CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022445Orig1s000

PRODUCT QUALITY REVIEW(S)

Memorandum

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

Date: **August 4, 2016**

From: **Danuta Gromek-Woods, Ph.D.**

Through: **Moo-Jhong Rhee, Ph.D.**
Chief, Branch V
Division of New Drug Product II
ONDP

To: **CMC Review #3 of NDA 22445**

Subject: **Final Recommendation**

The CMC review #3 dated 22-Dec-2015 has indicated the following two pending issues:

1. Final recommendation from the Office of Process and Facilities was pending.
2. CDRH/ODE consult was pending.

The memorandum dated 13-Jan-2016 indicated the following:

1. On January 13, 2016, the Office of Compliance issued the "Withhold Approval" recommendation for the (b) (4) involved in the NDA.

2. On December 22, 2015, CDRH/ODE issued a memorandum with the following recommendation: "Insufficient Device Performance Information to Support Approval".

And because of these deficiencies, this NDA was not recommended for approval from the OPQ perspective.

On March 4th, 2016, the Office of Compliance issued the "Approve" recommendation for the facilities involved in the NDA (see the **Attachment-1**).

On April 4th, 2016, CDRH/ODE issued a memorandum with the following recommendation: "Device Constituent Parts are Approvable" (see the **Attachment-2**).

On August 1, 2016, Dr. Zhengfang Ge issued a memorandum stating that labels are deemed adequate from the CMC perspective (see the **Attachment-3**).

Recommendation:

This NDA is **now** recommended for approval from the OPQ perspective.

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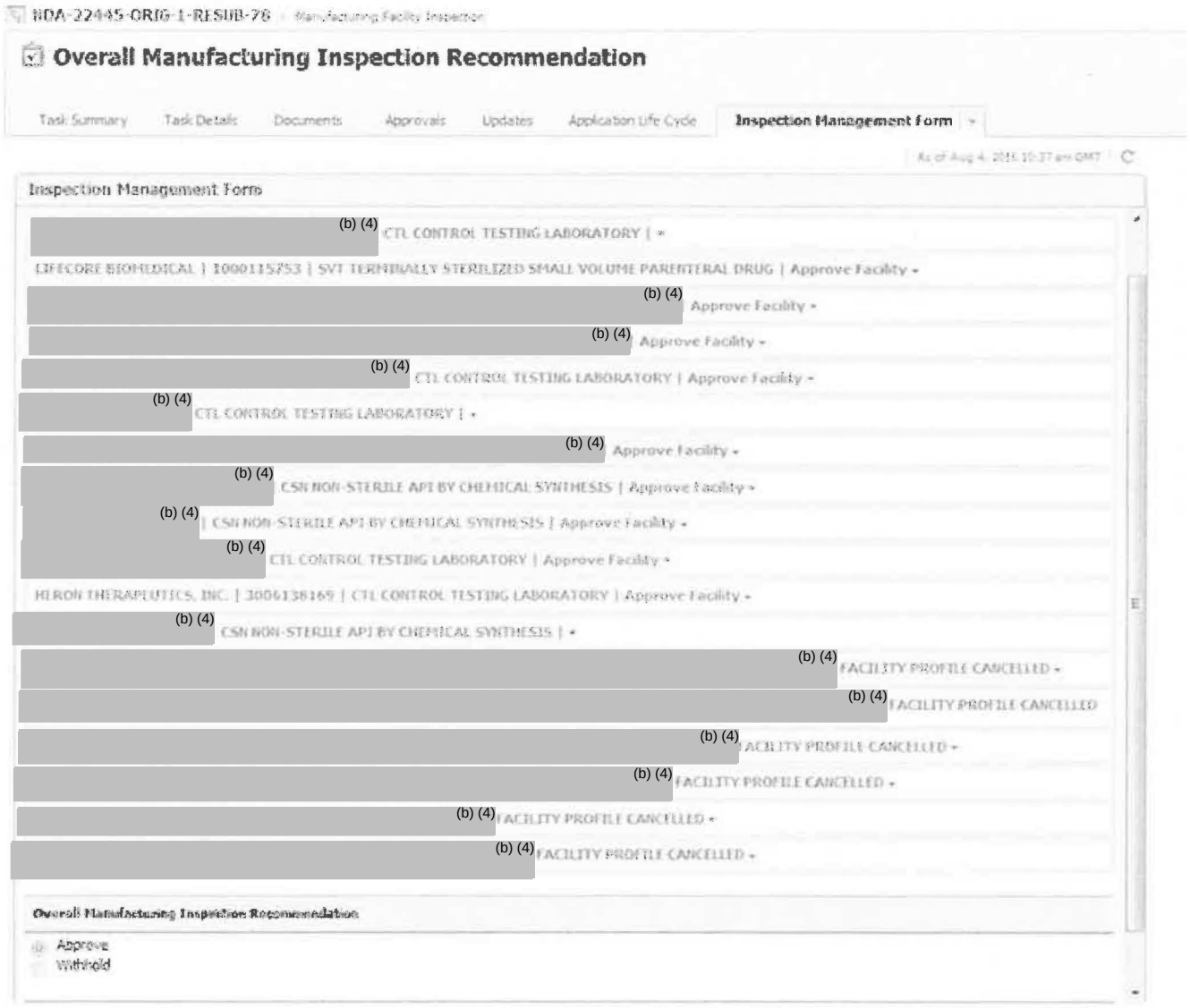
Attachments:

Attachment-1: Overall Manufacturing Inspection Recommendation



Attachment-2: Intercenter Consult Memorandum, CDER NDA 022445 - CDRH ICC1500527

Sustol CDRH Memo.pdf

Attachment-3:

NDA 22445
memo_labeling.pdf

APPEARS THIS WAY ON ORIGINAL

Danuta
Gromek-Woods

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Memorandum

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

Date: **March 27, 2013**

From: **Zhengfang Ge, Ph. D.**

Through: **Moo-Jhong Rhee, Ph.D.**
Chief, Branch IV
New Drug Quality Assessment Division II
ONDQA

To: **CMC Review #2 of NDA 22445**

Subject: **Final Recommendation**

The CMC Review #2 dated 27-Feb-2013 had noted the following three pending issues:

1. This NDA has ***not*** provided sufficient CMC information to assure identity, strength, purity, and quality of the drug product.
    - The specification is not complete pending resolution of In-Vitro Release (IVR) testing
2. Labels/labeling have ***not*** been finalized
3. An overall "Acceptable" recommendation from the Office of Compliance has ***not*** been made for the facilities involved.

And because of these deficiencies, in the CMC Review #2, this NDA was not recommended for approval from the ONDQA perspective.

On March 19, 2013, the Biopharm reviewer, Dr. T. Ghosh, concluded that the applicant has ***not*** resolved the deficiency for the *In-Vitro* release testing (see Biopharm Review by Dr. T. Ghosh, dated March 16, 2010, regarding Deficiencies for *IVR* testing in the CR letter of the original submission), rendering the specification for the drug product is inadequate.

Other than that, the applicant has resolved all other CMC related deficiencies adequately (see CMC Review #2 dated 27-Feb-2013).

Labeling issues have ***not*** been finalized pending resolution of dosage form nomenclature.

On March 26, 2013, the Office of Compliance issued an overall "***Withhold***" recommendation for the inspections of the manufacturing facilities.

Final Recommendation:

From the ONDQA perspective, this NDA is ***not*** recommended for ***approval*** in its present form based on the following:

1. 21 CFR 314.125(b)(1)
    - Inadequate specification for the drug product due to inadequate IVR testing as described in the Biopharm Review dated 19-March-2013 (see Biopharm Review by Dr. T. Ghosh)

2. 21 CFR 314.125(b)(6)
    - Labeling issues have ***not*** been finalized pending resolution of dosage form nomenclature, “extended release injection” vs “injection, extended release”.

3. 21 CFR 314.125(b)(13)
    - The office of Compliance has issued the overall “***Withhold***” recommendation for the facilities involved in this application (see the **Attachment**).

Attachment

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application:	NDA 22445/000	**Sponsor:**	AP PHARMA
Org. Code:	180		123 SAGINAW DR
Priority:	5S		REDWOOD CITY, CA 94063
Stamp Date:	18-MAY-2009	**Brand Name:**	APF530
PDUFA Date:	27-MAR-2013	**Estab. Name:**	
Action Goal:		**Generic Name:**	GRANISETRON (b) (4)
District Goal:	26-JAN-2013	**Product Number; Dosage Form; Ingredient; Strengths**	
		001; INJECTABLE; GRANISETRON; 10MG	

FDA Contacts:	J. DAVID	Project Manager	3017964247
	Z. GE	Review Chemist	3017961358
	M. KOWBLANSKY	Team Leader	3017961390

Overall Recommendation:	WITHHOLD	on 27-MAR-2013	by D. SMITH	(HFD-323)	3017965321
	WITHHOLD	on 12-MAR-2010	by A. ALEXANDROW	(HFD-001)	3017965363

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/s/

ZHENGFANG GE
03/27/2013

MOO JHONG RHEE
03/27/2013
Chief, Branch IV

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

Memorandum

Date: March 26, 2013

From: Steven Hertz, Consumer Safety Officer
Division of Good Manufacturing Practice Assessment (DGMPA)

Subject: Concurrence with District Office Withhold Recommendation
NDA 22445, Granisetron subcutaneous injection, 10mg

Through: Tara Gooen, Branch Chief (Acting)
New Drug Manufacturing Assessment Branch
Division of Good Manufacturing Practice Assessment (DGMPA)

To: OMPT/CDER/OND/ODEIII/DGIEP RPM

To: (b) (4) DO) Pre-Approval Manager

Applicant: A.P. Pharma
123 Saginaw Dr
Redwood City, CA 94063

Manufacturer: (b) (4)

The Office of Manufacturing and Product Quality (OMPQ) has completed its review of the establishment inspection report (EIR) for the inspection ending on (b) (4) (b) (4) Pre-approval coverage for NDA 22445 was provided during this inspection. The profile covered during this inspection was SVS.

OMPQ concurs with the (b) (4) DO recommendation to withhold approval of the subject application due to significant GMP deficiencies. The deficiencies uncovered during the inspection that warrant withholding approval of the subject application include the following:

- Electronic records do not meet access limitation and control requirements to ensure that they are secure and unaltered. On the recent inspection, investigators observed that laboratory liquid chromatograph data can be accessed, modified, and deleted by users with unauthorized system access. In their response, the firm provided SOPs for system security, but did not provide raw data and calculations for manual analysis to show that data previously generated in support of this application was accurate.

- On the recent inspection, investigators observed the firm in process of implementing changes to it's manufacturing process regarding installation of critical process equipment (b) (4) and modifying it's process flow documented in it's product application (b) (4) . This equipment had not been installed at the time of inspection. Additionally, this new equipment and process flow had not been communicated to the Agency

for review. Data from these changes and modifications have not been collected, but the firm admitted that the changes would affect product quality (b) (4) .

For these reasons and per FDA CPGM 7346.832 “Pre-Approval Inspections” Part V, specifically the lack of capacity to manufacture the drug product, we recommend to withhold approval for NDA 22445 until corrections are determined to be adequate.

If you have any questions, please contact me at 301-796-3203.

Steven Hertz
Consumer Safety Officer

Cc:

HFD-320 \\Cdsnas\ocs1\OC_320\HFD-323\Domestic PAI Case Management\2013\
CMS CASE ID: 67906

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/s/

STEVEN B HERTZ
03/26/2013

TARA R GOOEN
03/26/2013

Memorandum

Date: March 26, 2013

From: Steven Hertz, Consumer Safety Officer
Division of Good Manufacturing Practice Assessment (DGMPA)

Subject: Concurrence with District Office Withhold Recommendation
NDA 22445, Granisetron subcutaneous injection, 10mg

Through: Tara Gooen, Branch Chief (Acting)
New Drug Manufacturing Assessment Branch
Division of Good Manufacturing Practice Assessment (DGMPA)

To: OMPT/CDER/OND/ODEIII/DGIEP RPM

To: San Fransisco District (SAN-DO) Pre-Approval Manager

Applicant: A.P. Pharma
123 Saginaw Dr
Redwood City, CA 94063

Manufacturer: A.P. Pharma
123 Saginaw Dr
Redwood City, CA 94063
FEI: 3006138169

The Office of Manufacturing and Product Quality (OMPQ) has completed its review of the establishment inspection report (EIR) for the inspection ending on October 19th, 2012 of A.P. Pharma in Redwood City, CA. Pre-approval coverage for NDA 22445 was provided during this inspection. The profile covered during this inspection was CTL. During the inspection, it was noted that there are no approved products tested at this facility and so the firm does not have existing profile history.

A nine-item FDA 483 was issued to the firm on October 19th, 2012. The San Francisco District Office (SAN-DO) received a response letter from the firm on November 9th, 2012. The firm's response to one observation, concerning accuracy and robustness of test methods, was adequate. The firm's responses to the other eight observations were inadequate.

OMPQ concurs with the SAN-DO recommendation to withhold approval of the subject application due to significant GMP deficiencies. The deficiencies uncovered during the inspection that warrant withholding approval of the subject application include the following:

Systemic CGMP deficiencies:

- Electronic records do not meet validation or audit trail requirements to ensure that they are accurate, reliable, consistent, or unaltered. A retrospective assessment of a chromatograph system by the firm was not adequate because it did not ensure the security of the system during past analyses. Test results from this system, compared with manually re-calculated

results performed by the firm during the retrospective assessment, were in agreement; however the firm did not provide the Agency with raw data or example calculations for review.

- Electronic records do not meet access limitation and control requirements to ensure that they are secure and unaltered. The firm had responded that it had created two new SOPs concerning computer system and data security. However, on the recent inspection, investigators had determined that the firm had many instances of employees not following current SOPs. Additionally, these SOPs were not shown to be part of a standardized training method to ensure they would be adopted and followed by employees. Also, while the firm provided SOPs for QC Lab and Corporate IT security, there is no mention of additional computer systems (incoming materials and stability monitoring).

- On the recent inspection, investigators observed multiple instances of employees not following SOPs. The firm responded that it would improve employee training. However, the pervasiveness of the lack of following SOPs requires a follow-up inspection to ensure that employees are adequately trained and are actually following SOPs.

NDA 22445 specific deficiencies:

- Testing and release of drug product for distribution do not include appropriate laboratory determination and satisfactory conformance to the final specifications prior to release. For in-vitro release testing of drug product samples, carryover of active ingredients were observed in blank injections made between standard and sample injections in chromatographic run sequences. The firm responded by conducting an assessment on a lot of drug product, but did not perform an evaluation on other lots of the same drug product.

- Laboratory controls do not include the establishment of scientifically sound and appropriate specifications designed to assure that drug products conform to appropriate standards of identity, strength, quality, and purity. Drug product incubation sampling pull times were modified without supporting justification.

For these reasons and per FDA CPGM 7346.832 “Pre-Approval Inspections” Part V, we recommend to withhold approval for NDA 22445 until corrections are determined to be adequate.

If you have any questions, please contact me at 301-796-3203.

Steven Hertz
Consumer Safety Officer

Cc:

HFD-320 \\Cdsnas\ocs1\OC_320\HFD-323\Domestic PAI Case Management\2013\
CMS CASE ID: 59601

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/s/

STEVEN B HERTZ
03/26/2013

TARA R GOOEN
03/26/2013

Memorandum

Date: March 26, 2013

From: Steven Hertz, Consumer Safety Officer
Division of Good Manufacturing Practice Assessment (DGMPA)

Subject: Concurrence with District Office Withhold Recommendation
NDA 22445, Granisetron subcutaneous injection, 10mg

Through: Tara Gooen, Branch Chief (Acting)
New Drug Manufacturing Assessment Branch

Division of Good Manufacturing Practice Assessment (DGMPA)

To: OMPT/CDER/OND/ODEIII/DGIEP RPM

To: (b) (4) DO) Pre-Approval Manager

Applicant: A.P. Pharma
123 Saginaw Dr
Redwood City, CA 94063

Manufacturer: (b) (4)

The Office of Manufacturing and Product Quality (OMPQ) has completed its review of the establishment inspection report (EIR) for the inspection ending on (b) (4) (b) (4). Pre-approval coverage for NDA 22445 was provided during this inspection. The profile covered during this inspection was (b) (4).

A five-item FDA 483 was issued to the firm on January (b) (4) (b) (4) DO) received a response letter from the firm on January 24th, 2013. The firm's responses to one observation were inadequate.

OMPQ concurs with the (b) (4) DO recommendation to withhold approval of the subject application due to significant GMP deficiencies. The deficiencies uncovered during the inspection that warrant withholding approval of the subject application include the following:

- The firm failed to thoroughly review and investigate any unexplained discrepancy to its production and control records prior to batch release. The firm did not investigate multiple (b) (4) runs which exceeded specified down times when the load was interrupted during use. The firm's SOP regarding this issue specified that the firm must investigate any down time over it's specification to see if the (b) (4) exceeded its upper limit specification. The firm's response to this observation was inadequate in that it had not fully communicated to its customers the potential effects of (b) (4) runs which exceed

specified down times and how it may potentially impact the (b) (4) regulated products. Additionally, the firm did not perform an investigation into the product quality effect of exceeding downtime. While the firm did perform a retrospective analysis on 27 (b) (4) runs performed to date, relying on "historic (b) (4) data from previous technical exercises," the firm continues to work with customers to evaluate the potential impact to the respective quality of those products. The firm's investigation into the product quality impact of exceeding downtime during (b) (4) is not complete. The firm has not done an adequate study of the effects of (b) (4) run down time in which the (b) (4) but does not exceed its upper limit specification

For these reasons and per FDA CPGM 7346.832 "Pre-Approval Inspections" Part V, we recommend to withhold approval for NDA 22445 until corrections are determined to be adequate.

If you have any questions, please contact me at 301-796-3203.

Steven Hertz
Consumer Safety Officer

Cc:

HFD-320 \\Cdsnas\ocs1\OC_320\HFD-323\Domestic PAI Case Management\2013\
CMS CASE ID: 67808

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/s/

STEVEN B HERTZ
03/26/2013

TARA R GOOEN
03/26/2013

ONDQA - BIOPHARMACEUTICS REVIEW - ADDENDUM

NDA	22- 445 (Resubmission)
Applicant:	A. P. Pharma
Proposed Trade name:	Sustol®
Stamp Date	September 26, 2012
Amendment Date	October 18, 2012; February 22, 2013
Established Name:	Granisetron 2% (500mg drug product deliver 10 mg granisetron)
Dosage Form:	Extended Release Injection
Route of Administration:	Subcutaneous
Indication:	Prevention of nausea and vomiting associated with cancer chemotherapy
Primary Reviewer:	Tapash Ghosh, Ph. D.
Acting Team Leader:	John Duan, Ph. D.

Background: Please refer to the biopharmaceutics review (in DARRT dated March 13, 2013) for the resubmission for Granisetron Injection, extended release (APF530) dated September 26, 2012. The Biopharmaceutics commented on the evaluation of Biopharmaceutics deficiency No. 19, regarding the acceptance criteria for the IVR test. It was inferred that Deficiency No. 19 has been partially addressed and the information needed to set the final acceptance criteria for the IVR test can be provided at a later time as a Post Marketing Commitment.

However, in light of the fact that the resubmission will be getting another complete response (CR), the biopharmaceutics review will make this final recommendations as an amendment to the previous review in DARRT dated March 13, 2013.

RECOMMENDATION

ONDQA-Biopharmaceutics has reviewed the information provided in the resubmission of NDA 22-445 for Sustol® ER Injection to address Biopharmaceutics Deficiency No. 19, which was included in the Complete Response Letter issued by FDA on March 16, 2010.

From the Biopharmaceutics view point, the resubmission of NDA 22- 445 for Sustol® (granisetron 2%) Extended Release Injection is not recommended for approval.

Comments 1 to 3 below should be conveyed to the Applicant as appropriate.

COMMENTS (to be sent to the Applicant)

1. We noted that your proposed acceptance criteria of the *in vitro* drug release (IVR) test (b) (4) While we are aware of the complexity of the release of granisetron from this product, we also know that the acceptance criteria for the IVR test will be used as a major attribute to control the quality of your product. In this regard, we are concerned about the high level of variability for the different lots and especially (b) (4) the IVR profiles. Note that to reduce the variability that is currently observed at different time points of the drug release profile of your product, you may have to modify the IVR methodology. (b) (4)

2. Based on newly generated data, set the acceptance criteria for the IVR test of your product. Note that the criteria should also include specification-ranges for the (b) (4) release profile.

3. We will determine the final regulatory acceptance criteria for the IVR test of your product (b) (4) upon review of the IVR methodology information and data in the next submission.

Tapash K. Ghosh, Ph. D.
Primary Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

John Duan, Ph. D.
Acting Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

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/s/

TAPASH K GHOSH
03/19/2013

JOHN Z DUAN
03/19/2013

ONDQA - BIOPHARMACEUTICS REVIEW

NDA	22- 445 (Resubmission)
Applicant:	A. P. Pharma
Proposed Trade name:	Sustol®
Stamp Date	September 26, 2012
Amendment Date	October 18, 2012; February 22, 2013
Established Name:	Granisetron 2% (500mg drug product deliver 10 mg granisetron)
Dosage Form:	Extended Release Injection
Route of Administration:	Subcutaneous
Indication:	Prevention of nausea and vomiting associated with cancer chemotherapy
Primary Reviewer:	Tapash Ghosh, Ph. D.
Team Leader:	Angelica Dorantes, Ph. D.

SUMMARY

Background: Granisetron Injection, extended release (APF530) delivers 500.0 mg of polymeric formulation, containing 10.0 mg Granisetron base. The proposed drug product contains 2.0% (w/w) Granisetron base in 78.4% (w/w) Tri (ethylene glycol) poly (ortho ester) (TEG-POE, AP135) and 19.6% (w/w) Polyethylene Glycol Monomethyl Ether (MPEG-(b) (4)). The administered dose is 500mg.

Original Submission: The original NDA 22-445 for Sustol® (granisetron 2%) Extended Release Injection submitted on May 14, 2009, received a complete response action on March 16, 2012, due to several deficiencies from various reviewing disciplines. From the Biopharmaceutics perspective, the original Biopharmaceutics review (in DARRT 2/22/10) recommended non approval due to unacceptable *in vitro* release (IVR) specifications.

Resubmission: On September 26, 2012, the Applicant resubmitted NDA 22-445 providing their responses to the several deficiencies included in the CR letter. Deficiency No. 19 is the Biopharmaceutics deficiency.

Review: The Biopharmaceutics review is focused on the evaluation and acceptability of;

1) The information provided in the Applicant's response to Biopharmaceutics deficiency No. 19, regarding the acceptance criteria for the IVR test, and
2) The additional information provided in their subsequent responses dated October 18, 2012 and February 22, 2013, addressing additional information requests.

RECOMMENDATION

ONDQA-Biopharmaceutics has reviewed the information provided in the resubmission of NDA 22-445 for Sustol® ER Injection to address Biopharmaceutics Deficiency No. 19, which was included in the Complete Response Letter issued by FDA on March 16, 2010.

Deficiency No. 19

Your IVR specification proposing the following time points: (b) (4) *hours is not adequate.* (b) (4) *To address this deficiency, you should revise the dissolution specification with the suggested time points. You are advised to take into consideration the Agency's IVIVC guidance recommendation to select the specification range at any given time point.*

Based on the review of the provided information, Biopharmaceutics considers that,

A. Deficiency No. 19 has been partially addressed and,

B. The information needed to set the final acceptance criteria for the IVR test can be provided at a later time as a Post Marketing Commitment. The following comments should be conveyed to the Applicant.

COMMENTS (to be sent to the Applicant)

1. We noted that your proposed acceptance criteria of the *in vitro* drug release (IVR) test (b) (4) While we are aware of the complexity of the release of granisetron from this product, we also know that the acceptance criteria for the IVR test will be used as a major attribute to control the quality of your product. In this regard, we are concerned about the high level of variability for the different lots and especially (b) (4) the IVR profiles. Note that to reduce the variability that is currently observed at different time points of the drug release profile of your product, you may have to modify the IVR methodology. (b) (4)

2. At this point, we are willing to accept on an interim basis your proposed *in vitro* release test and latest proposed acceptance criteria, provided you agree to develop a less variable *in vitro* drug release testing methodology as a Post Marketing Commitment (PMC).

Interim IVR Method and Acceptance Criteria for Sustol® ER Injection

Drugs Name	Dosage Form	Apparatus	Temp.	Medium	Acceptance Criteria (% granisetron released)
Granisetron	Extended Release Injection (subcutaneous)	(b) (4)			

3. In essence, we want you to agree to the following post marketing commitment (PMC):

(b) (4)

4. We will determine the final regulatory acceptance criteria for the IVR test of your product at release and on stability upon review of the PMC's IVR data.

From the Biopharmaceutics view point, the resubmission of NDA 22- 445 for Sustol® (granisetron 2%) Extended Release Injection is recommended for approval, provided the Applicant agrees to the above post marketing commitment (PMC).

Comments 1 to 4 should be conveyed to the Applicant as appropriate.

Tapash K. Ghosh, Ph. D.
Primary Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Angelica Dorantes, Ph. D.
Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

BIOPHARMACEUTICS ASSESSMENT

Original NDA 22-445 for Sustol® (granisetron 2%) Extended Release Injection dated May 14, 2009, received a complete response action on March 16, 2012, due to several deficiencies from the various disciplines. Deficiency No. 19 was issued by Biopharmaceutics.

Deficiency No. 19.

Your IVR specification proposing the following time points: (b) (4) *hours is not adequate.* (b) (4) *To address this deficiency, you should revise the dissolution specification with the suggested time points. You are advised to take into consideration the Agency's IVIVC guidance recommendation to select the specification range at any given time point.*

Applicant's Response

In their response, the applicant states that they have revised the IVR test and acceptance criteria and their NDA resubmission incorporates FDA's request. The evaluation of the Applicant's response is presented in the following section.

In Vitro Release (IVR) Method:

(b) (4)

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(b) (4)

Based on the review of the overall information provided in the NDA resubmission and additional responses, Biopharmaceutics final recommendation for this NDA is as follows.

RECOMMENDATION

ONDQA-Biopharmaceutics has evaluated the information provided in the resubmission of NDA 22-445 to address Deficiency No. 19 and considers that this deficiency has been partially addressed by the Applicant. Biopharmaceutics considers that the information needed to set the final acceptance criteria for the IVR test can be provided at a later time as a Post Marketing Commitment. The following comments should be conveyed to the Applicant.

COMMENTS (to be sent to the Applicant)

1. We noted that your proposed acceptance criteria of the *in vitro* drug release (IVR) test (b) (4) While we are aware of the complexity of the release of granisetron from this product, we also know that the acceptance criteria for the IVR test will be used as a major attribute to control the quality of your product. In this regard, we are concerned about the high level of variability for the different lots and especially (b) (4) the IVR profiles. Note that to reduce the variability that is currently observed at different time points of the drug release profile of your product, you may have to modify the IVR methodology. (b) (4)

2. At this point, we are willing to accept on an interim basis your latest proposed acceptance criteria (highlighted below), provided you agree to develop a less variable *in vitro* drug release testing methodology as a Post Marketing Commitment (PMC).

(b) (4)

3.
. In essence, we are requesting that you agree to the following post marketing commitment (PMC):

4. We will determine the final regulatory acceptance criteria for the IVR test of your product at release and on stability upon review of the PMC's IVR data.

From the Biopharmaceutics view point, the resubmission of NDA 22- 445 for Sustol® (granisetron 2%) Extended Release Injection is recommended for approval, provided the Applicant agrees to the above post marketing commitment (PMC). Comments 1 to 4 should be conveyed to the Applicant as appropriate.

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/s/

TAPASH K GHOSH
03/13/2013

ANGELICA DORANTES
03/13/2013

NDA 22445

Sustol (granisetron) injection, extended release
10mg
A.P. Pharma

Zhengfang Ge, Ph.D.

Branch IV, Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment

For

Division of Gastroenterology and Inborn Errors Products

Table of Contents

Chemistry Review Data Sheet

1. NDA # 22445

2. REVIEW # 2

3. REVIEW DATE: Feb 27, 2013

4. REVIEWER: Zhengfang Ge, Ph. D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
See Review #1	Feb 23, 2010

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Resubmission	9/27/2012
Amendment	12/7/2012
Amendment	12/20/2012
Amendment	1/10/2013
Amendment	1/16/2013
Amendment	1/18/2013
Amendment	1/28/2013
Amendment	1/30/2013
Amendment	2/6/2013
Amendment	2/13/2013
Amendment	2/26/2013

7. NAME & ADDRESS OF APPLICANT:

Name:	A. P. Pharma
Address:	123 Saginaw Drive Redwood City, CA 94063
Representative:	John Barr
Telephone:	650-366-2626

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: SUSTOL
b) Non-Proprietary Name (USAN): Granisetron
c) CAS No: 109889-09-0
d) Code Name/# (ONDQA only): RM36, APF530
e) Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: 5
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

10. PHARMACOL. CATEGORY: 5-HT_3 Receptor Antagonist

11. DOSAGE FORM: injection, extended release

12. STRENGTH/POTENCY: 2% (500mg drug product deliver 10 mg granisetron)

13. ROUTE OF ADMINISTRATION: Subcutaneous Injection

14. Rx/OTC DISPENSED: _X_Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

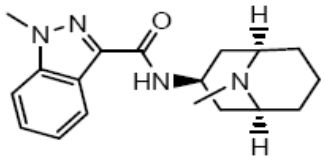
_____SPOTS product – Form Completed

___X__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

1-Methyl-N-[(1R,3r,5S)-9-methyl-9-azabicyclo[3.3.1]non-3-yl]-1H-indazole-3-carboxamide
or
endo-1-methyl-N-(9-methyl-9-azabicyclo[3.3.1]non-3-yl)-1H-indazole-3-carboxamide

Molecular Formula, Weight and Structure:



$C_{18}H_{24}N_4O$ m.w. 312.4

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	III	(b) (4)	Syringe component	3	Adequate	6/23/09	Reviewed by G. Arhin
	III		Syringe tip caps, stoppers. (b) (4)	3	Adequate	10/14/08 And 5/4/06	Reviewed by D. Klein for 4432/50 and by J. Salemme for 7025/65
	II		Sterilization of drug product	4	N/A		
	II		Drug substance manufacture	1	Adequate	Feb 4, 2010	Reviewed by Dr. J. Chang for this NDA
	II		Drug substance manufacture	1	Adequate	Jan 25, 2010	Reviewed by Dr. J. Chang for this NDA

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted

6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	68,213	

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Not Applicable		
EES	Pending		
Pharm/Tox	Acceptance criteria for impurities is acceptable, see review section P.5.1		Dr. T. Chakraborti
Biopharm	Acceptance criterion for dissolution test is pending		Dr. T. Ghosh
LNC	Not Applicable		
Methods Validation	Not Applicable		
DMEPA	See Labeling review		T. McMillan
EA	Categorical exclusion is granted		See review section IIB
Microbiology	Approval	1/29/2013	Dr. S. Donald

The Chemistry Review for NDA 22-445

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA has ***not*** provided sufficient CMC information to assure identity, strength, purity, and quality of the drug product (see section III. List of Deficiencies on page 75 of this review).

Labeling issues have ***not*** been finalized (see the List of Deficiencies on page 75 of this review).

An overall "Acceptable" recommendation from the Office of Compliance has ***not*** been made for the facilities involved.

Therefore, from the CMC perspective, this NDA is ***not*** ready for ***approval*** in its present form until all pending issues are resolved

1. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Substance:

The proposed drug substance is granisetron free base. Currently there are four granisetron drug products on the US market. Three of them contain granisetron HCl and one contains granisetron base.

The commercial drug substance suppliers include primary suppliers (b) (4) . The DMFs were reviewed by Dr. J. Chang for original submission and by this reviewer for the updated information and found adequate to support this NDA.

Drug Product:

The drug product is a viscous subcutaneous injection containing 2% w/w granisetron base (10mg) in 78.4% AP135 (tri(ethylene glycol) poly(ortho ester) polymer) and 19.6% MPEG- (b) (4)

(b) (4)

In the Agency's complete response for the original submission, the applicant was requested to include testing for low molecular weight impurities, unreacted monomers, and average molecular weight (Mn) or polydispersity ratio (PDI) in addition to weight average molecular weigh (Mw) in the novel excipient AP 135 specification and the drug product specification. The specifications for AP 135 and the drug product submitted in the resubmission have adequately addressed these issues. The final specification for the drug product is pending review for testing of In-Vitro release by biopharm reviewer Dr. T. Ghosh

Under the Agency's request, the container/closure system has been changed from 1.25mL glass syringe to 1mL glass syringe. The syringes are the same except the size difference. The manufacturing process of the drug product has been changed to terminal sterilization using gamma irradiation after filling the product into syringes (b) (4). The manufacturing process and process controls are revised accordingly and are adequate. Recommendation of the Approval has been received from Microbiology reviewer Dr. S. Donald.

Up to 24 months stability data are provided for the drug product using (b) (4) when stored at (2-8)ºC. The applicant was also requested to submit 3 months stability data for the drug product using terminal irradiation. The drug products are stable for 18 months based on the stability data for the (b) (4) batches. Out of specification is observed for In-Vitro release testing for the drug product using (b) (4) at month 24. Since the manufacturing process for the drug product using terminal irradiation (b) (4) is similar (b) (4), 18 months expiration dating period should be granted based on the stability data for the batches (b) (4).

The applicant proposed to use (b) (4) for established name. "granisetron" should be the established name. The name of the drug product should be expressed as Sustol(granisetron) Injection, extended release has been communicated to the applicant.

B. Description of How the Drug Product is Intended to be Used

The drug product is indicated for 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

The recommended dose is a single 10 mg subcutaneous injection approximately 30 minutes before the initiation of single-day chemotherapy. It may be given once every 7 days, and only on the day chemotherapy is given.

C. Basis for Not-Approval Recommendation

21 CFR 314.125 (b)(1)

- Inadequate specification for the drug product due to unresolved in-vitro release testing pending final Biopharm's recommendation.

21CFR314.125(b)(13)

- The overall "Acceptable" recommendation has ***not*** been issued from the Office of Compliance.

21CFR 314.125(b)(6)

- Labeling issues have ***not*** been finalized as of this review (see the **List of Deficiencies** on p. 75)

III. Administrative

A. Reviewer's Signature

In DFS

B. Endorsement Block

Chemist: Zhengfang Ge
Chemistry Branch Chief: Moo-Jhong Rhee

C. CC Block

Project Manager: J. Grewal
Pharmaceutical Assessment Lead: M. Kowblansky

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/s/

ZHENGFANG GE
03/05/2013

MOO JHONG RHEE
03/05/2013
Chief, Branch IV

Product Quality Microbiology Review

1/29/2013

NDA 022445:

Drug Product Name
Proprietary: Sustol Injection
Non-proprietary: granisetron (b) (4)

Review Number: 2

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
9/27/2012	9/27/2012	10/02/2012	10/05/2012
12/07/2012	12/07/2012	N/A	N/A
12/20/2012	12/20/2012	N/A	N/A
1/24/2013	1/25/2013	N/A	N/A

Submission History (for amendments only):

Submit	Received	Review Request	Assigned to Reviewer
5/16/2009	5/18/2009	N/A	N/A

Applicant/Sponsor
Name: A.P. Pharma, Inc.
Address: 123 Saginaw Drive
Redwood City, CA 94063

Representative: Michael A. Adam, Ph.D., Sr. Vice-President, R&D
Telephone: (650) 366 2626 x206

Name of Reviewer: Steven P. Donald, M.S.

Conclusion: Approval Recommended

Product Quality Microbiology Data Sheet

A. 1. TYPE OF SUBMISSION: NDA Resubmission

2. SUBMISSION PROVIDES FOR: New drug product and addressing deficiencies in Complete Response Letter (dated March 16, 2010).

3. MANUFACTURING SITE:

(b) (4)

4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY: Sterile, (b) (4) injectable formulation is provided in a 1.0 mL pre-filled (b) (4) long barrel glass syringes with 18 Gauge 5/8" thin wall needles for subcutaneous, abdominal administration; single use syringe.

5. METHOD(S) OF STERILIZATION: Terminal sterilization; gamma irradiation

6. PHARMACOLOGICAL CATEGORY: antiemetic

B. SUPPORTING/RELATED DOCUMENTS: N022445r1.doc, Product Quality Microbiology review of the original submission, dated 2/23/2010. DMF (b) (4)

September 12, 2011 submission; DMF (b) (4) review (b) (4)_2011Sept_12A1.doc, dated March 26, 2012.

C. REMARKS: The current submission is a resubmission to NDA 022445 (dated May 14, 2009) addressing deficiencies in Complete Response Letter (dated March 16, 2010). The applicant does not address each of the microbiology deficiencies separately, but provides new validation data and information in the resubmission that generally addresses the previous deficiencies. Data and information in the resubmission will be reviewed in the format of an original submission review. The subject drug product is referred to as granisetron (b) (4) APF530, or Sustol. An information request for product quality microbiology information was presented to the sponsor on November 14, 2012 and a response was received by the Agency on December 6, 2012. A review of the latest response is also included in this review.

A teleconference was held on December 18, 2012 between myself and A.P. Pharma representatives Michael Adam, Sr. VP, COO and Trisha Shimada, Project Manager. I informed them that 1.) terminal sterilization (b) (4) must be validated before approval and that they could not rely on dosing studies performed by the contractor using a general approach (b) (4) The representatives were also informed that 2.) samples on stability must represent the complete validated manufacturing process. To address these issues, the representatives agreed to provide dose mapping data (b) (4) Also requested during this Tcon were additional information for terminal sterilization lots 024502, 024503 and 024535 which have been placed on the stability protocol. This reviewer wanted to be sure that the lots on stability were representative of the validated manufacturing process. Information is to be provided on lot size, syringe filling location, terminal sterilization location, any supporting dose monitoring studies and an explanation of how the stability samples are representative of the manufacturing process. This last request was for clarification of the manufacturing process as there have been many process changes to date. These data for terminal sterilization validation and manufacturing history of the stability samples are provided in the 12/19/2012 submission. In the January 24, 2013, submission, the sponsor provides the results of dose mapping studies of an engineering lot performed at the (b) (4) location in order to show equivalency between the two terminal sterilization facilities.

filename: N022445r2.doc

Executive Summary

I. Recommendations

A. Recommendation on Approvability –

NDA 202245 is recommended for approval on the basis of product quality microbiology.

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable –N/A

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology -

(b) (4)

B. Brief Description of Microbiology Deficiencies

No product quality microbiology deficiencies were identified based upon the information provided.

C. Assessment of Risk Due to Microbiology Deficiencies – N/A

III. Administrative

A. Reviewer's Signature _____

Steven P. Donald, M.S.

B. Endorsement Block_____

Bryan Riley, Ph.D.
Team Leader

C. CC Block

N/A

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/s/

STEVEN P DONALD
01/30/2013

BRYAN S RILEY
01/30/2013
I concur.

OPS-MICROBIOLOGY REVIEW OF NDA MEETING PACKAGE (NDA 22-445)

I. NDA 22-445

REVIEW DATE:	25-APR-2011
MICROBIOLOGIST:	Steven Fong, Ph.D.
DRUG NAME:	Sustol (APF530, Granistron Injection)
SPONSOR:	A.P. Pharma, Inc. 123 Saginaw Drive Redwood City, CA 94063 Contact Person: John Barr 949-743-9228
DOCUMENT DATE:	30-MAR-2011 **CONSULT DATE:** 15-MAR-2011
DATE ASSIGNED:	15-MAR-2011
DOSAGE FORM:	Sterile, (b) (4) injectable

II. MANUFACTURER:

(b) (4)

III. REVIEW NOTES:

1. BACKGROUND

On 16-DEC-2010 and 23-DEC-2010 A.P. Pharma submitted requests for face-to-face, Type B meetings with the Agency to address clinical and CMC deficiencies, respectively, that were cited in a 16-MAR-2010 Complete Response letter for NDA 22-445. The requests for clinical and CMC meetings were granted 06-JAN-2011 and 17-JAN-2011, respectively, and the meetings were held 16-FEB-2011 and 31-MAR-2011. A Meeting Package dated 30-MAR-2011 for the 31-MAR-2011 CMC meeting was provided to the Reviewer on 16-MAR-2011. Answers to questions in the package were sent to the Applicant on 28-MAR-2011, and Applicant responses to the Agency's answers were received 30-MAR-2011.

The subject NDA describes a (b) (4) injectable gel intended for use as an anti-emetic in patients undergoing cancer chemotherapy. The original application proposed a manufacturing procedure (b) (4) Prior to injection the product was to be transferred to a 1 mL tuberculin syringe via a (b) (4) luer-to-luer connector. Microbiology quality concerns regarding this procedure were expressed by the Reviewer in teleconferences held 04-NOV-2009 and 02-DEC-2009. In response to these concerns, the Applicant submitted an NDA amendment on 02-FEB-2010 proposing an alternate manufacturing scheme in which the product is terminally sterilized (b) (4) by gamma irradiation at a dose of (b) (4) kGy. The amended NDA was assessed by the Reviewer in a 23-FEB-2010 microbiology quality review. This review cited deficiencies regarding the bioburden estimate used to calculate the irradiation dosage, and recommended that the minimum dose be increased to (b) (4) kGy based on guidelines presented in ANSI/AAMI 11137-2. The review also noted that insufficient justification was presented for the two syringe administration system, and recommended that terminal product sterilization (b) (4) Additional deficiencies

were cited regarding the identity of the gamma irradiation facility to be used for sterilization, dose mapping, and the method used for endotoxin testing. The cited deficiencies were conveyed to the Applicant in items 3a, 3b, 3c, and 4 of the 16-MAR-2010 Complete Response letter.

Responses to microbiology deficiencies 3a (b) (4) and 3c (proposed minimum irradiation dose too low) were included in the 16-MAR-2011 Meeting Package. The Applicant proposed that the two syringe system be discarded and replaced with a single, glass, (b) (4) 1.0 mL prefilled syringe that is directly used for patient injection. Drug product in these syringes will be terminally sterilized by gamma irradiation. The Applicant also proposed that bioburden testing be conducted (b) (4) as specified in ANSI/AAMI 11137-2. The maximum dose of (b) (4) kGy would be retained.

2. DISCUSSION

The Meeting Package contained two questions related to CMC-microbiology quality. These questions are copied below in bold font. Microbiology quality responses to the questions that were provided in the Agency's 28-MAR-2011 Meeting Package response are presented in regular font.

Revision of the Manufacturing Process to Use Terminal Sterilization.

1. Does the Agency agree with the terminal sterilization dose of (b) (4) kGy?

FDA Microbiology Quality 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 (b) (4) and the average bioburden is determined to be within (b) (4) CFU.

Drug Product

2. Does the FDA agree the switch (b) (4) to irradiation of the filled syringes produces product of equivalent quality?

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

Topics pertinent to microbiology quality were not discussed at the 31-MAR-2011 meeting.

Steven Fong, Ph.D.
Review Microbiologist

John Metcalfe, Ph.D.
Senior Microbiologist

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/s/

STEVEN E FONG
04/25/2011

JOHN W METCALFE
04/25/2011
I concur.

Memorandum

Date: March 12, 2010
From: Zhengfang Ge, Ph.D., Reviewer
Through: Moo-Jhong Rhee, Ph.D., Branch Chief
To: NDA 22-445
Subject: Addendum to Review #1 regarding manufacturing facility inspections

The pending CMC issues and labeling issues noted in the Review #1 are still unresolved. On March 12, 2010, the Office of Compliance issued an overall "Withhold" recommendation for the inspections of the manufacturing facilities.

Therefore, from the CMC perspective, this NDA is not recommended for approval in its present form.

(b) (4)

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

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/s/

ZHENGFANG GE
03/12/2010

MOO JHONG RHEE
03/12/2010
Chief, Branch III

NDA 22-445

Sustol (granisetron) injection, extended release
10mg
A.P. Pharma

Zhengfang Ge, Ph.D.

Branch III, Division of Pre-Marketing Assessment II
Office of New Drug Quality Assessment

For

Division of Gastroenterology Products

Table of Contents

Chemistry Review Data Sheet

1. NDA # 22-445

2. REVIEW # 1

3. REVIEW DATE: Feb 23, 2010

4. REVIEWER: Zhengfang Ge

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
None	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original submission	5/14/2009
Amendment 0001	7/9/2009
Amendment 0002	8/3/2009
Amendment 0004	9/16/2009
Amendment 0007	9/21/2009
Amendment 00013	1/25/2010
Amendment 00014	2/1/2010

Chemistry Assessment Section

7. NAME & ADDRESS OF APPLICANT:

Name:	A. P. Pharma
Address:	123 Saginaw Drive Redwood City, CA 94063
Representative:	John Barr
Telephone:	650-366-2626

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: SUSTOL
b) Non-Proprietary Name (USAN): Granisetron
c) CAS No: 109889-09-0
d) Code Name/# (ONDQA only): RM36, APF530
e) Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

10. PHARMACOL. CATEGORY: 5-HT_3 Receptor Antagonist

11. DOSAGE FORM: injection, extended release

12. STRENGTH/POTENCY: 2% (500mg drug product deliver 10 mg granisetron)

13. ROUTE OF ADMINISTRATION: Subcutaneous Injection

14. Rx/OTC DISPENSED: _X_Rx ___OTC

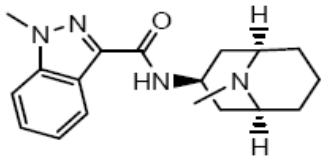
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

__X__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

1-Methyl-N-[(1R,3r,5S)-9-methyl-9-azabicyclo[3.3.1]non-3-yl]-1H-indazole-3-carboxamide
or
endo-1-methyl-N-(9-methyl-9-azabicyclo[3.3.1]non-3-yl)-1H-indazole-3-carboxamide

Molecular Formula, Weight and Structure:



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17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	III	(b) (4)	Syringe component	3	Adequate	6/23/09	Reviewed by G. Arhin
	III		Syringe tip caps, stoppers. (b) (4)	3	Adequate	10/14/08 And 5/4/06	Reviewed by D. Klein for 4432/50 and by J. Salemme for 7025/65
	II		Sterilization of drug product	4	N/A		
	II		Drug substance manufacture	1	Adequate	Feb 4, 2010	Reviewed by Dr. J. Chang for this NDA
	II		Drug substance manufacture	1	Adequate	Jan 25, 2010	Reviewed by Dr. J. Chang for this NDA
	II		Granisetron HCl manufacture	1	Not Adequate	Feb 17, 2010	Reviewed by Dr. J. Chang for this NDA

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application

5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	68,213	

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Not Applicable		
EES	Pending		
Pharm/Tox	Not Applicable		
Biopharm	Deficient	Feb 22, 2010	Dr. T. Ghosh
LNC	Not Applicable		
Methods Validation	Not Applicable		
DMEPA	Deficient	Feb 22, 2010	T. Jones-Smith
EA	Categorical exclusion is granted		See review section IIB
Microbiology	Deficient	Feb 23, 2010	Dr. S. Fong

The Chemistry Review for NDA 22-445

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA has ***not*** provided sufficient CMC information to assure identity, strength, purity, and quality of the drug product (see section III List of Deficiencies at the end of this review).

Labeling issues are still pending and facilities involved are also pending overall "Acceptable" recommendation from the Office of Compliance. Therefore from the CMC perspective, this NDA is ***not*** recommended for "***Approval***" in its present form until all pending issues are resolved

1. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Substance:

The proposed drug substance is granisetron free base. Currently there are four granisetron drug products on the US market. Three of them contain granisetron HCl and one contains granisetron base.

The commercial drug substance suppliers include primary suppliers (b) (4), and secondary supplier (b) (4). The DMFs are reviewed by Dr. J. Chang. DMF (b) (4) have been found adequate to support this NDA. However, there are still deficiencies unresolved for DMF (b) (4). Specification for the drug substance is provide in this NDA. The acceptance limits for Impurities (b) (4) in the drug substance specification are much higher than the limits provided in the drug product specification. Therefore, the applicant was requested to tighten the limits for impurity (b) (4) to be comparable to the drug product specification.

Drug Product:

The drug product is a viscous subcutaneous injection containing 2% w/w granisetron base (10mg) in 78.4% AP135 (tri(ethylene glycol) poly(ortho ester) polymer) and 19.6% MPEG- (b) (4)

(b) (4)

The proposed specification for AP135 includes controlling weight average molecular weigh (Mw), however, no control of polydispersity ratio (PDI) or number average molecular weigh (Mn) is proposed. Mw ($Mw= \Sigma_i NiMi^2/ \Sigma_i NiMi$ i=1 to ∞) is the average molecular weight weighted according to weight fraction. Mn ($Mn=\Sigma_i NiMi/ \Sigma_i Ni$ i=1 to ∞) is the average molecular weight weighted according to number fraction. Polydispersity ratio (PDI=Mw/Mn) is a fraction of a certain function group i that has reacted at a given polymerization stage. Unlike small molecules, the molecular weight of a polymer is not one unique value. Rather, a given polymer has a distribution of molecular weights depending on the way the polymer is produced. Polymer physical properties are functions of the molecular weight distribution. It depends on the number of polymer molecules as well as on the size of each polymer molecule. Therefore, controlling Mw alone is not sufficient. The applicant was requested to include a test for PDI or Mn in addition to Mw. Also, no data for low molecular weight impurities and unreacted monomers are provided as requested at the end-of-phase II meeting. The applicant was requested to include a test for low molecular weight impurities and unreacted monomers in the specification for this novel excipient.

API 135 for the drug product used in the clinical studies is manufactured at (b) (4) but it will be manufactured at (b) (4) for the commercial drug product. It is discovered that PDI and Mn results for AP135 batches used in the clinical studies are significantly different from the batches that are manufactured at the facility for the commercial batches. Since PDI and Mn can have a role in release of the active ingredient from the drug product, the applicant was requested to explain how to bridge the products that are different in these parameters and how the in-vitro release (IVR) test can discriminate the drug product with different Mw, Mn and PDI. In addition, it is found that the IVR method and release specification are not adequate, see biopharm review by Dr. T. Ghosh dated 22-Feb-2010.

Gel permeation chromatograph (GPC) is used to determine the molecular weight distribution Mw, Mn and PDI of the drug product and excipient AP135. The applicant claimed that this method could also measure small molecular impurities in the polymer. However, no validation is provided for the impurity measurements and no data is provided for these impurities in the drug products.

The manufacturing process of the drug product consists of (b) (4) The applicant conducted a feasibility study using gamma irradiation as a terminal sterilization step after filling the product into syringes at the Agency's request. The study concluded that the terminal irradiation is feasible and therefore the (b) (4) proposed in the original NDA is not acceptable, see microbiological review by Dr. S. Fong dated 23-Feb-2010.

The drug product is filled in 1.25mL (b) (4) glass syringe containing a (b) (4) Tip Cap, a (b) (4) Stopper and (b) (4) plunger rod. The drug product is transferred to a 1mL (b) (4) tuberculin syringe through a transferring connector before injection. To accurately dispense 500mg drug product, (b) (4) mg drug product is overfilled in the glass syringe to compensate loss during the transfer. The applicant was requested to include a test for the fill weight in the drug product specification. The transferring connector, (b) (4) tuberculin

(b) (4)

DMEPA reviewer identified several potential medical errors with the devices including potential over dose by injecting the drug directly from the 1.25mL glass syringe and potential wrong route of administration. Information requests regarding potential medical errors were communicated to the applicant through DMEPA, see DMEPA review dated 22-Feb-2010. Microbiologic reviewer also identified potential contamination during the transferring of drug product between two syringes and requested to prefill the drug product in 1 mL syringe directly.

Up to 24 months stability data are provided for the drug product. Stability data related to the drug substance such as assay and related substances are consistent when the drug product is stored at (2-8)ºC. The applicant proposed (b) (4) months expiration dating period for the drug product. However, this needs to be decided after receiving stability data for Mn/PDI and degradation information from AP135. The applicant was also requested to conduct an in-use stability study for the drug product after transferred to the 1m (b) (4) uberculin syringe.

The CMC deficiencies were communicated to the applicant on 17-Nov-2009 (listed in review section IV Attachment), the applicant submitted response in the amendment dated 19-Feb-2010. Review of this amendment is deferred to next review cycle.

Based on the requirements for the changes in the sterilization process and container closure system, the applicant will need to update the description of the manufacturing process and process controls including master batch record. Information of the new container closure system should also be submitted. Stability data for three batches of the drug product manufactured with the revised manufacturing process at the commercial manufacture sites and packaged in the new container closure system should be submitted for review.

The applicant proposed to use (b) (4) on established name. Based on the physical appearance and nature of extended release, the established name should be "(granisetron) injection, extend release". The Agency's decision needs to be communicated to the applicant.

B. Description of How the Drug Product is Intended to be Used

The drug product is indicated for 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

The recommended dose is a single 10 mg subcutaneous injection approximately 30 minutes before the initiation of single-day chemotherapy. It may be given once every 7 days, and only on the day chemotherapy is given.

C. Basis for Approvability or Not-Approval Recommendation

Impurities contributed by novel polymeric excipient AP135 are not controlled. Molecular weight distribution of AP135 is inadequately controlled. Issues with analytical methods including gel permeation chromatograph (GPC) and in-vitro release have not been resolved. Issues with the co-packaged devices for drug administration have not been resolved. The proposed (b) (4) process for the drug product is inadequate (*see deficiencies listed in review section III. List of Deficiencies on p.71*).

Proposed nomenclature for the dosage form is not acceptable.

The overall "Acceptable" recommendation has not been issued from the Office of Compliance.

III. Administrative

A. Reviewer's Signature

In DFS

B. Endorsement Block

Chemist: Zhengfang Ge
Chemistry Branch Chief: Moo-Jhong Rhee

C. CC Block

Project Manager: T. Phillips
Pharmaceutical Assessment Lead: M. Kowblansky

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22445	ORIG-1	AP PHARMA INC	APF530

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/s/

ZHENGFANG GE
02/25/2010

MOO JHONG RHEE
02/25/2010
Chief, Branch III

Product Quality Microbiology Review

23-FEB-2010

NDA 22-445/N-000

Drug Product Name
Proprietary: Sustol (proposed)
Non-proprietary: APF530 (granisetron injection)

Review Number: 1

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
19-FEB-2010	19-FEB-2010	N/A	N/A
01-FEB-2010	02-FEB-2010	N/A	N/A
16-MAY-2009	18-MAY-2009	N/A	22-MAY-2009

Applicant/Sponsor
Name: A.P. Pharma, Inc.
Address: 123 Saginaw Drive
Redwood City, CA 94063
Representative: John Barr
Sr. Vice-President, Research and Development
Patrick DeVillier
Sr. Director, Compliance
Telephone: 650-366-2626

Name of Reviewer: Steven Fong, Ph.D.

Conclusion: Recommended approvable pending resolution of microbiology quality deficiencies. Refer to review section 3 (page 18).

Product Quality Microbiology Data Sheet

A. 1. TYPE OF SUBMISSION: Original NDA.

2. SUBMISSION PROVIDES FOR: New drug product.

3. MANUFACTURING SITE: Provided in submission section 3.2.P.3.1.

(b) (4)

[redacted]

4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:

- Sterile, (b) (4) injectable formulation provided in a (b) (4) 1.25 mL Long (b) (4) glass syringe (1.25 mL (b) (4) syringe).
- Drug product is transferred from the 1.25 mL (b) (4) syringe to a 1.0 mL plastic tuberculin syringes prior to injection.

- (b) (4)
- Target dose is 500 mg of drug product with 10 mg of granisetron API in 0.4 mL.
- Subcutaneous, abdominal administration.

5. METHOD(S) OF STERILIZATION: Terminal gamma irradiation.

6. PHARMACOLOGICAL CATEGORY: Antiemetic.

B. SUPPORTING/RELATED DOCUMENTS: None.

C. REMARKS:

1) The proposed proprietary name, Sustol, was approved by DMEPA on 10-NOV-2009.

2) On 04-NOV-2009, the reviewer participated in a teleconference with the sponsor regarding its proposal (b) (4) rather than terminal gamma irradiation. The sponsor stated that it would report the results of terminal sterilization feasibility studies on 18-DEC-2009. On 16-DEC-2009, the sponsor notified the project manager that the results would not be available until January, 2010. As noted below in remarks item 5, an amendment detailing terminal sterilization feasibility was received 02-FEB-2010.

3) On 02-DEC-2009, the reviewer participated in a teleconference with the sponsor regarding its proposal that the product be transferred from a 1.25 mL (b) (4) syringe to a 1 mL tuberculin syringe prior to administration. Questions regarding the need for the transfer were posed by the reviewer and a representative from DMEPA. On 15-DEC-2009, DMEPA submitted an information request to the sponsor that included questions on the 2-syringe administration system. An amendment response was received 19-FEB-2010. The response contained information pertinent to microbiology quality issues and is considered in this review.

4) On 22-JAN-2010 the reviewer submitted an information request through the project manager to (b) (4) regarding the identity of the facilities in which the 1.25 mL (b) (4) syringe, syringe tip, and rubber stopper components (b) (4). A response was received 26-JAN-2010.

5) On 02-FEB-2010 the Agency received an amendment from the sponsor that provided the results of terminal sterilization feasibility studies. In the amendment cover letter, the sponsor requested that the portions of the original

application specific for (b) (4) be withdrawn and superseded with the terminal sterilization protocol and data presented in the amendment. In a subsequent telephone conversation with the project manager, the sponsor stated that it would submit a formal withdrawal request in March, 2010. This was beyond the deadline at which the review could be submitted before the PDUFA goal date. Given this consideration, the reviewer elected to disregard the (b) (4) information in the original submission, and review in its place the terminal sterilization information in the 02-FEB-2010 amendment.

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Executive Summary

I. Recommendations

A. Recommendation on Approvability – Recommended approvable pending resolution of microbiology quality deficiencies. Refer to microbiology deficiencies and comments presented on review page 18.

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable – N/A

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology – (b) (4)

B. Brief Description of Microbiology Deficiencies –

- Product filled into 1.25 mL (b) (4) syringes must be transferred to a 1 mL tuberculin syringes prior to dosing. Inadequate justification is provided for why the product cannot be filled into a syringe that permits direct product administration. Dosing and microbiology quality control studies should be performed with a syringe that allows for direct administration.
- Dose determinations based on ISO 11137-2 Method 1 utilized a (b) (4). The determination should be based on a higher estimate that allows for potential fluctuations in average bioburden.
- Inadequate information is provided regarding the location and description of the irradiation facility intended for commercial production, and the terminal sterilization irradiation process. Dosing determination and dose mapping studies should be performed at the facility intended for commercial irradiation.
- Inadequate information was provided regarding the most valid dilution and routine dilution to be used for product endotoxin determination.

C. Assessment of Risk Due to Microbiology Deficiencies - Failure to address the product quality microbiology deficiencies could result in an increased risk of product contamination.

III. Administrative

A. Reviewer's Signature _____

Steven E. Fong, Ph.D.
Microbiology Reviewer

B. Endorsement Block _____

James McVey
Team Leader, New Drug Microbiology

C. CC Block: N/A

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22445	ORIG-1	AP PHARMA INC	APF530

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/s/

STEVEN E FONG
02/23/2010
Recommended approvable pending resolution of microbiology quality deficiencies.

JAMES L MCVEY
02/23/2010
I concur.

ONDQA (Biopharmaceutics) Review

NDA: 22-445 (000)
Submission Date: 05/14/09
Product: 2% Granisetron Injection, extended release, for SC use
Type of Submission: Original Submission
Sponsor: A. P. Pharma, Inc.
Reviewer: Tapash K. Ghosh, Ph.D.

Background: The sponsor, A.P. Pharma, submitted an original New Drug Application (NDA) for drug product APF530 (granisetron injection, extended release, for subcutaneous use, a serotonin subtype 3 antagonist (5HT3) for the indication

- Moderately emetogenic cancer chemotherapy - prevention of acute and delayed nausea and vomiting associated with initial and repeat courses
- Highly emetogenic cancer chemotherapy - prevention of acute nausea and vomiting associated with initial and repeat courses.

The recommended dosage of APF530 is a single 10 mg SC dose administered approximately 30 minutes before the initiation of single-day chemotherapy. It may be given once every 7 days, and only on the day chemotherapy is given.

APF530 must be transferred to the supplied dosing syringe just prior to use. Thirty minutes prior to injection, APF530 needs to be removed from refrigerator (2° to 8°C (36° to 46 °F) to allow it to come to room temperature.

The sponsor developed an *in vitro* release (IVR) method (b) (4) . The following multi-point IVR specifications have been proposed by the sponsor:

Test Identity	***Acceptance Criteria***
In-vitro release of Granisetron @ 37^0C	(b) (4)

Recommendation: The *in-vitro* release study report as submitted is not complete.

The following comments should be sent to the sponsor:

- *IVR methodology includes sampling at time points* [redacted] *The sponsor is also advised to take into consideration the recommendation of the Agency's IVIVC guidance to select the specification range at any given time point.*

- *Please explain why you could not develop an IVIVC as you initially proposed.*

- *As shown in report DR-919-079, Mn and PDI are significantly different for AP135 batches manufactured at* [redacted]*. As these parameters can have a role in release of API from the product, which in turn will have an effect on systemic availability, please explain why you request the Agency to approve both sites and/or how you plan to bridge the products manufactured at these two sites. Traditionally, under similar situations, a BE study is needed unless it can be explained by an established IVIVC.*

- *Please explain how the proposed In-Vitro Release (IVR) methodology can discriminate products using polymeric excipient (AF135) with different Mw, Mn and PDI.*

Tapash K. Ghosh, Ph. D.
Primary Reviewer

FT by Patrick Marroum, Ph. D. _____

Description and Composition of the Drug Product [APF530, Subcutaneous Injectable]

The drug product, APF530, is a Tri(ethylene glycol) poly(ortho ester) polymer (known as TEG-POE)-based formulation containing Granisetron base. APF530 is a sterile (b) (4) injectable formulation supplied in 1.25 ml glass syringes containing amounts of drug product targeted to deliver 500 mg of drug product, i.e. 10 mg of Granisetron. An overfill mass of (b) (4) mg is contained in each dose unit to compensate for hold up of drug product in the transfer from primary container closure syringe to dose administration syringe.. The density of APF530 is 1.18 g/mL.

The complete statement of the components and quantitative composition of APF530, 500 mg, the proposed commercial drug product, is tabulated below.

Table 1: Composition of APF530, 500 mg

Component	Concentration (% w/w)	To deliver Concentration (mg/unit)	To fill Concentration (mg/unit)	Function	Reference to Quality Standard
AP135	78.4	392	(b) (4)	Excipient	Manufacturer[1]
MPEG (b) (4)	19.6	98		Excipient	NF
Granisetron[4]	2	10		Active	Manufacturer[2]
Totals	100	500			

[1] Acceptance Criteria developed by manufacturer and A.P. Pharma
[2]Acceptance Criteria based on manufacturer specifications
[3]Polyethylene Glycol Monomethyl Ether, A.P. Pharma compositional code: (b) (4)
[4]A.P. Pharma compositional code: RM36

OVERVIEW OF DISSOLUTION TESTING

(b) (4)

Reviewer's Comments:

The validation studies conducted have demonstrated the applicability of In-Vitro Release method (b) (4) [redacted]

However, the following issues need to be addressed:

- *IVR methodology includes sampling at time points* (b) (4) [redacted] *. The sponsor is also advised to take into consideration the recommendation of the Agency's IVIVC guidance to select the specification range at any given time point.*

- *The sponsor needs to clearly identify the clinical batches used to establish the proposed IVR specifications. Raw data on in-vitro release from those batches needs to be submitted preferably in electronic format.*

- *A full description of the method proposed for the IVR needs to be submitted.*

- *According to the sponsor,* (b) (4) [redacted]

- *Full details of HPLC method to quantitate granisetron* (b) (4) *with data demonstrating the stability of granisetron* (b) (4) *following sampling until analysis needs to be submitted.*

- *As statistical interpolations have been used, full report on the statistical regression analysis used for interpolation should be submitted.*

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
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/s/

TAPASH K GHOSH
02/22/2010

PATRICK J MARROUM
02/22/2010