in the formulated product. Also, the proposed range is quite broad when correlated with your in vitro release data: for M_w , (b) (4) % of the drug is released in (b) (4), approximately (b) (4) % of the drug is released.*

The in vitro release test proposes an upper limit of (b) (4) % of granisetron released in (b) (4) hours. The specification should be expressed in terms of an upper and lower limit.

You will need to identify the source of (b) (4) in the formulation.

What is the bacterial endotoxin specification for the drug product? Please provide the specification and how it was determined.

Does the Agency agree with the proposed dissolution method and the proposed approach to development of *in vitro* release specifications for drug product release and stability testing?

Response: *Yes, your approach is generally acceptable.*

8.2.4 Stability plan

Does the Agency agree with the plan drug product stability protocol is satisfactory to support NDA submission and a (b) (4) expiration date.

Response: *Yes*

Please clarify the method of the container closure integrity test in the stability protocol.

*Meeting Recorder: Betsy Scroggs, Pharm.D., RHPM
Meeting Chair: Marie Kowblansky, Ph.D., PAL, ONDQA*

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

/s/

Betsy Scroggs
1/13/2006 04:27:54 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 68,213

A.P. Pharma

(b) (4)

Dear (b) (4):

Please refer to your Investigational New Drug Application (IND) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for APF530 (granisetron, (b) (4)).

We also refer to the Type C meeting between representatives of your firm and the FDA on August 4, 2005 to seek the Division's perspective on your preclinical and clinical program for APF530 for regulatory approval of acute-onset and delayed-onset chemotherapy induced nausea and vomiting (CINV) via a 505(b)(2) application.

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 Betsy Scroggs, Pharm.D., Regulatory Project Manager, at (301) 827-1250.

Sincerely,

{See appended electronic signature page}

Betsy Scroggs, Pharm.D.
Regulatory Health Project Manager
Division of Gastrointestinal and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure