

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**022445Orig1s000**

**OTHER REVIEW(S)**

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## MEMORANDUM

### REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)  
Office of Medication Error Prevention and Risk Management (OMEPRM)  
Office of Surveillance and Epidemiology (OSE)  
Center for Drug Evaluation and Research (CDER)

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**Date of This Memorandum:** August 2, 2016  
**Requesting Office or Division:** Division of Gastroenterology & Inborn Error Products (DGIEP)  
**Application Type and Number:** NDA 22445  
**Product Name and Strength:** Sustol (granisetron) injection, extended release 10 mg/0.4 mL  
**Submission Date:** May 24, 2016 & July 6, 2016  
**Applicant/Sponsor Name:** Heron Therapeutics, Inc.  
**OSE RCM #:** 2015-1643  
**DMEPA Primary Reviewer:** Matthew Barlow, RN, BSN  
**DMEPA Team Leader:** Mishale Mistry, PharmD, MPH

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#### 1 PURPOSE OF MEMO

DGIEP requested that we review the revised carton and container labels and revised IFU for Sustol (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.<sup>1</sup>

#### 2 CONCLUSION

The revised carton and container labeling and revised IFU for Sustol are acceptable from a medication error perspective. We have no further recommendations at this time.

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<sup>1</sup> Barlow, M. Label and Labeling Review for Sustol (NDA 22445). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2016 Apr 25. 15 p. OSE RCM No.: 2015-1643.

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/s/  
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MATTHEW J BARLOW  
08/03/2016

MISHALE P MISTRY  
08/03/2016

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology**

**Drug Utilization Review**

Date: July 11, 2016

Reviewer(s): Patty Greene, Pharm.D., Drug Utilization Analyst  
Division of Epidemiology II (DEPI II)

Acting Team Leader: Travis Ready, Pharm.D.  
Division of Epidemiology II (DEPI II)

Deputy Director:  
for Drug Utilization Grace Chai, LCDR, Pharm.D.  
Division of Epidemiology II (DEPI II)

Drug Name(s): Ondansetron, Granisetron, and Palonosetron

Application Type/Number: Multiple

Applicant/sponsor: Multiple

OSE RCM #: 2016-923

**\*\*This document contains proprietary drug use data obtained by FDA under contract. The drug use data/information cannot be released to the public/non-FDA personnel without contractor approval obtained through the FDA/CDER Office of Surveillance and Epidemiology.\*\***

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## EXECUTIVE SUMMARY

This review was prompted by the Division of Gastroenterology and Inborn Error Products (DGIEP) in response to a new drug application (NDA) resubmission for Sustol (granisetron) injection, extended release. Sustol injection is pending approval for the proposed indication of the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of cancer chemotherapy, including, but not limited to, highly emetogenic chemotherapy. The Sponsor submitted (b) (4) a deferred pediatric study request for pediatric patients (b) (4) to 18 years of age. As a result, DGIEP requested the Division of Epidemiology II (DEPI II) provide estimates for the number of pediatric patients who received granisetron, palonosetron, and ondansetron during recent years for chemotherapy-related nausea and vomiting.

In support of this request, utilization of granisetron, palonosetron, and ondansetron in the respective primary settings of distribution was assessed for years 2012 through 2015. For ondansetron, approximately (b) (4) with a hospital discharge billing for ondansetron in the U.S. non-federal hospital setting were pediatric patients ages 0-17 years in year 2015. Among the pediatric patients with a billing for ondansetron, the proportion of use was slightly higher among pediatric patients aged 0-5 years compared to pediatric patients aged 6-12 years or 13-17 years. In terms of the location of billing of ondansetron by hospital unit, the oncology department accounted for less than (b) (4) % of pediatric patients with a hospital discharge billing for ondansetron over the examined time. However, hospital location of care (e.g. oncology wards) data as a marker for ondansetron use in CINV should not be overstated as patients can be treated for CINV in other departments such as the outpatient department. In addition, pediatric utilization of ondansetron may be underestimated in this study as it does not include utilization in standalone pediatric or pediatric oncology hospitals.

We also examined pediatric utilization of granisetron and palonosetron in the primary settings of distribution for these drugs based on healthcare claims from a **sample** of outpatient pharmacies, facilities, physician practices, and outpatient hospital settings from 2012 through 2015, cumulative. Across the 4-year period in this sample population, the proportion of pediatric patients with a healthcare claim for granisetron was low at (b) (4) % of total patients while pediatric utilization of palonosetron was (b) (4) . Location of care utilization data for granisetron and palonosetron were not available at this time.

In conclusion, although the extent of pediatric utilization of 5HT-3 receptor antagonist for CINV is unclear, a large number of pediatric patients are administered oral or injectable ondansetron.

## 1 INTRODUCTION

### 1.1 BACKGROUND

The Division of Gastroenterology and Inborn Error Products (DGIEP) is reviewing a new drug application (NDA) resubmission for Sustol (granisetron) injection, extended release.

(b) (4)  
a deferred pediatric study for pediatric patients<sup>(b) (4)</sup> to 18 years of age was requested by the Sponsor due to the recent completion of adult studies which are pending approval.

In support of their assessment, DGIEP requested the Division of Epidemiology II (DEPI II) provide drug utilization data for ondansetron as well as other 5HT-3 receptor antagonist used in the treatment of chemotherapy-induced nausea and vomiting. For this request, DEPI II is providing national estimates of unique patients with a hospital discharge billing for ondansetron, as well as a **sample** of patients with a claim for granisetron and palonosetron in the primary settings of care where these products are sold. Because of the differences in the primary settings of care where these products are distributed, national use estimates are available only for ondansetron. In addition, due to the lack of specificity in the available medical diagnosis codes, we are providing hospital discharge billing for ondansetron stratified by hospital location of care. Hospital location of care or services may serve as a marker for possible chemo-related treatment of nausea and vomiting. Location of care for granisetron and palonosetron were not available at this time.

### 1.2 PRODUCT INFORMATION

Ondansetron, granisetron, and palonosetron are selective 5HT-3 receptor antagonists indicated for the prevention of chemotherapy-induced and post-operative nausea and vomiting in adults and pediatric patients. Ondansetron was the first selective serotonin antagonist approved for marketing on January 4, 1991 under NDA 20-007. Product information for ondansetron, granisetron, and palonosetron are provided in Table 1.<sup>1</sup>

| Molecule           | Product | Application | Formulation | Pediatric Age Indication |
|--------------------|---------|-------------|-------------|--------------------------|
| <b>Ondansetron</b> |         |             |             |                          |
|                    | Zofran  | NDA 020007  | Injectable  | 1 month to 12 years      |
|                    |         | NDA 020403  |             | 6 months to 18 years     |
|                    |         | NDA 020103  | Tablet      | 4 to 18 years            |
|                    |         | NDA 020605  | Solution    | 4 to 18 years            |
|                    |         | Multiple    | Multiple    | 6 months to 18 years     |

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<sup>1</sup> U.S. Food and Drug Administration: Drugs@FDA. Accessed May 2016. Available at: [http://www.accessdata.fda.gov/drugsatfda\\_docs](http://www.accessdata.fda.gov/drugsatfda_docs)

|                     |                |                       |                                                    |
|---------------------|----------------|-----------------------|----------------------------------------------------|
|                     | ANDAs          | formulations          | 4 to 18 years                                      |
| Zofran ODT          | NDA 020781     | Tablet                | 4 to 18 years                                      |
|                     | Multiple ANDAs | Tablet                | 4 to 18 years                                      |
| Zuplenz             | NDA 022524     | Film                  | 4 to 11 years                                      |
| <b>Palonosetron</b> |                |                       |                                                    |
| Aloxi               | NDA 021372     | Injectable            | 1 month to 16 years                                |
|                     | Multiple ANDAs | Injectable            | 1 month to 16 years                                |
| <b>Granisetron</b>  |                |                       |                                                    |
|                     | Multiple ANDAs | Multiple formulations | Injectable: 2 to 16 years<br>Tablet: Not indicated |
| Sancuso             | NDA 022198     | Film                  | Not indicated                                      |

## 2 METHODS AND MATERIAL

Proprietary drug utilization databases available to the Agency were used to conduct this analysis (see the **Appendix** for the database descriptions).

### 2.1 DETERMINING SETTINGS OF CARE

The IMS Health, IMS National Sales Perspectives™ (NSP) database was used to determine the various retail and non-retail channels of distribution by the manufacturers for ondansetron, granisetron, and palonosetron. Sales data for year 2015 indicated that approximately (b) (4)% of ondansetron packages were distributed to non-retail pharmacy settings (mainly non-federal hospitals), (b) (4)% to outpatient retail pharmacy, and (b) (4) to mail-order/specialty pharmacies.<sup>2</sup> For the same period, approximately (b) (4)% of granisetron packages were distributed to non-retail pharmacy settings (mainly clinics), (b) (4)% to outpatient retail pharmacy, and (b) (4)% to mail-order/specialty pharmacies. In 2015, nearly (b) (4)% of palonosetron packages sold were distributed to non-retail pharmacy settings (mainly clinics), while less than (b) (4)% were distributed to outpatient retail and mail-order/specialty pharmacies combined. As a result, only U.S. non-federal hospital settings were examined for ondansetron utilization. Outpatient healthcare claims from a sample of clinic settings, outpatient pharmacies, and physician's offices were assessed for granisetron and palonosetron.

### 2.2 DATA SOURCES USED

IMS, Inpatient HealthCare Utilization System (IHCareUS) was used to provide national estimates of patients with a hospital discharge billing for ondansetron from U.S. non-federal hospitals, stratified by patient age (0-5, 6-12, 13-17, and 18+ years), from 2012 through 2015 annually. We also examined the nationally estimated number of pediatric patients with a hospital discharge billing for ondansetron from U.S. non-federal hospitals,

<sup>2</sup> IMS Health, IMS National Sales Perspectives™. 2015. Extracted May 2016. File: NSP 2016-923 5HT3 channels 5-6-16.xlsx

stratified by patient age and location of care, from 2012 through 2015 cumulative. Location is the area in the hospital where the patient was on the day of treatment. Because a patient can be in multiple locations on the same day or across multiple days during the same inpatient stay, the percentage of patients across locations is much higher than the total unique patients in each age group.

Symphony Health Solutions' IDV (Integrated Dataverse) was used to provide the number of patients with an outpatient prescription or medical claim for granisetron or palonosetron from a **sample** of 18,303 pharmacies and 5,825 clinics, outpatient hospital settings, outpatient facilities, physician's offices, stratified by patient age (0-5, 6-12, 13-17, and 18+ years), from 2012 through 2015 cumulative. Patient selection was based on the presence of prescription claims and/or medical claims using the National Drug Codes (NDCs) and/or Healthcare Common Procedure Coding System (HCPCS) for granisetron and palonosetron. Projections of these data for national-level estimates were not available at the time of this review.

### 3 RESULTS

(b) (4)



## 4 DISCUSSION

DEPI II was requested to provide estimates for the number of pediatric patients who received granisetron, palonosetron, and ondansetron during recent years for chemotherapy-related nausea and vomiting. For this assessment, we examined the extent of pediatric use for ondansetron, granisetron, and palonosetron based on the primary setting of care where these products are sold. Ondansetron was primarily sold to non-federal hospitals while granisetron and palonosetron were primarily sold to outpatient clinics.

National estimates of use were available in the non-federal hospital setting for ondansetron only. Our findings show that approximately (b) (4) pediatric patients aged 0-17 years were administered injectable or oral ondansetron in the hospital setting in 2015, accounting for approximately (b) (4) of total patients with a hospital discharge billing for ondansetron. The proportion of use was slightly higher among pediatric patients aged 0-5 years compared to pediatric patients aged 6-12 years or 13-17 years.

However, there are no ICD diagnosis codes to identify the extent of pediatric use for 5HT-3 receptor antagonists in chemotherapy-induced nausea and vomiting (CINV) versus post-operative nausea and vomiting (PINV). As a possible proxy of utilization for these indications, utilization by the location of care was used to help distinguish administration in the oncology and surgery departments. We found that the vast majority of ondansetron administration was billed from the outpatient hospital department, followed by the surgical department. Administration of ondansetron in the oncology department based on billing data was very low. However, it should be noted that outpatient hospital department likely includes encounters from patients with general nausea and vomiting, CINV, or PINV from scheduled outpatient visits on the hospital campus.

Of note, the pediatric utilization identified in our analyses is likely an underestimation of pediatric utilization of ondansetron in the hospital setting. IMS Hospital CDM database does not include data from children's hospitals, children's oncology hospitals, Federal hospitals, including VA facilities, and some other specialty hospitals in their sample and does not necessarily represent all acute care hospitals in the U.S. in all markets. Caveats of the IMS CDM data source are common to this type of hospital charge information, but are mostly limited to limitations of charge descriptions and what is actually entered by the sample hospitals. However, validations of IMS' Hospital CDM data using both the National Hospital Discharge Survey (NHDS) and the AHRQ HCUP data have shown IMS' patient level data to be representative and accurate across multiple therapeutic areas.

A different data source containing unprojected data from a sample of pharmacies and healthcare settings was used to assess the utilization of granisetron and palonosetron based on the primary setting of distribution for these drugs to outpatient clinics. At the time of this review, national estimates of use were not available in the outpatient clinic setting. Therefore, we examined healthcare claims to provide the number of patients with an outpatient prescription or medical claim for granisetron or palonosetron from a **sample** of 18,303 pharmacies and 5,825 clinics, outpatient hospital settings and facilities, and physician's offices across a 4-year period from 2012 through 2015. Our findings show that for granisetron and palonosetron, pediatric patients aged 0-17 years accounted for a small proportion of the patient population. Pediatric patients aged 0-17 years accounted for (b) (4) of the total use for granisetron, of which the proportion of use was slightly higher among pediatric patients aged 13-17 years compared to pediatric patients aged 0-5 years or 6-12 years. The use of palonosetron among pediatric patients was negligible. Of note, these results may not be generalizable to other settings of care such as inpatient settings and may underrepresent use captured by other payment methods such as cash or Medicaid. Further analysis of administration by type of facility (e.g. oncology clinics) was not available at the time of this review.

## 5 CONCLUSION

Although the extent of pediatric utilization for CINV is unclear, a large number of pediatric patients are administered ondansetron when compared to granisetron or palonosetron. In 2015, approximately (b) (4) pediatric patients aged 0-17 years were administered oral or injectable ondansetron in the U.S. non-federal hospital setting. Pediatric utilization of ondansetron may be underestimated in this study as it does not include utilization in standalone pediatric or pediatric oncology hospitals.

## 6 APPENDIX

### DRUG USE DATABASE DESCRIPTIONS

#### **IMS Health, IMS National Sales Perspectives™: Retail and Non-Retail**

The IMS Health, IMS National Sales Perspectives™ measures the volume of drug products, both prescription and over-the-counter, and selected diagnostic products moving from manufacturers into various outlets within the retail and non-retail markets. Volume is expressed in terms of sales dollars, eaches, extended boxes, and share of market. These data are based on national projections. Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings.

#### **IMS, Inpatient HealthCare Utilization System (IHCareUS)**

The IMS, Inpatient HealthCare Utilization System (IHCareUS) provides hospital inpatient and outpatient emergency department encounter transactions and patient level data drawn from hospital operational files and other reference sources. Encounter information is available from mid-2001, are collected weekly and monthly and are available 25-30 days

after the end of each monthly period. This robust data set includes >620 hospitals with hospital inpatient and outpatient encounter data linked to each appropriate patient as well as to select individual hospital departments by anonymized, consistent, longitudinal patient identifiers. These data include >16 million patients and >65 million annual hospital encounters (including ED visits) representing acute care, short-term hospital inpatient sites, and their associated hospital emergency departments in order to measure and track the near term health care utilization of hospitalized patients. Each hospital patient encounter includes detailed drug, procedure, device, diagnosis, and applied charges data as well as location of initiation of each service within the hospital setting of care (e.g. Pediatric, ICU) by day for each patient's entire stay, as well as patient demographics and admission/discharge characteristics. IMS' datasets are geographically representative, and include claims across all third-party payer types, including commercial insurers, Medicare, Medicare Part D, Medicaid and other payer types.

**Symphony Health Solutions' IDV® (Integrated Dataverse)**

Symphony Health Solutions' IDV (Integrated Dataverse) contains longitudinal patient data sources that capture adjudicated prescription, medical, and hospital claims across the United States for all payment types, including commercial plans, Medicare Part D, cash, assistance programs, and Medicaid. The IDV contains over 10 billion prescriptions claims linked to over 220 million unique prescription patients of with an average of 4.2 years of prescription drug history. Claims from hospital and physician practices include over 190 million patients with CPT/HCPCS medical procedure history as well as ICD-9 diagnosis history of which nearly 140 million prescription drug patients are linked to a diagnosis. The overall sample represents over 54,000 pharmacies, 1,500 hospitals, 800 outpatient facilities, and 80,000 physician practices.

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/s/  
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PATTY A GREENE

07/11/2016

drug use data cleared by database vendors 7/11/16

TRAVIS W READY

07/18/2016

GRACE CHAI

07/18/2016



**DEPARTMENT OF HEALTH & HUMAN SERVICES** Public Health Service

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Food and Drug Administration  
Office of New Drugs/Office of Drug Evaluation IV  
Division of Pediatric and Maternal Health  
Silver Spring, MD 20993  
Telephone 301-796-2200  
FAX 301-796-9855

**MEMORANDUM TO FILE**

**Pediatric Labeling Review**

**From:** Amy M. Taylor, MD, MHS Medical Officer  
Division of Pediatric and Maternal Health

**Through:** Hari Cheryl Sachs, MD, Team Leader  
Division of Pediatric and Maternal Health

Lynne P. Yao, MD, Director  
Division of Pediatric and Maternal Health

**NDA Number:** 22-445

**Sponsor:** Heron Therapeutics

**Drug:** Sustol<sup>®</sup> (granisetron) Injection, extended release

**Dosage form and route of administration:** Injection for subcutaneous use

**Proposed Indication:** For the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of cancer chemotherapy, including, but not limited to, highly emetogenic chemotherapy

**Consult request:** The Division of Gastroenterology and Inborn Errors Products (DGIEP) requests DPMH's assistance with labeling.

**Background**

The sponsor submitted an original NDA (22-445) on May 7, 2009. The application received a complete response (CR) on March 16, 2010 for multiple CMC and clinical deficiencies and again on March 27, 2013 based on concerns with the human factors

study, lack of support for the proposed indication, and continued CMC issues. The current submission was submitted on July 15, 2015.

The sponsor does not have an agreed Pediatric Study Plan (PSP) because the original submission of the NDA was prior to 2012 when FDASIA (which required an agreed upon PSP before NDA submission) was enacted. . In the September 2012 submission resulting in a March 2013 CR, (b) (4)

The sponsor requested a deferral of studies for ages (b) (4) to 18 years. In this most recent submission (July 15, 2015), the sponsor did not update their request for (b) (4) deferral.

(b) (4)

*Currently, DGIEP is reviewing safety data related to injection site reactions in adults. If this or another safety issue impacting pediatric patients is identified (b) (4)*

*The safety concern must be reflected in labeling.*

#### Additional granisetron dosage forms

Granisetron is approved as an intravenous injection, oral tablets, oral solution and an extended release transdermal patch.

The intravenous dosage form is approved for use in chemotherapy-induced nausea and vomiting in pediatric patients 2 to 16 years of age. This dosage form is not approved for prevention of postoperative nausea and vomiting in pediatric patients.

The oral tablet dosage form is not approved in pediatric patients. The original approval and a subsequent new indication predated PREA.

The oral solution dosage form is currently not being marketed.

The transdermal dosage form, marketed as Sancuso, is not approved in pediatric patients. The product has a requirement under PREA for studies in ages 2 to 17 years for the

prevention of nausea and vomiting in patients receiving moderately and/or highly emetogenic chemotherapy for up to 5 consecutive days.

### **Sponsor proposed labeling**

#### **8.4 Pediatric Use**

The safety and effectiveness of SUSTOL in patients under 18 years of age have not been established.

### **DPMH Recommendations:**

#### **8.4 Pediatric Use**

The safety and effectiveness of SUSTOL have not been established in pediatric patients. ~~under 18 years of age have not been established.~~

If a safety concern specifically impacting pediatric patients is identified, DPMH recommends that the pediatric use section reflect the safety concern, including cross-reference to Contraindications or Warning and Precautions as appropriate.

These recommendations were communicated to DGIEP during labeling meetings. Labeling negotiations are ongoing. The final labeling may differ as a result of those negotiations.

### **Addendum**

 (b) (4)  
 DGIEP proposed PREA PMRs for pediatric patients 2 to 17 years to which PeRC concurred.

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/s/  
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AMY M TAYLOR  
06/29/2016

HARI C SACHS  
06/29/2016  
I agree with these recommendations.

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Medical Policy**

**PATIENT LABELING REVIEW**

Date: June 2, 2016

To: Donna Griebel, MD  
Director  
**Division of Gastroenterology and Inborn Errors  
Products (DGIEP)**

Through: LaShawn Griffiths, MSHS-PH, BSN, RN  
Associate Director for Patient Labeling  
**Division of Medical Policy Programs (DMPP)**  
  
Shawna Hutchins, MPH, BSN, RN  
Team Leader, Patient Labeling  
**Division of Medical Policy Programs (DMPP)**

From: Karen Dowdy, RN, BSN  
Patient Labeling Reviewer  
**Division of Medical Policy Programs (DMPP)**  
  
Meeta Patel, Pharm.D.  
Regulatory Review Officer  
**Office of Prescription Drug Promotion (OPDP)**

Subject: Review of Patient Labeling: Medication Guide (MG)

Drug Name (established name): SUSTOL (granisetron)

Dosage Form and Route: extended-release injection, for subcutaneous use

Application Type/Number: NDA 022445

Applicant: Heron Therapeutics, Inc.

## 1 INTRODUCTION

On July 17, 2015, Heron Therapeutics, Inc. re-submitted for the Agency's review a 505(b)(2) New Drug Application (NDA) 022445 for SUSTOL (granisetron) extended-release injection. The Division of Gastroenterology and Inborn Errors Products (DGIEP) considers the Applicant's submission to be a complete, class 2 response to the Agency's Complete Response Letter issued on March 27, 2013. The Agency issued a previous Complete Response Letter to this NDA on March 16, 2010. The Division of Medical Policy Programs (DMPP) entered a Review Deferral Memorandum for the Applicant's July 17, 2015 proposed Package Insert (PPI) on January 4, 2016, however, DGIEP ultimately did not issue a Complete Response Letter. The proposed indication for SUSTOL (granisetron) extended-release injection is for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of cancer chemotherapy, including, but not limited to, highly emetogenic chemotherapy.

This collaborative review is written by DMPP and the Office of Prescription Drug Promotion (OPDP) in response to requests by DGIEP on April 20, 2016, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for SUSTOL (granisetron) extended-release injection.

## 2 MATERIAL REVIEWED

- Draft SUSTOL (granisetron) extended-release injection MG received on April 15, 2016 and received by DMPP and OPDP on May 20, 2016.
- Draft SUSTOL (granisetron) extended-release injection Prescribing Information (PI) received on July 17, 2015, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on May 20, 2016.

## 3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6<sup>th</sup> to 8<sup>th</sup> grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8<sup>th</sup> grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APhont to make medical information more accessible for patients with vision loss. We have reformatted the MG document using the Arial font, size 10.

In our collaborative review of the MG we have:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information

- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

#### **4 CONCLUSIONS**

The MG is acceptable with our recommended changes.

#### **5 RECOMMENDATIONS**

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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/s/  
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KAREN M DOWDY  
06/02/2016

MEETA N PATEL  
06/03/2016

SHAWNA L HUTCHINS  
06/03/2016

LASHAWN M GRIFFITHS  
06/03/2016



# Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH  
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: May 26, 2016

From: CDER DCRP QT Interdisciplinary Review Team

Through: Christine Garnett, Pharm.D.  
Clinical Analyst  
Division of Cardiovascular and Renal Products /CDER

To: Brian Strongin, RPM  
DGIEP

Subject: QT-IRT Consult to NDA 22445

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

This memo responds to your consult to us dated 4/30/2016 regarding Sustol QT-related labeling. The QT-IRT received and reviewed the following materials:

- Your consult;
- Sustol draft label;
- QT-IRT's previous review (dated 1/2/2013); and
- KYTRIL and ALOXI labels.

## QT-IRT Comments for DGIEP

### Question from the division

The SUSTOL TQT study did not show an effect on QT prolongation for either SUSTOL (at two times the recommend dose) or intravenous granisetron hydrochloride (at five times the recommended dose). However, intravenous granisetron hydrochloride is known to be associated with postmarketing events of QT prolongation, and was labeled for these events.

Please provide recommendations for the wording (including in Section 12.2 Pharmacodynamics, Section 5 Warnings and Precautions, and Section 6.2 Postmarketing Experience) that should be included in the SUSTOL labeling in order to convey any remaining uncertainty about the risk for

QT prolongation with SUSTOL in patients receiving cancer chemotherapy, considering the postmarketing experience and previous labeling for intravenous granisetron hydrochloride (Kytril).

#### QT-IRT's response

The TQT study demonstrated that granisetron administered by both the IV and SC routes did not prolong the QTc interval. There was no evidence of a concentration-response relationship over the observed exposure range. The mean  $C_{max}$  achieved was 35 ng/mL and 36 ng/mL for the IV and SC routes, respectively. This exposure is 2-fold the mean  $C_{max}$  of 18 ng/mL observed in 3 studies in cancer patients taking APF530 500 mg.

The Applicant collected ECGs in a subset of cancer patients in Cycle 1 of study C2006-01 and in all patients in study C2007-01. Mean change from baseline QTcF exceeded 10 ms at 8 h, 12 h, and 16 h post-dosing for both the 250 mg and 500 mg APF530 dose groups as well as in the ALOXI 0.25 mg IV control arm. ALOXI also had a negative TQT study at doses up to 2.25 mg IV. Given the lack of dose-response in the APF530 arms, a similar time course of increases in the mean change from baseline QTcF between APF530 and ALOXI arms, and negative TQT studies for both APF530 and ALOXI, we think that the increases in QTcF interval may be related to the patient population and/or chemotherapy treatment.

Based on these data and the KYTRIL and ALOXI labels, we have the following recommendations for the SUSTOL label, but defer the final decisions to the Division. We are not recommending any Warning & Precaution statements about QT prolongation. This is consistent with the ALOXI label.

#### 12.2 Pharmacodynamics

The effect of granisetron extended release on QTc prolongation was evaluated in a double-blind, randomized, four-way crossover, placebo and positive (moxifloxacin) controlled study in 51 adult men and women healthy subjects. At 2-fold the (b) (4) dose of SUSTOL, (b) (4) no significant effect on the QTcF interval.

In (b) (4) cancer patients, 24-hour Holter monitor and 12-lead ECGs for 142 patients were evaluated. QTcF greater than 450 ms were seen in a total of (b) (4) (%) patients (b) (4) SUSTOL and (b) (4) (%) patients (b) (4) intravenous palonosetron. One patient (b) (4) had QTcF interval greater than 500 ms and 4 patients had change from baseline QTcF greater than 60 ms.

*Reviewer's comment: Values were obtained from Table 81 in 2.7.4 Summary of Clinical Safety.*

#### 6.2 Granisetron Experience

Adverse events reported in clinical trials and post-marketing reports with other formulations of granisetron include the following:

Cardiovascular: **QT prolongation**, Hypertension, hypotension, angina pectoris, atrial fibrillation and syncope have been observed rarely.

*Reviewer's comment: QT prolongation was reported in the post-marketing reports in the KYTRIL label.*

## BACKGROUND

SUSTOL (granisetron) for Injection is an extended-release serotonin-3 (5-HT<sub>3</sub>) receptor antagonist indicated for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of cancer chemotherapy. The NDA was submitted May 16, 2009 and a Complete Response action was taken on March 16, 2010 and March 27, 2013. The latest resubmission is dated July 17, 2015. The division plans to take an Approval action this cycle.

QT-IRT previously reviewed the results of the TQT study of SUSTOL (granisetron extended-release injection) and intravenous granisetron hydrochloride and concluded no significant QTc prolongation effect of granisetron at the clinically relevant exposure and no evident relationship between granisetron concentrations and  $\Delta\Delta\text{QTcF}$  (dated January 2, 2013).

### Relevant Background on IV Granisetron Formulation

On October 7, 2009, the label for Kytril (granisetron hydrochloride injection) was updated to include information regarding the risk of QT prolongation with the product in response to the sponsor's report containing a comprehensive assessment of clinical events, including spontaneous reports, which may indicate QT prolongation in patients, including pediatric patients administered Kytril before undergoing tonsillectomy or adenotonsillectomy.

This QT information was also reviewed by the QT-IRT (see review dated June 4, 2009 by Suchitra Balkrishnan). The IRT reviewer concluded:

For the cardiac arrest cases, the indication of granisetron was CINV in 48 cases and PONV in 5 cases. Thirty-seven came from a clinical trial (43694A) where Kytril had already been stopped at the time of the event, making a causal relationship unlikely. Sixteen cases were spontaneous. There was one positive re-challenge with and without the taxane (b)(6) and one case occurred in a child (b)(6).

The two cases of ventricular fibrillation were spontaneously reported in 2 patients. In both cases the indication of Kytril was PONV. The two cases of ventricular tachycardia occurred in patients receiving Kytril for CINV.

In summary, on review of all the narratives there was confounding due to co-morbidities and concomitant medications (including cardiotoxic chemotherapy agents) but relationship to study drug could not be excluded.

Since then, Kytril has been discontinued from the market (not for reasons of safety or efficacy). The most recent version of the Kytril label was approved in 2011 and discusses the QT risk in

various sections, as noted below. Events of QT prolongation were also noted in the context of the postoperative nausea and vomiting study in pediatrics in the Clinical Studies section.

Thank you for requesting our input into the development of this product under NDA 22445. We welcome more discussion with you now and in the future. Please feel free to contact us via email at [cderderpqt@fda.hhs.gov](mailto:cderderpqt@fda.hhs.gov)

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/s/  
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JIANG LIU  
05/26/2016

CHRISTINE E GARNETT  
05/26/2016

FOOD AND DRUG ADMINISTRATION  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion

Memorandum

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**\*\*PRE-DECISIONAL AGENCY MEMO\*\***

**Date:** May 23, 2016

**To:** Brian Strongin  
Senior Regulatory Project Manager  
Division of Gastroenterology and Inborn Errors Products

**From:** Meeta Patel, PharmD  
Regulatory Review Officer  
Office of Prescription Drug Promotion (OPDP)

**Subject:** NDA 022445  
OPDP Comments for draft SUSTOL (granisetron) extended-release injection, for subcutaneous use, PI and carton/container labeling

---

OPDP has reviewed the proposed draft PI and carton/container labeling for SUSTOL (granisetron) extended-release injection, for subcutaneous use, sent to us on May 20, 2016, and have the following comment on the PI and no comments on the carton/container labeling. Comments on the draft patient labeling will be sent as a joint review with DMPP under separate cover.

Thank you for the opportunity to comment on the proposed PI and carton/container labeling.

If you have any questions or concerns, please contact Meeta Patel at 301-796-4284 or [meeta.patel@fda.hhs.gov](mailto:meeta.patel@fda.hhs.gov).

22 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/  
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MEETA N PATEL  
05/23/2016



**DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service**

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Food and Drug Administration  
Office of New Drugs, Office of Drug  
Evaluation IV  
Division of Pediatric and Maternal Health  
Silver Spring, MD 20993  
Telephone 301-796-2200  
FAX 301-796-9744

**Division of Pediatric and Maternal Health Review**

**Date:** May 16, 2016      **Consult Received:** May 12, 2016

**From:** Carol H. Kasten, MD, Medical Officer  
Division of Pediatric and Maternal Health, Maternal Health Team  
Office of Drug Evaluation IV (ODE IV)

**Through:** Tamara Johnson, MD, MS, Team Leader  
Maternal Health Team  
Division of Pediatric and Maternal Health, ODE IV

Lynne P. Yao, MD, Director  
Division of Pediatric and Maternal Health, ODE IV

**To:** Division of Gastroenterology and Inborn Errors Products

**Drug:** Sustol® (granisetron (b) (4)) Injection, NDA 22-445

**Sponsor:** Heron Therapeutics

**Proposed Indication:** indicated in adults with cancer for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic chemotherapy (MEC) or anthracycline and cyclophosphamide (AC) combination chemotherapy.

**Subject:** Labeling review for compliance with PLLR

## INTRODUCTION

This Class 2 resubmission to NDA 22-445, Sustol<sup>®</sup> (granisetron extended release) Subcutaneous Injection from Heron Therapeutics was received on July 17, 2015. The response is intended to address the deficiencies enumerated in the Agency's Complete Response letter of March 27, 2013. On May 12, 2016 the Division of Gastroenterology and Inborn Errors Products (DGIEP) consulted the Division of Pediatric and Maternal Health Staff - Maternal Health Team (DPMH-MHT) to review and provide labeling recommendations for the Sustol Pregnancy (8.1) and Lactation (8.2) subsections.

## BACKGROUND

The original NDA was received on May 18, 2009 as a 505(b)(2) application and referenced Kytril<sup>®</sup> injection (NDA 20-239) as the reference listed drug (RLD). Granisetron was first approved for injection in December, 1993 for the prevention of chemotherapy induced nausea and vomiting (CINV). There are multiple formulations of granisetron marketed currently with indications to prevent radiation induced nausea and vomiting (RINV), post-operative nausea and vomiting (PONV), in addition to CINV.

### Mechanism of Action

Granisetron, a serotonin receptor antagonist, blocks signaling of serotonin (5-HT) via its 5-HT<sub>3</sub> receptor.<sup>1</sup> 5-HT receptor subtypes are the largest known family of neurotransmitter receptors. The binding affinity of granisetron to the 5-HT<sub>3</sub> receptor is 4,000 to 40,000 times greater than its affinity to other serotonin receptors. 5-HT<sub>3</sub> receptors are found centrally in the chemotherapy trigger zone (CTZ) and peripherally at vagal nerve terminals in the intestines.<sup>2,3</sup> It is this particular 5-HT<sub>3</sub> receptor distribution which may provide the basis for the anti-emetogenic action of granisetron.<sup>4,5</sup>

### Sustol

This drug product contains 2% granisetron in the polymer vehicle TEG-POE and an excipient MPEG. The polymer is intended to permit granisetron to undergo extended release. The drug – vehicle combination is viscous and is supplied in a pre-filled glass syringe which requires pre-warming in order to be injected subcutaneously. The applicant states that the granisetron is intended to be delivered over a 120 hour period. There are multiple formulations of granisetron marketed currently approved to prevent nausea and/or vomiting induced by chemotherapy (CINV) or radiation (RINV) or that which may occur post-operatively (PONV).

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<sup>1</sup> Sanders-Bush E, Hazelwood L. Goodman & Gilman's The Pharmacological Basis of Therapeutics, 12e. [book auth.] Chabner BA, Knollmann BC. Brunton L.L., Chabner B.A., Knollmann B.C. (Eds Brunton LL. *Goodman & Gilman's The Pharmacological Basis of Therapeutics*, 12e. 12. New York : McGraw-Hill, 2011, 13.5.

<sup>2</sup> See Sanders-Bush, *et al.*

<sup>3</sup> KR, McQuaid KRm McQuaid. Drugs Used in the Treatment of Gastrointestinal Diseases. [ed.] Masters SB, Trevor AJ. Katzung B.G., Masters S.B., Trevor A.J. eds Katzung BG. *Basic & Clinical Pharmacology*. New York : McGraw-Hill, 2012, 62.

<sup>4</sup> See Sanders-Bush, *et al.*

<sup>5</sup> See McQuaid, *et al.*

## REVIEW

### Applicant Pharmacovigilance Data

No pharmacovigilance data was available from the applicant as this is a new formulation of granisetron with no data regarding pregnancy exposures.

### Reproductive Toxicology Databases and Pregnancy Literature Review

The Reprotox<sup>6</sup> database review stated that based on the animal data, use of granisetron during pregnancy did not appear to produce an increased risk of congenital malformations. Reprotox did report one case of a woman diagnosed during the third trimester of pregnancy with a Ewing's sarcoma infiltrating the right sacro-iliac joint and psoas muscle. The mother was treated with doxorubicin, ifosfamide, mesna and granisetron for CINV.<sup>7</sup> The exposed infant (sex not specified) was delivered at 34 weeks gestation weighing 1.3 kilograms which is approximately one standard deviation below the third percentile for male and female neonates delivered at 34 weeks gestation. The infant had intrauterine growth restriction (IUGR) which may have been secondary to the chemotherapy, uterine crowding from the tumor or possibly the granisetron. The reference reported that the exposed child appeared to be developing normally at four years of age.

A PubMed search using the terms pregnant or pregnancy and granisetron yielded 18 publications. Only one described an instance of prenatal exposure to granisetron and its outcome. This publication is described above.<sup>8</sup> The other publications were *in vitro* studies, a new lab assay to measure granisetron levels or described the results of granisetron used to prevent nausea following cesarean section.

The TERIS<sup>9</sup> database review concluded that the magnitude of teratogenic risk was undetermined based on very limited data. The review noted that no epidemiological studies have been published on prenatal exposure to granisetron. The TERIS review also cited the same publication as that discussed above.<sup>10</sup>

### Lactation Database and Literature Review

There was no review found in LactMed<sup>11</sup> for granisetron. One publication was identified using search terms lactating, lactation or breastfeeding and granisetron. This

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<sup>6</sup> Reprotox® Website: [www.Reprotox.org](http://www.Reprotox.org). REPROTOX® system was developed as an adjunct information source for clinicians, scientists, and government agencies. Accessed December 12, 2015.

<sup>7</sup> Merimsky O, Le Chevalier T, et al., Management of cancer in pregnancy: A case of Ewing's sarcoma of the pelvis in the third trimester. *Annals Oncology* 1999;10:345-350.

<sup>8</sup> See Merimsky.

<sup>9</sup> TERIS is the TERatology Information Service located at University of Washington. It is an online database designed to assist physicians or other healthcare professionals in assessing the risks of possible teratogenic exposures in pregnant women.  
[http://www.micromedexsolutions.com/micromedex2/librarian/ND\\_T/evidencexpert/ND\\_PR/evidencexpert/CS/](http://www.micromedexsolutions.com/micromedex2/librarian/ND_T/evidencexpert/ND_PR/evidencexpert/CS/) Accessed 3/21/2014

<sup>10</sup> See Merimsky.

<sup>11</sup> LACTMED®: The LactMed database is a National Library of Medicine database with information on drugs and lactation geared toward healthcare practitioners and nursing women.

publication<sup>12</sup> provided no information on granisetron and lactation. The most frequent adverse event (AE) from Sustol administration is injection site reaction which included bruising, pain, erythema, mass or nodule and capillary bleeding. The breastfeeding infant will not experience this. The other AEs associated with Sustol administration include gastrointestinal disorders such as constipation and ileus. Some of the patients administered Sustol were treated concomitantly with opioids and/or had undergone abdominal surgery which may have contributed to these AEs. If granisetron is present in breast milk, the risk to the breastfeeding infant appears to be low.

### **Nonclinical Review**

The initial nonclinical review was completed on May 16, 2009.<sup>13</sup> The review states that the animal reproduction studies demonstrated no evidence of embryo-fetal toxicity or impaired fertility in pregnant rats and rabbits administered granisetron IV at approximately 7 times (rats) and 5 times (rabbits) the maximum recommended weekly human dose of granisetron. In 2009, prior to implementation of the Pregnancy and Lactation Labeling Rule (PLLR), granisetron was determined to be a Pregnancy Category B drug.

The applicant also completed embryo-fetal and pre- postnatal studies in pregnant rats and rabbits with the polymer vehicle alone and no teratogenic findings or abnormal developmental parameters were demonstrated. Fertility was also unimpaired in both male and female rats.

## **DISCUSSION**

### **Pregnancy and Lactation Labeling Rule**

On December 4, 2014, the Food and Drug Administration (FDA) announced the publication of the “Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling,”<sup>14</sup> also known as the Pregnancy and Lactation Labeling Rule (PLLR). The PLLR requirements include a change to the structure and content of labeling for human prescription drug and biologic products with regard to pregnancy and lactation, and create a new subsection for information with regard to females and males of reproductive potential. Specifically, the pregnancy categories (A, B, C, D and X) will be removed from all prescription drug and biological product labeling and a new format will be required for all products that are subject to the 2006 Physicians Labeling Rule<sup>15</sup> format to include information about the risks and benefits of using these products during pregnancy and lactation.

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<sup>12</sup> Mattioli V, Pisoni G, *et al.* Oral granisetron as prophylaxis for nausea and vomiting during fluorescein angiography. A multicentre, double-blind, randomised, parallel group, placebo-controlled study. *Minerva Anesthesiol.* 1998 Dec;64(12):553-61.

<sup>13</sup> Pharmacology/Toxicology Review and Evaluation, NDA 22-445. Primary author, Tamal K. Chakraborti, Ph.D. dated May 16, 2009.

<sup>14</sup> *Content and Format of Labeling for Human Prescription Drug and Biological Products, Requirements for Pregnancy and Lactation Labeling* (79 FR 72063, December 4, 2014).

<sup>15</sup> *Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products*, published in the Federal Register (71 FR 3922; January 24, 2006).

## CONCLUSION

The Pregnancy and Lactation subsections of labeling were structured to be consistent with the PLLR.

## DPMH LABELING RECOMMENDATIONS

DPMH presented our labeling recommendations to the Division on May 11, 2016. DPMH recommendations are below and reflect our discussions with DGIEP. See the final labeling for all of the labeling revisions negotiated with the applicant.

## SUSTOL® (granisetron) extended-release injection, for subcutaneous use

### INDICATIONS AND USAGE

SUSTOL, in combination with other anti-emetic agents is indicated in adults for the prevention of acute and delayed nausea and vomiting associated with moderately emetogenic chemotherapy (MEC) or anthracycline and cyclophosphamide (AC) combination chemotherapy.

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

#### Risk Summary

Limited published data on granisetron use during pregnancy are not sufficient to inform a drug-associated risk. In animal reproduction studies, (b) (4) observed in pregnant rats and rabbits administered granisetron during organogenesis at intravenous doses up to (b) (4) times and up to (b) (4) times, respectively, the maximum recommended human dose (MRHD) of SUSTOL 10mg [see Data].

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

#### Data

##### Animal Data

Reproduction studies with granisetron hydrochloride have been performed in pregnant rats following administration during the period of organogenesis at intravenous doses up to 9 mg/kg/day (approximately (b) (4) times the maximum recommended human dose of SUSTOL, 10mg, based on body surface area) and oral doses up to 125 mg/kg/day (approximately (b) (4) times the recommended (b) (4) human dose based on body surface area). Reproduction studies have been performed in pregnant rabbits in which granisetron hydrochloride was administered during the period of organogenesis at intravenous doses up to 3 mg/kg/day (approximately (b) (4) times the recommended (b) (4) human dose based on body surface area) and at oral doses up to 32 mg/kg/day (approximately (b) (4) times the

recommended (b) (4) human dose based on body surface area). These studies did not reveal any evidence of impaired fertility or harm to the fetus due to granisetron.

Reproduction studies with the polymer vehicle for Sustol have been performed in pregnant rats and rabbits following administration of the polymer vehicle during the period of organogenesis at subcutaneous doses up to 0.295 and 1.18 g per day, respectively, (approximately (b) (4) and (b) (4) times, respectively, the recommended (b) (4) human dose based on body surface area). These studies did not reveal any evidence of impaired fertility or harm to the fetus due to the polymer vehicle. A pre and postnatal development study with the polymer vehicle for Sustol in rats showed no evidence of any adverse effects on pre and postnatal development at subcutaneous doses (administered on gestation days 7 through lactation day 20) up to 0.295 g per day (approximately (b) (4) times the recommended (b) (4) human dose based on body surface area).

## 8.2 Lactation

### Risk Summary

There are no data on the presence of granisetron in human milk, the effects of granisetron on the breastfed infant, or the effects of granisetron on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for (b) (4) and any potential adverse effects on the breastfed infant from granisetron or from the underlying maternal condition.

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CAROL H KASTEN  
05/16/2016

TAMARA N JOHNSON  
05/17/2016

LYNNE P YAO  
05/18/2016

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### **LABEL AND LABELING REVIEW**

Division of Medication Error Prevention and Analysis (DMEPA)  
Office of Medication Error Prevention and Risk Management (OMEPRM)  
Office of Surveillance and Epidemiology (OSE)  
Center for Drug Evaluation and Research (CDER)

**\*\*\* This document contains proprietary information that cannot be released to the public\*\*\***

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|                                       |                                                              |
|---------------------------------------|--------------------------------------------------------------|
| <b>Date of This Review:</b>           | April 25, 2016                                               |
| <b>Requesting Office or Division:</b> | Division of Gastroenterology & Inborn Error Products (DGIEP) |
| <b>Application Type and Number:</b>   | NDA 022445                                                   |
| <b>Product Name and Strength:</b>     | Sustol (granisetron (b) (4)) Injection<br>10 mg/0.4 mL       |
| <b>Product Type:</b>                  | Combination Product                                          |
| <b>Rx or OTC:</b>                     | Rx                                                           |
| <b>Applicant/Sponsor Name:</b>        | Heron Therapeutics, Inc.                                     |
| <b>Submission Date:</b>               | July 17, 2015                                                |
| <b>OSE RCM #:</b>                     | 2015-1643                                                    |
| <b>DMEPA Primary Reviewer:</b>        | Matthew Barlow, RN, BSN                                      |
| <b>DMEPA Team Leader:</b>             | Mishale Mistry, PharmD, MPH                                  |
| <b>DMEPA Deputy Director:</b>         | Lubna Merchant, PharmD, MS                                   |

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## 1 REASON FOR REVIEW

This review is in response to DGIEP's request for DMEPA to review the submitted proposed labels and labeling for any areas that may lead to medication errors. The proposed labels were submitted on July 17, 2015 under the application NDA 22445, as a part of the applicant's resubmission package.

### 1.1 REGULATORY HISTORY

This application was first submitted as NDA 22445 in 2009. In March 2010, this application received a Complete Response for several reasons related to drug product quality, clinical, statistics, clinical pharmacology, and container closure of the drug product. The applicant resubmitted the application on September 27, 2012. The submission received a second Complete Response due to Clinical issues and concerns involving the Human Factors study results on March 2013. The application was then resubmitted on July 17, 2015 for a third review.

## 2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

| <b>Table 1. Materials Considered for this Label and Labeling Review</b> |                                                   |
|-------------------------------------------------------------------------|---------------------------------------------------|
| <b>Material Reviewed</b>                                                | <b>Appendix Section (for Methods and Results)</b> |
| Product Information/Prescribing Information                             | A                                                 |
| Previous DMEPA Reviews                                                  | B                                                 |
| Human Factors Study                                                     | N/A-C                                             |
| ISMP Newsletters                                                        | D                                                 |
| FDA Adverse Event Reporting System (FAERS)*                             | E                                                 |
| Other                                                                   | N/A-F                                             |
| Labels and Labeling                                                     | G                                                 |

N/A=not applicable for this review

\*We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine post-market safety surveillance

## 3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

The applicant submitted the proposed syringe label, carton, warmer, clamshell, labeling and prescribing information for review on July 17, 2015 as a part of the applicant's resubmission. DMEPA previously reviewed and evaluated the summative usability studies for the Sustol prefilled syringe, which demonstrated that end users are able to use the product safely and effectively with the availability of labeling (i.e., Instructions for Use).<sup>1</sup> We performed a risk

assessment of the submitted labels and labeling for areas of vulnerability that may lead to medication errors. We searched the FDA Adverse Event Reporting System (FAERS) for medication errors that may be associated with the label and labeling of the referenced product, Kytril, but no relevant cases were found. We note that the proposed labels and labeling can be improved to increase the prominence of important information. We note the use of the term (b) (4) in the labels, which is inconsistent with the draft guidance<sup>2</sup>. We defer to Office of Pharmaceutical Quality/CMC for the appropriateness of the term (b) (4) on the labels and labeling. We provide recommendations in Section 4.1 to address these deficiencies.

## **4 CONCLUSION & RECOMMENDATIONS**

DMEPA concludes that the proposed labels and labeling can be improved to increase the readability and prominence of important information and promote the safe use of the product and mitigate any confusion.

### **4.1 RECOMMENDATIONS FOR HERON THERAPEUTICS, INC.**

We recommend the following be implemented prior to approval of this NDA:

- A. Container Label (Syringe barrel) – 1-pack and 6-pack
  - 1. Include the “Rx only” statement on the syringe barrel label per Section 503(b)(4)(A) of the Federal Food, Drug, and Cosmetic Act.
  - 2. Increase the prominence (use bold font type) of the statement “Highly viscous, (b) (4) subcutaneous injection only” to mitigate the risk that this important information is overlooked by end users.
- B. Clamshell Labeling:
  - 1. As displayed, the font color selection (b) (4) of the established name contrasted against the (b) (4) does not afford adequate contrast and makes this information difficult to read. We recommend changing the font color to increase readability.
- C. Single Unit Carton Labeling – 1-pack and 6-pack
  - 1. As displayed, the font color selection (b) (4) of the established name contrasted against the white background does not afford adequate contrast and makes this

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<sup>1</sup> Barlow, M. Human Factors Study Results Review for Sustol NDA 22445. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 Jan 12. RCM No.: 2015-1795.

<sup>2</sup> Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use (Draft Guidance). October 2015.

information difficult to read. We recommend changing the font color to increase readability.

D. Six-Pack Carton Labeling

1. As displayed, the font color selection (b) (4) of the established name contrasted against the white background does not afford adequate contrast and makes this information difficult to read. We recommend changing the font color to increase readability.
2. We recommend increasing the size of the statements “For subcutaneous use only. (b) (4)” and “Remove carton from refrigerator and unpack (b) (4) at least 60 minutes prior to use” to emphasize the importance of this information and ensure that the product is used correctly.
3. We recommend decreasing the prominence of the statement “6 single-dose” statement on the right side of the PDP. The current size and font competes in prominence with important information on the labeling (i.e., proprietary name, established name, strength, and route of administration).
4. We recommend adding the statement “Must be refrigerated” in bold text to the bottom left of the PDP with the rest of the storage information to provide complete storage techniques for this product.
5. We recommend relocating the manufacturer, patent, and trademark information from the PDP to another panel (i.e., back panel) of the carton labeling to reduce clutter and increase readability of the important information.

## APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

### APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Sustol that Heron Therapeutics, Inc. submitted on July 17, 2015, and the listed drug (LD).

| Table 2. Relevant Product Information for Sustol and the Listed Drug |                                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
|----------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Product Name</b>                                                  | <b>Sustol</b> [NDA 22445]                                                                                                                                                                                                                                                         | <b>Kytril</b> [NDA 20239]                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| <b>Initial Approval Date</b>                                         | N/A                                                                                                                                                                                                                                                                               | December 29, 1993                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| <b>Active Ingredient</b>                                             | Granisetron (b) (4)                                                                                                                                                                                                                                                               | Granisetron hydrochloride                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| <b>Indication</b>                                                    | Indicated for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of cancer chemotherapy, including, but not limited to, highly emetogenic chemotherapy.                                                                           | Indicated for: <ul style="list-style-type: none"> <li>The prevention of nausea and/or vomiting associated with initial and repeat courses of emetogenic cancer therapy, including high-dose cisplatin.</li> <li>The prevention and treatment of postoperative nausea and vomiting in adults. As with other antiemetics, routine prophylaxis is not recommended in patients in whom there is little expectation that nausea and/or vomiting will occur postoperatively. In patients where nausea and/or vomiting must be avoided during the postoperative period, KYTRIL Injection is recommended even where the incidence of postoperative nausea and/or vomiting is low.</li> </ul> |
| <b>Route of Administration</b>                                       | Subcutaneous Injection                                                                                                                                                                                                                                                            | Intravenous Injection                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| <b>Dosage Form</b>                                                   | Pre-filled Syringe for Injection                                                                                                                                                                                                                                                  | Single-Use and Multi-Use Vials for Injection                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| <b>Strength</b>                                                      | 10 mg/0.4 mL                                                                                                                                                                                                                                                                      | 1 mg/mL; 0.1 mg/mL                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| <b>Dose and Frequency</b>                                            | The recommended dose of SUSTOL (10 mg granisetron/0.4 mL) is a single subcutaneous injection in the upper arm or abdomen administered at least 30 minutes before the initiation of chemotherapy. Sustol was administered, in clinical trials, as frequently as once every 7 days. | <b>Prevention of Chemotherapy-Induced Nausea and Vomiting</b> <ul style="list-style-type: none"> <li><b>Adult Patients:</b> the recommended dosage for KYTRIL Injection is 10 mcg/kg administered intravenously within 30 minutes before initiation of chemotherapy, and only on the day(s) chemotherapy is given.</li> <li><b>Pediatric Patients:</b> the</li> </ul>                                                                                                                                                                                                                                                                                                                |

|                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|---------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | <p>recommended dose in pediatric patients 2 to 16 years of age is 10 mcg/kg. Pediatric patients under 2 years of age have not been studied.</p> <p><b>Prevention and Treatment of Postoperative Nausea and Vomiting</b></p> <ul style="list-style-type: none"> <li>• <b>Adult Patients:</b> the recommended dosage for prevention of postoperative nausea and vomiting is 1 mg of KYTRIL, undiluted, administered intravenously over 30 seconds, before induction of anesthesia or immediately before reversal of anesthesia. The recommended dosage for the treatment of nausea and/or vomiting after surgery is 1 mg of KYTRIL, undiluted, administered intravenously over 30 seconds.</li> </ul> |
| <b>How Supplied</b> | <p>SUSTOL is supplied in cartons of six kits (NDC 47426-101-06); single dose kit (NDC 47426-101-01) contains:</p> <ul style="list-style-type: none"> <li>• One sterile (b) (4) colored glass syringe which contains 10 mg granisetron/0.4 mL,</li> <li>• One sterile 18 Ga 5/8" special thin walled administration needle,</li> <li>• Two sodium acetate syringe warming pouches,</li> <li>• One Point Lok® needle protection device, and</li> <li>• Instructions for Use and Package Insert.</li> </ul> | <p>KYTRIL Injection, 1 mg/mL (free base), is supplied in 1 mL Single-Use Vials and 4 mg/4 mL Multi-Use Vials. KYTRIL Injection, 0.1 mg/mL (free base), is supplied in 1 mL Single-Use Vials. Contains no preservative.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| <b>Storage</b>      | <p>Store SUSTOL in the refrigerator at 2° to 8°C (36° to 46°F). SUSTOL can remain at room temperature for up to 7 days. Leaving SUSTOL at room temperature and then placing back in the refrigerator has no impact on product quality. SUSTOL can be re-warmed if needed.</p> <p>Protect from light.</p>                                                                                                                                                                                                 | <p>Store single-use vials and multi-use vials at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F). [See USP Controlled Room Temperature].</p> <p>Once the multi-use vial is penetrated, its contents should be used within 30 days. Do not freeze. Protect from light.</p>                                                                                                                                                                                                                                                                                                                                                                                                            |

## **APPENDIX B. PREVIOUS DMEPA REVIEWS**

### **B.1 Methods**

On January 1, 2016, we searched the L:drive using the terms, Sustol, to identify reviews previously performed by DMEPA.

### **B.2 Results**

Our search identified four previous reviews<sup>3,4,5,6</sup>, and we confirmed that our previous recommendations have been implemented.

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<sup>3</sup> Tobenkin, A. Usability Protocol Review for Sustol NDA 22445. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2012 May 22. RCM No.: 2012-747.

<sup>4</sup> McMillan, T. Label and Labeling & Human Factors Protocol Review for Sustol NDA 22445. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2013 Jan 30. RCM No.:2012-2316.

<sup>5</sup> Calderon, M. Human Factors Protocol Review Memo for Sustol NDA 22445. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2014 Feb 24. RCM No.: 2014-309.

<sup>6</sup> Barlow, M. Human Factors Study Results Review for Sustol NDA 22445. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 Jan 12. RCM No.: 2015-1795

## APPENDIX C. HUMAN FACTORS STUDY – N/A

### APPENDIX D. ISMP NEWSLETTERS

#### D.1 Methods

On January 1, 2016, we searched the Institute for Safe Medication Practices (ISMP) newsletters using the criteria below, and then individually reviewed each newsletter. We limited our analysis to newsletters that described medication errors or actions possibly associated with the label and labeling.

| ISMP Newsletters Search Strategy |                                                                                                                                                                                                               |
|----------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| ISMP Newsletter(s)               | Joint Commission Sentinel Event Alert; QAA Community; QAA Acute Care; PA Patient Safety Advisory; ISMP Canada Safety Bulletin; ISMP Nursing Newsletter; ISMP Community Newsletter; ISMP Acute Care Newsletter |
| Search Strategy and Terms        | Match Exact Word or Phrase: Granisetron                                                                                                                                                                       |

#### D.2 Results

The search criteria listed above yielded no results.

## APPENDIX E. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

### E.1 Methods

We searched the FDA Adverse Event Reporting System (FAERS) on January 1, 2016 using the criteria in Table 3, and then individually reviewed each case. We limited our analysis to cases that described errors possibly associated with the label and labeling. We used the NCC MERP Taxonomy of Medication Errors to code the type and factors contributing to the errors when sufficient information was provided by the reporter.<sup>7</sup>

| Table 3: FAERS Search Strategy |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|--------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Date Range                     | December 29, 1993 to January 1, 2016                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| Product                        | Kytril; Sancuso [active ingredient]<br>Granisetron; Granisetron Hydrochloride [product name]                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| Event (MedDRA Terms)           | <b>DMEPA Official FBIS Search Terms Event List:</b><br>Contraindicated Drug Administered (PT)<br>Drug Administered to Patient of Inappropriate Age (PT)<br>Inadequate Aseptic Technique in Use of Product (PT)<br>Medication Errors (HLGT)<br>Overdose (PT)<br>Prescribed Overdose (PT)<br>Prescribed Underdose (PT)<br>Product Adhesion Issue (PT)<br>Product Compounding Quality Issue (PT)<br>Product Formulation Issue (PT)<br>Product Label Issues (HLT)<br>Product Packaging Issues (HLT)<br>Product Use Issue (PT)<br>Underdose (PT) |

### E.2 Results

Our search identified 27 cases, of which no case described errors relevant for this review. We excluded 27 cases because they described issues not related to medication errors relevant to this review or this drug formulation.

---

<sup>7</sup> The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Taxonomy of Medication Errors. Website <http://www.nccmerp.org/pdf/taxo2001-07-31.pdf>.

### **E.3 List of FAERS Case Numbers**

Below is a list of the FAERS case number and manufacturer control numbers for the cases relevant for this review.

### **E.4 Description of FAERS**

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's postmarket safety surveillance program for drug and therapeutic biologic products. The informatic structure of the FAERS database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. FDA's Office of Surveillance and Epidemiology codes adverse events and medication errors to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Product names are coded using the FAERS Product Dictionary. More information about FAERS can be found at: <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm>.

### **APPENDIX F. OTHER – N/A**

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/s/  
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MATTHEW J BARLOW  
04/25/2016

MISHALE P MISTRY  
04/26/2016

LUBNA A MERCHANT  
04/26/2016



Food and Drug Administration  
Office of Device Evaluation  
White Oak Building 66  
10903 New Hampshire Ave.  
Silver Spring, MD 20993

**Intercenter Consult Memorandum****CDER NDA 022445 - CDRH ICC1500527**

**Date:** April 4, 2016

**To:** James Carr  
Division of Gastroenterology and Inborn Errors Products (DGIEP),  
Office of Drug Evaluation III (ODEIII),  
Office of New Drugs (OND),  
Center for Drug Evaluation and Research (CDER)

**From:** John McMichael  
General Hospital Devices Branch (GHDB),  
Division of Anesthesiology, General Hospital, Respiratory,  
Infection Control, & Dental Devices (DAGRID),  
Office of Device Evaluation (ODE),  
Center for Devices and Radiological Health (CDRH)

**Subject:** CDER/ODE III/DGIEP requests the assistance of the CDRH Engineering team in the review of the Sustol (NDA 022445) CR resubmission.

**Intended Use:** Granisetron Injection, extended release (APF530) is a sterile viscous subcutaneous injectable formulation supplied in 1.0 mL (b) (4) pre-filled long barrel glass syringes for the prevention of chemotherapy induced nausea and vomiting. The drug product is stored refrigerated at 2-8 degrees Celsius prior to use.

**Recommendation: Device Constituent Parts are Approvable**

---

**I. Purpose**

CDER/OND/ODEIII/DGIEP has requested CDRH/ODE's assistance in assessing the acceptability of any changes that have been made to the Sponsor's pre-filled syringe presentation since the original application. This product has undergone two previous review cycles. The Sponsor provided engineering study reports, memos with re-design rationale, human factors study reports (submission date 7/17/2015) supporting changes to the combination product since the original application. Please note that DMEPA was consulted to review any human factors information regarding this combination product.

This memo represents a complete review of all device information submitted to date.

**II. Background**

Sustol-Heron submitted an NDA resubmission in September 2015. CDRH/ODE was previously consulted and found the submission inadequate to support approval in April of 2012 before a CR was issued by the Agency. This combination product involves the subcutaneous injection of granisetron via a pre-filled syringe. The injection is to be executed by a trained health care provider. The scope of this

review covers the device constituent parts of the combination product, which includes the pre-filled syringe, the syringe warmers, and the packaging of the syringe and syringe warmers.

The consultant delivered several information requests to the Sponsor and all additional information received by the Agency in regards to this request has been reviewed under this memo. Please see Section VII of this memo.

After an internal review team meeting it was determined that a teleconference would be held with the Sponsor in an attempt to resolve any device review issues prior to reaching a final decision. A teleconference was held on February 11, 2016 with the Sponsor to discuss the remaining device deficiencies. The deficiencies were communicated to the Sponsor via email on February 12, 2016 and the Sponsor provided new data for review in response to the deficiencies on February 18, 2016. This information and the reviewer's comments regarding the new information can be found in Section VI of this memo.

### **III. Documents Reviewed**

The following documents were considered in the review of the device constituent parts of the combination product:

- TRD-ENG-01 Rev 01 – Technical Requirement Document for Sustol Delivery System
- TRD-ENG-02 – Technical Requirements Document, Sustol Syringe Warmer
- 3.2.P.7 – Container Closure System
- 3.2.P.2.4 – Container Closure System
- RPT-0117 – Engineering Report, Sodium Acetate Warmers, Real-time Long term Storage Performance Testing
- ETR-ENG-05 – Engineering Study, Refrigerated Stability of Point-Lok Needle Safety Devices
- RPT-ENG-07 – Breaking Force for the (b) (4) 1 mL Long Syringes
- VALR-ENG-13 – Design Validation Report, Sustol Syringe Warmer (SSW), One Year Real Time Aging
- RPT-0101 – Design Validation Report, Sustol Syringe Warmer (SSW), (b) (4) One Year Real Time Aging (R(1))
- RA-ENG-04 rev 01 – Failure Analysis Failure Modes, Effects, & Criticality Analysis (FMECA) Sustol Syringe Warmer
- TM-ENG-05 – Risk Management Report, Sustol Syringe Warmer
- TM-ENG-04 – Risk Management Report, Sustol Delivery System
- TM-ENG-03 – Design History File Summary: Sustol Delivery System & Sustol Syringe Warmer
- TM-ENG-02 – Verification and Validation Traceability Matrix And Program Summary, Sustol Syringe Warmer
- TM-ENG-01 - Verification and Validation Traceability Matrix And Program Summary, Sustol Delivery System
- RPT-ENG-14 – CAPA #0174 Report, Sustol Device Components Out of Specification Validation Results, Accelerated Aging Testing
- RPT-ENG-13 - CAPA #0173 Report, Sustol Device Components Out of Specification Validation Results, Syringe Warmer Surface Temperature Measurements
- RPT-ENG-13 - CAPA #0172 Report, Sustol Device Components Out of Specification Validation Results, Tip Cap Removal Force Testing
- RPT-ENG-11 – Summary Report of Sustol Device Components Validation and Verification Out of Specification Results
- RA-ENG-03 – Hazard Analysis, Sustol Syringe Warmer
- RA-ENG-01 – Hazard Analysis, Sustol Delivery System
- PRD-ENG-02 – Product Requirements Document, Sustol Syringe Warmer
- VALR-ENG-06 – Design Validation Report, Sustol Packaging, Shipping and Handling, ASTM 4169
- VALR-ENG-04 – Design Validation Report, Sustol Syringe Warmer (SSW)
- VALR-ENG-03 – Design Validation Report, Sustol Delivery System
- STBR-ENG-02 – Sustol Device Components, Shelf Life Study Report
- RPT-ENG-05 – Warming and Cooling of Sustol Syringes
- RPT-ENG-04 – Force Required to Inject Sustol

### **IV. Device Description**

The following was provided by the Sponsor as a description of the overall drug-delivery device “SUSTOL Delivery System”:

The SUSTOL Delivery System (SDS) are the device components of the SUSTOL (granisetron injection, extended release) drug product. The SDS is comprised of the following:

- (b) (4) 1 ml (long) glass syringe with (b) (4) Cap
- (b) (4) Grey stopper
- (b) (4) Flange
- (b) (4)
- (b) (4) Plunger (b) (4)
- (b) (4) needle, 18 ga x 5/8" (b) (4) Thin Wall (b) (4)
- (b) (4)
- Smiths Medical Point-Lok<sup>®</sup> Needle Safety Device

The (b) (4) glass syringe with tip cap is filled with the SUSTOL drug product, then the (b) (4) The assembly is then sterilized by gamma irradiation. (b) (4)

(b) (4) The syringe assembly, injection needle and Point-Lok are placed together in a (b) (4) tray with an Instructions for Use (IFU) and a Product Insert (PI), along with two syringe warmers (which are covered under separate Design History File – DHF-SSW-01). The tray is packaged in a paperboard unit box.

The product is stored at refrigeration temperatures of 2 - 8° C and then is warmed to 37 - 40° C prior to use.

The following is taken from 3.2.P.7:

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(b) (4)

Needle:

**3.2.P.7.3.2 Needle**

The product is delivered using a (b) (4) 18 Gauge 5/8-inch thin-wall needle. The 5/8 inch length was selected (b) (4)

Heron Therapeutics provided Letters of Authorization (b) (4)

Sustol Syringe Warmer:

The Sponsor submitted the following information comparing the two manufacturers of their proposed syringe warmers:

**Table 23: Comparison of (b) (4) Warmers**

| Parameter            | (b) (4)                 |                         |
|----------------------|-------------------------|-------------------------|
| Dimensions           | 125 ± 5 mm x 85 ± 5 mm  | 120 ± 5 mm x 85 ± 5 mm  |
| Pouch Material       | (b) (4)                 |                         |
| Fill Solution        | Sodium Acetate, (b) (4) | Sodium Acetate, (b) (4) |
| Activation Mechanism | Stainless Steel Button  | Stainless Steel Button  |
| Fastener             | Hook & Loop Strips      | Hook & Loop Strips      |

## **VI. CDRH Review**

This review is limited in scope to the device constituent parts of the combination product. Please note that all documents referenced by the Sponsor are held under the NDA.

The Sponsor provided the following Design History File for review of the pre-filled syringe and syringe warmer components of the combination product:

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**VIII. Concurrence Table**

| <b>Digital Signature Concurrence Table</b> |                                                                                                                                                                                                                                    |
|--------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Reviewer Sign-Off                          | John C. Mcmichael -S Date: 2016.04.04<br>12:45:49 -04'00'                                                                                                                                                                          |
| Branch Sign-Off                            | Alan M. Stevens -S<br>Digitally signed by Alan M. Stevens -S<br>DN: c=US, o=U.S. Government,<br>ou=HHS, ou=FDA, ou=People,<br>0.9.2342.19200300.100.1.1=13001892<br>11, cn=Alan M. Stevens -S<br>Date: 2016.04.04 13:01:04 -04'00' |

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/s/  
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BRIAN K STRONGIN  
04/04/2016



**DEPARTMENT OF HEALTH & HUMAN SERVICES** Public Health Service

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Food and Drug Administration  
CDER/OND/Office of Drug Evaluation IV  
Division of Pediatric and Maternal Health  
Silver Spring, MD 20993  
Telephone 301-796-2200  
FAX 301-796-9858

**M E M O R A N D U M**

**DATE:** March 25, 2016

**FROM:** Matthew Bacho, Senior RHPM  
Division of Pediatric and Maternal Health (DPMH)

**TO:** James Carr, MPAS, PA-C, RHPM  
Division of Gastroenterology and Inborn Errors  
Products (DGIEP)

**NDA:** 022445

**DRUG:** Sustol (granisetron) Injection, extended release

On 9/21/15 DPMH received a consult from DGIEP requesting assistance with the labeling of this product.

DPMH attended a number of internal meetings with DGIEP on 10/5, 10/27, 11/19, 12/14, 12/17/15, and 2/4/16. In December 2015, (b) (4)

A pediatric review from DPMH was finalized on 1/14/16; however, (b) (4), the Maternal Health Team has no further comment at this time, so this memorandum will close out the consult request.

DPMH Maternal Health Reviewer – Carol Kasten  
DPMH RPM – Matthew Bacho

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/s/  
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MATTHEW A BACHO  
03/25/2016



**DEPARTMENT OF HEALTH & HUMAN SERVICES** Public Health Service

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Food and Drug Administration  
Office of New Drugs/Office of Drug Evaluation IV  
Division of Pediatric and Maternal Health  
Silver Spring, MD 20993  
Telephone 301-796-2200  
FAX 301-796-9855

**MEMORANDUM TO FILE**

**Pediatric Labeling Review**

**From:** Amy M. Taylor, MD, MHS Medical Officer  
Division of Pediatric and Maternal Health

**Through:** Hari Cheryl Sachs, MD, Team Leader  
Division of Pediatric and Maternal Health

Lynne P. Yao, MD, Director  
Division of Pediatric and Maternal Health

**NDA Number:** 22-445

**Sponsor:** Heron Therapeutics

**Drug:** Sustol<sup>®</sup> (granisetron) Injection, extended release

**Dosage form and route of administration:** Injection for subcutaneous use

**Proposed Indication:** For the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of cancer chemotherapy, including, but not limited to, highly emetogenic chemotherapy

**Consult request:** The Division of Gastroenterology and Inborn Errors Products (DGIEP) requests DPMH's assistance with labeling.

**Background**

The sponsor submitted an original NDA (22-445) on May 7, 2009. The application received a complete response (CR) on March 16, 2010 for multiple CMC and clinical deficiencies and again on March 27, 2013 based on concerns with the human factors

study, lack of support for the proposed indication, and continued CMC issues. The current submission was submitted on July 15, 2015.

The sponsor does not have an agreed Pediatric Study Plan (PSP) because the original submission of the NDA was prior to 2012 when FDASIA (which required an agreed upon PSP before NDA submission) was enacted. . In the September 2012 submission resulting in a March 2013 CR, (b) (4)



The sponsor requested a deferral of studies for ages (b) (4) to 18 years. In this most recent submission (July 15, 2015), the sponsor did not update their request for partial waiver or deferral.



#### Additional granisetron dosage forms

Granisetron is approved as an intravenous injection, oral tablets, oral solution and an extended release transdermal patch.

The intravenous dosage form is approved for use in chemotherapy-induced nausea and vomiting in pediatric patients 2 to 16 years of age. This dosage form is not approved for prevention of postoperative nausea and vomiting in pediatric patients.

The oral tablet dosage form is not approved in pediatric patients. The original approval and a subsequent new indication predated PREA.

The oral solution dosage form is currently not being marketed.

The transdermal dosage form, marketed as Sancuso, is not approved in pediatric patients. The product has a requirement under PREA for studies in ages 2 to 17 years for the

prevention of nausea and vomiting in patients receiving moderately and/or highly emetogenic chemotherapy for up to 5 consecutive days.

### **Sponsor proposed labeling**

#### **8.4 Pediatric Use**

The safety and effectiveness of SUSTOL in patients under 18 years of age have not been established.

### **DPMH Recommendations:**

#### **8.4 Pediatric Use**

The safety and effectiveness of SUSTOL have not been established in pediatric patients. ~~under 18 years of age have not been established.~~

If a safety concern specifically impacting pediatric patients is identified, DPMH recommends that the pediatric use section reflect the safety concern, including cross-reference to Contraindications or Warning and Precautions as appropriate.

These recommendations were communicated to DGIEP during labeling meetings. Labeling negotiations are ongoing. The final labeling may differ as a result of those negotiations.

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/s/  
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AMY M TAYLOR  
01/11/2016

HARI C SACHS  
01/11/2016  
I agree with these recommendations.

LYNNE P YAO  
01/14/2016

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## HUMAN FACTORS STUDY RESULTS REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)  
Office of Medication Error Prevention and Risk Management (OMEPRM)  
Office of Surveillance and Epidemiology (OSE)  
Center for Drug Evaluation and Research (CDER)

\*\*\* This document contains proprietary information that cannot be released to the public\*\*\*

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|                                       |                                                              |
|---------------------------------------|--------------------------------------------------------------|
| <b>Date of This Review:</b>           | January 12, 2015                                             |
| <b>Requesting Office or Division:</b> | Division of Gastroenterology & Inborn Error Products (DGIEP) |
| <b>Application Type and Number:</b>   | NDA 22445                                                    |
| <b>Product Name and Strength:</b>     | Sustol (granisetron (b) (4)) Injection<br>10 mg/0.4 mL       |
| <b>Product Type:</b>                  | Combination Product                                          |
| <b>Rx or OTC:</b>                     | Rx                                                           |
| <b>Applicant/Sponsor Name:</b>        | Heron Therapeutics, Inc.                                     |
| <b>Submission Date:</b>               | July 17, 2015                                                |
| <b>OSE RCM #:</b>                     | 2015-1795                                                    |
| <b>DMEPA Primary Reviewer:</b>        | Matthew Barlow, BSN, RN                                      |
| <b>DMEPA Team Leader:</b>             | Mishale Mistry, PharmD, MPH                                  |
| <b>DMEPA Deputy Director:</b>         | Lubna Merchant, PharmD, MS                                   |

---

## 1 REASON FOR REVIEW

This review is in response to DGIEP's request for DMEPA to review and evaluate the Human Factors results submitted on July 17, 2015 as a part of the applicant's resubmission package. The Human Factors studies and the subsequent results were resubmitted under application NDA 22445. Additionally, DGIEP requested DMEPA to review the submitted proposed label and labeling.

### 1.1 REGULATORY HISTORY

This application was first submitted as NDA 22445 in 2009. In March 2010, this application received a Complete Response for several reasons related to drug product quality, clinical, statistics, clinical pharmacology, and container closure of the drug product. The applicant resubmitted the application on September 27, 2012. The submission received a second Complete Response due to Clinical issues and concerns involving the Human Factors study results on March 2013. Specifically, the Human Factors validation study (XP-1179-045) did not confirm that users could adequately administer the product with the proposed product design and its labeling, along with the Instructions for Use (IFU). According to the Complete Response, participants in the study reported difficulty pushing the plunger due to the viscosity of the product, and this led to a concern for administration errors. Additionally, CDRH had concerns related to the amount of pressure needed to administer the drug product (due to its viscosity) and subsequent potential of syringe breakage. The application was then resubmitted on July 17, 2015 for a third review.

## 2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

| <b>Table 1. Materials Considered for this Human Factors Study Review</b> |                                                   |
|--------------------------------------------------------------------------|---------------------------------------------------|
| <b>Material Reviewed</b>                                                 | <b>Appendix Section (for Methods and Results)</b> |
| Product Information/Prescribing Information                              | A                                                 |
| Previous DMEPA Reviews                                                   | B                                                 |
| Human Factors Study                                                      | C                                                 |
| ISMP Newsletters                                                         | N/A-D                                             |
| FDA Adverse Event Reporting System (FAERS)*                              | N/A-E                                             |
| Other                                                                    | N/A-F                                             |
| Labels and Labeling                                                      | G                                                 |

N/A=not applicable for this review

\*We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine post-market safety surveillance.

### 3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

This resubmission of the application NDA 22445 on July 17, 2015 is the third submission of this application. In the previous human factors study (XP-1179-045 Report), there was a concern that participants would not be able to administer the drug via the prefilled syringe due to the viscosity of the product. Study participants reported difficulty pushing the plunger due to the viscosity of the product, leading to a concern that administration errors may occur.

Subsequently, to address these concerns, the Applicant modified the device by:

(b) (4)

Following the above modifications to the product, the applicant performed three additional Human Factors Studies: a two-part formative study, a summative test, and a summative usability test. See Appendix C for more information on the formative study results and subsequent modifications.

#### **Summative Test (HTI.2014. APF.ST.503 Rev. A):**

The first Summative Test included a total of fifteen participants. The study included the performance and completion of two trials with the same fifteen participants for each. In this study, errors occurred in the following tasks:

1. **Failure to wait for the gel pack to warm the syringe for 5-6 minutes:** Three participants failed to warm the syringe for the full five to six minutes during their second injection attempt. One participant warmed the syringe for 1:52 minutes, as they thought that they did not need to “wait in real time” since this was a simulated study. Two other participants warmed the syringe for 4:30 minutes and 4:35 minutes, but noted in their post-test interview that the syringe should be warmed for five to six minutes. One of these participants thought that they had warmed the syringe for five minutes, as they had used the clock to keep track of time. The Sponsor states that the reduced warming time may be attributed to the fact that this was a simulation and no other activity was provided to occupy the participants during this wait time. Further analysis of this error is provided in the discussion of the Summative Usability Test Study ((HTI.2014.APF.ST2.503 Rev. 02).
2. **Syringe handling:** One participant received a needle-stick injury while attempting to insert the needle into the injection pad for the first injection. The participant missed the pad and hit their finger. In the post-test interview, the participant attributed the error to the awkward “physical layout” of the simulation. This error, in addition to feedback from all participants regarding the lack of a safety needle, led to the Applicant adding a Point-Lok needle-safety device to the Sustol Administration Kit, which needed to be validated by a summative usability study.
3. **Failure to remove the hub cover from the needle:** One participant failed to remove the hub cover from the needle on their second injection attempt. The participant attempted to remove only the hexagonal end piece of the hub, and their fingers covered the junction between the hub and needle. Failure to remove the hub cover would result in a delay of treatment. Additionally, the participant was successful in removing the hub cap

in their first injection attempt. We note that the IFU does not include a step regarding removal of the hub cover. Therefore, we recommend including a step clarifying that the user must remove the hub cover from the needle.

4. **Advancing the needle during injection:** One participant had difficulty with this task in both injections. On their first injection, the participant pulled up slightly on the needle, causing some medication to leak onto the injection pad. The participant then advancing the need back into the skin to stop the leakage. On the second injection, the participant did not insert the needle fully, resulting in some medication to leak onto the injection pad. The Instructions for Use state in bold text “Do NOT advance or reposition the syringe...”. Therefore, no additional modifications to the proposed IFU are needed to mitigate this type of error.

#### **Summative Usability Test Study (HTI.2014. APF.ST2.503 Rev. 02):**

DMEPA evaluated the modifications to the drug product and the Summative Usability Test Study (HTI.2014. APF.ST2.503 Rev. 02) to determine whether the changes mitigated the previously identified concerns, do not introduce any additional use errors, and if participants are able to use the product safely and effectively. Based upon the results of the Human Factors study, the prefilled syringe appears to be safe and effective when used by healthcare professionals. Furthermore, during the Summative Usability study, seven participants noted being prepared for the difficulty of administering the product due to the provided IFU.

In the Summative Usability Test, seven failures occurred within the following tasks of the study:

1. Failure to activate gel-warming pack (2 failures, on first and second injection)
2. Failure to wait for the gel pack to warm the syringe for 5-6 minutes (5 failures on second injection)

#### **Failure to activate the gel warming pack:**

An error associated with the failure to activate the gel warming pack occurred with one participant on both of their injection attempts. The participant flexed the disk inside the warming pouch only twice during the first trial and crystallization did not occur. The second trial involved the participant only flexing the disc once. The participant stated that they did not expect to feel any warmth when activated, and thought that the device would start warming sometime after the click. Overall, the participant did not have any difficulty administering the product. According to the Applicant, this participant did not fully understand how often to flex the discs inside the warming pouch. The proposed Instructions for Use state, “Flex (bend) the metal disc rapidly until crystals begin to form (fluid will start to turn white).” Users are provided with a visual cue (white fluid) to help them determine if the warming pouch is activated. Therefore, no additional modifications to the proposed IFU are needed to mitigate this type of error.

#### **Failure to wait 5 to 6 minutes for the gel pack to warm the syringe:**

Errors associated with failure to wait for the gel pack to warm the syringe occurred with five participants during their 2<sup>nd</sup> injection. These five participants only warmed the syringe for less than five minutes during the second trial, despite performing it correctly during the first trial. The Applicant attributed the error to the following reasons: miscalculation of time; participants grew impatient waiting; and during the waiting period, participants were not given other tasks

to do. According to the Applicant, the participants understood that five minutes is needed to warm the syringe. Additionally, the Applicant states that although the optimum warming time is five to six minutes, “the force to inject the product was significantly reduced even with a warming time of less than the instructed time.” Therefore, no additional modifications to the device or proposed IFU are needed to mitigate this type of error.

Overall, despite the aforementioned use errors, we do not believe the risks present a safety concern as users were able to administer the product without additional errors as demonstrated by the human factor study. (b) (4)

#### **4 CONCLUSIONS AND RECOMMENDATIONS**

The Summative Usability studies for the Sustol prefilled syringe demonstrated that end users (health care providers) are able to use the product safely and effectively with the availability of labeling (i.e., Instructions for Use). Although some errors occurred with the prefilled syringe, these errors would not result in serious harm.

##### **A. Recommendation for Heron Therapeutics, Inc.**

1. We recommend modifying the IFU to include a step clarifying that the user must remove the hub cover from the needle. The addition of this step will emphasize the need for this task and help mitigate any errors/issues related to not removing the hub cover.

## APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

### APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Sustol that Heron Therapeutics, Inc. submitted on July 17, 2015, and the Reference Listed Drug (RLD).

| <b>Table 2. Relevant Product Information for Sustol and the Listed Drug</b> |                                                                                                                                                                                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|-----------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Product Name</b>                                                         | <b>Sustol</b>                                                                                                                                                                                           | <b>Kytril (NDA 020239; NDA 020305; NDA 021238)</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| <b>Initial Approval Date</b>                                                | N/A                                                                                                                                                                                                     | December 29, 1993                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| <b>Active Ingredient</b>                                                    | Granisetron (b) (4)                                                                                                                                                                                     | Granisetron hydrochloride                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| <b>Indication</b>                                                           | Indicated for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of cancer chemotherapy, including, but not limited to, highly emetogenic chemotherapy. | indicated for: <ul style="list-style-type: none"> <li>• The prevention of nausea and/or vomiting associated with initial and repeat courses of emetogenic cancer therapy, including high-dose cisplatin.</li> <li>• The prevention and treatment of postoperative nausea and vomiting in adults. As with other antiemetics, routine prophylaxis is not recommended in patients in whom there is little expectation that nausea and/or vomiting will occur postoperatively. In patients where nausea and/or vomiting must be avoided during the postoperative period, KYTRIL Injection is recommended even where the incidence of postoperative nausea and/or vomiting is low.</li> </ul> |
| <b>Route of Administration</b>                                              | Subcutaneous Injection                                                                                                                                                                                  | Intravenous Injection                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| <b>Dosage Form</b>                                                          | Pre-filled Syringe for Injection                                                                                                                                                                        | Single-Use and Multi-Use Vials for Injection                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |

|                           |                                                                                                                                                                                                                                                                                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|---------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Strength</b>           | 10 mg/0.4 mL                                                                                                                                                                                                                                                                             | 1 mg/mL; 0.1 mg/mL                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| <b>Dose and Frequency</b> | <p>The recommended dose of SUSTOL (10 mg granisetron/0.4 mL) is a single subcutaneous injection in the upper arm or abdomen administered at least 30 minutes before the initiation of chemotherapy. Sustol was administered, in clinical trials, as frequently as once every 7 days.</p> | <p><b>Prevention of Chemotherapy-Induced Nausea and Vomiting</b><br/> <b>Adult Patients:</b> the recommended dosage for KYTRIL Injection is 10 mcg/kg administered intravenously within 30 minutes before initiation of chemotherapy, and only on the day(s) chemotherapy is given.<br/> <b>Pediatric Patients:</b> the recommended dose in pediatric patients 2 to 16 years of age is 10 mcg/kg. Pediatric patients under 2 years of age have not been studied.</p> <p><b>Prevention and Treatment of Postoperative Nausea and Vomiting</b><br/> <b>Adult Patients:</b> the recommended dosage for prevention of postoperative nausea and vomiting is 1 mg of KYTRIL, undiluted, administered intravenously over 30 seconds, before induction of anesthesia or immediately before reversal of anesthesia. The recommended dosage for the treatment of nausea and/or vomiting after surgery is 1 mg of KYTRIL, undiluted, administered intravenously over 30 seconds.</p> |
| <b>How Supplied</b>       | SUSTOL is supplied in cartons of six kits (NDC 47426-101-06);                                                                                                                                                                                                                            | KYTRIL Injection, 1 mg/mL (free base), is supplied in 1                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |

|                |                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                                                                                                                                                                                                                                                                   |
|----------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                | <p>single dose kit (NDC 47426-101-01) contains:</p> <ul style="list-style-type: none"> <li>• One sterile (b) (4) colored glass syringe which contains 10 mg granisetron/0.4 mL,</li> <li>• One sterile 18 Ga 5/8" special thin walled administration needle,</li> <li>• Two sodium acetate syringe warming pouches,</li> <li>• One Point Lok® needle protection device, and</li> <li>• Instructions for Use and Package Insert.</li> </ul> | <p>mL Single-Use Vials and 4 mg/4 mL Multi-Use Vials. KYTRIL Injection, 0.1 mg/mL (free base), is supplied in 1 mL Single-Use Vials. Contains no preservative.</p>                                                                                                                |
| <b>Storage</b> | <p>Store SUSTOL in the refrigerator at 2° to 8°C (36° to 46°F).</p> <p>SUSTOL can remain at room temperature for up to 7 days. Leaving SUSTOL at room temperature and then placing back in the refrigerator has no impact on product quality. SUSTOL can be re-warmed if needed.</p> <p>Protect from light.</p>                                                                                                                            | <p>Store single-use vials and multi-use vials at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F). [See USP Controlled Room Temperature]. Once the multi-use vial is penetrated, its contents should be used within 30 days. Do not freeze. Protect from light.</p> |

## **APPENDIX B. PREVIOUS DMEPA REVIEWS**

### **B.1 Methods**

On December 4, 2015, we searched the L:drive using the terms, Sustol, to identify reviews previously performed by DMEPA.

### **B.2 Results**

Our search identified three previous reviews<sup>123</sup>, and we confirmed that our previous recommendations have been implemented.

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<sup>1</sup> Tobenkin, A. Usability Protocol Review for Sustol NDA 22445. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2012 May 22. RCM No.: 2012-747.

<sup>2</sup> McMillan, T. Label and Labeling & Human Factors Protocol Review for Sustol NDA 22445. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2013 Jan 30. RCM No.:2012-2316.

<sup>3</sup> Calderon, M. Human Factors Protocol Review Memo for Sustol NDA 22445. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2014 Feb 24. RCM No.: 2014-309.

## **APPENDIX C. HUMAN FACTORS STUDY**

### **C.1 Study Design & Results For the 2-Part Formative Study, Summative Test, & Summative Usability Test**

#### **Human Factors Formative Study [Part 1]**

- Participants: Final total of 7 participants tested
  - RNs working inpatient/outpatient oncology setting for at least 6 months
  - Chemotherapy administration, anti-emetic drug administration, and subcutaneous medication administration experience→performed syringe-based injections regularly
- Facilities-Data Collection-Study/Test Procedure
  - Objective Measures
    - Performance on each task was assessed by the investigator and scored as follows:
      - a) success with little to no effort
      - b)success with difficulties or effort
      - c) failure to complete the scenario OR failure to perform a critical/essential task correctly.
    - Any unanticipated issues that were observed (to create a critical safety risk) were also scored as performance failures→ Also any other observations of use issues were recorded and discussed in the Post-Test Inquiry.
  - Subjective Measures: These assessment methods were also used to investigate performance issues
    - During the Post-Test Inquiry, participants were asked:
      - If they recall having difficulties performing actions with the product.
      - About specific use issues, including those that led to failures or completion of an action correctly.
    - These inquiries were directed towards finding and understanding the root cause behind performance issues/difficulties, including aspects of the user interface (i.e. IFU, Carton Labeling, Gel Pack Use).
  - Study Procedure: See Table #2
  - Results: See Table #3
  - Analysis of Use Issues
    - Use of Gel Warming Packs: Several participants had difficulties with the packs.

- 3 participants (2, 3, and 8) used both packs to warm the syringe→These events were scored as “Success with difficulties” because the use of 2 packs does not affect the efficiency of warming the syringe.
  - 3 participants (2, 4, and 7) warmed the syringe before assembling the needle→These events were scored as “Success with difficulties.”
  - 2 participants (2 and 5) did NOT warm the syringe for 5 minutes before either injection→scored as Task Failures.
- Pressing the Plunger: 4 participants (1,2,4, and 5) said that it was hard to press the plunger.
  - According to the results time spent warming the syringe DOES NOT correlate well with participant experience pressing the plunger nor with injection time.
    - The shortest (2) and longest (5) injection times occurred after the shortest warming periods and both stated it was hard to press the plunger.
    - Participant 7 warmed for 5:55 and took 74 seconds to complete the injection, and Participant 1 warmed for over 5 minutes and required 7 re-grips to complete the 1<sup>st</sup> injection.
    - The sponsor concluded one reason for the poor correlation between warming and injection *could be due to the lack of tactile feedback while injecting*
- Injection Angle and Medication Leakage
  - 1 Participant (5) appeared to insert needle at less than 30 degrees and some medication leaked onto the injection pad→ Per sponsor, appeared to be an isolated incident and claimed it could be artifact due to the use of artificial skin.
- Conclusions
  - Overall, participants performed well on most tasks and 6 of 7 participants successfully completed both injections.
    - Participants demonstrated unanticipated use of warming packs (use of 2 packs at once to warm syringe)→this did not result in a critical safety risk.
    - The 2 participants (2 and 7) warming the syringe before assembling the needle. 2 participants (2 and 5) warmed the syringe for less than the expected 5-6 minutes, while 2 participants required prompting by the Investigator to wait the 5-6 minutes to warm. One reason was developed as a possibility for these events:

syringe prep took place in the same area as patient location because several RNs stated they'd prepare the syringe in a "med prep area" away from the patient; thus, the lack of separation was thought to be a reason to cause an unexpected behavior in the participants.

- 4 participants said it was hard to press the plunger to give the medicine.
  - 2 participants delivered the drug long before they stopped pressing the plunger.
  - At least 1 other participant took a long time (74 seconds) to give the drug.
  - These events led to the idea of a lack of tactile feedback as the reason behind them.

Table 2: Study Procedure

| Steps                               | Description of Activity                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Time Allocated |
|-------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------|
| <b>1. Participant Enrollment</b>    | Upon arrival, Informed Consent was obtained and participants were given a demographic questionnaire, to verify that they meet the study inclusion and exclusion criteria.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | 10 minutes     |
| <b>2. Introduction to the Study</b> | Participants were given a short verbal introduction to the study and the Investigator fielded questions about the study at this time.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | 5 minutes      |
| <b>3. Performance Testing</b>       | <p>Participants were given the product and allotted time to familiarize themselves with the product. When they had indicated they were ready to proceed, participants were asked to administer SUSTOL® to a "patient" following the description provided in the patient's Medication Administration Record (MAR). A mannequin served as the patient. The mannequin was clothed, seated in a chair, and connected to an IV drip similar to a patient awaiting chemotherapy treatment. The mannequin was equipped with a hidden/covered injection pad in the area of the abdomen suitable for administration of SUSTOL® injections.</p> <p>This injection scenario was repeated twice, with at least a 5-minute break between injections.</p> | 20 minutes     |

|                                       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |            |
|---------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------|
| <b>4. Post-Test Inquiry</b>           | <p>A Post-Test Inquiry session was conducted with each participant to:</p> <ul style="list-style-type: none"> <li>a. evaluate their understanding of the drug product requirements that could not be easily evaluated by user performance;</li> <li>b. identify any issues they may have experienced that were not observed by the Investigator, including issues with the Instructions for Use;</li> <li>c. facilitate the determination of the root cause of any use issues observed by the Investigator or reported by the participant by exploring the issue with the participant.</li> </ul> | 25 minutes |
| <b>5. Debriefing and Compensation</b> | Participants were compensated for their participation and dismissed.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | 5 minutes  |

**Table 3: Performance Results**

Table 1: Performance on Critical and Essential Tasks

| Critical and Essential Tasks                                                       | Scoring                              | Inj 1       | Inj 2       | Observations                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|------------------------------------------------------------------------------------|--------------------------------------|-------------|-------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 1. Remove the carton from the refrigerator at least 60 minutes prior to injection. | Success<br>Suc. with Dif.<br>Failure |             |             | Not scored during the injection sequence because participants were not asked to remove the carton from the refrigerator. Instead, participant understanding was assessed through the Post-Test Inquiry                                                                                                                                                                                                                                                                                |
| 2. Remove Syringe warmers, syringe and needle from kit tray.                       | Success<br>Suc. with Dif.<br>Failure | 7<br>0<br>0 | 7<br>0<br>0 | All participants removed the contents of the carton without difficulties.                                                                                                                                                                                                                                                                                                                                                                                                             |
| 3. Choose administration route.                                                    | Success<br>Suc. with Dif.<br>Failure | 7<br>0<br>0 | 7<br>0<br>0 | All participants selected a subcutaneous injection into the abdomen.                                                                                                                                                                                                                                                                                                                                                                                                                  |
| 4. Unscrew cap from the end of the prefilled syringe.                              | Success<br>Suc. with Dif.<br>Failure | 7<br>0<br>0 | 7<br>0<br>0 | All participants unscrewed the end cap from the syringe without difficulty.                                                                                                                                                                                                                                                                                                                                                                                                           |
| 5. Remove the hub cover from the needle.                                           | Success<br>Suc. with Dif.<br>Failure | 7<br>0<br>0 | 7<br>0<br>0 | All participants successfully removed the hub cover from the needle without difficulty.                                                                                                                                                                                                                                                                                                                                                                                               |
| 6. Attach the needle (to the syringe).                                             | Success<br>Suc. with Dif.<br>Failure | 7<br>0<br>0 | 7<br>0<br>0 | All participants attached the needle without difficulty.                                                                                                                                                                                                                                                                                                                                                                                                                              |
| 7a. Activate gel warming pack.                                                     | Success<br>Suc. with Dif.<br>Failure | 7<br>0<br>0 | 7<br>0<br>0 | All participants activated the warming packs without difficulties.                                                                                                                                                                                                                                                                                                                                                                                                                    |
| 7b. Apply warming pack to syringe.                                                 | Success<br>Suc. with Dif.<br>Failure | 4<br>3<br>0 | 6<br>1<br>0 | <p>Three participants, scored as Success with Difficulties (#2, #8, and #5), used both warming packs to sandwich the syringe, instead of just one warming pack wrapped around the syringe. The task was scored as Success with Difficulties because the use of two gel packs does not affect the effectiveness of warming but use of two gel packs was unexpected.</p> <p>Participant #2 quickly discovered on her own that the syringe could be wrapped in only one warming pack</p> |

|                                                                   |                                      |             |             |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|-------------------------------------------------------------------|--------------------------------------|-------------|-------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                                   |                                      |             |             | <p>and held in place with the velcro strips; she used only one warmer on the second injection.</p> <p>Participant #8 activated both warming packs and placed the syringe between them; she then read through the Instructions For Use during the first warming period and realized that only one warming pack should be used for warming. She used only one warmer on the second injection.</p> <p>Participant #5 initially laid one warming pack on top of the syringe on the table then picked the syringe up and held it between two warming packs. She did not use the Velcro strips. Participant #5 used both warming packs on the syringe for the second injection.</p>                                          |
| 7c. Wait for the gel pack to warm the syringe for 5-6 minutes.    | Success<br>Suc. with Dif.<br>Failure | 5<br>0<br>2 | 5<br>0<br>2 | <p>Two participants did not wait five minutes to warm the syringe. Participant #2 (scored as a failure) began the injection after waiting about 1 ½ minutes on the first injection and one minute for the second injection.</p> <p>Participant #5 (failure) said she would not wait five minutes in a real life setting and warmed the syringe each time for about 1 ½ minutes.</p> <p>Participants #4 and #7 mentioned that the syringe should be warmed for 5-6 minutes but indicated their intention to start the injection before the time was up. The Investigator noted this, then prompted them to wait the full five minutes.</p> <p>All other participants warmed the syringes for at least five minutes.</p> |
| 7d. Remove syringe from the gel pack.                             | Success<br>Suc. with Dif.<br>Failure | 7<br>0<br>0 | 7<br>0<br>0 | <p>All participants removed the syringe from the warming pack without difficulties.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| 8. Remove blue needle cover.                                      | Success<br>Suc. with Dif.<br>Failure | 7<br>0<br>0 | 7<br>0<br>0 | <p>All participants removed the blue needle cover without difficulties.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| 9. Insert needle at                                               | Success                              | 6           | 6           | Participant #5 appeared to inject at an angle less than                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| 30-45 degrees.                                                    | Suc. with Dif.<br>Failure            | 0<br>1      | 0<br>1      | <p>30 degrees on both injections; as a result, some medication leaked onto the injection pad. This was considered a task failure.</p> <p>All other participants appeared to insert the needle at an appropriate angle.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| 10. Press plunger to deliver all the medication, slow and steady. | Success<br>Suc. with Dif.<br>Failure | 7<br>0<br>0 | 7<br>0<br>0 | <p>All syringes were examined by the Investigator after each injection. In all cases the medication was fully expelled as indicated by the position of the stopper at the bottom of the syringe barrel.</p> <p>Injection time and number of times the participant re-gripped the syringe during the injection are reported below.</p>                                                                                                                                                                                                                                                                                                                                                                                  |
| 11. Withdraw the needle.                                          | Success<br>Suc. with Dif.<br>Failure | 7<br>0<br>0 | 7<br>0<br>0 | <p>All participants withdraw the needle from the injection pad without difficulty.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| 12. Syringe handling.                                             | Success<br>Suc. with Dif.<br>Failure | 7<br>0<br>0 | 7<br>0<br>0 | <p>All participants handled the syringes properly and safely. No participant received a needlestick injury.</p> <p>All syringes were examined by the Investigator after each injection for cracking or breakage on the plunger shaft and the flange. No plunger or flange was broken or came loose. There was no visual evidence of cracking on either the plunger shaft or the flange.</p>                                                                                                                                                                                                                                                                                                                            |

## Table 4: Post-Test Inquiry Responses

Table 2: Summary of Participant Responses To Post-Test Inquiry Questions

| Question                                                                                                     | Participant Responses                                                                                                                                                                                                                                                                                                                                                                    |
|--------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 1. Where on the body is it appropriate to inject SUSTOL®?                                                    | All participants indicated the abdomen.                                                                                                                                                                                                                                                                                                                                                  |
| 2. Is it okay to inject SUSTOL® intravenously?                                                               | All participants indicated 'no' to all three questions.                                                                                                                                                                                                                                                                                                                                  |
| What about intramuscular or intraperitoneal?                                                                 |                                                                                                                                                                                                                                                                                                                                                                                          |
| 3. Should SUSTOL® be administered cold or warm? (Why?)                                                       | All participants indicated that SUSTOL® should be administered warm. Six of seven indicated SUSTOL® should be warm because it was thick or viscous. Participant #2 thought that warming was required "to activate this viscous ... medication".                                                                                                                                          |
| 4. How long should SUSTOL® be at room temperature before applying the warming pack?                          | All participants indicated that SUSTOL® should be at room temperature for 60 minutes before applying the gel pack.                                                                                                                                                                                                                                                                       |
| 5. Were the instructions to warm SUSTOL® immediately prior to injection clear?                               | All participants indicated that the instructions on warming were clear.                                                                                                                                                                                                                                                                                                                  |
| 6. Did the Instructions For Use prepare you for the viscous nature of SUSTOL®?                               | All participants indicated the Instructions For Use prepared them for the viscous nature of SUSTOL®.<br><br>Four participants (#1, #2, #4, #5) mentioned that they had expected the injection to be difficult or to experience resistance during the injection based on information in the Instructions For Use.                                                                         |
| 7. Finally, do you feel confident that you could safely and effectively administer SUSTOL® to your patients? | Six participants gave an immediate yes to the question. One participant (#2) said that after the second injection she was confident; she said "That (warming) confused me the first time. The first time I was like uncertain. The second time I was kind of like yeah it's kind of easy. But the first time..."                                                                         |
| 8. Do you recall having any difficulties with any of the following:                                          |                                                                                                                                                                                                                                                                                                                                                                                          |
| a. Removing the warmers, syringe or needle from the carton.                                                  | Six participants said they had no problems removing the contents. One participant (#5) misunderstood the question and did not give a relevant answer.                                                                                                                                                                                                                                    |
| b. Locating and checking the expiration date.                                                                | Four participants said they had no difficulty checking the expiration date. Participant #5 said "I didn't see one". Participant #7 said, "I didn't see one on the box" and "then up on the syringe it's tiny...though I maybe it's my vision". Participant #8 did not check but said, "in a clinical setting I would do that. It just didn't prompt me until I read these (IFU) closer". |
| c. Choosing an administration route.                                                                         | All participants said they had no difficulties choosing an administration route.                                                                                                                                                                                                                                                                                                         |

|                                                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|----------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| d. Choosing an injection site.                           | All participants said they had no difficulties choosing an injection site.                                                                                                                                                                                                                                                                                                                                                                                                                   |
| e. Understanding the pre-caution label on the syringe.   | All participants said they had no difficulties understanding the pre-caution label.                                                                                                                                                                                                                                                                                                                                                                                                          |
| f. Removing the precaution label.                        | All participants said they had no difficulties removing the pre-caution label or administering with the pre-caution label in place.                                                                                                                                                                                                                                                                                                                                                          |
| g. Checking the dose volume.                             | Six participants said they had no difficulties checking the dose volume. Participant #7 said, "I really didn't check it. ... I just use syringes so much. You can just look at it and tell".                                                                                                                                                                                                                                                                                                 |
| h. Unscrewing the tip cap.                               | Seven participants said they had no difficulties unscrewing the tip cap. Participant #6 said, "I didn't realize it was just the gray part that came off so I was trying to get this whole plastic piece off. So that was a little confusing. But once I figured out that it was just the gray that came off, that was easy".                                                                                                                                                                 |
| i. Removing the clear cap from the needle cover.         | All participants said they had no difficulties removing the clear cap.                                                                                                                                                                                                                                                                                                                                                                                                                       |
| j. Attaching the needle to the syringe.                  | All participants said they had no difficulties attaching the needle to the syringe.                                                                                                                                                                                                                                                                                                                                                                                                          |
| k. Activating and applying the gel pack to warm SUSTOL®. | Five participants said they had no difficulties activating and warming the syringe. Participants #2 said the disk "confused me the first time". Participant #8 said "I've not ever been exposed to a system like this" and "it doesn't say (how to use the second warming pack) ... I mean you have to read down to the details to know that the second warming pack" is used "if it cools off. And maybe the (second) warming pack could say ... spare warming pad or something like that". |
| l. Waiting for the gel pack to warm SUSTOL®.             | Five participants said they didn't have any difficulties waiting for the gel pack to warm SUSTOL®. Participant #4 said he didn't have his watch on but "it normally wouldn't be a problem". Participant #5 said "realistically, time in the chemo room, five minutes is a long time. I'm just saying".                                                                                                                                                                                       |
| m. Removing the blue needle cover.                       | All participants said they had no difficulties removing                                                                                                                                                                                                                                                                                                                                                                                                                                      |

|                                                            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                            | the blue needle cover.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| n. Inserting the needle at a 30 to 45 degree angle.        | All participants said they had no difficulties inserting the needle.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| o. Pressing the plunger to inject the medication.          | Participant #8 said she had no difficulties pressing the plunger. Participant #6 said "I don't normally hold the syringe by the (flange); it was easier if I did hold it"; she used the flange. Participant #7 compared the injection to other viscous medications and said "I wouldn't say difficult...no not really". Participant #2 said it needs a lot of pushing but "it was okay" to deliver; participant #4 mentioned some resistance but "it (plunger) went all the way in"; participant #5 said "That's a problem. And I used different hands each time";. Participant #1 said "I actually felt it (the plunger) give". |
| p. Checking or knowing that the entire dose was delivered. | All participants said they had no difficulties checking or knowing that the entire dose was delivered.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| q. Removing the needle from our patient.                   | All participants said they had no difficulties removing the needle from the patient.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| r. Discarding the needle and syringe.                      | All participants said they had no difficulties discarding the needle and syringe.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| s. Discarding the Syringe Warmer gel pack.                 | All participants said they had no difficulties discarding the gel warmer pack.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |

## Human Factors Formative Study [Part 2]

- Participants: Total of 14 participants tested with the same criteria as the Part 1.
  - 13 female and 1 male with an average age of 43 years and 9.5 years of experience in Oncology.
- Facilities-Data Collection-Study/Test Procedure
  - Market research facility in (b) (4) → All sessions were in a large conference room with a 1-way mirror.
    - A divider was used to section off the room: 1 side was used as a supply area (this held the injection supplies within a nursing cart), while the other side was the patient therapy area.
    - Each session had audio and video recording and lasted approximately 60 minutes following the study/test procedure (see Table #5 ).
  - Objective Measures
    - Involved the same methods and scoring as Part 1
  - Subjective Measures
    - Involved the same methods and Post-Test Inquiries as Part 1
  - Results
    - Reading Times
      - Half the participants [Required Review Arm] were directed to review the IFU in detail, while the other half [Pre-Validation Arm] were asked only to "familiarize" themselves with the product.

- There were NO discernable differences in how long participants spent reviewing the IFU across the 2 groups. Additionally there were no differences in performance across the 2 arms. Thus, the results for the 2 groups are combined.
  - See Table #6(a)
- Performance on Critical/Essential Tasks
  - Same scoring as Part 1. (Task 1 was not scored).
  - See Table #6(b)
- Use Issues and Analysis of Root Cause
  - Not Warming the Syringe in the Gel Packs for full 5 minutes.
    - 4 participants (2,8,12, and 13) did not warm the 1<sup>st</sup> injection syringe for the 5 minute minimum warming period.
    - 2 participants (2 and 12) did not use a clock to time the warming period for their initial injection→Both used the clock for their 2<sup>nd</sup> injection as they realized the need for it.
    - 1 participant (8) claimed did not warm because study was artificial, but in real setting would have done it appropriately.
    - 1 participant (13) used the clock, but misread the start time or miscalculated the elapsed time.
    - All participants warmed the 2<sup>nd</sup> syringe for the 5 minute minimum period.
  - Uncertainty about when/if all medication has been expelled.
    - 1 participant (5) was uncertain whether all of drug had been expelled during her 1<sup>st</sup> injection, as she held syringe in placed and pressed on plunger for about 3 minutes after the med had been fully expelled.
      - This participant was unable to tell with her 1<sup>st</sup> injection when the plunger had reached its stop point given tactile and proprioceptive feedback.
      - “I just can’t tell because the medicine and syringe plungers are both kind of grayish, and I can’t tell if it’s at the end.”
  - Inserting Syringe at too High an Angle.
    - All participants injected into the SubQ layer of the injection pad→However, 2 participants (1 and 10) injected at an angle greater than 45 degrees for both injections, but had pinched a large amount of skin so it was deemed unlikely the needle would reach muscle tissue or the peritoneal cavity in a real patient.

- Not Finding the Exp. Date.
  - 2 participants did not attempt to check the date.
  - 2 other participants could not locate the exp. Date when asked→Both expected it to be on the carton, and a 3<sup>rd</sup> located it on the syringe but said they expected it to be on the carton
  - The exp. Date was NOT printed on the cartons used in this study.
- Conclusion
  - Overall participants were successful in administering the injections→All completed 2 injections and recognized the need to remove the carton from the fridge 1 hour prior to administration along with acknowledging the need to warm the syringe to body temp.
  - No participant had difficulty preparing and attaching the needle to the syringe.
  - All felt they could safely and effectively administer the drug to their patients.
  - The changes to the IFU appear to be effective in clarifying the use of the warming packs→Specifically, all participants activated a SINGLE warming pack and successfully wrapped the syringe to warm it.
  - Changes to the Directions for Use on the back of the carton may have had an effect of making them appear less like instructions→Unlike Part 1, participants in Part 2 spent very little time looking at these directions and almost ALL of their time with the IFU insert.

Table 5: Part 2 Study/Test Procedure

| Steps                                 | Description of Activity                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | Time Allocated |
|---------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------|
| <b>1. Participant Enrollment</b>      | Upon arrival, Informed Consent was obtained and participants were given a demographic questionnaire, to verify that they met the study inclusion and exclusion criteria.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 10 minutes     |
| <b>2. Introduction to the Study</b>   | Participants were given a short verbal introduction (see Appendix D) to the study and the Investigator fielded questions about the study at this time.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | 5 minutes      |
| <b>3. Performance Testing</b>         | <p><b>Pre-Validation Arm</b><br/>Participants were given the product in its commercial packaging and allotted time to “familiarize themselves” with the product.</p> <p><b>Required Review Arm</b><br/>Participants were given the product in its commercial packaging and asked to review the Instructions for Use thoroughly.</p> <p><b>Both Arms</b><br/>When the participants for both arms indicated they were ready to proceed, they were asked to administer SUSTOL® to a “patient” following the description provided in the patient’s Medication Administration Record (MAR). A mannequin served as the patient. The mannequin was clothed, seated in a chair, and connected to an IV drip similar to a patient awaiting chemotherapy treatment. The mannequin was equipped with a hidden/covered injection pad in the area of the abdomen suitable for administration of SUSTOL® injections.</p> <p>This injection scenario was repeated twice, with a 5-minute break between injections.</p> | 20 minutes     |
| <b>4. Post-Test Inquiry</b>           | <p>A Post-Test Inquiry session was conducted with each participant to:</p> <ul style="list-style-type: none"> <li>a. evaluate their understanding of the drug product requirements that could not be easily evaluated by user performance;</li> <li>b. identify any issues they may have experienced that were not observed by the investigator, including</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | 25 minutes     |
|                                       | <ul style="list-style-type: none"> <li>c. issues with the Instructions for Use;</li> <li>c. facilitate the determination of the root cause of any use issues observed by the investigator or reported by the participant by exploring the issue with the participant.</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                |
| <b>5. Debriefing and Compensation</b> | Participants were compensated for their participation and dismissed.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | 5 minutes      |

Table 6(a) and (b): Part 2 Reading Time Results & Performance Results

| Pre-Validation Arm |                      | Required Review Arm |                      |
|--------------------|----------------------|---------------------|----------------------|
| Participant ID     | Reading Time (mm:ss) | Participant ID      | Reading Time (mm:ss) |
| 1                  | 8:17                 | 2                   | 5:35                 |
| 3                  | 12:00                | 4                   | 12:30                |
| 5                  | 8:40                 | 6                   | 6:46                 |
| 8                  | 6:50                 | 7                   | 7:07                 |
| 10                 | 4:30                 | 9                   | 5:50                 |
| 12                 | 7:10                 | 11                  | 6:00                 |
| 14                 | 6:00                 | 13                  | 4:49                 |
| Average            | 7:38                 | Average             | 6:49                 |

| Critical and Essential Tasks                                                       | Scoring                              | Inj 1 | Inj 2        | Observations                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|------------------------------------------------------------------------------------|--------------------------------------|-------|--------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 1. Remove the carton from the refrigerator at least 60 minutes prior to injection. | Success<br>Suc. with Dif.<br>Failure | ns    | 14<br>0<br>0 | <p>Participants were given the SUSTOL® kit for the first injection and therefore did not remove it from the refrigerator.</p> <p>For the second injection sequence, all participants selected a warm kit located on top of the refrigerator. Participant #5 removed a carton from the refrigerator, opened it and read the IFU. She then asked if she needed to wait for one hour. The investigator asked what she would do in her clinical</p> |

|                                                              |                                      |              |              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
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|                                                              |                                      |              |              | setting. She said she would take it out and wait 60 minutes. The investigator then gave her a carton that had been at room temperature for 60 minutes.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| 2. Remove syringe warmers, syringe and needle from kit tray. | Success<br>Suc. with Dif.<br>Failure | 14<br>0<br>0 | 14<br>0<br>0 | All participants successfully removed the tray from the carton and removed the contents from the plastic tray for both injections.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| 3. Choose administration route.                              | Success<br>Suc. with Dif.<br>Failure | 14<br>0<br>0 | 14<br>0<br>0 | All participants selected a subcutaneous injection in the abdomen for all injections.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| 4. Do not remove air bubbles.                                | Success<br>Suc. with Dif.<br>Failure | 14<br>0<br>0 | 14<br>0<br>0 | No participant attempted to remove air bubbles from the syringe.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| 5. Unscrew cap from the end of the prefilled syringe.        | Success<br>Suc. with Dif.<br>Failure | 14<br>0<br>0 | 14<br>0<br>0 | No participant had difficulties unscrewing the end cap from the syringe.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| 6. Remove the hub cover from the needle.                     | Success<br>Suc. with Dif.<br>Failure | 14<br>0<br>0 | 14<br>0<br>0 | No participant had difficulties removing the hub cover from the needle.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| 7. Attach the needle (to the syringe).                       | Success<br>Suc. with Dif.<br>Failure | 14<br>0<br>0 | 14<br>0<br>0 | No participant had difficulties attaching the needle to the syringe.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| 8. Activate and apply gel warming pack.                      | Success<br>Suc. with Dif.<br>Failure | 14<br>0<br>0 | 14<br>0<br>0 | <p>No participant had difficulties activating the gel pack and applying it to the syringe.</p> <p>Three participants (#2, 3, 9) did not put the needle on the syringe but put the needle in the warming pouch with the syringe for both warming sequences. One participant (#6) put the needle in the warming pouch with the syringe to warm it on the second warming sequence but not the first.</p> <p>Participant #8 did not attach the needle to the syringe before placing the syringe in the warming pouch for either injection, so warmed the syringe but not the needle. Participants #6 and 7 did not attach the needle for the first warming sequence but did so on the second. Participant #7 attached the needle to the second syringe after warming for about 2:40 minutes.</p> |

|                                                               |                                      |              |              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|---------------------------------------------------------------|--------------------------------------|--------------|--------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 9. Wait for the gel pack to warm the syringe for 5-6 minutes. | Success<br>Suc. with Dif.<br>Failure | 10<br>0<br>4 | 14<br>0<br>0 | <p>Four participants (#2, 8, 12, 13) did not warm the first syringe for the minimum of five minutes. All participants warmed the second syringe for a minimum of five minutes.</p> <p>Participant #2 warmed the syringe for 3:22 minutes. When asked in the PTI how long she warmed the first syringe, participant #2 said, "I'm thinking about four to five minutes. Honestly, I don't remember really timing it with the first one. ... And the second I made sure it was the full five minutes." The investigator asked if she remembered looking at the clock when warming the first syringe. Participant #2 said "Well, I already started warming it before I looked at the clock and then I went, oh, I should have looked at the clock immediately before."</p> <p>Participant #8 warmed the syringe for 3:50 minutes. In the PTI he said "I didn't know if we were playing with real time or not. I think I should have left it in there a minute longer."</p> <p>Participant #12 warmed the syringe for 2:01 minutes. When asked in the PTI, the participant said "I think when I did it the very first time it was probably less than the five minutes. ... But the second time it lasted maybe six minutes. ... Probably the first time doing it I was a little nervous." The participant warmed the second syringe for 5:00 minutes. When asked in the PTI, how she kept track of the time for the second injection, she said "The clock". The investigator then asked if she used the clock on the first one? The participant replied "I didn't even notice we had a clock in the room. I was going by my memory, you know, counting. Alarm clock in my brain was what I was going on."</p> <p>Participant #13 said it should be warmed for 5-6 minutes and checked the clock several times during the warming period. However, she must have misread the start time or miscalculated the end time because the warming time was only 3:35 minutes.</p> |
|---------------------------------------------------------------|--------------------------------------|--------------|--------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

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|--------------------------------------------------------------------------------------------|--------------------------------------|--------------|--------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 10. Remove syringe from the gel pack.                                                      | Success<br>Suc. with Dif.<br>Failure | 14<br>0<br>0 | 14<br>0<br>0 | All participants removed the warming pack without difficulties for both injection sequences.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| 11. Remove blue needle cover.                                                              | Success<br>Suc. with Dif.<br>Failure | 14<br>0<br>0 | 14<br>0<br>0 | All participants removed the needle cover without difficulties for both injection sequences.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| 12. Insert needle at 30-45 degrees.                                                        | Success<br>Suc. with Dif.<br>Failure | 12<br>0<br>2 | 12<br>0<br>2 | All participants injected into the subcutaneous layer of the injection pad.<br><br>For both injections, two participants (#1 and #10) injected at an angle closer to 90 degrees but had pinched a large amount of skin such that the injection would not have reached muscle tissue or the peritoneal cavity.                                                                                                                                                                                                                                                                                                                                     |
| 13. Press plunger with the thumb or palm using a slow and steady push until plunger stops. | Success<br>Suc. with Dif.<br>Failure | 13<br>1<br>0 | 14<br>0<br>0 | Participant #5 delivered all of the medication in less than 25 seconds but continued to press the plunger for an additional 3:30 minutes. When asked in the PTI, she said, "It was hard ... like I'm not doing this right! ... I couldn't really tell whether it was all out of the valve (syringe) because of the gray. I can't tell." She completed the second injection in 38 seconds.<br><br>All other participants completed the injection without difficulty. Participant #4 took 74 seconds to complete the injection. During the injection, she said "I am going to take my time and administer it slowly... the medicine is very thick". |
| 14. Withdraw the needle.                                                                   | Success<br>Suc. with Dif.<br>Failure | 14<br>0<br>0 | 14<br>0<br>0 | No participant had difficulties withdrawing the syringe from the patient.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| 12. Syringe handling. (Check for evidence of cracking or breaking of syringe and plunger.) | Success<br>Suc. with Dif.<br>Failure | 14<br>0<br>0 | 14<br>0<br>0 | The investigator examined all syringes after each session. No syringe showed signs of cracking and no syringe broke during the injections.<br><br>In all syringes, the plunger was at the bottom of the syringe, indicating that all of the medication was delivered during the injection.                                                                                                                                                                                                                                                                                                                                                        |

Table 7: Post-Test Inquiries

| Question                                                                                                     | Participant Responses                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|--------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 1. Where on the body is it appropriate to inject SUSTOL®?                                                    | All participants indicated the injection should be in the abdomen.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| 2. Is it okay to inject SUSTOL® intravenously? What about intramuscular or intraperitoneal?                  | All participants indicated 'no' to all three questions.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| 3. Should SUSTOL® be administered cold or warm?                                                              | All participants indicated that SUSTOL® should be administered warm.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| 4. How long should SUSTOL® be at room temperature before applying the warming pack?                          | Six of seven participants indicated that SUSTOL® should be at room temperature for 60 minutes before applying the gel pack.<br><br>Participant #12 appeared to misunderstand the question and said ten to fifteen minutes. The investigator asked the question in a different way a second time. The participant looked at the IFU and repeated ten to fifteen minutes.                                                                                                                                                                                                                                                      |
| 5. Were the instructions to warm SUSTOL® immediately prior to injection clear?                               | All participants indicated that the instructions on warming were clear.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| 6. How long should SUSTOL® be warmed in the warming blanket before administration?                           | All participants indicated that SUSTOL® should be warmed for 5-6 minutes in the warming blanket.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| 7. Did the IFU prepare you for the viscous nature of SUSTOL®?                                                | All participants indicated that the IFU prepared them for the viscous nature of SUSTOL®.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| 8. Finally, do you feel confident that you could safely and effectively administer SUSTOL® to your patients? | All participants answered 'yes' to the question.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| 9. Do you recall having any difficulties with any of the following:                                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| a. Removing the warmers, syringe or needle from the carton?                                                  | No participant reported having any difficulties removing the components from the carton.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| b. Locating or checking the expiration date?                                                                 | Participant #10 said that in her place of work the pharmacy checks the expiration date. Participant #12 said she could not find the expiration date on the carton.<br><br>NOTE: The expiration date was not printed on the carton.<br><br>Participant #4 said she did not check the expiration date because the pharmacy checks it; Participant #9 said she could not find the expiration date; she expected it to be on the carton; Participant #2 also mentioned she expected to see the expiration date on the carton.<br><br>No other participant reported having difficulties locating or checking the expiration date. |
| c. Choosing the administration route?                                                                        | No participant reported having difficulties choosing the administration route.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| d. Choosing the injection site?                                                                              | No participant reported having difficulties choosing the injection site.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| e. Understanding the precautionary label on the syringe?                                                     | No participant reported having difficulties understanding the precaution label.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| f. Removing the precaution label?                                                                            | No participant had difficulties with the precaution label.<br><br>Participants #2, 10, and 11 said she would like to see the label perforated.<br><br>Seven participants (#3, 4, 5, 6, 7, 8, and 12) did not remove it; it was not in the way.                                                                                                                                                                                                                                                                                                                                                                               |
| g. Checking the dose volume?                                                                                 | No participant reported difficulties checking the dose volume on the carton.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| h. Unscrewing the tip cap?                                                                                   | No participant reported having difficulties unscrewing the tip cap.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| i. Removing the clear cap from                                                                               | No participant reported having difficulties removing the clear cap                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |

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| the needle cover?                                          | from the needle cover.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| j. Attaching the needle to the syringe?                    | No participant reported having difficulties attaching the needle to the syringe.                                                                                                                                                                                                                                                                                                                                                                                                                      |
| k. Activating and applying the gel pack to warm SUSTOL®?   | Participant #11 'popped' the first disk to start the warming pack; she could not feel it getting warm and attempted to mix the contents of the pack but after three minutes it still was not getting warm; she 'popped' the disk again and mixed it ("mashed it") and it started to warm. She said it did not 'pop' the second time but she continued to mix it. She said she was comfortable working through the problem. In the PTI, she tried another warming pack and it warmed on the first try. |
| l. Waiting for the gel pack to warm SUSTOL®?               | Four participants (#5,8,12,14) said they would have other things to do while the syringe was warming. Participant #10 said that a five minute wait was long but not unrealistic; she mentioned taking the medication out of the refrigerator 60 minutes before warming, warming it, and making sure it was given 30 minutes before he chemotherapy, a lot of steps. But, she said that the steps were not difficult for her.                                                                          |
| m. Removing the blue needle cover?                         | No participant reported having difficulties removing the blue needle cover.                                                                                                                                                                                                                                                                                                                                                                                                                           |
| n. Inserting the needle at a 30 to 45 degree angle?        | No participant reported having difficulties inserting the needle at the correct angle.                                                                                                                                                                                                                                                                                                                                                                                                                |
| o. Pressing the plunger to inject the medication?          | No participant reported having difficulties pressing the plunger.<br><br>Participants #6, 7, 11, and 12 said they expected it to be hard because of the viscous nature of the medicine; participants #2 and 3 expected it to be hard because the IFU had advised them; participant #8 said she knew it would take 20 to 30 seconds to complete the injection; participant #9 said it was hard but was not a problem for her.                                                                          |
| p. Checking or knowing that the entire dose was delivered? | No participant reported having difficulties checking or knowing that the entire dose was delivered.<br><br>Participant #5 mentioned that the drug and the plunger were almost the same color; it would be easier to tell that all of the drug was delivered if the plunger was a different color. On the other hand, participants #8 and #10 said it was easy to tell because the syringe was clear and it was easy to see the medication.                                                            |
| q. Removing the needle from our                            | No participant reported having difficulties removing the needle                                                                                                                                                                                                                                                                                                                                                                                                                                       |

| Question                                                                                                                 | Participant Response                                                                                                                                                                                                                            |
|--------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 1. Did the instructions adequately guide you through the setup and injection process?                                    | All participants indicated that the Instructions for Use adequately guided them. Participants specifically mentioned:<br>- helpful images<br>- clear explanations<br>- easy to read instructions<br>- highlighting of important steps<br>- tips |
| 2. Was there any part of the process for which the instructions did not prepare you or provide you with enough guidance? | No participant indicated that the instructions did not prepare him or her for the injection. Participants specifically mentioned:<br>- straight forward instructions<br>- clear language<br>- helpful images                                    |
| 3. Were you confused by any step in the instructions? If so, which one(s)?                                               | No participant mentioned any confusion related to the instructions.                                                                                                                                                                             |

## Human Factors Summative Test Results

- Simulated-Use Test Type
  - The following reasons are why this test type was chosen:
    - Simulated-Use enabled detailed observation of user performance on almost all critical and essential tasks
    - Clinical scenarios were used to engage participants in a realistic drug administration→Only difference being that participants injected the drug into a [patient model] mannequin and not a live patient.
    - Allowed for video-recording
    - Simulated environment allowed for considerations of use environment that may affect user performance
    - Simulated-Use permitted interviewing participants immediately after use, in form of Post-Test Interview, while the details of their interactions were still fresh in their memory
    - Post-Test Interview questions were used to evaluate whether participants understand all critical/essential aspects of the drug product (since some aspects of drug may not effectively evaluated via performance testing)
- Participants
  - Total of 15 participants included in study
    - All RNs working in either inpatient or outpatient oncology settings within this setting for at least 6 months.
    - Experience in administration of chemotherapy, anti-emetics, subQ meds, and syringe-based injections.
    - 14 females and 1 male with an average age of 42.3 years and 12.7 years in Oncology.
- Facility/Use Environment-Task Categorization-Scenario-Training
  - Testing was conducted at a market research facility in a room with comparable levels of lighting, noise, temperature, and humidity→No interruptions or distractions were employed during sessions.
    - Mannequin was clothed, seated in a chair, and connected to an IV drip similar to a patient awaiting chemo treatment→Additionally it was equipped with a hidden/covered injection pad in the area of the abdomen.
    - Sustol product was prepared using commercial product components at the proposed commercial manufacturing facility.
  - All critical/essential tasks were evaluated in the Validation testing→See Table #9

- Use Scenario involved asking each participant to inject Sustol 2 times with a different MAR provided for each injection.
  - Each MAR specified the patient was to be given 10 mg of granisetron via SubQ injection 30 minutes prior to the start of chemo.
- No training was provided to the nurses on administration of Sustol.
- Study/Test Procedure: See Table #8
- Data Collection
  - Capture of Unanticipated Use Errors: Participants were monitored for any obvious signs of hesitation or confusion that may suggest other, unanticipated use issues.
    - These events were explored during the Post-Test Interview.
    - Additionally, participants were asked if they experienced difficulties during performance of the task and actions that may not have been obvious to the Investigator.
  - Subjective Assessment of Task Failures: these methods were used to investigate performance issues, which involved participants being asked during the Post-Test Interview if they recalled having difficulties performing actions with the drug.
    - The investigator asked about specific use issues, including those that led to failures to complete a scenario or action correctly.
    - These were done to direct us toward understanding the root cause of performance difficulties, including aspects of the user interface (IFU, Gel Packs, and Carton Labeling) that may have been confusing, difficult to read etc.
  - Task Failures/Difficulty
    - Participant performance was categorized the same as the previous formative tests: a) success with little to no effort b) success with difficulties or effort c) failure to complete the scenario OR failure to perform a critical/ essential task correctly.
- Validation Results
  - According to the study report, all 15 participants successfully completed 2 injections (See tables #10 & 11).
    - Per the report, during the 1<sup>st</sup> injection all 15 participants completed the injection with a performance categorization for each task as a) success with little to no effort.
    - However, during the 2<sup>nd</sup> injection, there were 2 tasks that some participants ended up with a failure to complete scenario OR failure to perform a critical essential task.
      - Task 5: Remove the hub cover from the needle: 1 participant had a task failure

- Task 9: Wait for the gel pack to warm the syringe for 5-6 minutes: 3 participants had a task failure.
- Analysis
  - Per the report:
    - All participants indicated that the instructions on warming were clear.
    - All participants stated that Sustol should be warmed in the packs for 5-6 minutes.
    - All participants warmed the syringe in the packs for at least 5 minutes in 1<sup>st</sup> injection.
    - All participants felt the IFU was very clear and prepared the mfor the viscous nature of Sustol.
    - All participants stated that they were able to hold the syringe steady throughout.
    - All participants stated they could administer Sustol as safely as other viscous meds they were familiar with.
  - Warming
    - According to the report all participants verbalized understanding of the warming process and requirements surrounding its proper use and unction during the Post-Test Interview.
      - 13 participants said it should be warmed before administering and 2 stated it'd be difficult to administer if it was not warm.
    - No participant reported having issues/difficulties activating the gel packs, applying them to the syringe, warming for at least 5 minutes, or removing the syringe from the gel pack.
    - 3 participants didn't warm the syringe for the minimum 5 minutes before the 2<sup>nd</sup> injection
      - 1 participant (2) warmed it for 1:52 and attributed her not waiting as to it being a test and not real.
      - 2 participants warmed for 4:30 (6) and 4:35 (11) minutes, and both said the syringe should be warmed for 5-6 minutes→Participant 11 thought she had warmed the syringe for 5 minutes and stated using the clock to time it.
      - No activity was provided to the participants during the warming period to occupy them, and this was a possible reason, per the report, that may have contributed to their reduced awareness of actual warming time.

- Maintaining the Angle of Injection
  - No participant reported having difficulties inserting the needle at an appropriate angle.
    - No participant used 2 hands to press the plunger.
    - 6 participants stabilized the syringe throughout the injection by supporting the barrel of the syringe near the point of entry with their non-dominant hand.
    - 3 other participants stabilized the injection site throughout the injection by maintaining their hold on the pinched skin with their non-dominant hand.
  - All participants appeared to maintain a stable injection angle while pressing the plunger.
- Administering all of the Medication
  - In earlier formative studies, a small number of participants appeared to have difficulties discerning when the syringe had reached the base of the plunger and kept pushing with the needle in place.
    - Before this study, the IFU was modified to direct users to check to make sure that the entire drug was delivered by checking the position of the stopper at the base of the plunger.
    - None of the participants in THIS study were observed or reported having issues knowing when the syringe plunger had reached the base of the syringe such that the drug was fully expelled → the moderator confirmed, by direct inspection of the syringes, that the plunger was at the base of the syringe barrel after each session.
- Review of Task Failures and Observed Issues
  - Not Warming Syringe in the Pack for 5 minutes during 2<sup>nd</sup> Injection.
    - 1 participant (1) knew the syringe should be warmed to body temp, thought it was at body temp, but didn't wait b/c she felt the simulation was "NOT real time."
    - Participant 11 thought she had warmed it for five minutes but misread the clock.

- Participant 6 didn't have any activity to keep her busy during the simulation as she felt she would have had one in the real setting.
- Difficulty removing the Needle Hub Cover.
  - 1 participant (13) had issues removing the needle hub cover on the 2<sup>nd</sup> injection despite not having any issues with the 1<sup>st</sup> injection.
    - His fingers covered the junction between the hub and needle so he didn't notice the dividing line that would indicate the entire clear cap should come off.
    - The needle is manufactured by Covidien.
  - 1 participant received a needle stick injury while attempting to insert the needle into the pad.
    - The participant stated that the “physical layout” of the simulation was awkward for her→Specifically she said the layout required her to kneel to give the injection
    - Participant said she did NOT “...think it was Sustol's fault.
  - All participants mentioned, at some point, that the product did NOT have a safety needle.

Table #8: Study Procedure

|                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|--------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 1. Participant Enrollment      | Upon arrival, Informed Consent was obtained and participants were given a demographic questionnaire, to verify that they met the study inclusion and exclusion criteria.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| 2. Introduction to the Study   | Participants were given an oral introduction to the study (see <a href="#">Appendix</a> ). The Investigator answered questions about the study at this time.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| 3. Performance Testing         | <p>After a brief introduction to describe the goals of the study, participants were given the product and allotted time to familiarize themselves with the product. Once they were ready to proceed, participants were asked to administer SUSTOL® to a “patient” following the description provided in the patient’s Medication Administration Record (MAR).</p> <p>This injection scenario was repeated twice, with at least a 5-minute interval between injections.</p>                                                                                                                                                                                                       |
| 4. Post-Test Interview         | <p>A Post-Test Interview session was conducted with each participant to:</p> <ul style="list-style-type: none"> <li>a) evaluate participant understanding of the drug product requirements that could not be easily evaluated by user performance;</li> <li>b) identify any issues participants may have experienced that were not observed by the Investigator, including issues with the Instructions for Use;</li> <li>c) facilitate the determination of the root cause of any unexpected behaviors or problems observed during performance of tasks by reviewing performance with participants.</li> </ul> <p>See <a href="#">Appendix</a> for the Post-Test Interview.</p> |
| 5. Debriefing and Compensation | After the Post-Test Interview, participants were compensated for their participation and dismissed. The Investigator inspected the syringes for evidence of cracking or breaking (see <a href="#">6.4.3</a> above).                                                                                                                                                                                                                                                                                                                                                                                                                                                              |

Table #9: Critical/Essential Tasks

Table 17. Critical and essential task and definitions of task failure

| Critical or Essential Task                                                     | Comment                                                                                                                         | HF Validation Method                                                                                                                                                              | Definition of Task Failure                                                                                                                                  |
|--------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Remove the carton from the refrigerator at least 60 minutes prior to injection | Essential to remove carton from the refrigerator at least 60 minutes prior to injection to allow it to come to room temperature | Participant performance was monitored for recognizing that SUSTOL® should be brought to room temperature prior to using the Syringe Warmers to prepare the syringe for injection. | Participant did not recognize that SUSTOL® should be removed from refrigeration at least 60 minutes before administration or warmed prior to administration |
| Remove Syringe                                                                 | Essential to remove                                                                                                             | For each of two                                                                                                                                                                   | Participant was                                                                                                                                             |

| Critical or Essential Task                          | Comment                                                                                                                                                | HF Validation Method                                                                                                                                                                                                                                        | Definition of Task Failure                                                                                  |
|-----------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------|
| warmers, syringe and needle from kit tray.          | kit components from packaging to give injection.                                                                                                       | injection scenarios, participants were provided an unopened SUSTOL® kit box for administration. Participant performance was monitored for issues opening the carton and tray and removing the components.                                                   | unable to remove components from tray.                                                                      |
| Choose administration route.                        | Critical and Essential. Medication must be delivered through the correct route to avoid harm to the patient and ensure an effective injection outcome. | A mannequin attached to an IV drip was used for all injection scenarios. Participant performance was monitored for whether they inject SUSTOL® subcutaneously. In a Post-Test Interview, participants were asked what administration routes are acceptable. | Participant chose an inappropriate route or suggests an inappropriate route during the Post-Test Interview. |
| Unscrew cap from the end of the pre-filled syringe. | Essential to allow the needle to be attached to the syringe body.                                                                                      | Participant performance was monitored for whether they unscrew the tip cap.                                                                                                                                                                                 | Participant failed to unscrew the tip cap.                                                                  |
| Remove the hub cover from the needle.               | Essential because the needle hub cover must be removed to attach the needle to the syringe to give the injection.                                      | Participant performance was monitored for whether they remove the cover from the needle.                                                                                                                                                                    | Participant failed to remove the needle hub cover.                                                          |

| Critical or Essential Task                    | Comment                                                                                                                                                 | HF Validation Method                                                                                                                                                  | Definition of Task Failure                                                                                                                                    |
|-----------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Attach the needle (to the syringe).           | Essential. Attaching the needle to the syringe body is necessary to give the injection.                                                                 | Participant performance was monitored for whether they attach the needle.                                                                                             | Participant failed to attach the needle, the liquid leaks from the needle connection during injection, or the needle inadvertently detaches from the syringe. |
| Activate the warming gel pack.                | Critical. The Syringe Warmer must be activated in order to warm the syringe.                                                                            | Participant performance was monitored for whether they activate the gel pack.                                                                                         | Participant failed to activate the gel pack.                                                                                                                  |
| Apply the warming gel pack.                   | Critical. Applying the warming gel pack will ensure that SUSTOL® is sufficiently warm to promote an easy and safe injection.                            | Participant performance was monitored for whether they apply the gel pack prior to administration.                                                                    | Participant failed to apply the gel pack to the syringe.                                                                                                      |
| Wait five to six minutes to warm the syringe. | Critical. The syringe must be warmed in the gel pack for at least five minutes to ensure that SUSTOL® reaches body temperature.                         | Participant performance was timed to determine if they warm the syringe for the minimal required time of five minutes.                                                | Participants warmed the syringe for less than five minutes.                                                                                                   |
| Remove the syringe from the gel pack.         | Essential. The syringe must be removed from the gel pack in order to administer SUSTOL®.                                                                | Participant was monitored for whether they removed the syringe from the gel pack.                                                                                     | Participant did not remove the syringe from the gel pack before attempting to inject.                                                                         |
| Remove the (blue) needle                      | The sheath must be removed before an                                                                                                                    | Participant performance was monitored for                                                                                                                             | Participant failed to remove the needle                                                                                                                       |
| Critical or Essential Task                    | Comment                                                                                                                                                 | HF Validation Method                                                                                                                                                  | Definition of Task Failure                                                                                                                                    |
| practices.                                    | aseptic technique is advisable for any injection and critical for reducing the risk of infection, especially in immuno-compromised patient populations. | standard nursing practice. In addition, participants may not have assumed, given the simulated nature of the study, that normal aseptic practices should be followed. |                                                                                                                                                               |
| Syringe handling.                             | Critical to handle syringe appropriately after injection to avoid needle stick and possible infection.                                                  | Participant performance was monitored for evidence of difficulties handling the SUSTOL® syringe (including needle sticks).                                            | Participant experienced an issue with a moderate or higher level of harm.                                                                                     |

**Table #10: Summary of Performance on Critical/Essential Tasks**

Table 18. Summary of Participant performance on critical and essential tasks

| Critical or Essential Task                                                         | Injection 1 |    |   | Injection 2 |    |   |
|------------------------------------------------------------------------------------|-------------|----|---|-------------|----|---|
|                                                                                    | S           | SD | F | S           | SD | F |
| 1. Remove the carton from the refrigerator at least 60 minutes prior to injection. | 15          | 0  | 0 | 15          | 0  | 0 |
| 2. Remove Syringe warmers, syringe and needle from kit tray.                       | 15          | 0  | 0 | 15          | 0  | 0 |
| 3. Choose administration route.                                                    | 15          | 0  | 0 | 15          | 0  | 0 |
| 4. Unscrew cap from the end of the prefilled syringe.                              | 15          | 0  | 0 | 15          | 0  | 0 |
| 5. Remove the hub cover from the needle.                                           | 15          | 0  | 0 | 14          | 0  | 1 |
| 6. Attach the needle (to the syringe).                                             | 15          | 0  | 0 | 15          | 0  | 0 |
| 7. Activate gel warming pack.                                                      | 15          | 0  | 0 | 15          | 0  | 0 |
| 8. Apply warming pack to syringe.                                                  | 15          | 0  | 0 | 15          | 0  | 0 |
| 9. Wait for the gel pack to warm the syringe for 5-6 minutes.                      | 15          | 0  | 0 | 12          | 0  | 3 |
| 10. Remove syringe from the gel pack.                                              | 15          | 0  | 0 | 15          | 0  | 0 |
| 11. Remove blue needle cover.                                                      | 15          | 0  | 0 | 15          | 0  | 0 |
| 12. Insert needle into the subcutaneous tissue.                                    | 15          | 0  | 0 | 15          | 0  | 0 |
| 13a. Press plunger to deliver all the medication, slow and steady.                 | 15          | 0  | 0 | 15          | 0  | 0 |

| Critical or Essential Task                                           | Injection 1 |    |   | Injection 2 |    |   |
|----------------------------------------------------------------------|-------------|----|---|-------------|----|---|
|                                                                      | S           | SD | F | S           | SD | F |
| 13b. Participant maintains the injection plane during the injection. | 15          | 0  | 0 | 15          | 0  | 0 |
| 13c. Participant does not advance the needle during the injection.   | 14          | 1  | 0 | 14          | 1  | 0 |
| 14. Check that the entire dose has been administered to the patient. | 15          | 0  | 0 | 15          | 0  | 0 |
| 15. Discard the used needle and syringe.                             | 15          | 0  | 0 | 15          | 0  | 0 |
| 16. Syringe handling.                                                | 14          | 0  | 1 | 15          | 0  | 0 |

**Table #11: In-Depth Performance of Critical/Essential Tasks**

Table 19: Detailed review of performance across critical and essential tasks

| Critical and Essential Tasks                                                       | Scoring                          | Inj 1        | Inj 2        | Observations                                                                                                                                                                                                                                                                                                                                                                                                                            |
|------------------------------------------------------------------------------------|----------------------------------|--------------|--------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 1. Remove the carton from the refrigerator at least 60 minutes prior to injection. | Success<br>Suc/w Diff<br>Failure |              |              | Not scored during the injection sequence because participants were not asked to remove the carton from the refrigerator. Instead, participant understanding was assessed through the Post-Test Interview.<br><br>Before opening the carton, all participants indicated that the carton should have been out of the refrigerator for at least one hour (60 minutes) to allow the contents to come to room temperature before continuing. |
| 2. Remove Syringe warmers, syringe and needle from kit tray.                       | Success<br>Suc/w Diff<br>Failure | 15<br>0<br>0 | 15<br>0<br>0 | All participants removed the contents without difficulty.                                                                                                                                                                                                                                                                                                                                                                               |

| Critical and Essential Tasks                          | Scoring                          | Inj 1        | Inj 2        | Observations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|-------------------------------------------------------|----------------------------------|--------------|--------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 3. Choose administration route.                       | Success<br>Suc/w Diff<br>Failure | 15<br>0<br>0 | 15<br>0<br>0 | All participants selected a subcutaneous injection into the abdomen.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| 4. Unscrew cap from the end of the prefilled syringe. | Success<br>Suc/w Diff<br>Failure | 15<br>0<br>0 | 15<br>0<br>0 | All participants successfully unscrewed the end cap from the syringe.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| 5. Remove the hub cover from the needle.              | Success<br>Suc/w Diff<br>Failure | 15<br>0<br>0 | 14<br>0<br>1 | <p>Fourteen participants removed the hub cover from the needle without difficulty.</p> <p>One participant (#13) required assistance from the Investigator on their second injection, despite having no issues on their first. For the second injection scenario, the participant expected to remove only the hexagonal end piece of the hub and attempted to twist it while holding onto the opposite end. Consequently, the hub cover did not rotate and break loose from the plastic weld holding the hub onto the needle cap. His fingers covered the junction between the hub and needle so he did not notice the dividing line that would indicate the entire clear cap should come off. This needle is a standard, off-the-shelf, Covidien needle approved for use and widely marketed throughout the US.</p> |
| 6. Attach the needle (to the syringe).                | Success<br>Suc/w Diff<br>Failure | 15<br>0<br>0 | 15<br>0<br>0 | All participants successfully attached the needle to the syringe.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| 7. Activate gel warming pack.                         | Success<br>Suc/w Diff            | 15<br>0      | 15<br>0      | All participants successfully activated the warming packs.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |

| Critical and Essential Tasks                                  | Scoring                          | Inj 1        | Inj 2        | Observations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|---------------------------------------------------------------|----------------------------------|--------------|--------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                               | Failure                          | 0            | 0            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| 8. Apply warming pack to syringe.                             | Success<br>Suc/w Diff<br>Failure | 15<br>0<br>0 | 15<br>0<br>0 | <p>All participants wrapped the syringe in the warming gel pack.</p> <p>One participant (#1) did not use the Velcro strips on the first syringe but held it in her hands while waiting for the 5 minute warming period. In the PTI, she said she "didn't realize it (Velcro) was there ... Now that I know it's there I would leave it in there for five minutes and not worry about it". This participant used the Velcro strips on the second syringe.</p>                                                                                                                                                                                                                                                                                                                                                                                              |
| 9. Wait for the gel pack to warm the syringe for 5-6 minutes. | Success<br>Suc/w Diff<br>Failure | 15<br>0<br>0 | 12<br>0<br>3 | <p>All participants warmed the syringe for a minimum of five minutes on the first injection. Moreover, all participants explicitly mentioned that the syringe should be warmed for 5 to 6 minutes prior to administration.</p> <p>On the second injection, one participant (#1) warmed for 1:52 minutes and in the PTI said "I guess I figured I didn't need to (warm it for five minutes) because we were just doing this I didn't need to wait in real time".</p> <p>Two other participants warmed for 4:30 (#6) and 4:35 (#11) minutes; both said, in the Post Test Interview, the syringe should be warmed for five to six minutes. Participant #6 said he did not mind waiting and could do other things while waiting. Participant #11 thought she had warmed the syringe for five minutes and that she had used the clock to keep track of the</p> |

| Critical and Essential Tasks                                       | Scoring                          | Inj 1        | Inj 2        | Observations                                                                                                                                                                                                                                                        |
|--------------------------------------------------------------------|----------------------------------|--------------|--------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                                    |                                  |              |              | warming period. The simulation did not provide any activity to occupy participants during the syringe warming time; this may have contributed to their reduced warming time. Several other participants commented that they would be busy during the waiting time.  |
| 10. Remove syringe from the gel pack.                              | Success<br>Suc/w Diff<br>Failure | 15<br>0<br>0 | 15<br>0<br>0 | All participants removed the syringe from the warming pack without difficulty.                                                                                                                                                                                      |
| 11. Remove blue needle cover.                                      | Success<br>Suc/w Diff<br>Failure | 15<br>0<br>0 | 15<br>0<br>0 | All participants removed the blue needle cover without difficulty.                                                                                                                                                                                                  |
| 12. Insert needle into the subcutaneous tissue.                    | Success<br>Suc/w Diff<br>Failure | 15<br>0<br>0 | 15<br>0<br>0 | All participants successfully inserted the needle into the subcutaneous tissue of the injection pad.                                                                                                                                                                |
| 13a. Press plunger to deliver all the medication, slow and steady. | Success<br>Suc/w Diff<br>Failure | 15<br>0<br>0 | 15<br>0<br>0 | All participants successfully delivered all the medication. The Investigator inspected the syringes after each injection. In all cases the medication was fully expelled as indicated by the position of the stopper at the bottom of the syringe barrel.           |
| 13b. Maintains the injection plane during the injection.           | Success<br>Suc/w Diff<br>Failure | 15<br>0<br>0 | 15<br>0<br>0 | All participants appeared to maintain a stable injection angle while pressing the plunger; movement of the syringe angle during the injection appeared to be minimal, based on visual inspection. This observation was confirmed by independent review of the video |

| Critical and Essential Tasks                         | Scoring                          | Inj 1        | Inj 2        | Observations                                                                                                                                                                                                                                                                   |
|------------------------------------------------------|----------------------------------|--------------|--------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                      |                                  |              |              | by two reviewers.                                                                                                                                                                                                                                                              |
|                                                      |                                  |              |              | All participants used only their dominant hand on the plunger during the injection; no participant used two hands on the plunger.                                                                                                                                              |
|                                                      |                                  |              |              | Six participants (#5, #6, #9, #13, #14, #15) stabilized the syringe throughout the injection by supporting the barrel of the syringe near the point where the needle entered the skin with their non-dominant hand.                                                            |
|                                                      |                                  |              |              | Three participants (#1, #4, #12) stabilized the injection site throughout the injection by maintaining the skin pinch with their non-dominant hand.                                                                                                                            |
| 13c. Do not advance the needle during the injection. | Success<br>Suc/w Diff<br>Failure | 14<br>1<br>0 | 14<br>1<br>0 | Once the injection started, no participant appeared to advance the needle further into the skin more than approximately 1mm. This observation was confirmed by independent review of the video by two reviewers.                                                               |
|                                                      |                                  |              |              | There was no visible surface deflection of the artificial skin even in those cases where the barrel of the syringe contacted the skin.                                                                                                                                         |
|                                                      |                                  |              |              | On the first injection, participant #2 pulled up slightly on the needle and some medication leaked on to the skin; participant #2 then advanced the needle back into the skin to stop the leakage. On the second injection, participant #5 did not insert the needle fully and |

| Critical and Essential Tasks                                         | Scoring                          | Inj 1        | Inj 2        | Observations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|----------------------------------------------------------------------|----------------------------------|--------------|--------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                                      |                                  |              |              | allowed some medication to leak on the skin.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| 14. Check that the entire dose has been administered to the patient. | Success<br>Suc/w Diff<br>Failure | 15<br>0<br>0 | 15<br>0<br>0 | All syringes were inspected by the Investigator.<br><br>For all syringes, the plunger was at the base of the syringe indicating that all medication had been expelled.                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| 15. Discard the used needle and syringe.                             | Success<br>Suc/w Diff<br>Failure | 15<br>0<br>0 | 15<br>0<br>0 | All participants discarded the syringe in the sharps container.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| 16. Syringe handling.                                                | Success<br>Suc/w Diff<br>Failure | 14<br>0<br>1 | 15<br>0<br>0 | One participant (#12) received a needle stick while attempting to insert the needle into the injection pad for the first injection; she just missed the pad and hit her finger. In the Post Test Interview, the participant said she didn't "think it was SUSTOL®'s fault. I think it was just one of those things". She stated that the "physical layout" of the simulation was awkward for her; that the layout required that she kneel to give the injection; she offered that she was "physically in an awkward position" prior to giving the injection. The participant completed the second injection without difficulty. |

Table #11: Responses to Post-Test Interview Questions

| Question                                                                                                    | Participant Responses                                                                                                                                                            |
|-------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 1. Where on the body is it appropriate to inject SUSTOL®?                                                   | All 15 participants indicated the injection should be subcutaneous in the abdomen; most mentioned 1" away from the navel.                                                        |
| 2. Is it okay to inject SUSTOL® intravenously? What about intramuscular or intra-peritoneal administration? | All 15 participants indicated 'no' to all three questions.                                                                                                                       |
| 3. Should SUSTOL® be administered cold or warm?                                                             | All 15 participants indicated that SUSTOL® should be administered warm.                                                                                                          |
| 4. (If warm) Why should SUSTOL® be warm before administering.                                               | All 15 participants said that warming reduces viscosity.<br><br>Eleven specifically mentioned warming makes it easier to administer.                                             |
| 5. Is it okay to use SUSTOL® if it has not been warmed first?                                               | Thirteen participants said SUSTOL® should be warmed before administering.<br><br>Two participants (#3, #13) said it would be difficult to administer SUSTOL® if it was not warm. |
| 6. How long should SUSTOL® be out of the refrigerator to allow it to come to room temperature?              | All 15 participants said that SUSTOL® should be out of the refrigerator for 60 minutes.                                                                                          |
| 7. Were in instructions to warm SUSTOL® immediately prior to injection clear?                               | All 15 participants said yes.                                                                                                                                                    |
| 8. Did the Instructions For Use prepare you for the viscous nature of SUSTOL®?                              | All 15 participants indicated that the IFU prepared them for the viscous nature of SUSTOL®.                                                                                      |
| 9a. Do you feel you were able                                                                               | Fourteen participants said yes they maintained the angle of                                                                                                                      |

| Question                                                                                                                       | Participant Responses                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
|--------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| to maintain the angle of injection throughout?                                                                                 | <p>the syringe without difficulty.</p> <p>One participant (#4) said "I think I realized the force that I then needed to place on the syringe was sort of jolting my angle ... causing my hand, to slightly move the angle a little away ... but I wouldn't say I caused a problem that I think the patient would notice". The video of this participant does not show any significant angular motion to the syringe during either injection.</p>                                                                                                                                                                                                                                                                                                                                                                                                                           |
| 9b. Do you feel you were able to hold the syringe steady throughout?                                                           | All 15 participants said "yes".                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| 9c. Do you feel you were able to administer this medication as safely as with other viscous medications you have administered? | <p>Fourteen participants said "yes".</p> <p>One participant (#12) said she did not have any experience with other viscous medications.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| 9d. Do you feel you were able to administer this medication as safely as with other medications administered subcutaneously?   | <p>Eleven participants said "yes" or "very similar to other medications" when asked if they were able to administer this medication as safely as other subcutaneous medications.</p> <p>Participant #2 said it could be "hard to get (to) the subcutaneous tissue" in an "emaciated patient...mainly because of the needle size" but said it would be "fine if you have body weight".</p> <p>Participant #4 compared the injection to other liquid (non-viscous) injections and said that it took longer to deliver than expected and that "I felt like my positioning wasn't the best"; she would have positioned herself differently, at a less "awkward angle". She stated that the second injection was more comfortable for her.</p> <p>Participant #13 said that while he felt the injection could be given safely, he was concerned about the absence of safety</p> |
| Question                                                                                                                       | Participant Responses                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
|                                                                                                                                | <p>needle.</p> <p>Participant #1 was not asked this question.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| 10. Do you recall having any difficulties with any of the following:                                                           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| a. Removing the warmers, syringe or needle from the carton?                                                                    | One participant (#1) said, "The carton was a little hard to open. I think just because I'm not used to it." The remaining participants reported opening the carton without difficulties.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| b. Locating or checking the expiration date?                                                                                   | <p>Twelve participants said they had no trouble locating and checking the expiration date.</p> <p>Two participants (#4, #8) reported multiple dates and initially were not sure which one was the expiration date.</p> <p>One participant (#7) said she did not check the expiration date but found the date very quickly during the interview.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| c. Choosing the administration route?                                                                                          | <p>None of the participants reported having difficulties choosing the administration route.</p> <p>Two participants (#10, #12) said the instructions were so clear on this point they felt they didn't have a choice on the administration route.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| d. Choosing the injection site?                                                                                                | All 15 participants chose the injection site without difficulty.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| e. Understanding the precautionary label on the syringe?                                                                       | All 15 participants said there were no difficulties understanding the precaution label.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| f. Removing the precaution label?                                                                                              | All 15 participants removed the precaution label or administered the medication with the label in place without difficulty. Five participants removed the label before                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |

| Question                                         | Participant Responses                                                                                                                                                                                                                                                                                                                                                                             |
|--------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                  | administering the medication and ten did not.                                                                                                                                                                                                                                                                                                                                                     |
| g. Checking the dose volume?                     | All 15 participants said they had no difficulties checking the dose volume.<br><br>Three participants (#6, #8, #10) mentioned there were no gradations on the syringe barrel; but all three acknowledged that the volume was indicated by the gray plunger above the black line.                                                                                                                  |
| h. Unscrewing the tip cap?                       | Fourteen participants reported having no difficulty unscrewing the tip cap.<br><br>One participant (#13) successfully removed the tip cap but claimed he had difficulties, "...I felt resistance trying ... to pull it". The instructions direct the user to "unscrew the tip cap".                                                                                                               |
| i. Removing the clear cap from the needle cover? | Fourteen participants said there were no difficulties removing the clear cap from the needle cover.<br><br>Participant #13 tried to twist the hexagonal end while holding the other end and required help from the Investigator. His fingers overlapped the clear cap and the needle hiding the junction between them. Again, this is a standard Covidien needle in widespread use across the US. |
| j. Attaching the needle to the syringe?          | All 15 participants said they attached the needle to the syringe without difficulty.                                                                                                                                                                                                                                                                                                              |
| k. Activating the gel pack to warm SUSTOL®?      | Thirteen participants said there were no difficulties activating the gel packs.<br><br>Two participants (#4, #6) mentioned it was a little difficult knowing what to do the first time with the activator disk although they activated the gel pack and warmed the syringe successfully.                                                                                                          |
| l. Applying the gel pack to warm SUSTOL®?        | All 15 participants said there were no difficulties applying the gel pack to SUSTOL®.                                                                                                                                                                                                                                                                                                             |

| Question                                                   | Participant Responses                                                                                                                                                                                                                                                                                                                                                                                                          |
|------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                            | however this did not change the angle of administration. A second participant (#6) reported "a little bit" of difficulty due to the position of the mannequin (not the syringe) and said patients are typically more supine.                                                                                                                                                                                                   |
| r. Using the finger flange?                                | All 15 participants reported having no difficulties using the finger flange.<br><br>Three participants (#5, #6, #11) mentioned it helped them apply more pressure.<br><br>Three participants (#3, #7, #12) said it helped stabilize the syringe.<br><br>As noted above, four other participants (#1, #4, #9, and #15) offered that the flange was helpful in response to the question about difficulties pressing the plunger. |
| s. Checking or knowing that the entire dose was delivered? | All 15 participants reported having no difficulties checking or knowing that the entire dose was delivered.<br><br>Seven participants (#1, #4, #5, #7, #9, #10, #15) said they could see the plunger at the bottom of the barrel.<br><br>Three others (#2, #11, #14) said they could feel it at the end.                                                                                                                       |
| t. Removing the needle from our patient?                   | All 15 participants reported having no difficulties removing the needle from the patient.                                                                                                                                                                                                                                                                                                                                      |
| u. Discarding the needle and syringe?                      | All 15 participants reported having no difficulties discarding the needle.                                                                                                                                                                                                                                                                                                                                                     |
| v. Discarding the syringe warmer gel pack?                 | All 15 participants reported having no difficulties discarding the syringe warmer pack.<br><br>All 15 participants knew it could go in the regular trash.                                                                                                                                                                                                                                                                      |

| Question                                          | Participant Responses                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|---------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                   | One participant (#1) mentioned she didn't use the Velcro strips the first time. She said she "just missed it; didn't read" all of the instructions.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| m. Waiting for the gel pack to warm SUSTOL®?      | <p>All 15 participants said it was not difficult waiting to warm SUSTOL®.</p> <p>Participants #6, #10, #12, and #13 said they would have other things to do while waiting.</p> <p>Participant #3 said it was "no trouble" waiting but "I was actually wondering if people would wait the full five minutes in ... (a) real setting"; he was uncertain "how critical that is" and said "my guess is that's easier to inject if you do wait the five minutes."</p> <p>Participants #2 and #5 mentioned it would be hard to wait five minutes in a healthcare setting (real life) and participant #7 said "you need to manage it (your time)".</p> |
| n. Removing the syringe from the gel pack?        | All 15 participants said they removed the syringe from the gel pack without difficulty.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| o. Removing the blue needle cover?                | All 15 participants said they removed the blue needle cover without difficulty.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| p. Inserting the needle at an appropriate angle?  | <p>All 15 participants said they inserted the needle at an appropriate angle without difficulty.</p> <p>One participant (#4) reported some difficulty pinching the injection pad.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| q. Pressing the plunger to inject the medication? | <p>Thirteen participants reported no difficulties pressing the plunger. Participants #1, #4, #9, and #15 stated that the finger flange was helpful.</p> <p>One participant (#14) stated that pressing was "...kind of harder than I thought..." and that "...it took me longer to do..." and "...my hand got tired...." so they "...took breaks";</p>                                                                                                                                                                                                                                                                                           |

## Human Factors Summative Usability Study

- Simulated-Use Test Type
  - This Test type was chosen for the same reasons as it was for the Validation Study.
- Participants
  - Total of 15 participants included in study
    - All RNs working in either inpatient or outpatient oncology settings within this setting for at least 6 months.
    - Experience in administration of chemotherapy, anti-emetics, subQ meds, and syringe-based injections.
- Facility/Use Environment-Task Categorization-Scenario-Training
  - Testing was conducted at a market research facility in a room with comparable levels of lighting, noise, temperature, and humidity→No interruptions or distractions were employed during sessions.
    - Mannequin was clothed, seated in a chair, and connected to an IV drip similar to a patient awaiting chemo treatment→Additionally it was

equipped with a hidden/covered injection pad in the area of the abdomen and the back of the arm.

- Sustol product was prepared using commercial product components at the proposed commercial manufacturing facility→Sustol Cartons were available in the fridge and on top of the fridge.
- All Critical/Essential tasks and the method of evaluation (see table #13).
- Use Scenario involved asking each participant to inject Sustol 2 times with a different MAR provided for each injection.
  - Each MAR specified the patient was to be given 10 mg of granisetron via SubQ injection 30 minutes prior to the start of chemo.
- No training was provided to the nurses on administration of Sustol.
- This study also added the assessment of Cracking or Breaking of the syringes due to concern expressed by the FDA related to how much pressure was needed to administer the drug could wind up cracking or breaking the syringe(s).
  - All syringes used by participants in the study were visually inspected at completion of each session for any evidence of cracking or breaking or for any evidence of the stopper separating from the plunger rod→This was coupled with the inspection that had already been occurring in the last study to make sure the plunger was at the bottom of the syringe to make sure all of the medication was delivered.
- Study/Test Procedure: see Table #12
- Data Collection
  - Capture of Unanticipated Use Errors: Participants were monitored for any obvious signs of hesitation or confusion that may suggest other, unanticipated use issues.
    - These events were explored during the Post-Test Interview.
    - Additionally, participants were asked if they experienced difficulties during performance of the task and actions that may not have been obvious to the Investigator.
  - Subjective Assessment of Task Failures: these methods were used to investigate performance issues, which involved participants being asked during the Post-Test Interview if they recalled having difficulties performing actions with the drug.
    - The investigator asked about specific use issues, including those that led to failures to complete a scenario or action correctly.
    - These were done to direct us toward understanding the root cause of performance difficulties, including aspects of the user interface (IFU, Gel Packs, and Carton Labeling) that may have been confusing, difficult to read etc.
  - Task Failures/Difficulty

- Participant performance was categorized the same as the previous formative tests: a) success with little to no effort b) success with difficulties or effort c) failure to complete the scenario OR failure to perform a critical/ essential task correctly.
- Validation Test Results
  - All 15 participants completed 2 injections, once into a pad on the abdomen of the mannequin, and once into a pad on the back of the upper arm.
    - All participants successfully prepared the syringe and attached the needle to the syringe.
    - All participants understood the role of the warming packs in warming the syringe prior to injection.
    - All participants successfully used the Point Lok needle safety device to cover the used needle and protect users from potential needle-stick
    - No cracks, breaks, or separation of the plunger from the rod were seen/noted for any syringe used in this study. Also, all participants maintained a steady injection plane during all injections→7 participants (2,5,6,8,9,14, and 15) stated they expected the injection to be difficult due to the medicine being so viscous, but they all stated the IFU prepared them for it→ 14 participants used 1 hand on the syringe during the entire injection and used second non-dominant hand to support the injection site/or barrel of the syringe. However, for both injections Participant 1 pinched the skin with the non-dominant hand then released the pinch when she started the injection; After a few minutes she placed her non-dominant on top of her dominant hand on the syringe, but the syringe remained stable.
    - New Administration Site
      - Administration to the back of the upper arm did not present any new usability issues.
    - Disposing the Used Syringe
      - 14 participants used the point lok needle safety device for both injections. Participant 8 didn't use the needle safety device after the 1<sup>st</sup> injection and disposed of needle into sharps container→She did use it correctly after the 2<sup>nd</sup> injection.
      - No participant received a needle stick injury, or had any [other?] difficulties using the needle safety device.
    - Warming Time
      - All participants in the 1<sup>st</sup> injection and 10 in the 2<sup>nd</sup> injection allowed the syringe to warm for a minimum of 5 minutes→Some

of these 5 nurses claim that in the real world nurses would occupy their time with something else why warming.

- Analysis of Use-Related Issues

- Warming the Syringe for Less than 5 minutes in the Warming Pack

- 5 out of 15 participants warmed the 2<sup>nd</sup> syringe in the gel warming pack for less than the recommended 5 minutes, even though these same participants warmed the 1<sup>st</sup> syringe for at least 5 minutes.
    - Per the report there are a few reasons that could have possibly caused this:
      - Miscalculation of time
      - Participants may have grown impatient
      - During the wait the participants were not given other tasks to do and the moderator didn't initiate conversation
    - The optimum warming time with the warmers was determined to be 5-6 minutes as indicated in the IFU, however the force to inject the drug was significantly reduced even with a warming time of less than the instructed time.

- Not Activating the Gel Warming Pack

- Participant 4 attempted but did not activate a warming pack for either injection scenario→1<sup>st</sup> scenario #4 flexed the disc inside the warming pouch only twice (up then down), and crystallization did NOT occur→In the 2<sup>nd</sup> scenario #4 only flexed it once.
    - Participant 4 still did not have issues with either injection, and both syringes were given at room temp.
    - #4 stated that she didn't expect to feel any warmth and thought that the device would start warming sometime after the click
    - According to the report, the root cause of the use error appears to be that #4 didn't fully understand how often to flex the disks inside the warming packs to initiate crystallization.

- Conclusion

- Per the report, participants in the study were able to administer Sustol as directed without significant use issues→They held the syringe in a stable orientation during the injection and maintained the control of the syringe .

- 2 use issues were observed and were considered to be minor low risk results:
      - 5 participants warmed the syringe in the gel pack for 5 minutes minimum on their 1<sup>st</sup> injection, but during the 2<sup>nd</sup> it was less than 5 minutes.

- 1 participant was unable to activate the gel warming pack during the injection sequence. Still was able to give the drug.
- This study was conducted to assess 2 new changes: Back of upper arm as injection site & Point-Lok Needle Safety Device.

Table #12: Study Procedure

|                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|--------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 1. Participant Enrollment      | Upon arrival, Informed Consent was obtained and participants were given a demographic questionnaire, to verify that they met the study inclusion and exclusion criteria.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| 2. Introduction to the Study   | Participants were given an oral introduction to the study (see <a href="#">Appendix</a> ). The Investigator responded to questions about the study at this time.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| 3. Performance Testing         | <p>After a brief introduction to describe the goals of the study, participants were given an unopened SUSTOL carton and allowed time to familiarize themselves with the product. Once they were comfortable with the product and ready to proceed, participants were asked to administer SUSTOL to a “patient” following the description provided in the patient’s Medication Administration Record (MAR).</p> <p>This injection scenario was repeated twice, once in the abdomen and once in the back of the upper arm. There was at least a 5-minute interval between injections. Prior to the first injection, the moderator asked the participant about appropriate administration sites. If the participant listed the abdomen and back of the upper arm, the participant was permitted to choose either location for their first injection but directed to use the other location for their second. If the participant listed only one of these locations, the moderator asked, “Anywhere else?” and if no other location was identified, the participant was directed to give the second injection in the other location. If the participant listed other sites as appropriate, it was recorded as a use issue and explored in the Post-Test Interview, and the participant was directed to administer once in the abdomen and once in the back of the arm. All participants used the Point-Lok needle safety for at least one injection scenario.</p> |
| 4. Post-Test Interview         | <p>A Post-Test Interview session was conducted with each participant to:</p> <ul style="list-style-type: none"> <li>• evaluate participant understanding of the drug product requirements that could not be easily evaluated by user performance;</li> <li>• identify any issues participants may have experienced that were not observed by the Investigator, including issues with the Instructions for Use;</li> <li>• facilitate the determination of the root cause of any unexpected behaviors or problems observed during performance of tasks by reviewing performance with participants.</li> </ul> <p>See <a href="#">Appendix</a> for the Post-Test Interview.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| 5. Debriefing and Compensation | After the Post-Test Interview, participants were compensated for their participation and dismissed. The moderator inspected the syringes for evidence of cracking or breaking and evidence that all the medication was delivered (see <a href="#">Section 6.4.3</a> above).                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |

Table #13: Critical/Essential Tasks

| Critical or Essential Task                                                      | Comment                                                                                                                                                | Validation Method                                                                                                                                                                                                                                          | Definition of Performance Failure                                                                                                                              |
|---------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Remove the carton from the refrigerator at least 60 minutes prior to injection. | Essential to remove carton from the refrigerator at least 60 minutes prior to injection to allow it to come to room temperature.                       | Participant performance was monitored for recognizing that the SUSTOL should be brought to room temperature prior to using the Syringe Warmers to prepare the syringe for injection.                                                                       | Participant did not recognize that SUSTOL should be removed from refrigeration at least 60 minutes before administration or warmed prior to administration     |
| Remove Syringe warmers, syringe and needle from kit tray.                       | Essential to remove kit components from packaging to give injection.                                                                                   | For each of two injection scenarios, participants were provided an unopened SUSTOL kit box for administration. Participant performance was monitored for issues opening the carton and tray and removing the components.                                   | Participant was unable to remove components from tray.                                                                                                         |
| Choose administration route.                                                    | Critical and Essential. Medication must be delivered through the correct route to avoid harm to the patient and ensure an effective injection outcome. | A mannequin attached to an IV drip was used for all injection scenarios. Participant performance was monitored for whether they inject SUSTOL subcutaneously. In a Post-Test Interview, participants were asked what administration routes are acceptable. | Participant chose an inappropriate route or suggested an inappropriate route during the Post-Test Interview.                                                   |
| Unscrew cap from the end of the pre-filled syringe.                             | Essential to allow the needle to be attached to the syringe body.                                                                                      | Participant performance was monitored for whether they unscrewed the tip cap.                                                                                                                                                                              | Participant failed to unscrew the tip cap.                                                                                                                     |
| Remove the hub cover from the needle.                                           | Essential because the needle hub-cover must be removed to attach the needle to the syringe to give the injection.                                      | Participant performance was monitored for whether they removed the cover from the needle.                                                                                                                                                                  | Participant failed to remove the needle hub cover.                                                                                                             |
| Attach the needle (to the syringe).                                             | Essential. Attaching the needle to the syringe body is necessary to give the injection.                                                                | Participant performance was monitored for whether they attached the needle.                                                                                                                                                                                | Participant failed to attach the needle, the liquid leaked from the needle connection during injection, or the needle inadvertently detached from the syringe. |
| Activate the warming gel pack.                                                  | Critical. The Syringe Warmer must be activated in order to warm the syringe.                                                                           | Participant performance was monitored for whether they activated the gel pack.                                                                                                                                                                             | Participant failed to activate the gel pack                                                                                                                    |

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| Critical or Essential Task                                                             | Comment                                                                                                                        | Validation Method                                                                                                                                                                                                                                                      | Definition of Performance Failure                                                     |
|----------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|
| Apply the warming gel pack.                                                            | Critical. Applying the warming gel pack will ensure that SUSTOL is sufficiently warm to promote an easy and safe injection.    | Participant performance was monitored for whether they applied the gel pack prior to administration.                                                                                                                                                                   | Participant failed to apply the gel pack to the syringe.                              |
| Wait five to six minutes to warm the syringe.                                          | Critical. The syringe must be warmed in the gel pack for at least five minutes to ensure that SUSTOL reaches body temperature. | Participant performance was timed to determine if they warmed the syringe for the minimal required time of five minutes.                                                                                                                                               | Participant warmed the syringe for less than five minutes.                            |
| Remove the syringe from the gel pack.                                                  | Essential. The syringe must be removed from the gel pack in order to administer SUSTOL.                                        | Participant was monitored for whether they removed the syringe from the gel pack.                                                                                                                                                                                      | Participant did not remove the syringe from the gel pack before attempting to inject. |
| Remove the (blue) needle sheath.                                                       | The sheath must be removed before an injection can be given.                                                                   | Participant performance was monitored for whether they removed the needle sheath.                                                                                                                                                                                      | Participant failed to remove the needle sheath.                                       |
| Insert the needle into the subcutaneous tissue.                                        | Essential to insert the needle through the skin to deliver the medication.                                                     | Participant performance was monitored for whether they inserted the needle into the injection pad.                                                                                                                                                                     | Participant failed to insert the needle.                                              |
| Press the plunger with thumb or palm using a slow and steady push until plunger stops. | Essential to delivering the medication.                                                                                        | Participant performance was monitored for whether they pressed the plunger using a slow and steady push to deliver the all of the medication. The investigator also observed whether participants maintained a consistent plane and needle depth relative to the skin. | Participant failed to press the plunger to deliver the injection.                     |
| Withdraw the needle.                                                                   | Essential to withdraw the needle to complete the injection.                                                                    | Participant performance was monitored for whether they removed the needle from the "skin" after injection.                                                                                                                                                             | Participant failed to remove the needle.                                              |

| Critical or Essential Task                                                                    | Comment                                                                                                                                                                     | Validation Method                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | Definition of Performance Failure                                         |
|-----------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------|
| Discard the needle and syringe safely, according to standard biohazard disposable procedures. | Critical in preventing post administration needle stick injuries.                                                                                                           | Participant performance was monitored for how they disposed of the needle and syringe. The Point-Lok needle safety device was provided with the SUSTOL administration kit and a sharps container was available in the test room. While electing not to use the Point-Lok needle safety device is not a use error, given the objectives of the study, participants who did not use the Point-Lok needle safety device during the simulation, were asked to demonstrate its use during the Post-Test Interview. | Participant did not safely dispose of the used needle and syringe.        |
| Follow aseptic practices.                                                                     | Adherence to proper aseptic technique is advisable for any injection and critical for reducing the risk of infection, especially in immune-compromised patient populations. | Not evaluated. Part of standard nursing practice. In addition, participants may not assume, given the simulated nature of the study, that normal aseptic practices should be followed.                                                                                                                                                                                                                                                                                                                        | N/A                                                                       |
| Syringe handling.                                                                             | Critical to handle syringe appropriately after injection to avoid needle stick and possible infection.                                                                      | Participant performance was monitored for evidence of difficulties handling the SUSTOL syringe (including needle sticks).                                                                                                                                                                                                                                                                                                                                                                                     | Participant experienced an issue with a moderate or higher level of harm. |

Table #14: Summary of Critical/Essential Performance Tasks

| Critical or Essential Task                                                         | Injection 1 |    |   | Injection 2 |    |   |
|------------------------------------------------------------------------------------|-------------|----|---|-------------|----|---|
|                                                                                    | S           | SD | F | S           | SD | F |
| 1. Remove the carton from the refrigerator at least 60 minutes prior to injection. | 15          |    |   | 15          |    |   |
| 2. Remove syringe warmers, syringe, and needle from kit tray.                      | 15          |    |   | 15          |    |   |
| 3. Choose administration route.                                                    | 15          |    |   | 15          |    |   |
| 4. Choose appropriate administration site.                                         | 15          |    |   | 15          |    |   |
| 5. Do not remove air bubbles.                                                      | 15          |    |   | 15          |    |   |
| 6. Unscrew cap from the end of the prefilled syringe.                              | 15          |    |   | 15          |    |   |
| 7. Remove the hub cover from the needle.                                           | 15          |    |   | 15          |    |   |
| 8. Attach the needle (to the syringe).                                             | 15          |    |   | 15          |    |   |
| 9. Activate gel-warming pack.                                                      | 14          |    | 1 | 14          |    | 1 |
| 10. Apply warming pack to syringe.                                                 | 15          |    |   | 15          |    |   |
| 11. Wait for the gel pack to warm the syringe for 5–6 minutes.                     | 15          |    |   | 10          |    | 5 |
| 12. Remove syringe from the gel pack.                                              | 15          |    |   | 15          |    |   |
| 13. Remove blue needle cover.                                                      | 15          |    |   | 15          |    |   |
| 14. Insert needle into the subcutaneous tissue.                                    | 15          |    |   | 15          |    |   |
| 15. Press plunger to deliver all the medication, slow and steady.                  | 15          |    |   | 15          |    |   |
| 16. Participant maintains the injection plane during the injection.                | 15          |    |   | 15          |    |   |
| 17. Participant does not advance the needle during the injection.                  | 15          |    |   | 15          |    |   |
| 18. Withdraw the needle.                                                           | 15          |    |   | 15          |    |   |
| 19. Check that the entire dose has been administered to the patient.               | 15          |    |   | 15          |    |   |
| 20. Discard the used needle and syringe.                                           | 15          |    |   | 15          |    |   |
| 21. Syringe handling.                                                              | 15          |    |   | 15          |    |   |

Table #15: In-Depth Performance of Critical/Essential Tasks

| Critical and Essential Task                                                        | Scoring                             | Inj 1        | Inj 2        | Observations                                                                                                                                                                                                                                                                                                                                                                                                                  |
|------------------------------------------------------------------------------------|-------------------------------------|--------------|--------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 1. Remove the carton from the refrigerator at least 60 minutes prior to injection. | Success<br>Suc. with Dif<br>Failure | 15<br>0<br>0 |              | Not scored in the first scenario. Participants were allowed to choose between cartons in the refrigerator or cartons that had been left out overnight in the second scenario. All participants selected cartons left out overnight and confirmed that they were acceptable to use. In the Post-Test Interview, all participants indicated that the carton should be out of the refrigerator for at least one hour before use. |
| 2. Remove syringe warmers, syringe and needle from kit tray.                       | Success<br>Suc. with Dif<br>Failure | 15<br>0<br>0 | 15<br>0<br>0 | All participants removed the contents from the carton without difficulty.                                                                                                                                                                                                                                                                                                                                                     |
| 3. Choose administration route.                                                    | Success<br>Suc. with Dif<br>Failure | 15<br>0<br>0 | 15<br>0<br>0 | All participants selected a subcutaneous injection in either the abdomen or the back of the upper arm.                                                                                                                                                                                                                                                                                                                        |
| 4. Choose appropriate administration site.                                         | Success<br>Suc. with Dif<br>Failure | 15<br>0<br>0 | 15<br>0<br>0 | All participants chose either the abdomen or the back of the upper arm as appropriate injection sites. No participant indicated that any other site was appropriate.                                                                                                                                                                                                                                                          |
| 5. Do not remove air bubbles.                                                      | Success<br>Suc. with Dif<br>Failure | 15<br>0<br>0 | 15<br>0<br>0 | No participant attempted to remove air bubbles from the syringe.                                                                                                                                                                                                                                                                                                                                                              |
| 6. Unscrew cap from the end of the prefilled syringe.                              | Success<br>Suc. with Dif<br>Failure | 15<br>0<br>0 | 15<br>0<br>0 | All participants successfully unscrewed the end cap from the syringe.                                                                                                                                                                                                                                                                                                                                                         |

| Critical and Essential Task              | Scoring       | Inj 1 | Inj 2 | Observations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|------------------------------------------|---------------|-------|-------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 7. Remove the hub cover from the needle. | Success       | 15    | 15    | All participants successfully removed the hub cover from the needle.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|                                          | Suc. with Dif | 0     | 0     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|                                          | Failure       | 0     | 0     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| 8. Attach the needle (to the syringe).   | Success       | 15    | 15    | All participants successfully attached the needle to the syringe.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
|                                          | Suc. with Dif | 0     | 0     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|                                          | Failure       | 0     | 0     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| 9. Activate gel-warming pack.            | Success       | 14    | 14    | <p>Fourteen participants successfully activated the gel warming pack for both injection scenarios.</p> <p>Participant (4) completed both injections without difficulty. However, she did not successfully activate the gel pack during the warming step. She flexed the metal disk in the gel pack only twice for the first injection and once for the second injection. This was insufficient to start crystallization in either pack.</p> <p>In the Post-Test Interview, the participant said she assumed she had prepared the gel packs correctly; she did not detect this error as she did not expect to feel the gel pack warming. However, she was able to describe the use of the gel pack as a means to warm the syringe. The moderator demonstrated the use of the gel pack in the Post-Test Interview and asked the participant to attempt to initiate warming in the original gel pack. She was able to initiate crystallization by clicking the disk several times. (See <a href="#">Section 7.9.</a>)</p> |
|                                          | Suc. with Dif | 0     | 0     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|                                          | Failure       | 1     | 1     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| 10. Apply warming pack to syringe.       | Success       | 15    | 15    | All participants successfully wrapped the syringe in the warming pack and used the Velcro strips to hold the gel pack in place.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|                                          | Suc. with Dif | 0     | 0     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|                                          | Failure       | 0     | 0     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |

| Critical and Essential Task                                       | Scoring       | Inj 1 | Inj 2 | Observations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
|-------------------------------------------------------------------|---------------|-------|-------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 11. Wait for the gel pack to warm the syringe for 5–6 minutes.    | Success       | 15    | 10    | <p>Fifteen participants in the first scenario and ten in the second scenario allowed the syringe to warm for a minimum of five minutes before administering.</p> <p>In the second injection scenario, five participants (2, 4, 8, 9, 10) did not wait a minimum of five minutes to warm the syringe before administering. After wrapping the syringe in the gel pack, four of these participants (2, 4, 8, 9) stated that they needed to wait 5–6 minutes before giving the injection and all thought that they had waited the full five minutes. Wait times were between 3:40 and 4:40 seconds. Details of individual performances are given below. Participant 10 appeared to look at the clock during the warming period and removed the syringe from the gel pack after 4 minutes and 30 seconds. (See <a href="#">Section 7.9</a>.)</p> |
|                                                                   | Suc. with Dif | 0     | 0     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|                                                                   | Failure       | 0     | 5     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| 12. Remove syringe from the gel pack.                             | Success       | 15    | 15    | All participants successfully removed the syringe from the gel pack.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|                                                                   | Suc. with Dif | 0     | 0     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|                                                                   | Failure       | 0     | 0     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| 13. Remove blue needle cover.                                     | Success       | 15    | 15    | All participants successfully removed the blue needle cover.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
|                                                                   | Suc. with Dif | 0     | 0     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|                                                                   | Failure       | 0     | 0     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| 14. Insert needle into the subcutaneous tissue.                   | Success       | 15    | 15    | All participants successfully inserted the needle into the injection pad.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|                                                                   | Suc. with Dif | 0     | 0     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|                                                                   | Failure       | 0     | 0     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| 15. Press plunger to deliver all the medication, slow and steady. | Success       | 15    | 15    | <p>All participants successfully pressed the plunger and delivered all the medication.</p> <p>The moderator confirmed that the plunger was at the bottom of the syringe barrel after each participant session to provide evidence that all the medication was delivered.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
|                                                                   | Suc. with Dif | 0     | 0     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|                                                                   | Failure       | 0     | 0     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |

| Critical and Essential Task                                                | Scoring       | Inj 1 | Inj 2 | Observations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|----------------------------------------------------------------------------|---------------|-------|-------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 16. Participant maintains the injection plane during the injection.        | Success       | 15    | 15    | Based on moderator and observer observations, all participants maintained a steady injection plane during both injections. The observations were confirmed by reviewing the video recordings of each session.                                                                                                                                                                                                                                                                                                                                                            |
|                                                                            | Suc. with Dif | 0     | 0     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|                                                                            | Failure       | 0     | 0     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| 17. Participant maintains the position of the needle during the injection. | Success       | 15    | 15    | A review of the session videos confirmed that all participants maintained the position of the needle during both injections. While pressing the plunger to administer, no participant advanced the needle tip beyond the initial insertion depth.                                                                                                                                                                                                                                                                                                                        |
|                                                                            | Suc. with Dif | 0     | 0     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|                                                                            | Failure       | 0     | 0     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| 18. Withdraw the needle.                                                   | Success       | 15    | 15    | All participants successfully withdrew the needle from the injection pad.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|                                                                            | Suc. with Dif | 0     | 0     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|                                                                            | Failure       | 0     | 0     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| 19. Check that the entire dose has been administered to the patient.       | Success       | 15    | 15    | All participants administered the entire dose for both injections. The moderator confirmed that the plunger was at the base of the syringe for both syringes after each session.                                                                                                                                                                                                                                                                                                                                                                                         |
|                                                                            | Suc. with Dif | 0     | 0     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|                                                                            | Failure       | 0     | 0     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| 20. Discard the used needle and syringe.                                   | Success       | 15    | 15    | All participants successfully discarded the used needle and syringe in the proper manner. Fourteen participants inserted the needle into the Point Lok needle safety device before placing the syringe and needle into the sharps container for both injections. Participant 8 placed the first syringe and needle in the sharps container without first inserting the needle into the needle safety device. Participant 8 inserted the needle into the Point Lok needle safety device and put the syringe and needle into the sharps container on the second injection. |
|                                                                            | Suc. with Dif | 0     | 0     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|                                                                            | Failure       | 0     | 0     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| Critical and Essential Task                                                | Scoring       | Inj 1 | Inj 2 | Observations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| 21. Syringe handling.                                                      | Success       | 15    | 15    | All participants handled syringes without difficulty.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|                                                                            | Suc. with Dif | 0     | 0     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|                                                                            | Failure       | 0     | 0     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |

Table #15: Post-Test Interview Question Responses

| Questions                                                                                                   | Participant Responses                                                                                                                             |
|-------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------|
| 1. Where on the body is it appropriate to inject SUSTOL?                                                    | All 15 participants indicated that the injection should be given only as a subcutaneous injection in the abdomen or in the back of the upper arm. |
| 2. Is it okay to inject SUSTOL intravenously? What about intramuscular or intra-peritoneal administration?  | All 15 participants responded with “no” to all three questions.                                                                                   |
| 3. Should SUSTOL be administered cold or warm?                                                              | All 15 participants indicated that SUSTOL should be administered warm. All 15 participants said that warming reduces viscosity of the medication. |
| 4. How long should SUSTOL be out of the refrigerator to allow it to come to room temperature?               | All 15 participants said that SUSTOL should be out of the refrigerator for at least 60 minutes before use.                                        |
| 5. Were in instructions to warm SUSTOL immediately prior to injection clear?                                | All 15 participants said the instructions to warm the syringe were clear.                                                                         |
| 6. How long should SUSTOL be warmed in the warming blanket before administration?                           | All 15 participants indicated that the syringe should be warmed for five to six minutes before administration.                                    |
| 7. Did the Instructions For Use prepare you for the viscous nature of SUSTOL?                               | All 15 participants indicated that the IFU prepared them for the viscous nature of SUSTOL.                                                        |
| 8. Finally, do you feel confident that you could safely and effectively administer SUSTOL to your patients? | All 15 participants said they felt they were able to administer the medication safely and effectively to their patients.                          |

| Questions                                                           | Participant Responses                                                                                                                                                                                                                                                                           |
|---------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 9. Do you recall having any difficulties with any of the following: |                                                                                                                                                                                                                                                                                                 |
| a. Removing the warmers, syringe or needle from the carton?         | All 15 participants said they were able to remove the warmers, syringe and needle from the carton without difficulty.                                                                                                                                                                           |
| b. Locating or checking the expiration date?                        | All 15 participants found the expiration date on the syringe. Three participants said it was a little hard; participant 8 said it was "not in a good place," participant 10 said it was "hard to see the black print on the gray background," and participant 15 said she "just found it hard." |
| c. Choosing the administration route?                               | All 15 participants said they chose the administration site without difficulty.                                                                                                                                                                                                                 |
| d. Choosing the injection site?                                     | All 15 participants said they chose the injection site without difficulty.                                                                                                                                                                                                                      |
| e. Understanding the precautionary label on the syringe?            | All 15 participants said there were no difficulties understanding the precaution label.                                                                                                                                                                                                         |
| f. Removing the precaution label?                                   | Eight participants (2, 3, 4, 5, 6, 7, 8, 11) who removed the precaution label said they removed it without difficulty. Seven participants who did not remove the label said it did not interfere when administering the product.                                                                |
| g. Checking the dose volume?                                        | All 15 participants said they had no difficulties checking the dose volume.                                                                                                                                                                                                                     |
| h. Unscrewing the tip cap?                                          | Fourteen participants reported having no difficulty unscrewing the tip cap. One participant (12) successfully removed the tip cap but said it was a little difficult gripping the soft rubber base. The difficulty gripping the base did not significantly affect preparation of the syringe.   |
| i. Removing the clear cap from the needle cover?                    | All 15 participants said they had no difficulties removing the clear cap from the needle cover.                                                                                                                                                                                                 |

| Questions                                        | Participant Responses                                                                                                                                                                                                                                                                      |
|--------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| j. Attaching the needle to the syringe?          | All 15 participants said they attached the needle to the syringe without difficulty.                                                                                                                                                                                                       |
| k. Activating the gel pack to warm SUSTOL?       | All 15 participants said there were no difficulties activating the gel packs. Participant (4) is included in those who said they had no difficulties activating the gel pack. At this point in the interview, she was unaware that the gel packs that she had used had not been activated. |
| l. Applying the gel pack to warm SUSTOL?         | All 15 participants said they had no difficulties applying the gel pack to the syringe.                                                                                                                                                                                                    |
| m. Waiting for the gel pack to warm SUSTOL?      | All 15 participants said it was not difficult waiting to warm the syringe.                                                                                                                                                                                                                 |
| n. Removing the syringe from the gel pack?       | All 15 participants said they removed the syringe from the gel pack without difficulty.                                                                                                                                                                                                    |
| o. Removing the blue needle cover?               | All 15 participants said they removed the blue needle cover without difficulty.                                                                                                                                                                                                            |
| p. Inserting the needle at an appropriate angle? | All 15 participants said they inserted the needle at an appropriate angle without difficulty.                                                                                                                                                                                              |

## **APPENDIX D. ISMP NEWSLETTERS**

### **D.1 Methods**

N/A

### **D.2 Results**

N/A

## **APPENDIX E. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)**

### **E.1 Methods**

N/A

### **E.2 Results**

N/A

### **E.3 List of FAERS Case Numbers**

N/A

### **E.4 Description of FAERS**

N/A

## **APPENDIX F.**

### **F.1      Methods**

N/A

### **F.2      Results**

N/A

## **APPENDIX G. LABELS AND LABELING**

### **G.1 List of Labels and Labeling Reviewed**

Using the principles of human factors and Failure Mode and Effects Analysis,<sup>4</sup> along with postmarket medication error data, we reviewed the following Sustol labels and labeling submitted by Heron Therapeutics, Inc. on July 17, 2015.

- Instructions for Use

### **G.2 Label and Labeling Images**

#### **A. IFU**

4 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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<sup>4</sup> Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/  
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MATTHEW J BARLOW  
01/12/2016

MISHALE P MISTRY  
01/13/2016

LUBNA A MERCHANT  
01/13/2016

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Medical Policy Initiatives  
Division of Medical Policy Programs**

**REVIEW DEFERRAL MEMORANDUM**

Date: January 4, 2016

To: Donna Griebel, MD  
Director  
**Division of Gastroenterology and Inborn Errors  
Products (DGIEP)**

Through: LaShawn Griffiths, MSHS-PH, BSN, RN  
Associate Director for Patient Labeling  
**Division of Medical Policy Programs (DMPP)**  
Marcia Williams, PhD  
Team Leader, Patient Labeling  
**Division of Medical Policy Programs (DMPP)**

From: Karen Dowdy, RN, BSN  
Patient Labeling Reviewer  
**Division of Medical Policy Programs (DMPP)**

Subject: Review Deferred: Patient Package Insert (PPI)

Drug Name (established name): SUSTOL (granisetron)

Dosage Form and Route: injection, for subcutaneous use

Application Type/Number: NDA 022445

Applicant: Heron Therapeutics

## 1 INTRODUCTION

On July 17, 2015, Heron Therapeutics, Inc., formerly A.P. Pharma, Inc., re-submitted for the Agency's review Original New Drug Application (NDA) 022445 for SUSTOL (granisetron) injection in response to the Agency's Complete Response Letter that was issued March 27, 2013. The Agency issued a previous Complete Response Letter to this NDA on March 16, 2010. The proposed indication for SUSTOL (granisetron) injection is for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of cancer chemotherapy, including, but not limited to, highly emetogenic chemotherapy. On December 8, 2015, the Division of Gastroenterology and Inborn Errors Products (DGIEP) requested that the Division of Medical Policy Programs (DMPP) review the Applicant's proposed Patient Package Insert (PPI) for SUSTOL (granisetron) injection.

(b) (4) the Applicant's proposed Patient Package Insert (PPI) for SUSTOL (granisetron) injection.

## 2 CONCLUSIONS

(b) (4)

Please notify us if you have any questions.

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/s/  
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SHAWNA L HUTCHINS  
01/04/2016

MARCIA B WILLIAMS  
01/04/2016

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

---

DATE: 12/21/2015

TO: Division of Gastroenterology and Inborn Errors Products  
Office of Drug Evaluation III

FROM: Division of New Drug Bioequivalence Evaluation (DNDBE)  
Office of Study Integrity and Surveillance

SUBJECT: **Recommendation to accept data without on-site inspection**

RE: NDA 22445

The Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS) recommends accepting data without on-site inspection. The rationale for this decision is noted below.

**Rationale**

Although the last inspection was classified as a VAI, based on the inspectional outcome and our recommendation to the review division, an inspection is not needed at this time.

**Requested Site Inspection**

| Facility Type | Facility Name | Facility Address |
|---------------|---------------|------------------|
| Analytical    | (b) (4)       | (b) (4)          |

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

---

DATE: 12/21/2015

TO: Division of Gastroenterology and Inborn Errors Products  
Office of Drug Evaluation III

FROM: Division of New Drug Bioequivalence Evaluation (DNDBE)  
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Recommendation to accept data without on-site inspection**

RE: NDA 22445

The Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS) recommends accepting data without on-site inspection. The rationale for this decision is noted below.

**Rationale**

OSIS recently inspected the site listed below. The inspectional outcome from the inspection was classified as No Action Indicated (NAI).

**Inspection Site**

| Facility Type | Facility Name | Facility Address |
|---------------|---------------|------------------|
| Clinical      | (b) (4)       |                  |

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/s/  
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NICOLA M FENTY-STEWART  
12/22/2015

MEMORANDUM

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

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**CLINICAL INSPECTION SUMMARY**

DATE: December 9, 2015

TO: James Carr, Regulatory Project Manager  
Lauren Weintraub, M.D., Medical Officer  
Division of Gastroenterology and Inborn Errors Products

FROM: Susan Leibenhaut, M.D.  
Medical Officer  
Good Clinical Practice Assessment Branch  
Division of Clinical Compliance Evaluation  
Office of Scientific Investigations

THROUGH: Susan D. Thompson, M.D.  
Team Leader  
Good Clinical Practice Assessment Branch  
Division of Clinical Compliance Evaluation  
Office of Scientific Investigations

THROUGH: Kassa Ayalew, M.D., M.P.H  
Branch Chief  
Good Clinical Practice Assessment Branch  
Division of Clinical Compliance Evaluation  
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 022445

APPLICANT: Heron Therapeutics  
DRUG: Sustol® for injection (Granisetron subcutaneous injection)  
NME: No  
THERAPEUTIC CLASSIFICATION: Standard

INDICATION: For the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of cancer chemotherapy, including, but not limited to, highly emetogenic chemotherapy (HEC).

CONSULTATION REQUEST DATE: October 1, 2015  
INSPECTION SUMMARY GOAL DATE: December 15, 2015  
DIVISION ACTION GOAL DATE: January 15, 2016  
PDUFA DATE: January 15, 2016

## **I. BACKGROUND:**

Heron Therapeutics (formerly A.P. Pharma) submitted this NDA for SUSTOL<sup>®</sup> (also known as APF530) for the indication of the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of cancer chemotherapy, including, but not limited to, highly emetogenic chemotherapy (HEC). SUSTOL<sup>®</sup> is a long-acting granisetron formulation for subcutaneous (SC) injection. Granisetron hydrochloride is a selective 5-HT<sub>3</sub> receptor antagonist, and was approved by the FDA in 1994 under the name Kytril for the prevention and treatment of nausea and/or vomiting associated with initial and repeat courses of emetogenic cancer therapy, including high-dose cisplatin. The indication of prevention of postoperative nausea and vomiting was added in 2002.

The review division requested inspection of the four sites below for the clinical trial APPA C2013-01 entitled "A Prospective, Randomized, Placebo-Controlled, Double-Blind, Multicenter, Phase 3 Study of APF530 500 mg SC, Fosaprepitant 150 mg IV, and Dexamethasone vs. Ondansetron 0.15 mg/kg IV, Fosaprepitant 150 mg IV, and Dexamethasone for the Prevention of Chemotherapy-Induced Nausea and Vomiting in Subjects Receiving Highly Emetogenic Chemotherapy." Sites were chosen on the basis of high enrollment, previous inspectional history, and number of INDs in the OSI database.

## II. RESULTS (by Site):

| Type of Inspected Entity, Name, and Address                                                                             | Protocol #/<br>Site #/ # of<br>Subjects | Inspection<br>Date                    | Classification* |
|-------------------------------------------------------------------------------------------------------------------------|-----------------------------------------|---------------------------------------|-----------------|
| CI: Richy Agajanian, M.D.<br>The Oncology Institute of Hope and Innovation<br>11480 Brookshire Ave.<br>Downey, CA 90241 | APPA<br>C2013-01<br>Site 001/ 69        | October 20 to<br>November 5,<br>2015  | Pending NAI     |
| CI: Robert E. Smith, Jr. M.D.<br>South Carolina Oncology Associates, PA<br>166 Stoneridge Drive<br>Columbia, SC 29210   | APPA<br>C2013-01<br>Site 026/ 43        | November 30 to<br>December 2,<br>2015 | Pending NAI     |
| CI: Charles W. Taylor, M.D.<br>Tulsa Cancer Institute, PLLC<br>12697 East 51st Street South<br>Tulsa, OK 74146          | APPA<br>C2013-01<br>Site 031/ 42        | November 2 to<br>6, 2015              | Pending NAI     |
| CI: Sharon Wilks, M.D.<br>Cancer Care Centers of South Texas<br>2130 N.E. Loop 410 Suite 100<br>San Antonio, TX 78217   | APPA<br>C2013-01<br>Site 062/ 37        | November 2 to<br>13, 2015             | Pending NAI     |

### Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations.

Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending.

### 1. Richy Agajanian, M.D.

#### The Oncology Institute of Hope and Innovation, Downey, CA 90241

**Note:** Observations below for this clinical investigator (CI) inspection are based on communications with the FDA field investigator. An inspection summary addendum will be issued if conclusions change upon review of the final Establishment Inspection Report (EIR).

- a. **What was inspected:** At this site, 81 subjects were screened, 69 subjects were enrolled into the study, and 66 subjects completed the study. Consenting documents for 41 subjects were reviewed and source records for 26 subjects were reviewed. The source documents and subject diaries were compared with the eCRF entries and the line listings provided with the inspection assignment.

- b. **General Observations/Commentary:** There were no discrepancies noted between the subject diary entries and the line listings. There was no evidence of under-reporting of protocol deviations. Of the reviewed records, five subjects' records contained minor discrepancies concerning concomitant medication (not pain medication) or adverse events (AEs) (not injection site reactions).
- c. **Assessment of data integrity:** The study appears to have been conducted adequately, and the data generated by this site may be used in support of the respective indication.

**2. Robert E. Smith, Jr. M.D.**  
**South Carolina Oncology Associates, PA, Columbia, SC 29210**

**Note:** Observations below for this clinical investigator (CI) inspection are based on communications with the FDA field investigator. An inspection summary addendum will be issued if conclusions change upon review of the final Establishment Inspection Report (EIR).

- a. **What was inspected:** At this site, 45 subjects were screened, 43 subjects were enrolled into the study, and 41 completed the study. There was a review of all enrolled subjects' diaries for primary efficacy endpoint. There were in depth reviews of 20 subjects' charts for AE reporting. For the remaining 23 subjects, there was a spot check for AEs.
- b. **General observations/commentary:** There were no discrepancies noted between the subject diaries and the primary endpoint data listings submitted by the sponsor to the FDA and provided to the FDA field. Only one unreported AE was noted. This was an episode of resolved bilateral lower extremity edema reported by Subject (b) (6) at the final visit. As noted in the clinical study report submitted to the NDA by the sponsor, the site did have one issue with a subject not receiving the study drug. This was an isolated error in the pharmacy in which commercial ondansetron was mixed by the pharmacy technician instead of the study vial of drug. The site initiated an action plan to prevent future errors. No Form FDA 483 was issued.
- c. **Assessment of data integrity:** The study appears to have been conducted adequately, and the data generated by this site may be used in support of the respective indication.

**3. Charles W. Taylor, M.D.**  
**Tulsa Cancer Institute, PLLC, Tulsa, OK 74146**

**Note:** Observations below for this CI inspection are based on communications with the FDA field investigator. An inspection summary addendum will be issued if conclusions change upon review of the final EIR.

- a. **What was inspected:** At this site, a total of 47 subjects were screened, 42 subjects were enrolled into the study, and 41 subjects completed the study. The records for 35 enrolled subjects were reviewed. The records were compared with data listings for primary and secondary endpoints, AEs including injection site reactions, and eligibility criteria.
- b. **General Observations/Commentary:** The primary efficacy data were able to be verified. There was no evidence of under-reporting of AEs. A Form FDA 483 was not issued.
- c. **Assessment of data integrity:** The study appears to have been conducted adequately, and the data generated by these studies appear acceptable in support of the respective indications.

**4. Sharon Wilks, M.D.**  
**Cancer Care Centers of South Texas, San Antonio, TX 78217**

**Note:** Observations below for this CI inspection are based on communications with the FDA field investigator. An inspection summary addendum will be issued if conclusions change upon review of the final EIR.

- a. **What was inspected:** For this site, 46 subjects were screened. A total of 37 subjects were enrolled in and completed the study. The records for 21 enrolled subjects were reviewed and compared to primary and secondary endpoints, adverse events, eligibility criteria, and other selected data points against the line listings provided with the assignment.
- b. **General Observations/Commentary:** The primary efficacy data were able to be verified. There was no evidence of under-reporting of adverse events. No Form FDA 483 was issued. There were omissions of concomitant medications noted for three subjects. For Subject (b) (6), randomized to ondansetron, who experienced an injection site reaction with hematoma, the pain medications Meloxicam, acetaminophen, and hydrocodone were noted in the source document but not included in the concomitant medications.
- c. **Assessment of data integrity:** The site injection reactions appear to have been captured adequately. The underreporting of concomitant pain medication occurred in a single patient randomized to the comparator arm and did not appear to be biased to the test article treatment group. The study appears to have been conducted adequately, and the data generated by this study appear acceptable in support of the respective indications.

### III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Four clinical investigator sites were inspected for this application. All reviews are preliminary, based on e-mail communications and have a preliminary classification of NAI.

The study appears to have been conducted adequately, and the data generated by the study are acceptable in support of the respective indication. An inspection summary addendum will be issued if conclusions change upon review of the final EIR.

*{See appended electronic signature page}*

Susan Leibenhaut, M.D.  
Medical Reviewer  
Good Clinical Practice Assessment Branch  
Division of Clinical Compliance Evaluation  
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/s/  
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SUSAN LEIBENHAUT  
12/09/2015

SUSAN D THOMPSON  
12/10/2015

KASSA AYALEW  
12/10/2015

MEMORANDUM

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

**DATE:** March 1, 2014

**TO:** File

**FROM:** Mary Chung, Regulatory Project Manager

**SUBJECT:** CDRH/ODE/DAGID Consult Review of NDA 022445 revised Human Factors Study and Instructions-for-Use (dated 2/28/14)

**APPLICATION/DRUG:** NDA 022445 Sustol (granisetron) Injection, extended-release

On February 3, 2014, the Division of Gastroenterology Products submitted a request for consultation to the Office of Device Evaluation/Division of Anesthesiology, General Hospital, Infection Control, and Dental Devices (ODE/DAGID). The purpose of this consult request was to review the revised human factor validation protocol (received 1/22/14) which the sponsor indicated have incorporated FDA comments provided during the 10/30/13 End of Review Meeting and 3/26/13 General Advice letter. The attached consult response is the review for this consult.



DEPARTMENT OF HEALTH AND HUMAN SERVICES

MEMORANDUM

Food and Drug Administration  
Office of Device Evaluation  
10903 New Hampshire Avenue  
Silver Spring, MD 20993

**CDRH Human Factors Consult Review**

DATE: February 26, 2014

FROM: QuynhNhu Nguyen, Biomedical Engineer/Human Factors Reviewer, CDRH/ODE/DAGRID  
THROUGH: Ron Kaye, Human Factors and Device Use-Safety Team Leader, CDRH/ODE/DAGRID  
TO: Mary Chung, Project Manager, CDER/OND/ODEIII/DGIEP

SUBJECT: **NDA 22445**  
Applicant: AP Pharma  
Device Constituent: Prefilled Syringe Injection  
Drug Constituent: Sustol  
Intended Treatment: cancer chemotherapy  
CDRH CTS Tracking No: ICC1400082

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QuynhNhu Nguyen, Combination Products Human Factors Specialist

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Ron Kaye, Human Factors and Device Use-Safety Team Leader

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### ***Combination Product Device Information***

Submission No.: NDA 22445  
Applicant: AP Pharma  
Device Constituent: Prefilled Syringe Injection  
Drug Constituent: Sustol  
Intended Treatment: cancer chemotherapy

### ***CDRH Human Factors Involvement History***

- 3/20/13 CDRH HF provided final review of the NDA
- 10/30/13 CDRH HF participated in the End of Review Meeting with the Sponsor
- 1/14/2014 – CDRH HF was requested to review the draft human factors validation study protocol included in the NDA. The request states: “Per 10/30/13 End of Review (EOR) Meeting discussion with FDA, A.P. Pharma submitted a revised human factor validation protocol which incorporates FDA comments provided during the 10/30/13 EOR Meeting and 3/27/13 Complete Response letter for FDA review prior to the initiation of the study.” EDR Location: <\\CDSESUB1\evsprod\NDA022445\0069>

### ***Overview and Recommendation***

The Division of Gastroenterology and Inborn Errors Products, Office of Drug Evaluation III, Office of New Drugs, Center for Drugs Evaluation and Research requested a Human Factors consultative review of a draft human factors study protocol. CDRH Has been involved with the reivew of this submission since 2012. See Appendix 2 for more details.

This consultant found the revised study protocol to be generally acceptable. This consultant has two comments on the protocol and one advice to communicate to the Sponsor regarding CDRH HF’s expectation for the study report when it becomes available.

#### **Protocol Comment # 1:**

We appreciate the level of details (table 1, and specific tracked changes throughout) that you have included in your revised human factors study protocol. We note that you have made several modifications to the product including a (b) (4), and to the instructions for use. Ensure that your supplemental human factors study focus on evaluating the specific modifications that are being proposed such that the data collected can be used to confirm that the modifications are effective at reducing the use errors, and do not introduce any new hazards.

#### **Protocol Comment # 2:**

We note that your latest Instructions for Use continues to required that a health care professional (HCP) use a single hand to both push the plunger and stabilize the syringe while administering the product. Ensure that collect the necessary data to demonstrate that this technique can be performed safely and effectively, and that they users can maintain the injection in the correct tissue plane.

General Advice: Be advised that we expect that your study report conclude that the device is reasonably safe and effective for the intended users, uses and use conditions. A summary of relevant portions of preliminary analyses, evaluations, and validation testing are recommended for use in support of this conclusion. Discuss the test results, particularly failures or patterns of subjective reports of difficulty with the use of the device, with respect to identified risks and whether these risks were caused by aspects of the design of the device, its labeling, the content or proximity of training and whether modifications are required. Prioritize your data analysis according to identified risk and task priority to determine the magnitude and significance of the use errors, failures and difficulties that occurred during the testing. Discuss the residual risk associated with use that cannot be further reduced through modifications of training, labeling, or from modifications to the design of the user interface. Additionally, provide rationale to explain why the residual risk(s) cannot be further reduced. Be aware that your proposed plans to modify design flaws that could result in clinical impact on patients in future versions of the device are generally unacceptable.

## **Appendix 1: CDRH Human Factors Review**

As follow-up to the EOR Meeting of October 30, 2013, A.P. Pharma is submitting a revised human factors validation protocol which incorporate FDA comments and the critical tasks associated with the use of the syringe warmer (due to viscosity of the drug product). A redline version of the protocol with tracked changes to the previous validation protocol (SN0060) is also included (Attachment 2). A summary of the significant protocol changes is listed in Table 1 of the submission.

The human factors validation study will enroll a total of 15 oncology nurses. The study tasks have been evaluated based on previously conducted formative studies, an initial human factors validation study, and other preliminary analyses such as a task analysis and risk analysis.

During completion of scenarios, participant performance will be documented. In addition, unanticipated issues that create a critical safety risk will be considered a performance failure. All failures will be followed up with test participants via a formal debriefing to determine root cause and need for further mitigations. All use issues associated with moderate or higher levels of harm will be addressed through appropriate corrective measures (such as modifications to the pre-filled syringe design, Instructions for Use, or other labeling).

## Appendix 2: Previous CDRH Human Factors Review (3/20/2013)

### *Overview and Recommendations*

The Division of Gastroenterology and Inborn Error Products, Office of New Drugs, Center for Drugs Research and Evaluation, requested a Human Factors consultative review of a Human Factors validation study report submitted via NDA# 22445 by AP Pharma. This review provides CDRH's review and recommendations on the Human Factors related information contained in the NDA.

Since Sustol is a viscous drug product, and it is the first time it is delivered through a pre-filled syringe, CDRH and CDER have concerns associated with the force required to inject. While the Sponsor has modified the syringe components for use in the Human Factors validation study i.e. (b) (4), users continued to report difficulty in administering the drug product through the syringe. As a result, on 2/13/2013, the review team expressed these concerns to the Sponsor, and requested that the Sponsor provide a proposal to address these concerns. On 2/18/2013, the Sponsor proposed various labeling modifications to the Instructions for Use, syringe label, and carton label including the addition of a (b) (4) information to the Instructions for Use. On 2/20/2013, the review team provided feedback to the Sponsor's proposal and recommended that the drug administration be performed by two individuals.

The data obtained from the Human Factors validation study suggested there are issues associated with safe and effective use of the product. The performance data indicated that incomplete injection of the drug product could occur. In addition, users reported difficulty in generating the required force to perform the injection, which could result in injecting the drug product in unintended area that lead to intended patient reaction and/or bleeding. As a result, CDRH Human Factors team recommended that additional modifications either in the product labeling and/or product design are necessary and additional human factors study should be conducted to demonstrate that the product modifications are effective in reducing/minimizing patient harm.

A face-to-face meeting was held on March 1, 2013 between FDA and AP Pharma to discuss proposed plan to address administration concerns. Subsequently, AP Pharma provided test results of a formative Human Factors/usability study with 20 oncology nurses and a proposed Human Factors/usability validation study protocol. The formative Human Factors/usability study was conducted with the revised Instructions for Use (IFU). Review of the study results showed that there are still some concerns, which AP Pharma will need to address prior to conducting the validation study. In addition, review of the proposed validation showed some areas regarding study methodology that the Sponsor would make changes to the protocol prior to executing the study. Details on the review of the formative study and the proposed validation study can be found on page 7 of this memo.

This reviewer discussed the outstanding concerns with DMEPA and the following comments represent the consolidated comments based on the review of the formative study results and the proposed validation study protocol review:

#### A. Formative Study Results

1. Your formative study results showed that the products used during the testing did not represent the finalized commercial products, which generated issues related to device performance such as disengagement of the finger flanges and malfunctions of the plunger. Please note that in your Human Factors/Usability validation study, we expect that you use

products that have been assembled using a validated process and released under the Quality Management System.

2. Your formative study results showed that while four of the 20 users did not follow the specific technique stated in the Instructions for Use, they were able to administer the product. You did not discuss whether any of the techniques applied by these test participants had any potential negative consequences to the patient or the user. Please note that if any of the techniques applied could result in patient harm, the Instructions for Use/labeling should be modified to warn users of those potential consequences, and the modified Instructions for Use/labeling should be used for your Human Factors/usability validation study.
3. Your formative study results suggested that an additional cautionary statement be added to the Instructions for Use for not removing the white finger flanges. Please ensure that the data you collect from your Human Factors/usability validation study demonstrate that this mitigation is effective.

#### B. Validation Protocol

4. In the study introduction (b) (4)  
[REDACTED]  
[REDACTED] Please remove them from your moderator guide.
5. In addition, we expect that in your Human Factors/usability validation study, you should make the Instructions for Use available along with the product and let the study participants use them as they would normally use them.
6. In your Human Factors/usability validation study, if assistance is provided to study participants, please provide the nature of assistance provided along with the use scenario, and obtain feedback from test participants on the difficulty that they experience while using the product.
7. [REDACTED] (b) (4)  
[REDACTED]. Bringing this product to room temperature is a critical task to help promote ease of administration. Step 1 in your Instructions for Use specified that the user has to remove the product from the refrigeration at least 60 minutes prior to use and can be left overnight. We recognize the importance of warming up this type of product and understand the logistics of simulating this aspect of use in a Human Factors/usability validation study. We recommend that you ask test participants directly to assess their understanding and essential knowledge with regards to this step rather than simulating it in your study. We believe that it is equally critical that the user who performs the injection understand that they need to verify that the product has been warmed up to room temperature for at least 60 minutes. Please ensure that your Human Factors/usability validation study collect the necessary data to demonstrate that users understand these two steps.

### ***Combination Product Device Information***

Submission Number: NDA 22445  
Applicant: AP Pharma  
Drug Constituent: Sustol (granisetron) subcutaneous  
Device Constituent: Prefilled Syringe  
Intended treatment: cancer chemotherapy

### ***CDRH Human Factors Involvement History***

- 10/15/2012: CDRH Human Factors team was requested to review AP Pharma's Human Factors validation study report
- 2/13/2013: CDRH HF team participated in a teleconference with CDER representatives and Sponsor representatives to discuss product administration concerns (force required to inject the drug product). The Sponsor indicated that they will develop proposals to address the concerns and submit to FDA for review and concurrence
- 2/20/2013: CDRH HF team participated in an internal meeting to discuss Sponsor's proposed response to address product administration concerns. The review team found that the proposal did not address the concerns.
- 3/1/2013: CDRH HF team participated in a face-to-face meeting between FDA and AP Pharma to discuss approaches to address the product administration concerns. Subsequent to a face-to-face meeting, AP Pharma provided test results of a formative Human Factors/usability study and a proposed Human Factors/usability validation study protocol.
- 3/18/2013: CDRH HF team participated in an internal meeting and was requested to provide a list of outstanding concerns.

### ***Review Summary***

This application proposed the marketing of Sustol as a subcutaneous as a 10 mg subcutaneous injection in a (b) (4) glass syringe, co-packaged with the following items: (b) (4)

(b) (4). The drug product is a tri(ethylene glycol) poly(ortho ester) (TEG-POE) polymer-based formulation containing granisetron base and is designed to deliver the active pharmaceutical ingredient in an extended release manner). SUSTOL is an extended release formulation of granisetron that provides long-lasting antiemetic benefits to chemotherapy patients. SUSTOL is intended to be administered by an oncology nurse in inpatient and outpatient oncology settings. A.P. Pharma does not manufacture the syringe or needle. The components of the pre-filled syringe are sourced from third-party manufacturers. However, in selecting components for a suitable syringe for SUSTOL, A.P. Pharma considered features of syringe design and instructions that would mitigate known problems with similar products.



15 oncology nurses participated in the validation study without any training on the administration of Sustol. A patient mannequin in a seated position with an injection pad was used for the administrations. The study included all of the steps associated with the use of the product. Most of the steps are considered essential (i.e. use errors/failures do not result in patient harm). There are three steps that are considered critical (i.e. use errors/failures can result in patient harm). Those steps are: (1) choosing administration route; (2) discarding used needle and syringe; (3) handling syringe to avoid needle stick injuries and possible infection. Since Sustol is a very viscous drug, FDA had requested in prior communication that warming to room temperature be evaluated during validation testing. Warming to at least 60 minutes prior to use can reduce the force required to inject. (b) (4)

The study results showed that in examining the completion of injection, three participants did not appear to have expelled all of the medication from the syringe and had one or two droplets remaining. The Sponsor provided additional response indicating that an independent observer visually inspected all of the syringes after injection, and of the 45 syringes (15 participants, 3 injections), 44 of the syringes were judged to have the plunger stopper flush with the bottom of the syringe barrel, and one syringe had two droplets remaining. In addition, some participants reported use difficulties during the study: one participant in unscrewing the tip cap from the end of the prefilled syringe; one participant in removing the hub cover from the needle; and two participants removing the white finger flange from the syringe prior to injecting. In addition, five participants indicated that on their first trial, the syringe was much harder to push than expected, and four other participants indicated that they were expecting the harder pressure because of the drug viscosity. In examining the warming of the syringe to room temperature, all 15 participants acknowledged the need for warming the syringe before use, and they rolled the syringe in the palm of their hands before injection.

Subsequent to the face-to-face meeting on March 1, 2013 between FDA and AP Pharma to discuss proposed plan to address administration concerns, AP Pharma provided test results of a formative Human Factors/usability study with 20 oncology nurses and a proposed Human Factors/usability validation study protocol.

- The formative Human Factors/usability study was conducted with the revised Instructions for Use (IFU) that provided information prominently about the viscosity of the drug product and the tremendous force required to perform the injection. The revised IFU also suggested the user to use the technique of removing the non-dominant hand after pinching and using that hand to hold onto the syringe barrel for additional support as the other hand pushes the plunger. Review of the

study results showed that (1) the products used for the testing were not “finished products”, which resulted in issues related to device performance such as disengagement of the finger flanges and malfunctions of the plunger; (2) four of twenty users did not apply the suggested technique recommended in the IFU but they were able to perform the administration; (3) the IFU had to be revised with an additional cautionary statement for not removing the finger flanges during use.

- Review of the Human Factors/usability validation study protocol showed that there are some concerns associated with the study methodology. The concerns are associated with (1) (b) (4) (2) realistic use of Instructions for Use in the study, (3) level of assistance that will be provided to test participants in the study; and (4) the aspects of use associated with taking product from the refrigerator, and leaving it warm up to room temperature.

As a result, the reviewer recommends that AP Pharma provide additional information to address the outstanding concerns.

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/s/  
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MARY H CHUNG  
03/28/2014

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## HUMAN FACTORS PROTOCOL MEMO

Division of Medication Error Prevention and Analysis (DMEPA)  
Office of Medication Error Prevention and Risk Management (OMEPRM)  
Office of Surveillance and Epidemiology (OSE)  
Center for Drug Evaluation and Research (CDER)

\*\*\* This document contains proprietary information that cannot be released to the public\*\*\*

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|                                       |                                                                          |
|---------------------------------------|--------------------------------------------------------------------------|
| <b>Date of This Review:</b>           | February xx, 2014                                                        |
| <b>Requesting Office or Division:</b> | Division of Gastroenterology and Inborn Errors (DGIEP)                   |
| <b>Application Type and Number:</b>   | NDA 22445                                                                |
| <b>Product Name and Strength:</b>     | Sustol (granisetron (b) (4) Injection,<br>10 mg/0.4 mL Prefilled Syringe |
| <b>Product Type:</b>                  | Drug-Device Combination Product                                          |
| <b>Rx or OTC:</b>                     | Rx                                                                       |
| <b>Applicant/Sponsor Name:</b>        | A.P. Pharma                                                              |
| <b>Submission Date:</b>               | January 17, 2014                                                         |
| <b>OSE RCM #:</b>                     | 2014-309                                                                 |
| <b>DMEPA Primary Reviewer:</b>        | Mónica Calderón, PharmD BCPS                                             |
| <b>DMEPA Team Leader:</b>             | Lubna Merchant, MS, PharmD                                               |

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## 1. INTRODUCTION

This memo responds to a request from DGIEP to evaluate the adequacy of the Applicant's Human Factors Study Protocol and Instructions-for-Use that were submitted by A.P. Pharma for Sustol (granisetron (b) (4) NDA 22445. DMEPA had requested that prior to the Applicant initiating their Human Factors Validation Study, they submit a revised protocol and revised Instructions-for-Use for our review incorporating the comments provided by the Agency (EOR Meeting Minutes dated November 27, 2013 and General Advice Letter dated March 26, 2013).

## 2. CONCLUSIONS

We note that the Human Factors Protocol submitted adequately addressed the concerns presented to the Applicant in March and November 2013. Additionally, the revised Instructions-for-Use (IFU) submitted are clearly stated with appropriate pictorials demonstrating each step. Although previous recommendations have been incorporated into the Human Factors protocol, there remain areas for improvement to the protocol and the proposed syringe warmer labeling. DMEPA and the Center for Devices and Radiological Health (CDRH) provide recommendations below in Section 3.

## 3. RECOMMENDATIONS

DMEPA and CDRH provide the following recommendations to the Applicant:

### A. Human Factors Protocol

#### General Comments

1) We appreciate the level of details (table 1, and specific tracked changes throughout) that you have included in your revised human factors study protocol. We note that you have made several modifications to the product including (b) (4), and modifications to the instructions for use. Please ensure that your supplemental study focuses on the specific modifications that are being proposed such that the data collected can be used to confirm that the modifications are effective at reducing the use errors, and do not introduce any new hazards.

2) We note that your latest Instructions for Use continues to require a health care professional (HCP) (b) (4)

Please ensure the necessary data is collected to demonstrate this technique can be performed safely and effectively, and the users can maintain the injection in the correct tissue plane.

#### Specific Comments

1) Activation and application of the warming pouch was added as one task, but should be divided into the following separate Critical tasks:

- a) Activate the warming pouch.
- b) Apply the warming pouch to the syringe.
- c) Wait 5-6 minutes to warm the syringe.
- d) Remove the syringe from the warming pouch prior to injection.

2) Task Tables for Investigator Workbook

a) Separate the activation and application of the warming pouch into two tasks:

- i.) Activate the warming pouch.
- ii.) Apply the warming pouch to the syringe.

**B. Syringe Warmer Label**

1) Remove the (b) (4) statement from the warmer pouch. As currently displayed, it is much more prominent than the Syringe Warmer statement and may be confused (b) (4).

2) Revise the statement (b) (4) to **"Syringe Warmer for Sustol"** to emphasize the pouch provided is the warming device.

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/s/  
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MONICA M CALDERON  
02/24/2014

LUBNA A MERCHANT  
02/24/2014

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Medical Policy Initiatives  
Division of Medical Policy Programs**

**REVIEW DEFERRAL MEMORANDUM**

Date: March 27, 2013

To: Donna Griebel, MD  
Director  
**Division of Gastroenterology and Inborn Errors  
Products (DGIEP)**

Through: LaShawn Griffiths, MSHS-PH, BSN, RN  
Associate Director for Patient Labeling  
**Division of Medical Policy Programs (DMPP)**  
  
Sharon R. Mills, BSN, RN, CCRP  
Senior Patient Labeling Reviewer  
**Division of Medical Policy Programs (DMPP)**

From: Karen Dowdy, RN, BSN  
Patient Labeling Reviewer  
**Division of Medical Policy Programs (DMPP)**

Subject: Review Deferred: Patient Package Insert (PPI)

Drug Name (established name): SUSTOL (granisetron)

Dosage Form and Route: injection, for subcutaneous use

Application Type/Number: NDA 22-445

Applicant: A.P. Pharma Inc.

## **1 INTRODUCTION**

On September 27, 2012, A.P. Pharma Inc. re-submitted for the Agency's review their Original New Drug Application (NDA) 22-445 for SUSTOL (granisetron) injection in response to the Agency's Complete Response Letter that was issued on March 16, 2010. The proposed indications for SUSTOL (granisetron) injection are as follows:

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

On December 17, 2012, the Division of Gastroenterology and Inborn Errors Products (DGIEP) requested that the Division of Medical Policy Programs (DMPP) review the Applicant's proposed Patient Package Insert (PPI) for SUSTOL (granisetron) injection.

This memorandum documents the DMPP review deferral of the Applicant's proposed Patient Package Insert (PPI) for SUSTOL (granisetron) injection.

## **2 CONCLUSIONS**

Due to outstanding Facility Inspections, Container/Closure system, Clinical, and Product Quality deficiencies, DGIEP plans to issue a Complete Response (CR) letter. Therefore, DMPP defers comment on the Applicant's proposed patient labeling at this time. A final review will be performed after the Applicant submits a complete response to the Complete Response (CR) letter. Please send us a new consult request at such time.

Please notify us if you have any questions.

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/s/  
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KAREN M DOWDY  
03/27/2013

SHARON R MILLS  
03/27/2013

LASHAWN M GRIFFITHS  
03/27/2013

MEMORANDUM

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

**DATE:** March 21, 2013

**SUBJECT:** CDRH/ODE/DAGRID Human Factors Consult Review (final)

**APPLICATION/DRUG:** NDA 022445 Sustol (granisetron) injection, extended-release

Reference is made to the consult issued on October 15, 2013 from CDER/DGIEP to CDRH/ODE/DAGRID (Dr. Quynh Nhu Nguyen) requesting assistance with review of the device component of the Sustol (granisetron) injection drug product (NDA 022445). Of particular interest was the human factors validation study and associated materials submitted with and during the NDA resubmission cycle. Enclosed is CDRH/ODE/DAGRID's final human factors consult review.



DEPARTMENT OF HEALTH AND HUMAN SERVICES

MEMORANDUM

Food and Drug Administration  
Office of Device Evaluation  
10903 New Hampshire Avenue  
Silver Spring, MD 20993

DATE: March 20, 2013

FROM: QuynhNhu Nguyen, Biomedical Engineer/Human Factors Reviewer, CDRH/ODE/DAGRID  
THROUGH: Ron Kaye, Human Factors and Device Use-Safety Team Leader, CDRH/ODE/DAGRID  
CC: Molly Story, Human Factors and Accessible Medical Technology Specialist, DAGRID  
TO: Jagjit Grewal, Regulatory Project Manager, CDER/OND/ODEIII/DGIEP

SUBJECT: **NDA 22445 (ICC1200220/CON1221222)**  
**Applicant: AP Pharma**  
**Device Constituent: Prefilled Syringe Injection**  
**Drug Constituent: Sustol**  
**Intended Treatment: cancer chemotherapy**

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QuynhNhu Nguyen, Combination Products Human Factors Specialist

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Ron Kaye, Human Factors and Device Use-Safety Team Leader

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## CDRH Human Factors Review

### *Overview and Recommendations*

The Division of Gastroenterology and Inborn Error Products, Office of New Drugs, Center for Drugs Research and Evaluation, requested a Human Factors consultative review of a Human Factors validation study report submitted via NDA# 22445 by AP Pharma. This review provides CDRH's review and recommendations on the Human Factors related information contained in the NDA.

Since Sustol is a viscous drug product, and it is the first time it is delivered through a pre-filled syringe, CDRH and CDER have concerns associated with the force required to inject. While the Sponsor has modified the syringe components for use in the Human Factors validation study i (b) (4) users continued to report difficulty in administering the drug product through the syringe. As a result, on 2/13/2013, the review team expressed these concerns to the Sponsor, and requested that the Sponsor provide a proposal to address these concerns. On 2/18/2013, the Sponsor proposed various labeling modifications to the Instructions for Use, syringe label, and carton label (b) (4) to the Instructions for Use. On 2/20/2013, the review team provided feedback to the Sponsor's proposal and recommended that the drug administration be performed by two individuals.

The data obtained from the Human Factors validation study suggested there are issues associated with safe and effective use of the product. The performance data indicated that incomplete injection of the drug product could occur. In addition, users reported difficulty in generating the required force to perform the injection, which could result in injecting the drug product in unintended area that lead to intended patient reaction and/or bleeding. As a result, CDRH Human Factors team recommended that additional modifications either in the product labeling and/or product design are necessary and additional human factors study should be conducted to demonstrate that the product modifications are effective in reducing/minimizing patient harm.

A face-to-face meeting was held on March 1, 2013 between FDA and AP Pharma to discuss proposed plan to address administration concerns. Subsequently, AP Pharma provided test results of a formative Human Factors/usability study with 20 oncology nurses and a proposed Human Factors/usability validation study protocol. The formative Human Factors/usability study was conducted with the revised Instructions for Use (IFU). Review of the study results showed that there are still some concerns, which AP Pharma will need to address prior to conducting the validation study. In addition, review of the proposed validation showed some areas regarding study methodology that the Sponsor would make changes to the protocol prior to executing the study. Details on the review of the formative study and the proposed validation study can be found on page 7 of this memo.

This reviewer discussed the outstanding concerns with DMEPA and the following comments represent the consolidated comments based on the review of the formative study results and the proposed validation study protocol review:

#### A. Formative Study Results

1. Your formative study results showed that the products used during the testing did not represent the finalized commercial products, which generated issues related to device performance such as disengagement of the finger flanges and malfunctions of the plunger. Please note that in your Human Factors/Usability validation study, we expect that you use

products that have been assembled using a validated process and released under the Quality Management System.

2. Your formative study results showed that while four of the 20 users did not follow the specific technique stated in the Instructions for Use, they were able to administer the product. You did not discuss whether any of the techniques applied by these test participants had any potential negative consequences to the patient or the user. Please note that if any of the techniques applied could result in patient harm, the Instructions for Use/labeling should be modified to warn users of those potential consequences, and the modified Instructions for Use/labeling should be used for your Human Factors/usability validation study.
3. Your formative study results suggested that an additional cautionary statement be added to the Instructions for Use for not removing the white finger flanges. Please ensure that the data you collect from your Human Factors/usability validation study demonstrate that this mitigation is effective.

#### B. Validation Protocol

4. In the study introduction, (b) (4)  
[REDACTED]  
Please remove them from your moderator guide.
5. In addition, we expect that in your Human Factors/usability validation study, you should make the Instructions for Use available along with the product and let the study participants use them as they would normally use them.
6. In your Human Factors/usability validation study, if assistance is provided to study participants, please provide the nature of assistance provided along with the use scenario, and obtain feedback from test participants on the difficulty that they experience while using the product.
7. In the formative study, (b) (4)  
[REDACTED]. Bringing this product to room temperature is a critical task to help promote ease of administration. Step 1 in your Instructions for Use specified that the user has to remove the product from the refrigeration at least 60 minutes prior to use and can be left overnight. We recognize the importance of warming up this type of product and understand the logistics of simulating this aspect of use in a Human Factors/usability validation study. We recommend that you ask test participants directly to assess their understanding and essential knowledge with regards to this step rather than simulating it in your study. We believe that it is equally critical that the user who performs the injection understand that they need to verify that the product has been warmed up to room temperature for at least 60 minutes. Please ensure that your Human Factors/usability validation study collect the necessary data to demonstrate that users understand these two steps.

### ***Combination Product Device Information***

Submission Number: NDA 22445  
Applicant: AP Pharma  
Drug Constituent: Sustol (granisetron) subcutaneous  
Device Constituent: Prefilled Syringe  
Intended treatment: cancer chemotherapy

### ***CDRH Human Factors Involvement History***

- 10/15/2012: CDRH Human Factors team was requested to review AP Pharma's Human Factors validation study report
- 2/13/2013: CDRH HF team participated in a teleconference with CDER representatives and Sponsor representatives to discuss product administration concerns (force required to inject the drug product). The Sponsor indicated that they will develop proposals to address the concerns and submit to FDA for review and concurrence
- 2/20/2013: CDRH HF team participated in an internal meeting to discuss Sponsor's proposed response to address product administration concerns. The review team found that the proposal did not address the concerns.
- 3/1/2013: CDRH HF team participated in a face-to-face meeting between FDA and AP Pharma to discuss approaches to address the product administration concerns. Subsequent to a face-to-face meeting, AP Pharma provided test results of a formative Human Factors/usability study and a proposed Human Factors/usability validation study protocol.
- 3/18/2013: CDRH HF team participated in an internal meeting and was requested to provide a list of outstanding concerns.

### ***Review Summary***

This application proposed the marketing of Sustol as a subcutaneous as a 10 mg subcutaneous injection in a (b) (4) glass syringe, co-packaged with the following items: (b) (4)

The drug product is a tri(ethylene glycol) poly(ortho ester) (TEG-POE) polymer-based formulation containing granisetron base and is designed to deliver the active pharmaceutical ingredient in an extended release manner). SUSTOL is an extended release formulation of granisetron that provides long-lasting antiemetic benefits to chemotherapy patients. SUSTOL is intended to be administered by an oncology nurse in inpatient and outpatient oncology settings. A.P. Pharma does not manufacture the syringe or needle. The components of the pre-filled syringe are sourced from third-party manufacturers. However, in selecting components for a suitable syringe for SUSTOL, A.P. Pharma considered features of syringe design and instructions that would mitigate known problems with similar products.

15 oncology nurses participated in the validation study without any training on the administration of Sustol. A patient mannequin in a seated position with an injection pad was used for the administrations. The study included all of the steps associated with the use of the product. Most of the steps are considered essential (i.e. use errors/failures do not result in patient harm). There are three steps that are considered critical (i.e. use errors/failures can result in patient harm). Those steps are: (1) choosing administration route; (2) discarding used needle and syringe; (3) handling syringe to avoid needle stick injuries and possible infection. Since Sustol is a very viscous drug, FDA had requested in prior communication that warming to room temperature be evaluated during validation testing. Warming to at least 60 minutes prior to use can reduce the force required to inject. (b) (4)

The study results showed that in examining the completion of injection, three participants did not appear to have expelled all of the medication from the syringe and had one or two droplets remaining. The Sponsor provided additional response indicating that an independent observer visually inspected all of the syringes after injection, and of the 45 syringes (15 participants, 3 injections), 44 of the syringes were judged to have the plunger stopper flush with the bottom of the syringe barrel, and one syringe had two

droplets remaining. In addition, some participants reported use difficulties during the study: one participant in unscrewing the tip cap from the end of the prefilled syringe; one participant in removing the hub cover from the needle; and two participants removing the white finger flange from the syringe prior to injecting. In addition, five participants indicated that on their first trial, the syringe was much harder to push than expected, and four other participants indicated that they were expecting the harder pressure because of the drug viscosity. In examining the warming of the syringe to room temperature, all 15 participants acknowledged the need for warming the syringe before use, and they rolled the syringe in the palm of their hands before injection.

Subsequent to the face-to-face meeting on March 1, 2013 between FDA and AP Pharma to discuss proposed plan to address administration concerns, AP Pharma provided test results of a formative Human Factors/usability study with 20 oncology nurses and a proposed Human Factors/usability validation study protocol.

- The formative Human Factors/usability study was conducted with the revised Instructions for Use (IFU) that provided information prominently about the viscosity of the drug product and the tremendous force required to perform the injection. The revised IFU also suggested the user to use the technique of removing the non-dominant hand after pinching and using that hand to hold onto the syringe barrel for additional support as the other hand pushes the plunger. Review of the study results showed that (1) the products used for the testing were not “finished products”, which resulted in issues related to device performance such as disengagement of the finger flanges and malfunctions of the plunger; (2) four of twenty users did not apply the suggested technique recommended in the IFU but they were able to perform the administration; (3) the IFU had to be revised with an additional cautionary statement for not removing the finger flanges during use.
- Review of the Human Factors/usability validation study protocol showed that there are some concerns associated with the study methodology. The concerns are associated with (b) (4) (2) realistic use of Instructions for Use in the study, (3) level of assistance that will be provided to test participants in the study; and (4) the aspects of use associated with taking product from the refrigerator, and leaving it warm up to room temperature.

As a result, the reviewer recommends that AP Pharma provide additional information to address the outstanding concerns.

4 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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JAGJIT S GREWAL  
03/21/2013

MEMORANDUM

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

**DATE:** March 20, 2013

**SUBJECT:** CDRH/ODE/DAGID Review

**APPLICATION/DRUG:** NDA 022445 Sustol (granisetron) injection, extended-release

Reference is made to the consult dated October 15, 2012 from CDER/DGIEP to CDRH/ODE/DAGID requesting assistance with review of the device components and the proposed administration preparation process defined in the kit insert labeling for NDA 022445 Sustol (granisetron) injection, extended-release. Enclosed is CDRH/ODE/DAGID's review memo evaluating these issues for the NDA re-submission dated September 27, 2012.

**DEPARTMENT OF HEALTH AND HUMAN SERVICES****MEMORANDUM**

Food and Drug Administration  
Center for Devices and  
Radiological Health  
Office of Device Evaluation  
White Oak Building 66  
10903 New Hampshire Avenue  
Silver Spring, MD 20993

**Date:** March 20, 2013  
**From:** Jacqueline Ryan, Combination Products Team Leader,  
General Hospital Devices Branch, DAGID, ODE, CDRH, WO 66, Rm. 2556  
**To:** Jagjit Grewal, Senior RHPM, CDER/ OMPT/CDER/OND/ODEIII/DGIEP  
**Subject:** CDRH Consult, NDA 22445, pre-filled syringe and needle to deliver Sustol®(granisetron)

**1. Issue**

The: Center for Drug Evaluation and Research (CDER)]has requested a consult from the Center for Devices and Radiological Health (CDRH, regarding NDA 22445 The device constituent of this combination product consists of a pre-filled syringe to deliver Sustol®(granisetron)

**2. Documents Reviewed**

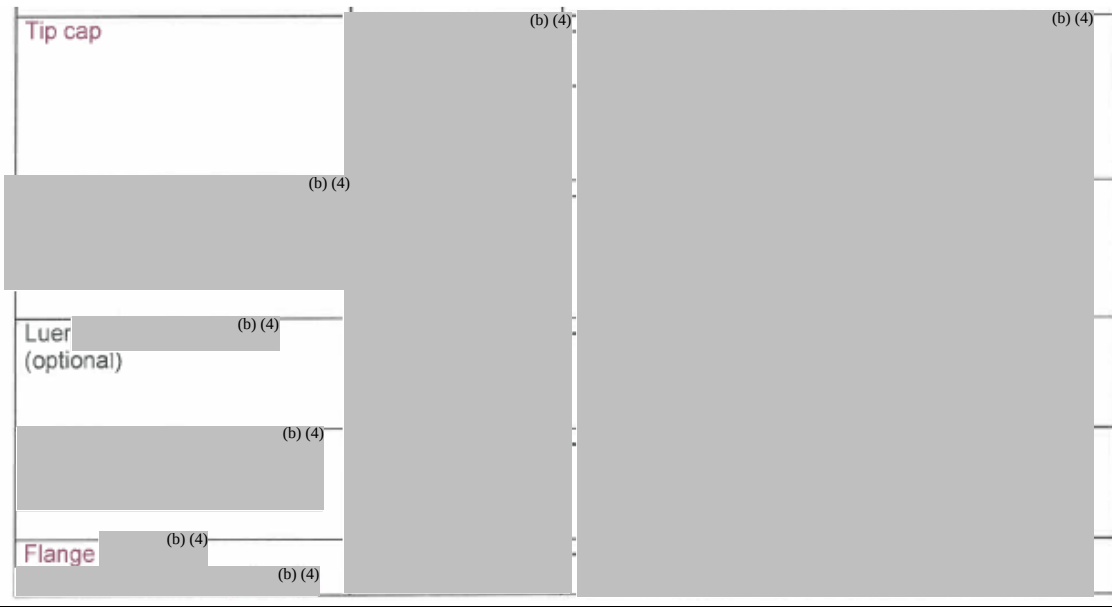
NDA 22445  
DMF (b) (4)

**3. Device Description**

The drug product is filled into sterile (b) (4) long syringes with Luer Lok Assembly (LLA). Each syringe unit contains a (b) (4) Gray (b) (4) Cap, a (b) (4) Gray Stopper and (b) (4) plunger rod. The manufacturer has performed Dye Leak Challenge testing to demonstrate the integrity of the primary container closure system components. The tip cap and stopper formulations are manufactured by (b) (4) (b) (4). A LOA to DMF (b) (4) (file located in Folder 1.4.1) is provided; the DMF (b) (4) applies to formulation (b) (4) Gray for the stopper and (b) (4) Gray for the tips.

**3.1 - Product description**

| PRODUCT        | MATERIAL      | CHARACTERISTICS                                                                      |
|----------------|---------------|--------------------------------------------------------------------------------------|
| Syringe barrel | (b) (4) glass | (b) (4) glass<br>(b) (4)<br>- function : container for pharmaceutical use<br>(b) (4) |



#### **4. CDRH Review and Comments**

CDRH's Review of the device constituent for this Combination Product consisted of an assessment of Device Performance. The following concerns were raised in the initial review cycle:

Several different needles were tested for compatibility and clinical performance. However, it is not clear which needle is included with the injection kit. The sponsor should clarify if the (b) (4) 18G 5/8" needle will be included with the injection kit.

The drug substance is extremely viscous and will probably require significant force for extrusion. The sponsor should provide performance data to demonstrate that the needle supplied with the injection kit will not separate from the syringe or leak when injecting drug product.

There is little information regarding the plunger rod (b) (4). The sponsor should provide the 510(k) number for the plunger rod (b) (4) or provide performance data to demonstrate that it is safe and effective for its intended use. They should include bench testing data with acceptance criteria and a rationale for the acceptance criteria, biocompatibility data for a device which has short term contact with intact skin and any applicable human factors/usability data.

There is little information regarding the flange (b) (4). The sponsor should identify the syringe flange (b) (4) and provide the 510(k) number for this part if applicable.

The sponsor should provide breakloose and extrusion force data for the terminally sterilized syringe with attached plunger (b) (4) and needle at room temperature, preferably at or near the end of shelf life.

#### **5. CDRH Initial Review Deficiencies November 14, 2012 and Sponsor Reply December 6, 2012 (NDA 022445\0036)**

a. Please clarify if the (b) (4) 18G 5/8" needle will be included with the injection kit.

**Sponsor Reply:**

A.P. Pharma intends on using the (b) (4) 18 gauge 5/8" needle. This needle will be included in the packaged product.

**Reviewer's Comment:**

**This needle was cleared under K** (b) (4)

b. Please provide performance data to demonstrate that the needle supplied with the injection kit will not separate from the syringe or leak when injecting drug product.

**Sponsor Reply**

Human Factors testing on terminally irradiated 1.0 mL pre-filled syringes was performed (XP-1179-045). Fifteen participants performed three successful injections each with the SUSTOL® product, 45 injections total, without failures. The validation test found no failures on critical or essential tasks. At the completion of each study session all syringes were examined for cracking or breaking of the syringe or syringe components. There was no evidence of tip cracking or stress to any of the used syringes or the syringe components.

Force to Operate testing (ISO 8537, Annex C) was performed on three lots of terminally irradiated, 1.0 mL pre-filled syringes Fully assembled syringes (with needle, flange, and plunger attached) were loaded into a test fixture and drug product was expelled at a rate of 1 mm/sec until the plunger bottomed out. Drug product was expelled at an initial average force of 106.0 Newtons and an average force of 83.5 Newtons. By comparison the median force of a three point grip was evaluated in 50 males and 50 females. The fiftieth percentile was found to be 86 and 125 Newtons in females and males, respectively (Ovan der Ploeg, Fidler, Oosterhuis. *Hand-held myometry: referenced values. Journal of Neurology, Neurosurgery, and Psychiatry*. 1991;54:244-247). No failures, defined as needle separation or drug product leakage from the syringe tip, were observed.

Injection Overload testing was performed with the intent to push the product to failure (XP-1157-179, XP-1179-060). Fully assembled syringes were loaded into a test fixture and tested at each crosshead speed (two syringes at a time); starting at 1.25 mm/sec and increasing until failure was observed or a maximum speed of 6.5 mm/sec was achieved. At delivery rates of 1.25-2.00 mm/sec, 241 Newtons was the maximum force required to expel the drug product.

When syringes were subjected to expulsion rates > 2.25 mm/sec, three types of failure were observed.

- The syringe cracked when the plunger bottomed out after test completion. These failures are a limitation of the test method, as the force increases dramatically at the end.
- The syringe failed at the attachment point between the finger flange and the glass syringe. Although the syringe body broke, the needle remained attached to the syringe tip; no leakage from the tip or needle was observed.
- The lock collar popped off. The lock collar is the threaded portion of the Luer, and when the lock collar fails, the needle goes with it, similar to separation force testing.

Thus, the 1.0 mL pre-filled syringe needle does not separate from the syringe or leak when injecting the drug product under normal use.

**CDHR Comment:**

The sponsor concluded that the Human Factors usability test was acceptable, however the report indicates that only 12 of the 15 subjects expelled all of the medication from

all of the syringes during their attempted injections. The sponsor should explain why the incomplete injections were considered acceptable.

For the Sustol syringe, the average initial peak force (breakloose) for injection, is quite high, (especially when the drug is delivered faster than the 1mm/sec recommended rate). The sponsor should indicate, citing normative data from the literature, if 95% percent of the US population can generate the required breakloose force using the thumb or hand, and can sustain the force needed to expel the drug from the syringe over the time needed to extrude the drug.

Given that the breakloose and glide forces are at the maximum achievable force for 50% of the population, this reviewer is concerned that users may not be able to achieve adequate control of the device to allow injection into the correct tissue plane. Proper subcutaneous injection technique requires using one hand to raise a skin fold. The sponsor should indicate how they have demonstrated or will demonstrate that the user is able raise a skin fold and inject the drug while keeping the needle in the correct tissue plane.

Device failures when the drug is delivered at faster than recommended rates are also concerning. Labeling will need to indicate that the drug is viscous and that pressure should be applied to the plunger over an extended period of time to avoid device failures.

c. Please provide the 510(k) number for the plunger rod (b) (4) or provide performance data to demonstrate that it is safe and effective for its intended use. You should include bench testing data with acceptance criteria and a rationale for the acceptance criteria, biocompatibility data for a device which has short term contact with intact skin and any applicable human factors/usability data.

*Sponsor Reply:*

The 1.0 mL (b) (4) Plunger Rod is a custom part designed and manufactured by (b) (4) for A.P. Pharma. A.P. Pharma keeps the design history file.

*Performance testing of the plunger rod was performed to compare baseline plungers to 3 year accelerated aged plungers (XP-1157-206, XP-1157-207). Plungers were assembled with the syringe device and subjected to drop, 3 point bend, and piston flexural testing. All testing completed successfully and confirmed that there was no variation in testing results that were statistically significant between the baseline plungers and the 3 year accelerated aged plungers. In addition, the plunger was compared to two commercially available plunger rods to determine performance parameters and assess the suitability of the plunger rod for its intended use. The 3 point bend, drop, and force to operate tests were performed. All testing was successfully completed and confirmed that the (b) (4) Plunger Rod matched or exceeded the performance of the tested commercially available plungers).*

*Performance bench testing (force to operate, stress cracking of Luer-Lok, drop testing, corrosion, injection overload) was also performed on the (b) (4) Plunger Rod integrated into the 1.0 mL Pre- Filled (b) (4) Long Barrel Syringe system to assure product performance).*

**CDHR Comment:**

**The performance testing was reviewed and deemed adequate.**

d. Please identify the syringe flange (b) (4) and provide the 510(k) number for this part if applicable.

*Sponsor Reply:*

(b) (4) refers to the syringe flange (b) (4) as the (b) (4) reference LOA), and is referenced in the Table of Contents in DMF# (b) (4). The (b) (4) is a container/closure component and subject to a Type III DMF.

**CDHR Comment:**

The master file was reviewed. The device description for the flange (b) (4) in the MAF is adequate. There was no performance testing provided in the MAF to indicate the removal force for the flange (b) (4). The sponsor asserts that when the drug is administered at the recommended extrusion rate, the flange does not detach.

e. Please provide breakloose and extrusion force data for the terminally sterilized syringe with attached plunger (b) (4) and needle at room temperature, preferably at or near the end of shelf life.

**Sponsor Reply:**

Break-loose and extrusion force data are provided in Query response #5 (XP-1157-179, XP-1179-060). Thirty pre-filled syringes from three lots were subjected to force to operate testing (ISO 8537, Annex C). All samples were kept in refrigerated storage conditions. The samples were then placed into the test storage condition  $22 \pm 2^{\circ}\text{C}$  for a minimum of 16 hours prior to testing. A fresh needle and plunger rod were attached to each pre-filled syringe. The syringe was then loaded into the test fixture and expelled at a rate of 1.0 mm/second until the plunger had bottomed out (Table 3). The syringes tested were obtained from three engineering lots, where 1 lot was stored for ~3 months and two lots were stored for ~5 months at  $2-8^{\circ}\text{C}$  prior to testing. The syringes performed similarly for each lot, independent of aging.

**Table 3: Sustol® Force to Operate Data**

| DDL # 205981<br>AP Pharm Lot #024366 |                        |                   | DDL # 210210<br>AP Pharm Lot #024376 |                        |                   | DDL # 210211<br>AP Pharm Lot #024501A |                        |                   |
|--------------------------------------|------------------------|-------------------|--------------------------------------|------------------------|-------------------|---------------------------------------|------------------------|-------------------|
| DDL Sample #                         | Initial Peak Force (N) | Average Force (N) | DDL Sample #                         | Initial Peak Force (N) | Average Force (N) | DDL Sample #                          | Initial Peak Force (N) | Average Force (N) |
| 1                                    | 126.2                  | 104.8             | 1                                    | 95.38                  | 73.39             | 1                                     | 102.2                  | 80.41             |
| 2                                    | 95.66                  | 72.89             | 2                                    | 88.89                  | 68.14             | 2                                     | 107.7                  | 78.73             |
| 3                                    | 95.54                  | 85.23             | 3                                    | 105.2                  | 81.42             | 3                                     | 102.5                  | 79.15             |
| 4                                    | 113.2                  | 101.4             | 4                                    | 107.3                  | 81.18             | 4                                     | 93.73                  | 73.36             |
| 5                                    | 116.3                  | 103.8             | 5                                    | 105.5                  | 82.77             | 5                                     | 120.1                  | 87.78             |
| 6                                    | 130.9                  | 114.6             | 6                                    | 98.89                  | 77.40             | 6                                     | 95.42                  | 69.10             |
| 7                                    | 143.4                  | 125.6             | 7                                    | 107.5                  | 82.05             | 7                                     | 84.98                  | 62.67             |
| 8                                    | 146.6                  | 126.4             | 8                                    | 101.7                  | 77.68             | 8                                     | 86.05                  | 65.56             |
| 9                                    | 149.8                  | 133.1             | 9                                    | 101.1                  | 77.74             | 9                                     | 92.59                  | 66.39             |
| 10                                   | 128.2                  | 110.4             | 10                                   | 100.4                  | 76.79             | 10                                    | 91.25                  | 67.53             |
| 11                                   | 115.9                  | 101.4             | 11                                   | 91.73                  | 72.91             | 11                                    | 101.0                  | 72.44             |
| 12                                   | 111.6                  | 98.50             | 12                                   | 92.40                  | 72.22             | 12                                    | 111.5                  | 78.65             |
| 13                                   | 125.0                  | 103.8             | 13                                   | 83.00                  | 66.60             | 13                                    | 109.0                  | 78.46             |
| 14                                   | 107.2                  | 95.68             | 14                                   | 102.1                  | 73.69             | 14                                    | 90.52                  | 69.81             |
| 15                                   | 123.5                  | 107.7             | 15                                   | 105.5                  | 77.90             | 15                                    | 99.92                  | 74.97             |
| 16                                   | 139.0                  | 120.3             | 16                                   | 97.25                  | 73.04             | 16                                    | 97.40                  | 74.74             |
| 17                                   | 128.5                  | 110.2             | 17                                   | 104.0                  | 76.40             | 17                                    | 102.7                  | 76.52             |

| DDL #205981<br>AP Pharm Lot #024366 |                              |                      | DDL #210210<br>AP Pharm Lot #024376 |                              |                      | DDL #210211<br>AP Pharm Lot #024501A |                              |                      |
|-------------------------------------|------------------------------|----------------------|-------------------------------------|------------------------------|----------------------|--------------------------------------|------------------------------|----------------------|
| DDL<br>Sample #                     | Initial<br>Peak<br>Force (N) | Average<br>Force (N) | DDL<br>Sample #                     | Initial<br>Peak<br>Force (N) | Average<br>Force (N) | DDL<br>Sample #                      | Initial<br>Peak<br>Force (N) | Average<br>Force (N) |
| 18                                  | 124.5                        | 106.5                | 18                                  | 100.4                        | 77.54                | 18                                   | 117.8                        | 82.99                |
| 19                                  | 131.5                        | 111.7                | 19                                  | 97.73                        | 70.18                | 19                                   | 99.68                        | 76.76                |
| 20                                  | 128.5                        | 107.9                | 20                                  | 105.4                        | 73.32                | 20                                   | 100.2                        | 72.17                |
| 21*                                 | 122.5                        | 99.16                | 21                                  | 104.8                        | 77.61                | 21                                   | 86.24                        | 62.79                |
| 22                                  | 95.97                        | 84.43                | 22                                  | 117.3                        | 91.25                | 22                                   | 89.92                        | 66.71                |
| 23                                  | 112.1                        | 87.02                | 23                                  | 110.3                        | 85.73                | 23                                   | 95.69                        | 66.59                |
| 24                                  | 92.89                        | 77.44                | 24                                  | 121.0                        | 84.67                | 24                                   | 105.7                        | 74.73                |
| 25                                  | 82.39                        | 68.34                | 25                                  | 108.7                        | 87.96                | 25                                   | 114.5                        | 78.86                |
| 26                                  | 73.41                        | 62.95                | 26                                  | 112.6                        | 89.54                | 26                                   | 97.57                        | 73.09                |
| 27                                  | 91.42                        | 76.57                | 27                                  | 104.8                        | 78.62                | 27                                   | 103.0                        | 76.92                |
| 28                                  | 82.31                        | 72.48                | 28                                  | 105.9                        | 81.40                | 28                                   | 97.25                        | 74.37                |
| 29                                  | 98.74                        | 87.69                | 29                                  | 107.4                        | 82.61                | 29                                   | 107.7                        | 79.24                |
| 30                                  | 100.7                        | 84.90                | 30                                  | 103.3                        | 75.23                | 30                                   | 112.7                        | 85.34                |

\*Sample syringe failed at the attachment point between the finger flange and the glass syringe.

**CDHR Comment:**

**Our concerns regarding breakloose and extrusion forces for the syringe have been described above. Additionally, the sponsor noted a device failure during the testing due to detachment of the finger flange from the glass syringe.**

**6. CDRH Request for Information December 14, 2012 and Sponsor Reply January 9, 2013**

**CDRH Deficiency:**

You concluded that your usability test was acceptable, however the report indicates that only 12 of the 15 subjects expelled all of the medication from all of the syringes during their attempted injections. Please explain why the incomplete injections were considered acceptable.

**Sponsor Reply:**

*The study design required each of the 15 participants to expel the drug product from three syringes, for a total of 45 syringes tested (HF Validation Protocol Sustol). After drug product was expelled from each syringe by the participants, an independent observer visually inspected the syringes to confirm that the plunger stopper was flush with the bottom of the syringe barrel. Upon inspection, forty-four of the 45 syringes were judged to have the plunger stopper flush with the bottom of the syringe. Additionally, the observer attempted to force additional material from the syringe even if it was visually empty. In three of these syringes, the independent observer could still force one small droplet out of the end of the needle of the visually empty syringe by applying additional forced pressure. In the last syringe, the plunger stopper was not fully flush with the bottom of the syringe barrel. When the independent observer applied additional forced pressure to the plunger, two small droplets were extruded from the end of the needle. Therefore, for 44 syringes, the drug product was observed to be successfully delivered from the syringe. In the one case, the syringe was not fully expelled. This was attributed to administration error.*

**CDHR Comment:**

**It appears that 3 subjects had difficulty assessing that the injection was completed. This again raises concerns that the breakloose and glide forces of the syringe are excessive and may lead to dosing errors.**

**CDRH Deficiency:**

For the Sustol syringe, the average initial peak force (breakloose) for injection was 114.4 N and glide force was 98N. Citing the literature, please indicate if 95% percent of the US population can generate the required breakloose force using the thumb or hand, and can sustain the force needed to expel the drug from the syringe over the time needed to extrude the drug.

**Sponsor Reply:**

*An average initial peak force for injection of 114.4 Newtons (N) and glide force of 98 N were determined at an expulsion rate of 1 mm per second (XP-1157-179, XP-1179-060). This expulsion rate is approximately three times the rate observed in the Human Factors studies. A similar study conducted at an expulsion rate of 16 mm per minute, or 0.27 mm per second, approximately one third the previous rate, gave an initial peak force of 37.4 N, approximately one third the force required previously (XP-1148-082). This confirms that the required expulsion force is, as expected, linearly proportional to the expulsion rate. Therefore, the peak force and glide force required to expel the recommended Sustol® dose within 30 seconds, as specified in the Instructions for Use, is calculated to be 76 N and 65 N, respectively. Sustol® is administered by positioning the index and middle finger underneath either side of the finger flange and pressing the plunger rod with the thumb or palm of the hand. Literature references show the median force of a three point grip evaluated in 50 adult males and 50 adult females was found to be 86 N and 125 N in females and males, respectively (Ovan der Ploeg RJO, Fidler V, Oosterhuis HJGH. Hand-held Myometry: Referenced Values. Journal of Neurology, Neurosurgery, and Psychiatry 54:244-247, 1991). The force for females and males in the 95th percentile was determined to be 65 N and 94 N, respectively. These values meet or exceed the force calculated for expelling Sustol.*

**CDHR Comment:**

**The sponsor will need to specify in the labeling that the drug should be delivered over 30 seconds to minimize the use of excessive force which could cause the needle to move out of the correct tissue plane, resulting in an intramuscular or intraperitoneal injection, especially in patients with minimal subcutaneous fat. CDRH is still concerned that the breakloose and injection forces are close to maximum achievable force for about half the population and is above maximum achievable pinch force for 5% of the population.**

**CDRH Deficiency:**

Proper subcutaneous injection technique requires using one hand to raise a skin fold. Please indicate how you have demonstrated or will demonstrate that the user is able raise a skin fold and inject the drug while keeping the needle in the correct tissue plane.

**Sponsor Reply:**

*The subcutaneous injection for Sustol® follows standard subcutaneous injection procedures ([NIH reference](#), [Rheum video reference](#)). Standard procedures and training are applicable for administration of Sustol®. Similar instructions ([Pharmacy Manual](#)) were used in the two most recent clinical trials that used the proposed needle for administration and no issues were*

*reported for 132 subcutaneous administrations of Sustol®. In the Human Factors Validation study all participants were able to either pinch or grasp the injection pad with one hand prior to injection and insert the needle at an angle of approximately 45 degrees with the other hand (IFU). The 45 degree angle was maintained until the injection was completed. A summary of the observations recorded for the subcutaneous injection techniques used during the validation study are provided below.*

- Eleven participants pinched the injection pad and held the pinch for the entire injection.*
- Four participants pinched the pad and once the needle penetrated the skin they released their pinch.*

**CDRH Device Evaluation has remaining concerns regarding the safety of the syringe used to administer Sustol. We are particularly concerned that based on the breakloose and glide forces for the syringe and normative data for pinch strength up to 5% of the user population may not be able to generate the force needed to safely extrude the drug. This may result either in failed injections or possible drug administration errors. Discussions with the sponsor and CDER, CDRH Human Factors, and DMEPA regarding labeling to mitigate such errors is ongoing.**

#### **7. CDRH Final Recommendations**

**CDRH ODE and Human Factors participated in a meeting with the sponsor regarding drug administration concerns on March 1, 2013. Both CDRH Human Factors and DMEPA determined that the original Human Factors study submitted by the applicant was not adequate due to administration difficulties which the subjects experienced that were not classified as administration failures. The sponsor agreed to perform new Human Factors testing to demonstrate ease of use of the syringe and that the drug can be safely administered by users with variable levels of experience.**

**The sponsor submitted a formative human factors validation study March 23, 2013 that will be reviewed by CDRH Human Factors and DMEPA. The sponsor included testing which demonstrated that the breakloose (expulsion force) for the syringe measured on the Instron Testing Device after 90 seconds of hand warming decreased significantly from 118N (refrigerated) to approximately 30N, which is below the maximum achievable pinch force for 95% of the population by normative data. CDRH ODE therefore believes that the device is appropriate for its intended use. However, safe and effective use of the device is dependent on several critical steps in the instructions for use, including removing the syringe from refrigeration, warming of the syringe with the hands, expelling the drug at the rate recommended by the sponsor, and not removing the finger flange prior to injection. Stabilization of the syringe with the non-dominant hand may also help to mitigate movement of the needle out of the tissue plane during injection. Validation of the instructions for use and remaining drug administration concerns will be addressed by CDRH Human Factors and DMEPA.**

If you have any questions, please contact Jacqueline Ryan at 301-796-9599.

| Digital Signature Concurrence Table |  |
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JAGJIT S GREWAL  
03/20/2013

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology  
Office of Medication Error Prevention and Risk Management**

**Label, Labeling, and Packaging Review Memo**

Date: March 20, 2013

Reviewer(s): Teresa McMillan, PharmD  
Division of Medication Error Prevention & Analysis

Team Leader: Lubna Merchant, PharmD, M.S.  
Division of Medication Error Prevention & Analysis

Drug Name(s) and Strength(s): Sustol (Granisetron) Injection, Extended-release  
10 mg/0.4 mL

Application Type/Number: NDA 022445

Applicant/sponsor: AP Pharma

OSE RCM #: 2012-2316-1

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## 1 INTRODUCTION

This review evaluates the formative study results summary, syringe labels, carton labeling, Instructions for Use, and validation protocol for NDA 022445 submitted by the Applicant in response to a meeting between the Agency and A.P. Pharma on March 1, 2013.

## 2 METHODS AND MATERIALS REVIEWED

The formative study results summary, syringe labels, carton labeling, Instructions for Use, and validation protocol submitted to the FDA on March 15, 2013 (See Appendix A for images of the syringe labels, carton labeling, and IFU) were evaluated to assess whether the revisions adequately address our concerns from a medication error perspective.

## 3 DISCUSSION

Our evaluation of the formative study determined that the revised labels and labeling appear to be effective in aiding the 20 participants to successfully complete all critical tasks (see Appendix B). However, there were areas of weakness in the formative study design that may affect the utility of these study results. For example, (b) (4)

which does not  
mimic actual practice. (b) (4)

Bringing this product to room temperature is a critical step and thus participants should be assessed on their understanding and essential knowledge with regards to this step. The participants also should understand that they need to verify that the product has been warmed up to room temperature for at least 60 minutes prior to use. In addition, the products used during formative testing did not represent the finalized commercial products, which caused issues with the plunger. The product to be tested should be identical to the proposed marketed product in every aspect. We reviewed the validation protocol to ensure that these areas have been addressed and will not affect the utility of the study results. In addition, there are areas of the IFU that can be improved to help promote the safe use of the product.

## 4 CONCLUSIONS AND RECOMMENDATIONS

We identified some areas of weakness in the validation study design that may affect the utility of the study results. We have the following additional comments to the protocol that need to be addressed by the Applicant prior to initiating the study. In addition, there are areas of the IFU that can be improved to help promote the safe use of the product. We provide comments for the validation protocol and the IFU in Sections 4.1 and 4.2. We also discussed the comments for the validation protocol with CDRH and both divisions concur.

## 4.1 COMMENTS TO THE DIVISION

### A. Validation Protocol

1. In the study introduction, (b) (4)  
[REDACTED]  
[REDACTED]  
[REDACTED] Please remove them from your moderator guide.
2. In addition, we expect that in your Human Factors/usability validation study, you should make the Instructions for Use available along with the product and let the study participants use them as they would normally use them.
3. In your Human Factors/usability validation study, if assistance is provided to the study participant, please provide the nature of assistance provided along with the use scenario, and obtain feedback from test participants on the difficulty that they experience while using the product.
4. (b) (4)  
[REDACTED] Bringing this product to room temperature is a critical task to help promote ease of administration. Step 1 in your Instructions for Use specified that the user has to remove the product from the refrigeration at least 60 minutes prior to use and can be left overnight. We recognize the importance of warming up this type of product and understand the logistics of simulating this aspect of use in a Human Factors/usability validation study. We recommend that you ask test participants directly to assess their understanding and essential knowledge with regards to this step rather than simulating it in your study. We believe that it is equally critical that the user who performs the injection understand that they need to verify that the product has been warmed up to room temperature for at least 60 minutes. Please ensure that your Human Factors/usability validation study collect the necessary data to demonstrate that users understand these two steps.
5. Ensure the product tested is identical to that intended to be marketed in every aspect.

### B. Patient Instructions for Use

1. Step 1, “Bring Sustol to room temperature” states that Sustol may be left out at room temperature overnight. Please specify the maximum amount of time Sustol can be left out at room temperature before it should be discarded.
2. Remove the negative statement (b) (4)  
[REDACTED] in Steps 2 and 3, under the “Inject Sustol” heading.

### C. Carton Labeling

1. Remove the negative statement (b) (4)  
[REDACTED] in Step 5.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications, please contact Phong (Pete) Do, OSE Project Manager, at 301-796-4795.

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TERESA S MCMILLAN  
03/21/2013

LUBNA A MERCHANT  
03/21/2013

MEMORANDUM

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

**DATE:** March 18, 2013

**SUBJECT:** CDRH/ODE/DAGID Human Factors Consult Interim Memo (February 25, 2013)

**APPLICATION/DRUG:** NDA 022445 Sustol (granisetron) injection, extended-release

Reference is made to the consult issued on October 15, 2013 from CDER/DGIEP to CDRH/ODE/DAGID (Dr. Quynh Nhu Nguyen) requesting assistance with review of the device component included in NDA 022445. Enclosed is CDRH/ODE/DAGID's interim review memo on the human factors validation report provided with the September 27, 2012 NDA resubmission.



DEPARTMENT OF HEALTH AND HUMAN SERVICES

MEMORANDUM

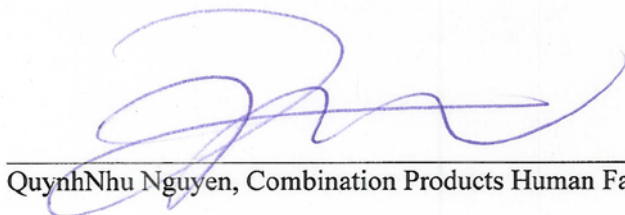
Food and Drug Administration  
Office of Device Evaluation  
10903 New Hampshire Avenue  
Silver Spring, MD 20993

DATE: February 25, 2013

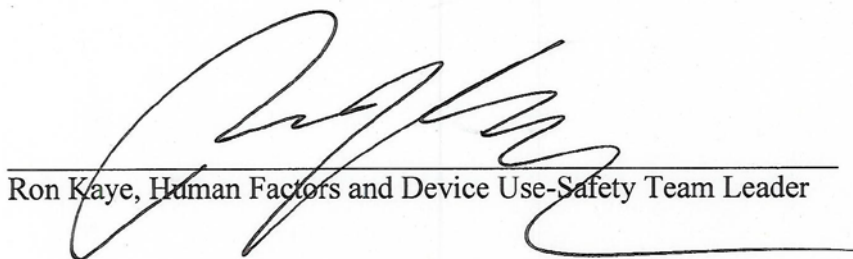
FROM: QuynhNhu Nguyen, Biomedical Engineer/Human Factors Reviewer, CDRH/ODE/DAGID  
THROUGH: Ron Kaye, Human Factors and Device Use-Safety Team Leader, CDRH/ODE/DAGID  
CC: Molly Story, Human Factors and Accessible Medical Technology Specialist, DAGID  
TO: Jagjit Grewal, Regulatory Project Manager, CDER/OND/ODEIII/DGIEP

SUBJECT: **NDA 22445**  
**Applicant: AP Pharma**  
**Device Constituent: Sustol Prefilled Syringe Injection**  
**Intended Treatment: cancer chemotherapy**

---

  
QuynhNhu Nguyen, Combination Products Human Factors Specialist

2/25/2013  
Date

  
Ron Kaye, Human Factors and Device Use-Safety Team Leader

2/25/2013  
Date

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## CDRH Human Factors Review

### ***Overview and Recommendations***

The Division of Gastroenterology and Inborn Error Products, Office of New Drugs, Center for Drugs Research and Evaluation, requested a Human Factors consultative review of a Human Factors validation study report submitted via NDA# 22445 by AP Pharma. This review provides CDRH's review and recommendations on the Human Factors related information contained in the NDA.

Since Sustol is a viscous drug product, and it is the first time it is delivered through a pre-filled syringe, CDRH and CDER have concerns associated with the force required to inject. While the Sponsor has modified the syringe components for use in the Human Factors validation study (b) (4)

(b) (4) As a result, on 2/13/2013, the review team expressed these concerns to the Sponsor, and requested that the Sponsor provide a proposal to address these concerns. On 2/18/2013, the Sponsor proposed various labeling modifications to the Instructions for Use, syringe label, and carton label (b) (4) information to the Instructions for Use. On 2/20/2013, the review team provided feedback to the Sponsor's proposal and recommended that the drug administration be performed by two individuals.

The data obtained from the Human Factors study suggested there are issues associated with safe and effective use of the product. The performance data indicated that incomplete injection of the drug product could occur. In addition, users reported difficulty in generating the required force to perform the injection, which could result in injecting the drug product in unintended area that lead to intended patient reaction and/or bleeding. As a result, CDRH Human Factors team recommends that additional modifications either in the product labeling and/or product design are necessary and additional human factors study should be conducted to demonstrate that the product modifications are effective in reducing/minimizing patient harm.

### ***Combination Product Device Information***

Submission Number: NDA 22445  
Applicant: AP Pharma  
Drug Constituent: Sustol (granisertron) subcutaneous  
Device Constituent: Prefilled Syringe  
Intended treatment: cancer chemotherapy

### ***CDRH Human Factors Involvement History***

- 10/15/2012: CDRH Human Factors team was requested to review AP Pharma's Human Factors validation study report
- 2/13/2013: CDRH HF team participated in a teleconference with CDER representatives and Sponsor representatives to discuss product administration concerns (force required to inject the drug product). The Sponsor indicated that they will develop proposals to address the concerns and submit to FDA for review and concurrence
- 2/20/2013: CDRH HF team participated in an internal meeting to discuss Sponsor's proposed response to address product administration concerns. The review team found that the proposal did not address the concerns.

### **Review Summary**

This application proposed marketing Sustol as a subcutaneous as a 10 mg subcutaneous injection in a (b) (4) glass syringe, co-packaged with the following items (b) (4)

. The drug product is a tri(ethylene glycol) poly(ortho ester) (TEG-POE) polymer-based formulation containing granisetron base and is designed to deliver the active pharmaceutical ingredient in an extended release manner). SUSTOL is an extended release formulation of granisetron that provides long-lasting antiemetic benefits to chemotherapy patients. SUSTOL is intended to be administered by an oncology nurse in inpatient and outpatient oncology settings. A.P. Pharma does not manufacture the syringe or needle. The components of the pre-filled syringe are sourced from third-party manufacturers. However, in selecting components for a suitable syringe for SUSTOL, A.P. Pharma considered features of syringe design and instructions that would mitigate known problems with similar products.



15 oncology nurses participated in the validation study without any training on the administration of Sustol. A patient mannequin in a seated position with an injection pad was used for the administrations. The study included all of the steps associated with the use of the product. Most of the steps are

considered essential (i.e. use errors/failures do not result in patient harm). There are three steps that are considered critical (i.e. use errors/failures can result in patient harm). Those steps are: (1) choosing administration route; (2) discarding used needle and syringe; (3) handling syringe to avoid needle stick injuries and possible infection. Since Sustol is a very viscous drug, FDA had requested in prior communication that warming to room temperature be evaluated during validation testing. Warming to at least 60 minutes prior to use can reduce the force required to inject. (b) (4)

The study results showed that in examining the completion of injection, three participants did not appear to have expelled all of the medication from the syringe and had one or two droplets remaining. The Sponsor provided additional response indicating that an independent observer visually inspected all of the syringes after injection, and of the 45 syringes (15 participants, 3 injections), 44 of the syringes were judged to have the plunger stopper flush with the bottom of the syringe barrel, and one syringe had two droplets remaining. In addition, some participants reported use difficulties during the study: one participant in unscrewing the tip cap from the end of the prefilled syringe; one participant in removing the hub cover from the needle; and two participants removing the white finger flange from the syringe prior to injecting. In addition, five participants indicated that on their first trial, the syringe was much harder to push than expected, and four other participants indicated that they were expecting the harder pressure because of the drug viscosity. In examining the warming of the syringe to room temperature, all 15 participants acknowledged the need for warming the syringe before use, and they rolled the syringe in the palm of their hands before injection.

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JAGJIT S GREWAL  
03/18/2013

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology  
Office of Medication Error Prevention and Risk Management**

**Label, Labeling, Packaging and Human Factors Study Review**

Date: January 30, 2013

Reviewer: Teresa McMillan, PharmD  
**Division of Medication Error Prevention and Analysis**

Team Leader: Lubna Merchant, PharmD, M.S.  
**Division of Medication Error Prevention and Analysis**

Deputy Director: Kellie Taylor, PharmD, MPH  
**Division of Medication Error Prevention & Analysis**

Drug Name(s): Sustol (Granisetron (b) (4) Injection

Strengths: 10 mg/0.4 mL

Application Type/Number: NDA 022445

Applicant/Sponsor: AP Pharma

OSE RCM #: 2012-2316

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## 1 INTRODUCTION

This review evaluates the proposed labels, labeling, product design and Human Factors Study for Sustol, NDA 022445 for areas of vulnerability that could lead to medication errors.

### 1.1 REGULATORY HISTORY

This NDA was previously reviewed by DMEPA in OSE Proprietary Name Review # 2009-1600, dated November 20, 2009, OSE Label and Labeling Review# 2009-1392, dated March 4, 2010, and OSE Product Design Review # 2009-1392, dated February 22, 2010. Our concerns regarding the medication error potential, due to the product design, were conveyed to the Division. These concerns were conveyed in the Complete Response letter dated March 2, 2010.

Subsequently, the Applicant revised the product design (b) (4)

[REDACTED] Additionally, the Applicant submitted a proposed Human Factors Validation Test Protocol and this was evaluated in OSE Label, Labeling, and Usability Study Reviews #2012-747, dated July 13, 2012 and May, 22, 2012.

On October 25, 2012, A.P. Pharma submitted a request to the Agency for an assessment of the proposed proprietary name, Sustol which is currently being evaluated in a separate review (OSE# 2012-2527). Additionally, the Applicant submitted the associated labels, labeling, and a Human Factors Study for the proposed product on October 25, 2012.

### 1.2 PRODUCT INFORMATION

The following product information is provided in the October 25, 2012 proprietary name submission.

- Active Ingredient: Granisetron
- Indication of Use: moderately-highly emetogenic cancer chemotherapy-prevention of acute (0-24 hr) and delayed(24-120 hr) nausea and vomiting associated with initial and repeat courses
- Route of Administration: Subcutaneous
- Dosage Form: Solution for Injection
- Strength: 10 mg/0.4 mL
- Dose and Frequency: 10 mg, 30 minutes prior to chemotherapy every 7 days
- How Supplied: A kit which contains a single-use pre-filled glass sterile syringe along with a dosing needle
- Storage: Refrigerated at 2°C to 8°C- may be removed form the refrigerator at least 60 minutes prior to use in order to ease administration and may be left at room temperature for up to 7 days. Protect from light.

## 2 METHODS AND MATERIALS REVIEWED

DMEPA searched the FDA Adverse Event Reporting System (FAERS) database for Granisetron medication error reports. We also reviewed the Granisetron labels and package insert labeling submitted by the Applicant.

### 2.1 SELECTION OF MEDICATION ERROR CASES

We searched the FDA Adverse Event Reporting System (FAERS) database using the strategy listed in Table 1. The date of our search was limited from our last search date of September 9, 2010 (OSE RCM # 2011-169)

| Table 1: FAERS Search Strategy |                                                                                                                                          |
|--------------------------------|------------------------------------------------------------------------------------------------------------------------------------------|
| Date                           | September 9, 2010 to January 3, 2013 (the search was limited to the date of our last search on September 9, 2010 in OSE RCM # 2010-1016) |
| Drug Names                     | *GRANISETRON*(active ingredient)                                                                                                         |
| MedDRA Search Strategy         | Medication Errors (HLGT)<br>Product Packaging Issues HLT<br>Product Label Issues HLT<br>Product Quality Issues (NEC) HLT                 |

The FAERS database search identified 5 cases, respectively. Each case was reviewed for relevancy and duplication. After individual review, all 5 cases were not included in the final analysis for the following reasons:

- Overdose unrelated to Granisetron
- Product quality issue or complaint with Sancuso (granisetron) adhesion
- Adverse Events unrelated to Granisetron

We also note that OSE Review #2010-1015 identified two (n=2) cases of medication error involving wrong route of administration of Kytril (granisetron). In one (n=1) case the patient received Kytril (granisetron) intramuscularly instead of intravenously. The second case involved a patient taking Kytril (granisetron) intravenous solution orally for undocumented reasons. No outcomes or root cause was reported for these cases. Additionally, there has been no other wrong route of administration cases reported.

### 2.2 LITERATURE SEARCH

We searched PubMed and the ISMP publications on January 3, 2012 for additional cases and actions concerning Granisetron. No additional cases were identified.

## **2.3 LABELS AND LABELING**

Using the principles of human factors and Failure Mode and Effects Analysis,<sup>1</sup> along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Syringe Labels submitted on October 25, 2012 (Appendix B)
- Carton Labeling submitted on October 25, 2012 (Appendix C)
- Insert Labeling submitted on October 25, 2012 (Appendix D Instructions for Use image, no image for PI)

## **2.4 PREVIOUSLY COMPLETED REVIEWS**

DMEPA had previously reviewed Sustol in OSE Proprietary Name Review # 2009-1600, dated November 20, 2009, OSE Label and Labeling Review# 2009-1392, dated March 4, 2010, and OSE Product Design Review # 2009-1392, dated February 22, 2010.

Additionally, we previously reviewed Kytril (Granisetron) on OSE Label and Labeling Review dated October 27, 2012. We looked at all previous reviews to ensure all our recommendation were implemented or considered for this review.

## **3 MEDICATION ERROR RISK ASSESSMENT**

The following sections describe our findings of the Sustol Human Factors Study and our risk assessment of the Sustol product design well as the associated label and labeling.

### **3.1 HUMAN FACTORS STUDY AND PRODUCT DESIGN RISK ASSESSMENT**

This Human Factors Study was conducted due to concerns with the viscosity of the product and its use in the (b) (4) container/closure system along with an 18-gauge needle attachment. This study consisted of 15 nurses who were given three trials to administer this product into an injection mannequin by using the proposed Instructions for Use. None of the participants received any training prior to administration.

The Applicant states that all participants successfully administered this product. However, 1 of the 15 participants failed to complete the first of three trial injections due to difficulty pushing the plunger which caused the participant to believe the drug was not being administered. This participant withdrew the syringe from the site of injection, inspected the syringe and then expelled the contents. Additionally, 3 of the 15 participants had one to two droplets of this product in the syringe after administration. It was also noted that 7 participants voiced concerns about the difficulty to push the plunger due to the viscosity of the product and regarding the needle size and how it may cause discomfort to the patient. This difficulty and discomfort may cause the healthcare professional administering this product and the patient to inadvertently move making it difficult to maintain the injection in the correct tissue plane. This risk could not have been evaluated in the simulated use study.

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<sup>1</sup> Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

We note that the proposed product must be warmed to room temperature prior to administration and therefore this task was also assessed during the study. Warming the proposed product prior to injection allows for a more comfortable injection and improves the flow of this viscous product. This task is critical because failure to do so can result in the need to place increase pressure on the syringe in order to administer the product. All participants acknowledged the need to warm the syringe prior to administration and all participants rolled the syringe in the palm of their hands for all injections. (b) (4)

However, we note that 11 participants rolled for less than 45 seconds. Three participants also indicated that the pharmacy would be responsible for making sure the product is at the required temperature. Although the Applicant has identified (b) (4) the room temperature requirement is prominently presented on the labels and labeling, this may not be sufficient to ensure the product is administered at room temperature.

In addition, the Applicant assessed the syringe for evidence of cracking or breaking which could result from the viscosity and increased pressure needed to administer this product. There was no evidence of any cracking or breakage noted to the syringe or its' components.

### **3.2 LABEL AND LABELING RISK ASSESMENT**

This product is the first extended-release subcutaneous injectable formulation of the currently marketed product Granisetron. We note that there are immediate-release oral (i.e. tablet and solution) and injectable (i.e. intravenous) formulations of Granisetron as well as a transdermal formulation of Granisetron. The oral formulations are administered once or twice daily 1 hour prior to chemotherapy and the injectable intravenous formulation is administered 30 minutes prior to chemotherapy. Additionally, the transdermal formulation can be administered at the same frequency of once every 7 days as the proposed product Sustol.

Even though we previously identified cases of wrong route of administration for Granisetron no new cases have been reported. Additionally, no wrong frequency of administration cases was identified amongst the currently marketed formulations of Granisetron. The Applicant has included the route of administration throughout the labels and labeling. However, this information can be more prominent to help further mitigate wrong route of administration errors. The Applicant also clearly identifies the frequency of administration in the Prescribing Information. However, this information is not present on the syringe labels and carton labeling. A "once weekly" statement should be added to the carton labeling and syringe labels to help minimize the risk of wrong frequency of administration errors amongst the Granisetron formulations.

## **4 CONCLUSIONS**

DMEPA concludes that the proposed label and labeling can be improved to increase the readability and prominence of important information on the label to promote the safe use of the product. Additionally, the Human Factors Study confirmed that users may encounter difficulties while administering this product due to the amount of pressure needed.

## 5 RECOMMENDATIONS

Based on this review, DMEPA recommends the following be implemented prior to approval of this NDA supplement:

### 5.1 COMMENTS TO THE DIVISION

#### A. General Comment

We have concerns regarding the potential difficulty in administration of this product. We note that the Applicant has adequately identified that this product is viscous and should be administered by a slow and sustained injection in the Prescribing Information and the Instructions For Use. However, participants in the Human Factors Study commented on the difficulty to push the plunger due to the viscosity of the product. They also raised concerns about attempting a subcutaneous injection with an 18-gauge needle and how it may cause discomfort to the patient. We are also concerned that due to the amount of force needed to administer this product and the discomfort it may cause, both the healthcare professional and the patient may inadvertently move during administration making it difficult to maintain the injection in the correct tissue plane. Because the HF study was a simulated study, the study was unable to evaluate whether these aspects would likely result in error during actual use. We recommend the Division consider these concerns in their evaluation of this NDA.

#### B. Prescribing Information

A. The Dosage and Administration sections in the Highlights and Full Prescribing Information do not include the 10 mg/0.4 mL strength.

1. Revise the Dosage and Administration section in the Highlights of the Prescribing Information to state the following:

A 10 mg/0.4 mL single subcutaneous injection administered in the abdomen, approximately 30 minutes before the start of chemotherapy.

2. Revise the Dosage and Administration section in the Full Prescribing Information to state the following:

The recommended dose of Sustol is a 10 mg/0.4 mL single subcutaneous injection administered in the abdomen, approximately 30 minutes before the initiation of chemotherapy.

B. The How Supplied/Storage and Handling Section do not include the granisetron dose in mg per mL.

Revised the How Supplied/Storage and Handling Section to state the following:

Sustol is provided as a kit consisting of a single-use, pre-filled, sterile syringe, containing 10 mg of granisetron per 0.4 mL, along with a 18 gauge X 5/8" dosing needle. Do not substitute any components.

C. Instructions For Use and Prescribing Information

Revise all instances of the abbreviations "SC", and "IV" throughout the Prescribing Information and the Instructions for Use. Revise to state subcutaneously, and intravenously respectively<sup>2</sup>. The abbreviation "SC" can be misinterpreted as SL or sublingual. The abbreviation IV can also be interpreted as "four", "ill" or "intravertebral". As part of a national campaign to prevent the use of error-prone abbreviations, FDA agreed not to approve error-prone abbreviations in labeling because they are carried to the prescribing practice.

**5.2 COMMENTS TO THE APPLICANT**

A. Syringe Label and Carton Labeling

1. The proprietary and established names and the strength should be presented as the following:

Sustol (granisetron (b) (4) Injection

10 mg/0.4 mL

2. Add a "Once weekly" statement to the principal display panel to denote the frequency of administration for this extended-release formulation of granisetron.

B. Carton Labeling

1. Increase the prominence of the following statement:

For Subcutaneous Use (b) (4)

2. Relocate the statement (b) (4) to appear in the white space above the (b) (4) statement on the principal display panel and increase the prominence of this statement.

3. Relocate the statement "DO NOT substitute any components" to appear in the blue space above the (b) (4) statement on the principal display panel and increase the prominence of this statement.

If you have further questions or need clarifications, please contact Phong (Pete) Do, OSE Project Manager, at 301-796-4795.

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<sup>2</sup> Institute for Safe Medication Practices, "List of Error-Prone Abbreviations, Symbols, and Dose Designations. [www.ismp.org](http://www.ismp.org)

## **APPENDICES**

### **APPENDIX A. DATABASE DESCRIPTIONS**

#### **FDA Adverse Event Reporting System (FAERS)**

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FDA implemented FAERS on September 10, 2012, and migrated all the data from the previous reporting system (AERS) to FAERS. Differences may exist when comparing case counts in AERS and FAERS. FDA validated and recoded product information as the AERS reports were migrated to FAERS. In addition, FDA implemented new search functionality based on the date FDA initially received the case to more accurately portray the follow up cases that have multiple receive dates.

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

8 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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TERESA S MCMILLAN  
01/30/2013

LUBNA A MERCHANT  
01/30/2013

KELLIE A TAYLOR  
01/30/2013

MEMORANDUM

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

**DATE:** March 18, 2013

**SUBJECT:** CDRH/ODE/OC Review Recommendation (January 9, 2013)

**APPLICATION/DRUG:** NDA 022445 Sustol (granisetron) injection, extended release

Reference is made to the October 23, 2012 consult request from CDER/DGIEP to CDRH/ODE/OC requesting assistance with facility inspections for the device component included with NDA 022445. Enclosed is CDRH/ODE/OC's consult evaluation dated January 9, 2013.

## DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service  
Food and Drug Administration  
Center for Devices and Radiological Health  
Office of Compliance, Division of Enforcement A  
General Hospital Devices Branch

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**DATE:** January 9, 2013

**TO:** Jagjit Grewal, Division of Gastroenterology Products, Office of Drug Evaluation III, Office of New Drugs, Center for Drug Evaluation and Research Division of Gastroenterology Products, WO22, Room 5109

**Cc:** Office of combination products at [combination@fda.gov](mailto:combination@fda.gov)

**THRU:** Carl Fischer, PhD., Chief, General Hospital Devices Branch, Division of Enforcement A, Office of Compliance, CDRH, WO-66, Room 3526  CF 1-9-13

**FROM:** Felicia L. Brayboy, General Hospital Devices Branch, Division of Enforcement A, Office of Compliance, CDRH, WO-66, Room 3453

**SUBJECT:** Inter-Center consult requested by CDER/OND for NDA re-submission 022445

**CONSULT INSTRUCTIONS:** DGIEP requests CDRH/OC assistance with facility inspections for the device component of this application.

---

### Objective

The Office of Compliance at CDRH received a consult request from CDER/DGIEP requesting CDRH/OC assistance with facility inspections for the device component associated with this application.

### Product Description

The product is: Sustol (granisetron) Injection, 10 mg/0.4 mL.

The intended use is:

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 of chemotherapy.

AP Pharma provided their NDA re-submission in response to the March 16, 2010 Complete Response letter. In their NDA re-submission, the sponsor indicates that they have changed the presentation of the product to a single, pre-filled 1.0 mL (b) (4) Long Barrel Syringe and an 18-gauge 5/8" (b) (4) needle.

### Consult Evaluation

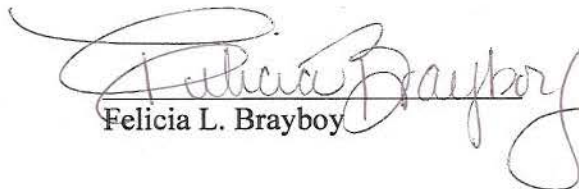
CDRH Office of Compliance has reviewed the list of manufacturing and testing sites.

Syringe filling (b) (4), packaging, and filling will take place at (b) (4). This facility had a medical device inspection in (b) (4) and was classified No Action Indicated (NAI).

Terminal sterilization (final drug product) will take place at (b) (4). The (b) (4) location had a medical device inspection in (b) (4) that was classified NAI (the (b) (4) inspection was also classified NAI). The (b) (4) location had a medical device inspection in (b) (4) and was classified NAI (the (b) (4) inspection was also classified NAI).

### CDRH Recommendation

Upon review of the available documentation, CDRH concludes that satisfactory inspections have been conducted at the above-mentioned facilities. CDRH will concur with CDER's decision regarding NDA re-submission 022445 approval.

  
Felicia L. Brayboy

Prepared/typed: FBrayboy 01/09/13  
Reviewed/approved: ~~DOE~~ For CF 1/9/13  
Finalized:

cc:  
WO66-3515 (DOE-A Firm File)  
WO66-3515 (Division Chron File)  
WO66-3453 (FBrayboy, Reviewer)

CTS No.: ICC1200202

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/s/  
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JAGJIT S GREWAL  
03/18/2013

**Interdisciplinary Review Team for QT Studies Consultation:  
Thorough QT Study Review**

|                                    |                                                         |
|------------------------------------|---------------------------------------------------------|
| <b>NDA</b>                         | 22445                                                   |
| <b>Brand Name</b>                  | Sustol                                                  |
| <b>Generic Name</b>                | Granisetron                                             |
| <b>Sponsor</b>                     | A.P. Pharma Inc.                                        |
| <b>Indication</b>                  | Chemotherapy-Induced Nausea and Vomiting (CINV)         |
| <b>Dosage Form</b>                 | Injection, extended release                             |
| <b>Granisetron Class</b>           | 5-hydroxytryptamine type 3 (5-HT3) receptor antagonists |
| <b>Therapeutic Dosing Regimen</b>  | 10 mg                                                   |
| <b>Duration of Therapeutic Use</b> | Acute                                                   |
| <b>Maximum Tolerated Dose</b>      | unknown                                                 |
| <b>Submission Number and Date</b>  | SDN 037 / Resubmission, 27 Sep 2012                     |
| <b>Review Division</b>             | DGIEP                                                   |

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

## **1 SUMMARY**

### **1.1 OVERALL SUMMARY OF FINDINGS**

No significant QTc prolongation effect of APF530 or granisetron was detected in this TQT study. The largest upper bounds of the 2-sided 90% CI for the mean difference between APF530 or granisetron and placebo were below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines. The largest lower bound of the two-sided 90% CI for the  $\Delta\Delta\text{QTcF}$  for moxifloxacin was greater than 5 ms, and the moxifloxacin profile over time is adequately demonstrated in Figure 7, indicating that assay sensitivity was established.

In this randomized, blinded, four-period crossover study, 56 healthy subjects received APF530, granisetron, placebo, and a single dose of moxifloxacin 400 mg. The overall summary of findings is presented in Table 1.

**Table 1: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for APF530 and Granisetron and the Largest Lower Bound for Moxifloxacin (FDA Analysis)**

| Treatment            | Time | $\Delta\Delta QTcF$ (ms) | 90% CI (ms) |
|----------------------|------|--------------------------|-------------|
| APF530               | 3    | 3.5                      | (0.8, 6.1)  |
| Granisetron          | 48   | 2.4                      | (-0.6, 5.4) |
| Moxifloxacin 400 mg* | 2    | 11.3                     | (8.9, 13.7) |
| Moxifloxacin 400 mg* | 3    | 11.6                     | (8.9, 14.2) |

- Multiple endpoint adjustment was not applied. The largest lower bounds after Bonferroni adjustment for 4 timepoints are 14.6 and 15.2 ms.

One g of APF530 in healthy volunteers produced comparable  $C_{max}$  to the anticipated  $C_{max}$  following the therapeutic dose of 500 mg in cancer patients. At these concentrations there are no detectable prolongations of the QT-interval. No intrinsic/extrinsic factors have been identified to affect pharmacokinetics of granisetron significantly.

## **2 PROPOSED LABEL**

### **2.1 SPONSOR'S PROPOSED LABEL**

#### **12.2 Pharmacodynamics**

The effect of granisetron extended release on QTc prolongation was evaluated in a double-blind, randomized, four-way crossover, placebo and positive (moxifloxacin) controlled study in 51 adult men and women.

(b) (4)

(b) (4)

#### **2.2 QT-IRT PROPOSAL**

*We defer final label language to the Division. Below is our recommendation.*

##### **12.6 Cardiac Electrophysiology**

At a concentration comparable to  $C_{\max}$  of the maximum recommended dose, granisetron does not prolong QTc to any clinically relevant extent.

### **3 BACKGROUND**

#### **3.1 PRODUCT INFORMATION**

Graisetron is a 5HT3 receptor antagonist approved to treat or prevent nausea and vomiting.

#### **3.2 MARKET APPROVAL STATUS**

Granisetron is approved as oral tablets, as oral solution, and as intravenous solution.

#### **3.3 PRECLINICAL INFORMATION**

A hERG assay or similar study is not described in the sponsor's protocol for the QT study.

#### **3.4 PREVIOUS CLINICAL EXPERIENCE**

Over 1000 subjects have received relevant doses of granisetron in clinical studies. Cardiovascular adverse events have been rare.

#### **3.5 CLINICAL PHARMACOLOGY**

Appendix 6.1 summarizes the key features of APF530's clinical pharmacology.

### **4 SPONSOR'S SUBMISSION**

#### **4.1 OVERVIEW**

The QT-IRT reviewed the protocol prior to conducting this study under IND 68213. The sponsor submitted the study report C2011-01 for granisetron, including electronic datasets and waveforms to the ECG warehouse.

#### **4.2 TQT STUDY**

##### **4.2.1 Title**

"A Randomized, Placebo-Controlled, Four-Period Crossover, Definitive QT Study of the Effects of APF530 Exposure, High-Dose IV Granisetron, and Moxifloxacin on QTc Prolongation"

##### **4.2.2 Protocol Number**

C2011-01

##### **4.2.3 Study Dates**

15 July 2011 - 07 October 2011

##### **4.2.4 Objectives**

This study had two primary objectives:

1. To evaluate the effect of APF530, 1 g (20 mg granisetron) given SC in normal volunteers on the placebo-subtracted change of QTc by Fridericia method (QTcF) from Baseline over 48 hours
2. To achieve a mean Cmax of granisetron and AUC exposure in normal volunteers equivalent to that achieved by APF530 500 mg (10 mg granisetron) given SC in patients

The secondary objectives were the following:

1. To evaluate the effect of APF530 compared with placebo on the QTc by Bazett's formula (QTcB), heart rate, PR interval, QRS interval, uncorrected QT interval, change in ST and T-wave morphology, and categorical change in QTc variables
2. To evaluate the effect of a high plasma concentration on QTcF, QTcB, PR interval, QRS interval, uncorrected QT interval, change in ST and T-wave morphology, and categorical change in QTc variables
3. To evaluate the correlation between the QTcF change from Baseline with plasma concentration, if mean change in QTcF is statistically significant at any time point
4. In a fashion identical to the primary objective, to evaluate the effect of high-dose IV granisetron on primary and secondary endpoints
5. To evaluate assay sensitivity (oral moxifloxacin was used as an active control)
6. To gather SC administration site reaction data

*Source: Sponsor's study report, pages 23-24.*

## **4.2.5 Study Description**

### **4.2.5.1 Design**

"This was a Phase 1, single-site, double-blind, randomized, 4-way crossover study in 56 healthy male and female subjects. Subjects received the following 4 treatments in random order: APF530 (SC), granisetron (IV), moxifloxacin (oral), and placebo (SC, IV, or oral). The central ECG laboratory was blinded to treatment."

*Source: Sponsor's study report, page 24.*

### **4.2.5.2 Controls**

The Sponsor used both placebo and positive (moxifloxacin) controls.

### **4.2.5.3 Blinding**

All treatment arms were administered blinded using a double dummy approach. Moxifloxacin tablets were overencapsulated.

## **4.2.6 Treatment Regimen**

### **4.2.6.1 Treatment Arms**

This study had four treatment arms.

- A. The primary active regimen (administered at time 0) consisted of APF530, 1 g (20 mg granisetron) administered as SC abdominal injections (0.84 mL in 2 injections [~1 inch apart] of 0.42 mL each), placebo (0.9% normal saline) administered as

- an IV infusion (total of 10 mL infused over 3 minutes), and a moxifloxacin placebo capsule administered orally.
- B. The secondary active regimen (administered at time 0) consisted of granisetron 50 µg/kg in 0.9% normal saline administered as an IV infusion (total of 10 mL infused over 3 minutes), placebo (0.9% normal saline) administered as SC abdominal injections (0.84 mL in 2 injections [~1 inch apart] of 0.42 mL each), and a moxifloxacin placebo capsule administered orally.
  - C. The placebo control regimen (administered at time 0) consisted of placebo (0.9% normal saline) administered as SC abdominal injections (0.84 mL in 2 injections [~1 inch apart] of 0.42 mL each), placebo (0.9% normal saline) administered as an IV infusion (total of 10 mL infused over 3 minutes), and a moxifloxacin placebo capsule administered orally.
  - D. The positive control regimen (administered at time 0) consisted of moxifloxacin (Avelox) administered orally as an overencapsulated 400 mg tablet (identical in appearance to the placebo capsule), placebo (0.9% normal saline) administered as an IV infusion (total of 10 mL infused over 3 minutes), and placebo (0.9% normal saline) administered as SC abdominal injections (0.84 mL in 2 injections [~1 inch apart] of 0.42 mL each).

Source: Sponsor's study report, page 31.

Subjects were randomized using a Williams Latin square design, balanced for first-order carryover effects.

**Table 2: Sponsor's Williams Latin Square**

| Treatment Sequence | Period 1 Treatment | Period 2 Treatment | Period 3 Treatment | Period 4 Treatment |
|--------------------|--------------------|--------------------|--------------------|--------------------|
| 1                  | A                  | B                  | D                  | C                  |
| 2                  | B                  | C                  | A                  | D                  |
| 3                  | C                  | D                  | B                  | A                  |
| 4                  | D                  | A                  | C                  | B                  |

Treatments: A = APF530 (granisetron; subcutaneous); B = granisetron hydrochloride (intravenous); C = placebo (subcutaneous, intravenous, or oral); D = moxifloxacin (oral)

Source: Sponsor's study report, page 33.

#### 4.2.6.2 Sponsor's Justification for Doses

The mean C<sub>max</sub> from 6 male healthy volunteers following 1 g of APF530 in a Phase 1 study was found to be 18.1 ng/mL and the mean C<sub>max</sub> in cancer patients following 500 mg APF530 in three studies was found to be 17.8 ng/mL. The sponsor expects double exposure of APF530 in patients compared to healthy volunteers based these observations and chose 1 g of APF530 in the current study which is the largest dose tested in humans and the double the proposed therapeutic dose.

The dose of IV granisetron was selected to achieve a mean plasma concentration of granisetron 4-fold the mean concentration of approximately 18 ng/mL observed in

patients receiving the clinical dose of 500 mg APF530 (10 mg of granisetron). Based on the PK profile studied in healthy volunteers given a single 40- $\mu$ g/kg dose of granisetron by 3-minute IV infusion [Allen et al, 1992; Allen et al, 1995; Kytril injection package insert, 2011] and the fact that the plasma concentration of granisetron after IV infusion is dose proportional [Allen et al, 1994; Zussman et al, 1987], the selected dose of 50  $\mu$ g/kg of granisetron by 3-minute IV infusion was chosen for this study.

*Reviewer's Comment: The  $C_{max}$  observed following the therapeutic dose in cancer patients (500 mg s.c.) in a previous study was 17.8 ng/mL. We think this  $C_{max}$  is likely to be underestimated because of the sparse sampling scheme (no PK samples between 6 and 24 hours post-dose). The 1-g s.c dose in healthy volunteers in this study was intended to generate similar exposure to that of the proposed therapeutic dose in cancer patients (500 mg). The 50- $\mu$ g/kg i.v. dose was intended to generate exposure 4-fold that of the proposed therapeutic dose in cancer patients (500 mg). However, the results of this study showed that both doses achieved  $C_{max}$  values ( $\sim$  35 ng/ml). We cannot say that this  $C_{max}$  is 2-fold that of the therapeutic dose because of the underestimation of the previously reported  $C_{max}$ . But by visual inspection of the concentration profile in the previously reported study, we can conclude the  $C_{max}$  of the therapeutic dose in cancer patients will not exceed the  $C_{max}$  observed from this QT study.*

*According to the summary of clinical pharmacology, no intrinsic/extrinsic factors have been identified to affect pharmacokinetics of granisetron significantly.*

#### **4.2.6.3 Instructions with Regard to Meals**

Subjects were confined to the clinical unit on the day of Check-in and during treatment days for each of the 4 treatments for a total of 12 days of confinement. Subjects received a menu for the dosing period to include 3 meals and an evening snack containing approximately 30% to 40% fat.

Based upon a 7:30 AM dosing time, breakfast started approximately 2 hours after dosing, lunch was served approximately 6 hours after the start of dosing, dinner was served approximately 10 hours after the start of dosing, and, if needed, a light snack was served 13.5 hours after the start of dosing. Subjects were allowed to consume water ad libitum throughout the study. All meal times and meal content were standardized to Baseline as appropriate.

*Reviewer's Comment: The effect of food on the pharmacokinetics of APF530 is not available. Since the route of administration of APF530 is subcutaneous, significant effect of food is not anticipated.*

#### **4.2.6.4 ECG and PK Assessments**

The ECGs were obtained digitally using a Mortara X12+ ECG continuous 12-lead digital recorder. Three 12-lead ECGs were captured approximately 1 minute apart (providing 3 ECGs for each time point). A window of  $\pm$ 3 minutes around each time point was utilized to capture ECGs of adequate quality. The ECG sampling time points were as follows:

- Days 1, 11, 21, and 31: before dosing and 5 minutes, 30 minutes, 1, 2, 3, 4, 10, 11, 12, 23, 24, and 25 hours after dosing
- Days 2, 12, 22, and 32: 47, 48, and 49 hours after dosing

*Reviewer's Comment: From previous studies,  $T_{max}$  of granisetron following 250 and 500 mg of APF530 in cancer patients was found to be approximately 23 hours post-dose. Considering that PK samples were collected less intensively in those studies (6-hour interval between 6 to 24 hours post-dose), the previously reported values might not be accurate. The PK sampling in the thorough QT study occurred more intensively than that in previous PK studies, which resulted in estimation of higher  $C_{max}$  and shorter  $T_{max}$  compared with the previously reported values. The median  $T_{max}$  observed in the TQT study was 11.1 hours post-dose and the ECG measurements were obtained around  $T_{max}$ . The ECG measurements seem to be sufficient to characterize potential QT/QTc prolongation in both absorption phase and the elimination phase of granisetron following subcutaneous injection of APF530.*

#### **4.2.6.5 Baseline**

The sponsor used a pre-dose, within-day baseline.

#### **4.2.7 ECG Collection**

Intensive 12-Lead Holter monitoring will be used to obtain digital ECGs. Subjects were to be supine and quiet around the nominal sampling times.

#### **4.2.8 Sponsor's Results**

##### **4.2.8.1 Study Subjects**

Fifty-six subjects enrolled and 51 completed all crossover phases.

##### **4.2.8.2 Statistical Analyses**

###### **4.2.8.2.1 Primary Analysis**

The primary statistical hypotheses were:

- $H_0: \{\mu_{\text{drug}}(i) - \mu_{\text{placebo}}(i) \geq 10, \text{ for at least one } i, i = \text{all after dose time points}\}$
- $H_1: \{\mu_{\text{drug}}(i) - \mu_{\text{placebo}}(i) < 10, \text{ for all } i, i = \text{all after dose time points}\}$

where "i" represented the post-treatment hours on Days 1, 2, 11, 12, 21, 22, 31, and 32, and where  $\mu_{\text{drug}}(i)$  and  $\mu_{\text{placebo}}(i)$  were the mean change from predose of QTcF for APF530 and placebo at ECG assessment time point (i), respectively.

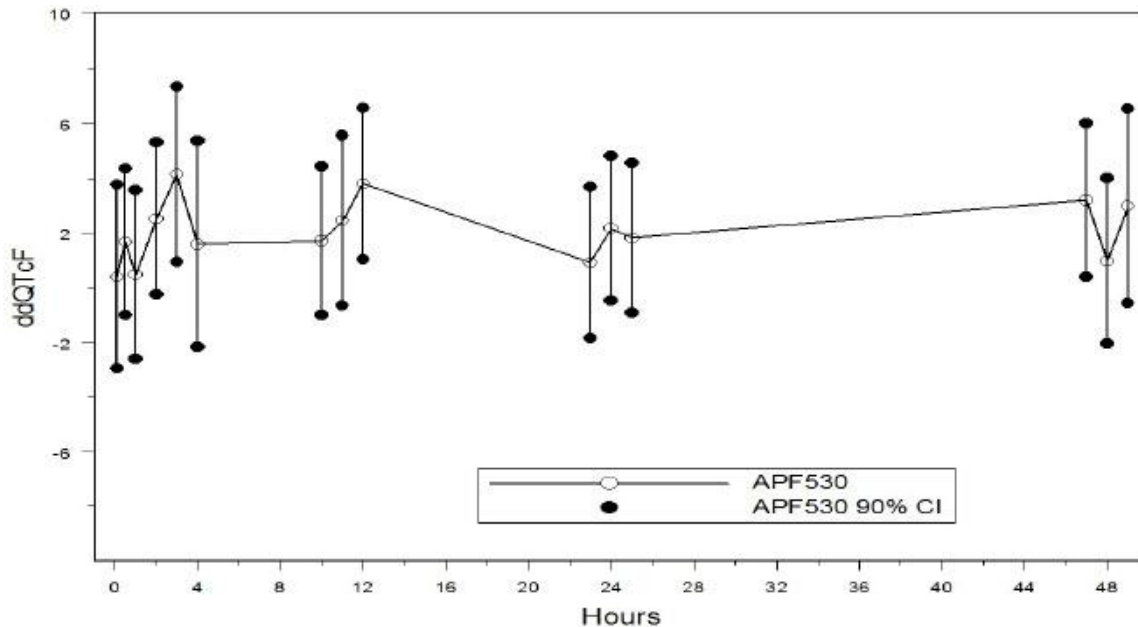
To investigate potential QTc interval prolongation associated with APF530, the primary endpoint was the difference between dQTcF for the groups receiving APF530 and placebo (i.e., ddQTcF). A mixed-effects model was used to evaluate the primary endpoint and included terms for dose sequence, subjects within sequence, study drug (APF530 or placebo), study period, postdose ECG assessment time point, study drug by postdose ECG time point interaction, and study period by postdose ECG time point interaction. An unstructured covariance structure was used for the model and the mean and upper 95% 1-sided CI of the baseline-adjusted difference (i.e., ddQTcF) between

QTcF for the APF530 and placebo groups was used to make the primary statistical comparison.

Source: Sponsor's study report, page 48.

The sponsor's results do not indicate an elongation in QT intervals. No upper bound of the 95% 1-sided CI's were above 10 ms.

**Figure 1: Sponsor's Timecourse for APF530**



Source: Sponsor's study report, page 57.

These results agree with our independent analysis. See section 5.2.

#### 4.2.8.2.2 Assay Sensitivity

The statistical hypotheses to evaluate assay sensitivity were:

H0:  $\{\mu_{\text{moxi}}(i) - \mu_{\text{placebo}}(i) \leq 5, \text{ for all } i, i = 1, 2, 3, 4$

H1:  $\{\mu_{\text{moxi}}(i) - \mu_{\text{placebo}}(i) > 5, \text{ for all } i, i = 1, 2, 3, 4$

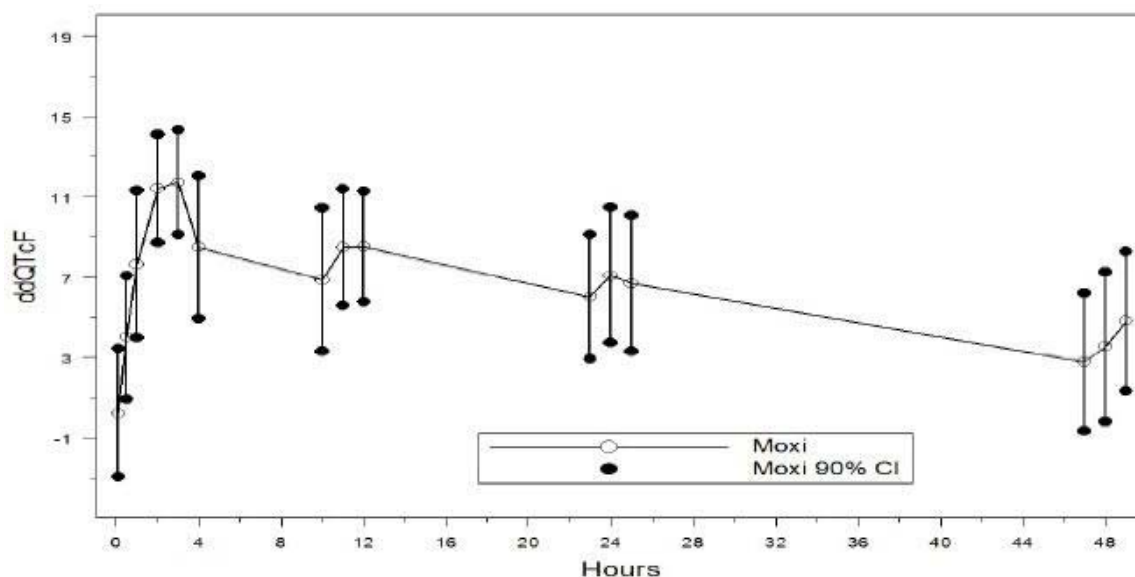
where "i" represented 1, 2, 3, and 4 hours after dosing, and where  $\mu_{\text{moxi}}(i)$  and  $\mu_{\text{placebo}}(i)$  were the mean change from predose of QTcF for moxifloxacin and placebo at ECG assessment time point (i), respectively.

The same mixed-effects model described previously was used to simultaneously determine the predicted mean difference (ddQTcF) across all subjects between dQTcF for moxifloxacin minus dQTcF for placebo and the associated lower 95% 1-sided CI. The assay sensitivity of the study was validated if the lower 95% 1-sided CI for ddQTcF (moxifloxacin - placebo) was greater than 5 ms for the mean time-matched baseline-adjusted difference for at least 1 time point after dosing for 1, 2, 3, or 4 hours.

Source: Sponsor's study report, page 49.

The sponsor's moxifloxacin timecourse followed the expected shape, and the largest lower bound of the 95% 1-sided CI was greater than 5 ms.

**Figure 2: Sponsor's Timecourse for Moxifloxacin**



Source: Sponsor's study report, page 60.

These results agree with our independent analysis. See section 5.2.

#### 4.2.8.3 Safety Analysis

No cardiovascular adverse events were reported.

#### 4.2.8.4 Clinical Pharmacology

##### 4.2.8.4.1 Pharmacokinetic Analysis

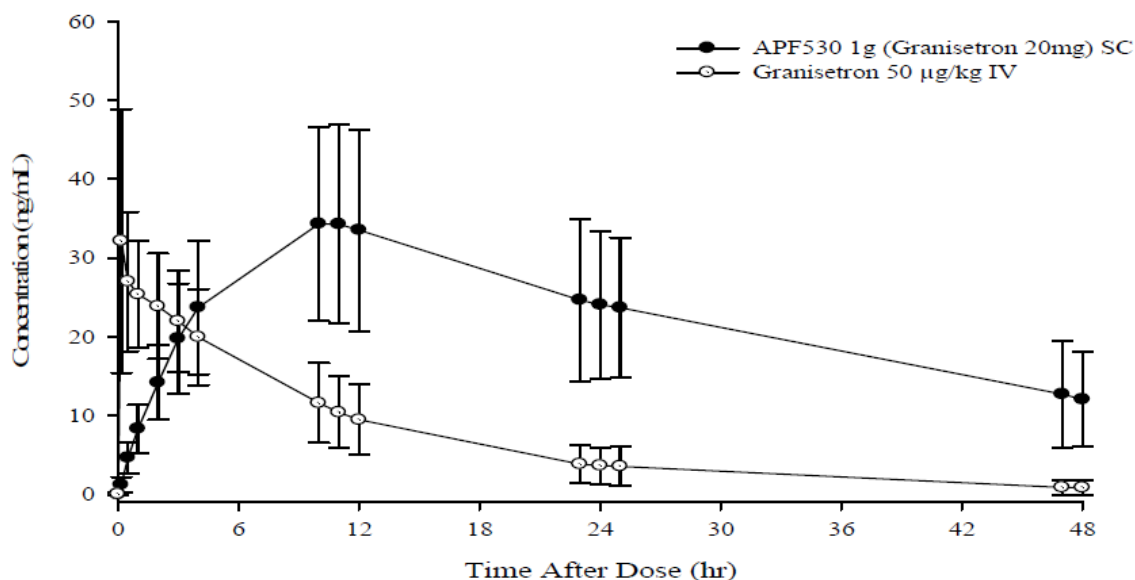
The PK results are presented in Figure 3 (APF530 SC and granisetron IV), Figure 4 (moxifloxacin PO), and Table 3 (all study drugs).  $C_{max}$  and AUC values in the thorough QT study were approximately 2-fold higher following administration of 1 g APF530 compared with 500 mg APF530, the intended clinical dose.

**Table 3. Summary of Pharmacokinetic Parameters**

| PK Parameter                    |        | APF530<br>SC 1 g | Granisetron IV<br>50µg/kg | Moxifloxacin<br>PO 400 mg |
|---------------------------------|--------|------------------|---------------------------|---------------------------|
| AUC <sub>0-inf</sub> (ng*hr/mL) | N      | 30               | 49                        | 49                        |
|                                 | Mean   | 1254             | 353                       | 31528                     |
|                                 | SD     | 578              | 153                       | 6321                      |
| C <sub>max</sub> (ng/mL)        | N      | 56               | 52                        | 53                        |
|                                 | Mean   | 35.8             | 34.6                      | 2123                      |
|                                 | SD     | 13.3             | 15.3                      | 502                       |
| T <sub>max</sub> (hr)           | N      | 56               | 52                        | 53                        |
|                                 | Median | 11.1             | 0.183                     | 2.08                      |
|                                 | Range  | 4.08-23.1        | 0.167-4.15                | 0.583-4.08                |
| T <sub>1/2</sub> (hr)           | N      | 31               | 49                        | 49                        |
|                                 | Mean   | 18.6             | 9.69                      | 13.8                      |
|                                 | SD     | 4.02             | 3.53                      | 1.65                      |

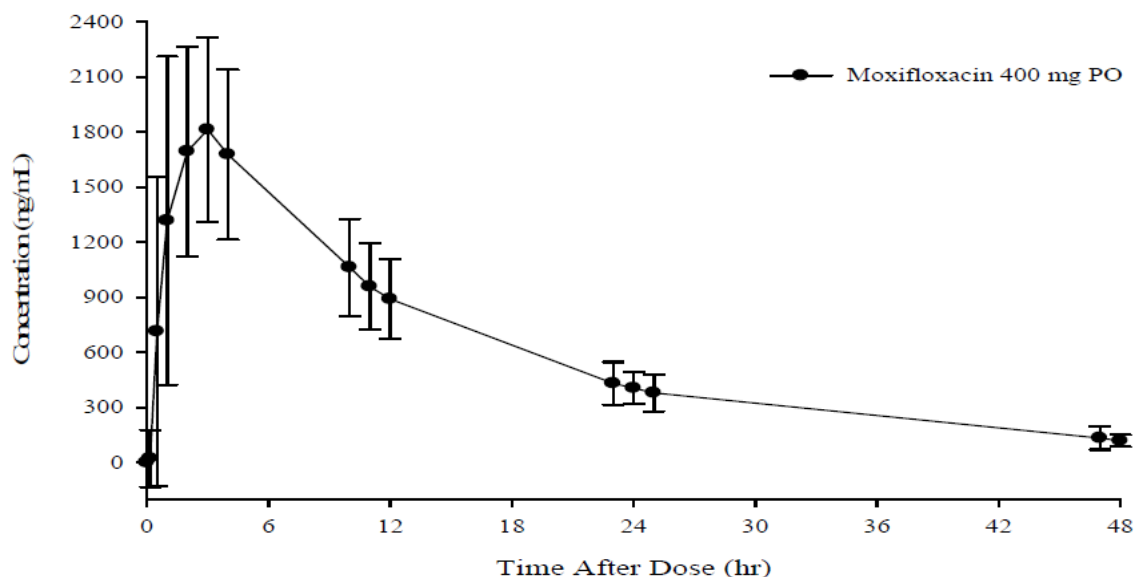
Source: Sponsor's study report, page 66

**Figure 3. Mean (±SD) Plasma Concentrations of Granisetron following APF530 1 g SC and Granisetron 50 µg/kg IV**



Source: Sponsor's study report, page 62

**Figure 4. Mean ( $\pm$ SD) Plasma Concentrations of Moxifloxacin following 400 mg Moxifloxacin PO**



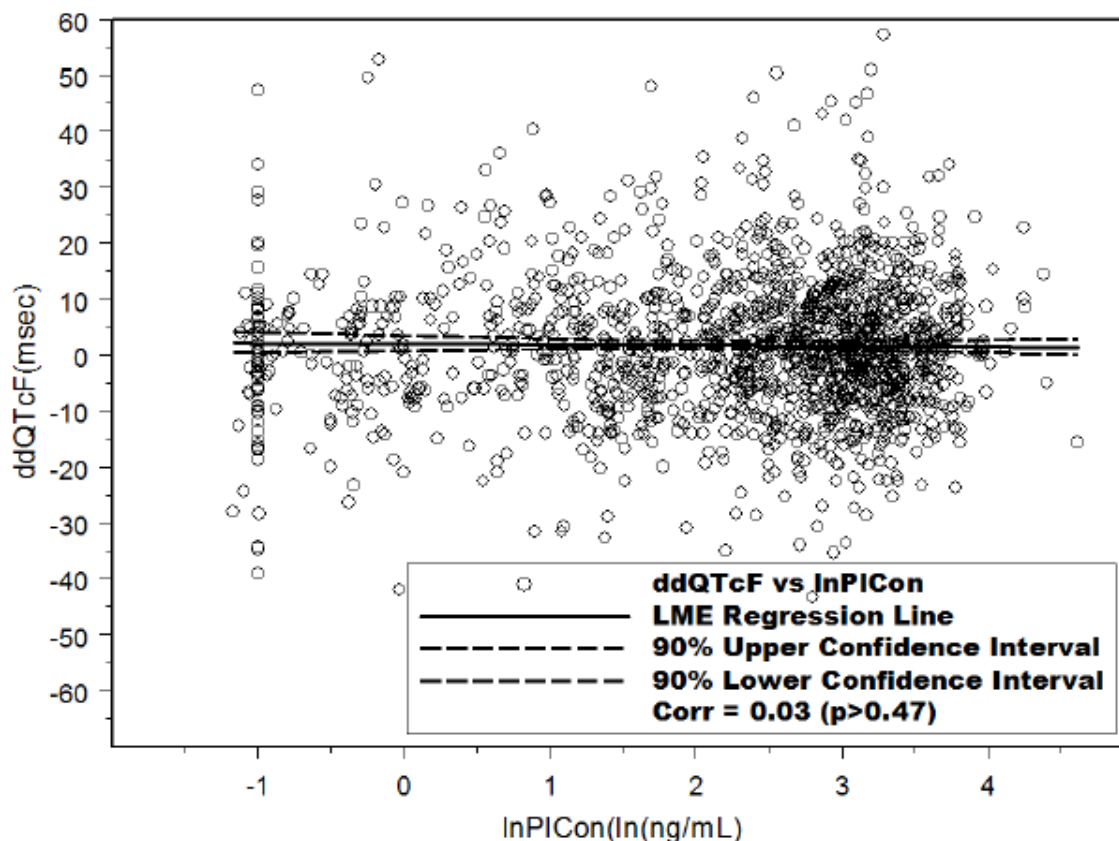
Source: Sponsor's study report, page 63

#### 4.2.8.4.2 Exposure-Response Analysis

The correlation between  $\Delta\Delta$ QTcF and natural log (ln) plasma concentrations of granisetron was low ( $R=0.03$ ) and the slope of the relationship was nearly flat. The relationship between  $\Delta\Delta$ QTcF and plasma concentration of granisetron was not statistically significant.  $\Delta\Delta$ QTcF rose anomalously immediately before subjects were discharged. Because of this, the ECG/PK model was repeated excluding Hours 47 through 49. Using a linear mixed-effects model, this analysis yielded a slightly positive slope (0.2910); however, the slope was nearly flat, statistically insignificant, and the correlation coefficient was small.

The scatterplots of overall  $\Delta\Delta$ QTcF versus natural log granisetron concentrations are shown in Figure 5.

**Figure 5.  $\Delta\Delta\text{QTcF}$  versus Natural Log of Granisetron Concentrations**



Source: Sponsor's study report, page 68

Reviewer's Analysis: A plot of  $\Delta\Delta\text{QTc}$  vs. granisetron concentrations is presented in Figure 8.

## 5 REVIEWERS' ASSESSMENT

### 5.1 EVALUATION OF THE QT/RR CORRECTION METHOD

We evaluated the appropriateness of the correction methods (QTcF and QTcB). Baseline values were excluded in the validation. Ideally, a good correction QTc would result in no relationship of QTc and RR intervals.

We used the mixed model of the pooled post-dose data of QTcF and QTcB distinguished by an indicator of correction method to evaluate the linear relationships between different correction methods and RR. The model included RR, correction type (QTcF or QTcB), and the interaction term of RR and correction type. The slopes of QTcF and QTcB versus RR are compared in magnitude as well as statistical significance in difference. As shown in Table 4, it appears that QTcF had smaller absolute slopes than QTcB. Therefore, QTcF is a better correction method for the study data.

**Table 4: Comparison of QTcB and QTcF Using the Mixed Model**

| Treatment Groups    | Slope of QTcB | Slope of QTcF | P-value |
|---------------------|---------------|---------------|---------|
| APF530              | -0.0568       | 0.0102        | 0.0000  |
| Granisetron         | -0.0570       | 0.0090        | 0.0000  |
| Moxifloxacin 400 mg | -0.0637       | 0.0056        | 0.0000  |
| Placebo             | -0.0596       | 0.0084        | 0.0000  |
| All                 | -0.0619       | 0.0056        | 0.0000  |

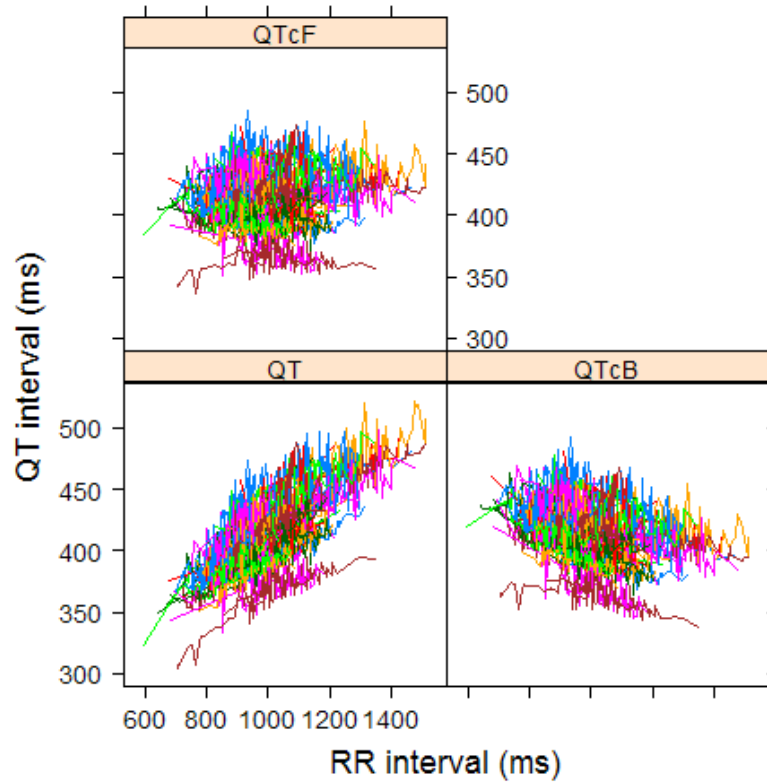
We also confirmed this conclusion by using the criterion of Mean Sum of Squared Slopes (MSSS) from individual regressions of QTc versus RR. The smaller this value is, the better the correction. Based on the results listed in Table 5, it also appears that QTcF is the best correction method. Therefore, this statistical reviewer used QTcF for the primary statistical analysis. This is consistent with the sponsor's choice of QTcF for their primary analysis.

**Table 5: Average of Sum of Squared Slopes for Different QT-RR Correction Methods**

| Treatment Group     | QTcB |        | QTcF |        |
|---------------------|------|--------|------|--------|
|                     | N    | MSSS   | N    | MSSS   |
| APF530              | 51   | 0.0046 | 51   | 0.0026 |
| Granisetron         | 51   | 0.0054 | 51   | 0.0019 |
| Moxifloxacin 400 mg | 51   | 0.0057 | 51   | 0.0024 |
| Placebo             | 51   | 0.0073 | 51   | 0.0051 |
| All                 | 51   | 0.0055 | 51   | 0.0016 |

The relationship between different correction methods and RR is presented in Figure 6.

**Figure 6: QT, QTcB, and QTcF vs. RR (Each Subject's Data Points are Connected with a Line)**



## 5.2 STATISTICAL ASSESSMENTS

### 5.2.1 QTc Analysis

#### 5.2.1.1 The Primary Analysis for APF530 and Granisetron

The statistical reviewer used mixed model to analyze the  $\Delta$ QTcF effect. The model includes treatment, sequence, and period as fixed effects and subject as a random effect. Baseline values are also included in the model as a covariate. The analysis results are listed in Table 6 and Table 7.

**Table 6: Analysis Results of  $\Delta$ QTcF and  $\Delta\Delta$ QTcF for Treatment Group A: APF530 x 2 days**

|      | $\Delta$ QTcF: APF530 |      |     | $\Delta$ QTcF: Placebo |      |     | $\Delta\Delta$ QTcF |      |     |             |
|------|-----------------------|------|-----|------------------------|------|-----|---------------------|------|-----|-------------|
| Time | N                     | Mean | SD  | N                      | Mean | SD  | N                   | Mean | SD  | 90% CI      |
| 0.1  | 51                    | -0.3 | 1.3 | 51                     | -0.4 | 1.3 | 51                  | 0.1  | 1.7 | (-2.6, 2.8) |
| 0.5  | 51                    | -1.1 | 1.2 | 51                     | -2.5 | 1.2 | 51                  | 1.4  | 1.6 | (-1.2, 4.0) |
| 1    | 51                    | -0.4 | 1.3 | 51                     | -0.5 | 1.3 | 51                  | 0.0  | 1.8 | (-2.9, 3.0) |
| 2    | 51                    | -0.6 | 1.2 | 51                     | -2.7 | 1.2 | 51                  | 2.2  | 1.5 | (-0.2, 4.6) |
| 3    | 51                    | -4.2 | 1.5 | 51                     | -7.6 | 1.5 | 51                  | 3.5  | 1.6 | (0.8, 6.1)  |
| 4    | 51                    | -6.5 | 1.6 | 51                     | -7.2 | 1.6 | 51                  | 0.7  | 1.8 | (-2.2, 3.6) |
| 10   | 51                    | -5.7 | 1.4 | 51                     | -6.9 | 1.4 | 51                  | 1.2  | 1.4 | (-1.2, 3.6) |
| 11   | 51                    | -3.6 | 1.3 | 51                     | -5.7 | 1.3 | 51                  | 2.1  | 1.6 | (-0.6, 4.7) |
| 12   | 51                    | 0.4  | 1.5 | 51                     | -2.8 | 1.5 | 51                  | 3.2  | 1.5 | (0.8, 5.6)  |
| 23   | 51                    | 4.1  | 1.2 | 51                     | 3.5  | 1.2 | 51                  | 0.6  | 1.5 | (-1.9, 3.1) |
| 24   | 51                    | 4.5  | 1.2 | 51                     | 2.4  | 1.2 | 51                  | 2.1  | 1.6 | (-0.5, 4.7) |
| 25   | 51                    | 2.6  | 1.3 | 51                     | 1.0  | 1.2 | 51                  | 1.6  | 1.5 | (-1.0, 4.1) |
| 47   | 51                    | 5.3  | 1.3 | 51                     | 2.1  | 1.3 | 51                  | 3.2  | 1.7 | (0.4, 5.9)  |
| 48   | 51                    | 1.6  | 1.4 | 51                     | 0.7  | 1.4 | 51                  | 0.9  | 1.8 | (-2.1, 3.8) |
| 49   | 51                    | 1.4  | 1.4 | 51                     | -1.2 | 1.4 | 51                  | 2.6  | 1.8 | (-0.4, 5.7) |

**Table 7: Analysis Results of  $\Delta$ QTcF and  $\Delta\Delta$ QTcF for Treatment Group B: Granisetron x 2 days**

|      | $\Delta$ QTcF: Granisetron |      |     | $\Delta$ QTcF: Placebo |      |     | $\Delta\Delta$ QTcF |      |     |             |
|------|----------------------------|------|-----|------------------------|------|-----|---------------------|------|-----|-------------|
| Time | N                          | Mean | SD  | N                      | Mean | SD  | N                   | Mean | SD  | 90% CI      |
| 0.1  | 51                         | 0.3  | 1.3 | 51                     | -0.3 | 1.3 | 51                  | 0.8  | 1.7 | (-2.0, 3.5) |
| 0.5  | 51                         | -3.5 | 1.2 | 51                     | -1.1 | 1.2 | 51                  | -1.0 | 1.6 | (-3.6, 1.6) |
| 1    | 51                         | -0.7 | 1.3 | 51                     | -0.4 | 1.3 | 51                  | -0.3 | 1.8 | (-3.2, 2.7) |
| 2    | 51                         | -1.5 | 1.2 | 51                     | -0.6 | 1.2 | 51                  | 1.2  | 1.5 | (-1.2, 3.6) |
| 3    | 51                         | -5.8 | 1.5 | 51                     | -4.2 | 1.5 | 51                  | 1.8  | 1.6 | (-0.8, 4.4) |
| 4    | 51                         | -6.9 | 1.6 | 51                     | -6.5 | 1.6 | 51                  | 0.2  | 1.8 | (-2.7, 3.2) |
| 10   | 51                         | -6.1 | 1.4 | 51                     | -5.7 | 1.4 | 51                  | 0.8  | 1.4 | (-1.6, 3.2) |
| 11   | 51                         | -3.9 | 1.3 | 51                     | -3.6 | 1.3 | 51                  | 1.8  | 1.6 | (-0.8, 4.5) |
| 12   | 51                         | -1.9 | 1.5 | 51                     | 0.4  | 1.5 | 51                  | 0.9  | 1.4 | (-1.5, 3.3) |
| 23   | 51                         | 5.1  | 1.2 | 51                     | 4.1  | 1.2 | 51                  | 1.5  | 1.5 | (-1.0, 4.0) |
| 24   | 51                         | 3.8  | 1.2 | 51                     | 4.5  | 1.2 | 51                  | 1.4  | 1.6 | (-1.2, 4.0) |
| 25   | 51                         | 1.6  | 1.2 | 51                     | 2.6  | 1.3 | 51                  | 0.6  | 1.5 | (-1.9, 3.2) |
| 47   | 51                         | 4.5  | 1.3 | 51                     | 5.3  | 1.3 | 51                  | 2.4  | 1.7 | (-0.4, 5.1) |
| 48   | 51                         | 3.1  | 1.4 | 51                     | 1.6  | 1.4 | 51                  | 2.4  | 1.8 | (-0.6, 5.4) |
| 49   | 51                         | 1.9  | 1.4 | 51                     | 1.4  | 1.4 | 51                  | 3.2  | 1.8 | (0.1, 6.2)  |

The largest upper bounds of the 2-sided 90% CI for the mean difference between APF530 and placebo, and between Granisetron and placebo were 6.1 ms and 5.4 ms, respectively.

### 5.2.1.2 Assay Sensitivity Analysis

The statistical reviewer used the same statistical model to analyze moxifloxacin and placebo data. The results are presented in Table 8. The largest unadjusted 90% lower confidence interval is 8.9 ms. When considering Bonferroni multiple endpoint adjustment, the largest lower confidence interval is 8.0 ms, which indicates that an at least 5 ms QTcF effect due to moxifloxacin can be detected from the study.

**Table 8: Analysis Results of  $\Delta$ QTcF and  $\Delta\Delta$ QTcF for Moxifloxacin**

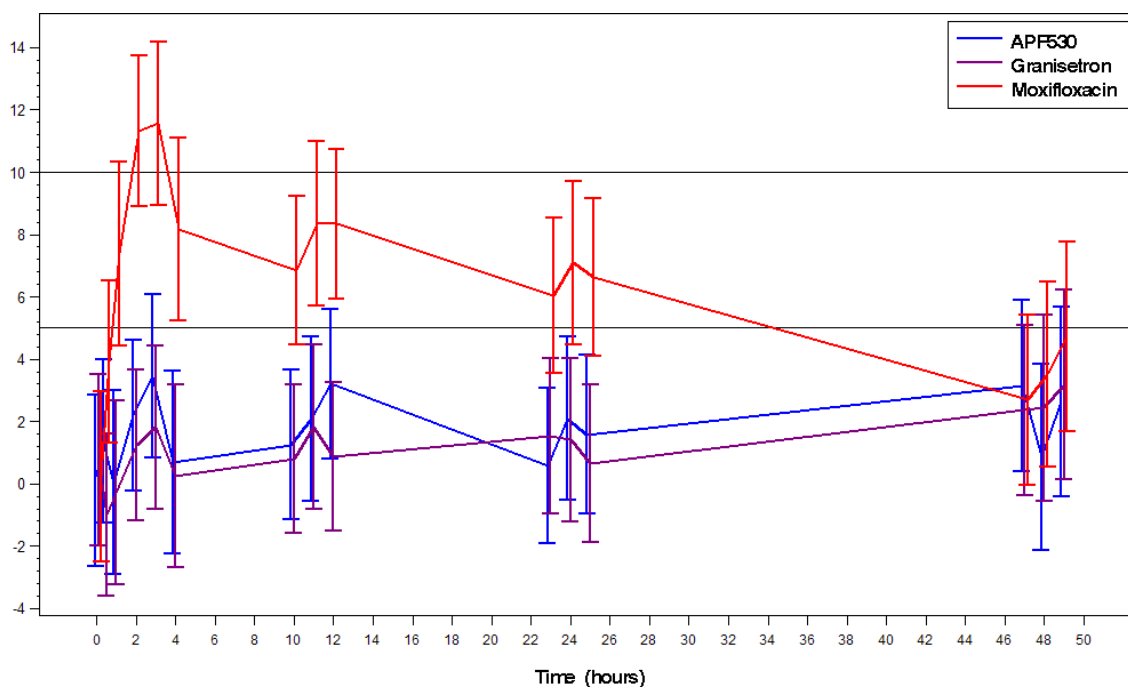
| Time | $\Delta$ QTcF: moxifloxacin |      |     | $\Delta$ QTcF: placebo |      |     | $\Delta\Delta$ QTcF |      |     |                   |                  |
|------|-----------------------------|------|-----|------------------------|------|-----|---------------------|------|-----|-------------------|------------------|
|      | N                           | Mean | SD  | N                      | Mean | SD  | N                   | Mean | SD  | Unadjusted 90% CI | Adjusted* 90% CI |
| 0.1  | 51                          | -0.2 | 1.3 | 51                     | -0.3 | 1.3 | 51                  | 0.2  | 1.7 | (-2.5, 3.0)       | (-3.5, 4.0)      |
| 0.5  | 51                          | 1.4  | 1.2 | 51                     | -1.1 | 1.2 | 51                  | 3.9  | 1.6 | (1.3, 6.5)        | (0.3, 7.5)       |
| 1    | 51                          | 6.9  | 1.3 | 51                     | -0.4 | 1.3 | 51                  | 7.4  | 1.8 | (4.4, 10.3)       | (3.4, 11.4)      |
| 2    | 51                          | 8.6  | 1.2 | 51                     | -0.6 | 1.2 | 51                  | 11.3 | 1.5 | (8.9, 13.7)       | (8.0, 14.6)      |
| 3    | 51                          | 4.0  | 1.5 | 51                     | -4.2 | 1.5 | 51                  | 11.6 | 1.6 | (8.9, 14.2)       | (8.0, 15.2)      |
| 4    | 51                          | 1.0  | 1.6 | 51                     | -6.5 | 1.6 | 51                  | 8.2  | 1.8 | (5.2, 11.1)       | (4.2, 12.2)      |
| 10   | 51                          | -0.1 | 1.4 | 51                     | -5.7 | 1.4 | 51                  | 6.8  | 1.4 | (4.5, 9.2)        | (3.6, 10.1)      |
| 11   | 51                          | 2.7  | 1.3 | 51                     | -3.6 | 1.3 | 51                  | 8.4  | 1.6 | (5.7, 11.0)       | (4.8, 12.0)      |
| 12   | 51                          | 5.6  | 1.5 | 51                     | 0.4  | 1.5 | 51                  | 8.3  | 1.4 | (5.9, 10.7)       | (5.1, 11.6)      |
| 23   | 51                          | 9.6  | 1.2 | 51                     | 4.1  | 1.2 | 51                  | 6.0  | 1.5 | (3.6, 8.5)        | (2.6, 9.5)       |
| 24   | 51                          | 9.5  | 1.2 | 51                     | 4.5  | 1.2 | 51                  | 7.1  | 1.6 | (4.5, 9.7)        | (3.5, 10.7)      |
| 25   | 51                          | 7.6  | 1.2 | 51                     | 2.6  | 1.3 | 51                  | 6.6  | 1.5 | (4.1, 9.2)        | (3.2, 10.1)      |
| 47   | 51                          | 4.8  | 1.3 | 51                     | 5.3  | 1.3 | 51                  | 2.7  | 1.7 | (-0.0, 5.4)       | (-1.1, 6.4)      |
| 48   | 51                          | 4.2  | 1.4 | 51                     | 1.6  | 1.4 | 51                  | 3.5  | 1.8 | (0.5, 6.5)        | (-0.6, 7.6)      |
| 49   | 51                          | 3.5  | 1.4 | 51                     | 1.4  | 1.4 | 51                  | 4.7  | 1.8 | (1.7, 7.8)        | (0.6, 8.9)       |

\* Bonferroni correction was applied for multiple endpoint adjustment for 4 time points.

### 5.2.1.3 Graph of $\Delta\Delta$ QTcF Over Time

The following figure displays the time profile of  $\Delta\Delta$ QTcF for different treatment groups.

**Figure 7: Mean and 90% CI  $\Delta\Delta$ QTcF Timecourse**



*All CIs are unadjusted, including moxifloxacin.*

#### 5.2.1.4 Categorical Analysis

Table 9 lists the number of subjects as well as the number of observations whose QTcF values are  $\leq 450$  ms, between 450 ms and 480 ms. There was 1 (2%) subject who experienced QTcF greater than 480 ms in the moxifloxacin group.

**Table 9: Categorical Analysis for QTcF**

|                     | N  | Value $\leq 450$ ms | 450 ms < Value $\leq 480$ ms | Value > 480 ms |
|---------------------|----|---------------------|------------------------------|----------------|
| Treatment Group     |    |                     |                              |                |
| APF530              | 51 | 46 (90.2%)          | 5 (9.8%)                     | 0 (0.0%)       |
| Granisetron         | 51 | 43 (84.3%)          | 8 (15.7%)                    | 0 (0.0%)       |
| Moxifloxacin 400 mg | 51 | 41 (80.4%)          | 9 (17.6%)                    | 1 (2.0%)       |
| Placebo             | 51 | 48 (94.1%)          | 3 (5.9%)                     | 0 (0.0%)       |

Table 10 lists the categorical analysis results for  $\Delta$ QTcF. No subject's change from baseline was above 60 ms.

**Table 10: Categorical Analysis of  $\Delta$ QTcF**

|                     | N  | Value $\leq$ 30 ms | 30 ms < Value $\leq$ 60 ms |
|---------------------|----|--------------------|----------------------------|
| Treatment Group     |    |                    |                            |
| APF530              | 51 | 49 (96.1%)         | 2 (3.9%)                   |
| Granisetron         | 51 | 49 (96.1%)         | 2 (3.9%)                   |
| Moxifloxacin 400 mg | 51 | 46 (90.2%)         | 5 (9.8%)                   |
| Placebo             | 51 | 49 (96.1%)         | 2 (3.9%)                   |

### 5.2.2 HR Analysis

The same statistical analysis was performed based on HR. The point estimates and the 90% confidence intervals are presented in Table 11 and Table 12. The largest upper limits of 90% CI for the HR mean differences between APF530 and placebo and Granisetron and placebo are 2.5 bpm and 1.1 bpm, respectively.

**Table 11: Analysis Results of  $\Delta$ HR and  $\Delta\Delta$ HR for Treatment Group A: APF530 x 2 days**

| Time | $\Delta$ HR: APF530 |      |     | $\Delta$ HR: Placebo |      |     | $\Delta\Delta$ HR |      |     |              |
|------|---------------------|------|-----|----------------------|------|-----|-------------------|------|-----|--------------|
|      | N                   | Mean | SD  | N                    | Mean | SD  | N                 | Mean | SD  | 90% CI       |
| 0.1  | 51                  | 2.3  | 0.7 | 51                   | 2.3  | 0.7 | 51                | -0.1 | 1.0 | (-1.7, 1.6)  |
| 0.5  | 51                  | 0.6  | 0.7 | 51                   | 2.4  | 0.7 | 51                | -1.8 | 1.0 | (-3.5, -0.1) |
| 1    | 51                  | 1.5  | 0.9 | 51                   | 3.1  | 0.9 | 51                | -1.7 | 1.2 | (-3.7, 0.3)  |
| 2    | 51                  | 1.6  | 0.7 | 51                   | 0.8  | 0.7 | 51                | 0.8  | 1.0 | (-0.9, 2.5)  |
| 3    | 51                  | 5.6  | 0.7 | 51                   | 5.7  | 0.7 | 51                | -0.1 | 1.0 | (-1.9, 1.6)  |
| 4    | 51                  | 6.7  | 0.8 | 51                   | 8.2  | 0.8 | 51                | -1.4 | 1.2 | (-3.4, 0.5)  |
| 10   | 51                  | 5.1  | 0.8 | 51                   | 5.5  | 0.8 | 51                | -0.5 | 1.1 | (-2.4, 1.4)  |
| 11   | 51                  | 4.2  | 0.8 | 51                   | 3.7  | 0.8 | 51                | 0.5  | 1.1 | (-1.3, 2.4)  |
| 12   | 51                  | 2.8  | 0.8 | 51                   | 3.6  | 0.8 | 51                | -0.8 | 1.1 | (-2.7, 1.0)  |
| 23   | 51                  | 1.4  | 0.8 | 51                   | 2.2  | 0.8 | 51                | -0.8 | 1.2 | (-2.8, 1.1)  |
| 24   | 51                  | 1.7  | 0.8 | 51                   | 1.6  | 0.8 | 51                | 0.1  | 1.1 | (-1.8, 2.0)  |
| 25   | 51                  | 1.6  | 0.8 | 51                   | 3.8  | 0.8 | 51                | -2.2 | 1.2 | (-4.2, -0.3) |
| 47   | 51                  | 1.6  | 0.9 | 51                   | 3.6  | 0.9 | 51                | -2.0 | 1.2 | (-4.1, -0.0) |
| 48   | 51                  | 1.3  | 0.9 | 51                   | 4.3  | 0.9 | 51                | -3.0 | 1.2 | (-5.1, -1.0) |
| 49   | 51                  | 4.0  | 0.9 | 51                   | 5.3  | 0.9 | 51                | -1.3 | 1.3 | (-3.4, 0.8)  |

**Table 12: Analysis Results of  $\Delta$ HR and  $\Delta\Delta$ HR for Treatment Group B: Granisetron  
x 2 days**

|      | $\Delta$ HR: Granisetron |      |     | $\Delta$ HR: Placebo |      |     | $\Delta\Delta$ HR |      |     |              |
|------|--------------------------|------|-----|----------------------|------|-----|-------------------|------|-----|--------------|
| Time | N                        | Mean | SD  | N                    | Mean | SD  | N                 | Mean | SD  | 90% CI       |
| 0.1  | 51                       | 1.4  | 0.7 | 51                   | 2.3  | 0.7 | 51                | -0.9 | 1.0 | (-2.6, 0.8)  |
| 0.5  | 51                       | -0.0 | 0.7 | 51                   | 2.4  | 0.7 | 51                | -2.4 | 1.0 | (-4.1, -0.8) |
| 1    | 51                       | 0.9  | 0.9 | 51                   | 3.1  | 0.9 | 51                | -2.2 | 1.2 | (-4.2, -0.2) |
| 2    | 51                       | 0.1  | 0.7 | 51                   | 0.8  | 0.7 | 51                | -0.6 | 1.0 | (-2.4, 1.1)  |
| 3    | 51                       | 4.4  | 0.7 | 51                   | 5.7  | 0.7 | 51                | -1.3 | 1.0 | (-3.0, 0.4)  |
| 4    | 51                       | 5.8  | 0.8 | 51                   | 8.2  | 0.8 | 51                | -2.3 | 1.2 | (-4.3, -0.4) |
| 10   | 51                       | 3.9  | 0.8 | 51                   | 5.5  | 0.8 | 51                | -1.7 | 1.1 | (-3.6, 0.2)  |
| 11   | 51                       | 2.1  | 0.8 | 51                   | 3.7  | 0.8 | 51                | -1.6 | 1.1 | (-3.5, 0.3)  |
| 12   | 51                       | 1.0  | 0.8 | 51                   | 3.6  | 0.8 | 51                | -2.7 | 1.1 | (-4.5, -0.8) |
| 23   | 51                       | -0.1 | 0.8 | 51                   | 2.2  | 0.8 | 51                | -2.3 | 1.2 | (-4.2, -0.3) |
| 24   | 51                       | 0.6  | 0.8 | 51                   | 1.6  | 0.8 | 51                | -0.9 | 1.1 | (-2.8, 0.9)  |
| 25   | 51                       | 0.5  | 0.8 | 51                   | 3.8  | 0.8 | 51                | -3.3 | 1.2 | (-5.2, -1.3) |
| 47   | 51                       | 0.9  | 0.9 | 51                   | 3.6  | 0.9 | 51                | -2.7 | 1.2 | (-4.7, -0.7) |
| 48   | 51                       | 1.5  | 0.9 | 51                   | 4.3  | 0.9 | 51                | -2.8 | 1.2 | (-4.8, -0.7) |
| 49   | 51                       | 4.0  | 0.9 | 51                   | 5.3  | 0.9 | 51                | -1.3 | 1.3 | (-3.4, 0.8)  |

### 5.2.3 PR Analysis

The same statistical analysis was performed based on PR interval. The point estimates and the 90% confidence intervals are presented in Table 13 and Table 14. The largest upper limits of 90% CI for the PR mean differences between APF530 and placebo and Granisetron and placebo are 4.5 ms and 5.3 ms, respectively.

The outlier analysis results for PR are presented in Table 15.

**Table 13: Analysis Results of  $\Delta$ PR and  $\Delta\Delta$ PR for Treatment Group A: APF530 X 2 days**

|      | $\Delta$ PR: APF530 |      |     | $\Delta$ PR: Placebo |      |     | $\Delta\Delta$ PR |      |     |             |
|------|---------------------|------|-----|----------------------|------|-----|-------------------|------|-----|-------------|
| Time | N                   | Mean | SD  | N                    | Mean | SD  | N                 | Mean | SD  | 90% CI      |
| 0.1  | 51                  | -2.6 | 0.9 | 51                   | -5.0 | 0.9 | 51                | 2.4  | 1.3 | (0.2, 4.5)  |
| 0.5  | 51                  | -2.4 | 0.8 | 51                   | -1.6 | 0.8 | 51                | -0.9 | 1.1 | (-2.7, 0.9) |
| 1    | 51                  | -2.4 | 0.8 | 51                   | -1.8 | 0.8 | 51                | -0.6 | 1.2 | (-2.5, 1.3) |
| 2    | 51                  | -1.8 | 0.8 | 51                   | -1.9 | 0.8 | 51                | 0.1  | 1.1 | (-1.7, 1.9) |
| 3    | 51                  | -2.5 | 1.0 | 51                   | -2.9 | 1.0 | 51                | 0.4  | 1.4 | (-2.0, 2.7) |
| 4    | 51                  | -5.4 | 1.0 | 51                   | -5.2 | 1.0 | 51                | -0.2 | 1.4 | (-2.5, 2.1) |
| 10   | 51                  | -7.5 | 0.9 | 51                   | -8.9 | 0.9 | 51                | 1.4  | 1.3 | (-0.7, 3.5) |
| 11   | 51                  | -6.8 | 1.0 | 51                   | -7.3 | 1.0 | 51                | 0.5  | 1.4 | (-1.8, 2.9) |
| 12   | 51                  | -6.4 | 1.2 | 51                   | -5.1 | 1.2 | 51                | -1.4 | 1.6 | (-4.1, 1.4) |
| 23   | 51                  | 0.3  | 1.3 | 51                   | 0.8  | 1.3 | 51                | -0.5 | 1.9 | (-3.6, 2.6) |
| 24   | 51                  | -1.0 | 1.0 | 51                   | -1.3 | 1.0 | 51                | 0.3  | 1.5 | (-2.2, 2.7) |
| 25   | 51                  | -2.2 | 1.1 | 51                   | -1.8 | 1.1 | 51                | -0.5 | 1.5 | (-3.0, 2.1) |
| 47   | 51                  | 1.6  | 1.1 | 51                   | 3.4  | 1.1 | 51                | -1.8 | 1.6 | (-4.4, 0.8) |
| 48   | 51                  | 0.2  | 1.3 | 51                   | 2.5  | 1.3 | 51                | -2.3 | 1.8 | (-5.3, 0.8) |
| 49   | 51                  | 0.0  | 1.1 | 51                   | -0.1 | 1.1 | 51                | 0.2  | 1.6 | (-2.5, 2.8) |

**Table 14: Analysis Results of  $\Delta$ PR and  $\Delta\Delta$ PR for Treatment Group B: Granisetron  
X 2 days**

| Time | $\Delta$ PR: Granisetron |      |     | $\Delta$ PR: Placebo |      |     | $\Delta\Delta$ PR |      |     |             |
|------|--------------------------|------|-----|----------------------|------|-----|-------------------|------|-----|-------------|
|      | N                        | Mean | SD  | N                    | Mean | SD  | N                 | Mean | SD  | 90% CI      |
| 0.1  | 51                       | -1.8 | 0.9 | 51                   | -5.0 | 0.9 | 51                | 3.2  | 1.3 | (1.1, 5.3)  |
| 0.5  | 51                       | -1.0 | 0.8 | 51                   | -1.6 | 0.8 | 51                | 0.6  | 1.1 | (-1.2, 2.4) |
| 1    | 51                       | -1.9 | 0.8 | 51                   | -1.8 | 0.8 | 51                | -0.1 | 1.2 | (-2.1, 1.8) |
| 2    | 51                       | -1.5 | 0.8 | 51                   | -1.9 | 0.8 | 51                | 0.4  | 1.1 | (-1.4, 2.2) |
| 3    | 51                       | -3.0 | 1.0 | 51                   | -2.9 | 1.0 | 51                | -0.1 | 1.4 | (-2.5, 2.3) |
| 4    | 51                       | -4.5 | 1.0 | 51                   | -5.2 | 1.0 | 51                | 0.6  | 1.4 | (-1.6, 2.9) |
| 10   | 51                       | -7.7 | 0.9 | 51                   | -8.9 | 0.9 | 51                | 1.3  | 1.3 | (-0.8, 3.3) |
| 11   | 51                       | -7.4 | 1.0 | 51                   | -7.3 | 1.0 | 51                | -0.1 | 1.4 | (-2.4, 2.3) |
| 12   | 51                       | -4.9 | 1.2 | 51                   | -5.1 | 1.2 | 51                | 0.2  | 1.6 | (-2.5, 2.9) |
| 23   | 51                       | -0.2 | 1.3 | 51                   | 0.8  | 1.3 | 51                | -1.0 | 1.9 | (-4.1, 2.1) |
| 24   | 51                       | 0.5  | 1.0 | 51                   | -1.3 | 1.0 | 51                | 1.8  | 1.5 | (-0.6, 4.2) |
| 25   | 51                       | -1.6 | 1.1 | 51                   | -1.8 | 1.1 | 51                | 0.2  | 1.5 | (-2.3, 2.8) |
| 47   | 51                       | 5.2  | 1.1 | 51                   | 3.4  | 1.1 | 51                | 1.8  | 1.6 | (-0.8, 4.4) |
| 48   | 51                       | 2.7  | 1.3 | 51                   | 2.5  | 1.3 | 51                | 0.2  | 1.8 | (-2.8, 3.2) |
| 49   | 51                       | 1.6  | 1.1 | 51                   | -0.1 | 1.1 | 51                | 1.7  | 1.6 | (-1.0, 4.3) |

**Table 15: Categorical Analysis for PR**

| Treatment Group | N  | PR < 200 ms | PR $\geq$ 200 ms |
|-----------------|----|-------------|------------------|
| APF530          | 51 | 50 (98.0%)  | 1 (2.0%)         |
| Granisetron     | 51 | 50 (98.0%)  | 1 (2.0%)         |
| Placebo         | 51 | 50 (98.0%)  | 1 (2.0%)         |

#### 5.2.4 QRS Analysis

The same statistical analysis was performed based on QRS interval. The point estimates and the 90% confidence intervals are presented in Table 16 and Table 17. The largest upper limits of 90% CI for the QRS mean differences between APF530 and placebo and Granisetron and placebo are 1.9 ms and 1.5 ms, respectively. There are 9 (17.6%) and 9 (17.6%) subjects who experienced QRS interval greater than 110 ms in APF530 and Granisetron, respectively.

The outlier analysis results for QRS are presented in Table 18.

**Table 16: Analysis Results of  $\Delta$ QRS and  $\Delta\Delta$ QRS for Treatment Group A: APF530  
X 2 days**

|      | $\Delta$ QRS: APF530 |      |     | $\Delta$ QRS: Placebo |      |     | $\Delta\Delta$ QRS |      |     |             |
|------|----------------------|------|-----|-----------------------|------|-----|--------------------|------|-----|-------------|
| Time | N                    | Mean | SD  | N                     | Mean | SD  | N                  | Mean | SD  | 90% CI      |
| 0.1  | 51                   | 0.3  | 0.6 | 51                    | 0.2  | 0.6 | 51                 | 0.1  | 0.9 | (-1.4, 1.6) |
| 0.5  | 51                   | 0.3  | 0.6 | 51                    | -0.1 | 0.6 | 51                 | 0.4  | 0.9 | (-1.0, 1.8) |
| 1    | 51                   | -0.1 | 0.6 | 51                    | -0.5 | 0.6 | 51                 | 0.4  | 0.8 | (-0.9, 1.7) |
| 2    | 51                   | -0.0 | 0.6 | 51                    | -0.6 | 0.6 | 51                 | 0.6  | 0.8 | (-0.7, 1.9) |
| 3    | 51                   | 1.4  | 0.7 | 51                    | 1.5  | 0.7 | 51                 | -0.1 | 0.8 | (-1.4, 1.2) |
| 4    | 51                   | -0.1 | 0.6 | 51                    | 0.0  | 0.6 | 51                 | -0.1 | 0.7 | (-1.3, 1.0) |
| 10   | 51                   | -1.2 | 0.7 | 51                    | -1.0 | 0.7 | 51                 | -0.2 | 0.7 | (-1.4, 1.0) |
| 11   | 51                   | -1.2 | 0.7 | 51                    | -1.7 | 0.7 | 51                 | 0.5  | 0.8 | (-0.7, 1.8) |
| 12   | 51                   | -1.1 | 0.7 | 51                    | -1.3 | 0.6 | 51                 | 0.3  | 0.7 | (-0.9, 1.5) |
| 23   | 51                   | 1.2  | 0.8 | 51                    | 1.1  | 0.8 | 51                 | 0.0  | 0.7 | (-1.3, 1.3) |
| 24   | 51                   | 0.8  | 0.6 | 51                    | 0.4  | 0.6 | 51                 | 0.5  | 0.8 | (-0.8, 1.8) |
| 25   | 51                   | 0.7  | 0.6 | 51                    | -0.0 | 0.6 | 51                 | 0.7  | 0.7 | (-0.4, 1.8) |
| 47   | 51                   | 2.2  | 0.6 | 51                    | 1.8  | 0.6 | 51                 | 0.4  | 0.8 | (-0.9, 1.6) |
| 48   | 51                   | 0.7  | 0.7 | 51                    | 1.1  | 0.7 | 51                 | -0.4 | 0.6 | (-1.5, 0.6) |
| 49   | 51                   | 0.5  | 0.7 | 51                    | 0.3  | 0.7 | 51                 | 0.2  | 0.7 | (-1.0, 1.4) |

**Table 17: Analysis Results of  $\Delta$ QRS and  $\Delta\Delta$ QRS for Treatment Group B: Granisetron X 2 days**

|      | $\Delta$ QRS: Granisetron |      |     | $\Delta$ QRS: Placebo |      |     | $\Delta\Delta$ QRS |      |     |              |
|------|---------------------------|------|-----|-----------------------|------|-----|--------------------|------|-----|--------------|
| Time | N                         | Mean | SD  | N                     | Mean | SD  | N                  | Mean | SD  | 90% CI       |
| 0.1  | 51                        | -0.5 | 0.6 | 51                    | 0.2  | 0.6 | 51                 | -0.7 | 0.9 | (-2.2, 0.8)  |
| 0.5  | 51                        | -0.8 | 0.6 | 51                    | -0.1 | 0.6 | 51                 | -0.6 | 0.9 | (-2.1, 0.8)  |
| 1    | 51                        | -1.0 | 0.6 | 51                    | -0.5 | 0.6 | 51                 | -0.5 | 0.8 | (-1.8, 0.8)  |
| 2    | 51                        | -0.8 | 0.6 | 51                    | -0.6 | 0.6 | 51                 | -0.2 | 0.8 | (-1.4, 1.1)  |
| 3    | 51                        | 0.6  | 0.7 | 51                    | 1.5  | 0.7 | 51                 | -1.0 | 0.8 | (-2.3, 0.3)  |
| 4    | 51                        | 0.2  | 0.6 | 51                    | 0.0  | 0.6 | 51                 | 0.2  | 0.7 | (-1.0, 1.3)  |
| 10   | 51                        | -2.2 | 0.7 | 51                    | -1.0 | 0.7 | 51                 | -1.2 | 0.7 | (-2.4, -0.0) |
| 11   | 51                        | -1.5 | 0.7 | 51                    | -1.7 | 0.7 | 51                 | 0.2  | 0.8 | (-1.0, 1.5)  |
| 12   | 51                        | -1.6 | 0.7 | 51                    | -1.3 | 0.6 | 51                 | -0.3 | 0.7 | (-1.5, 0.9)  |
| 23   | 51                        | 0.9  | 0.8 | 51                    | 1.1  | 0.8 | 51                 | -0.3 | 0.7 | (-1.6, 1.0)  |
| 24   | 51                        | -0.1 | 0.6 | 51                    | 0.4  | 0.6 | 51                 | -0.4 | 0.8 | (-1.7, 0.9)  |
| 25   | 51                        | -0.3 | 0.6 | 51                    | -0.0 | 0.6 | 51                 | -0.3 | 0.7 | (-1.4, 0.8)  |
| 47   | 51                        | 1.1  | 0.6 | 51                    | 1.8  | 0.6 | 51                 | -0.7 | 0.8 | (-2.0, 0.6)  |
| 48   | 51                        | 0.3  | 0.7 | 51                    | 1.1  | 0.7 | 51                 | -0.8 | 0.6 | (-1.9, 0.3)  |
| 49   | 51                        | -0.0 | 0.7 | 51                    | 0.3  | 0.7 | 51                 | -0.3 | 0.7 | (-1.5, 0.9)  |

**Table 18: Categorical Analysis for QRS**

|                 | N  | QRS < 110 ms | QRS ≥ 110 ms |
|-----------------|----|--------------|--------------|
| Treatment Group |    |              |              |
| APF530          | 51 | 42 (82.4%)   | 9 (17.6%)    |
| Granisetron     | 51 | 42 (82.4%)   | 9 (17.6%)    |
| Placebo         | 51 | 43 (84.3%)   | 8 (15.7%)    |

### 5.3 CLINICAL PHARMACOLOGY ASSESSMENTS

The relationship between  $\Delta\Delta\text{QTcF}$  and granisetron concentrations was investigated by linear mixed effects modeling. The following three linear models were considered:

Model 1 is a linear model with an intercept

Model 2 is a linear model with mean intercept fixed to 0 (with variability)

Model 3 is a linear model with no intercept

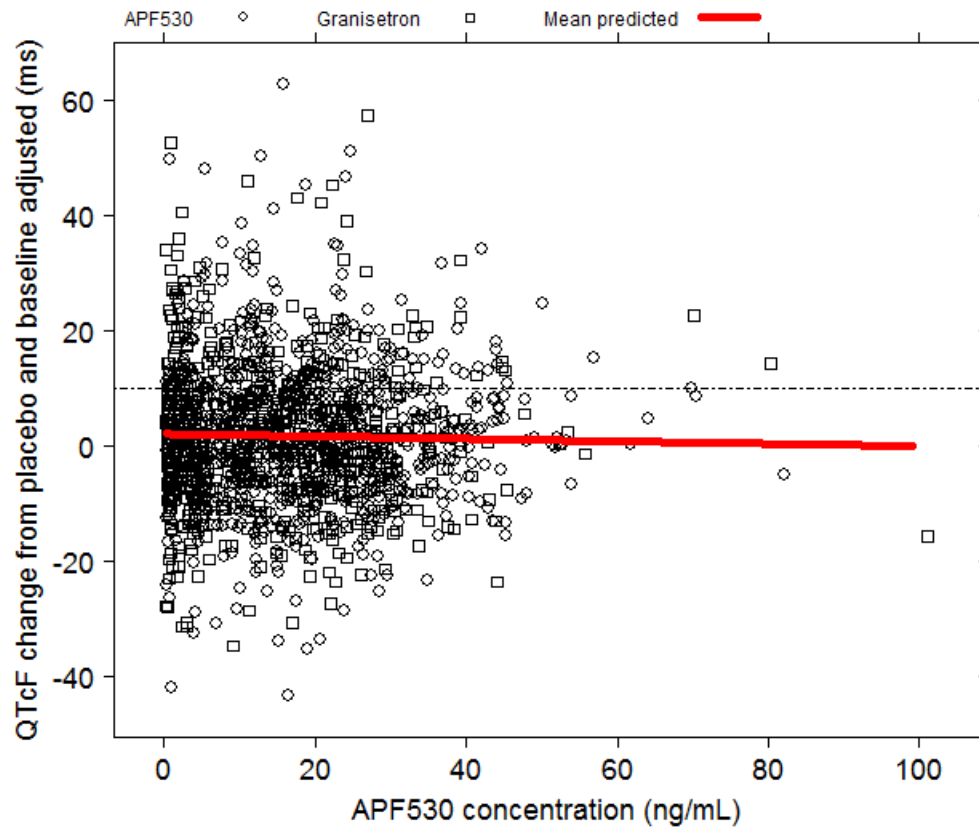
In all three models the slope was insignificant. Model 1 was used for further analysis since the model with an intercept was found to fit the data best based on AIC. Table 19 summarizes the results of APF530- $\Delta\Delta\text{QTcF}$  analyses.

**Table 19. Exposure-Response Analysis of APF530 Associated with  $\Delta\Delta\text{QTcF}$  Prolongation**

| Parameter                 | Estimate (90% CI)         | p-value | Inter-Individual Variability |
|---------------------------|---------------------------|---------|------------------------------|
| Intercept (ms)            | 2.05 (-0.15; 4.25)        | 0.1246  | 8.89                         |
| Slope (ms per ng/mL)      | -0.0214 (-0.0646; 0.0217) | 0.4068  | 0.1                          |
| Residual Variability (ms) | 9.33                      |         |                              |

The relationship between granisetron concentrations and  $\Delta\Delta\text{QTcF}$  is visualized in Figure 8 with no evident exposure-response relationship. The mean predicted  $\Delta\Delta\text{QTcF}$  at the median concentration following 1 g APF530 was below 5 ms (1.35 ms) and the upper limit of its 90% CI was below 10 ms (3.4 ms), concluding negative drug effects on  $\Delta\Delta\text{QTcF}$  within observed concentration range.

**Figure 8.  $\Delta\Delta Q_{TcF}$  vs. APF530 concentration with Population Prediction (Solid Red Line)**



The predicted  $\Delta\Delta Q_{TcF}$  values at the geometric mean peak granisetron concentrations are shown in Table 20.

**Table 20. Predicted  $\Delta\Delta Q_{TcF}$  at Geometric Mean Peak Granisetron Concentration with Model 1**

| <i>Treatment</i>        | <i>Concentration</i> | <i>Predicted <math>\Delta\Delta Q_{TcF}</math></i> | <i>90% CI</i> |
|-------------------------|----------------------|----------------------------------------------------|---------------|
| APF530 SC 1 g           | 32.9 ng/mL           | 1.35                                               | (-0.705, 3.4) |
| Granisetron IV 50 µg/kg | 32.3 ng/mL           | 1.36                                               | (-0.688, 3.4) |

## **5.4 CLINICAL ASSESSMENTS**

### **5.4.1 Safety assessments**

None of the events identified to be of clinical importance per the ICH E 14 guidelines i.e. syncope, seizure, significant ventricular arrhythmias or sudden cardiac death occurred in this study.

### **5.4.2 ECG assessments**

Waveforms from the ECG warehouse were reviewed. Overall ECG acquisition and interpretation in this study appears acceptable.

### **5.4.3 PR and QRS Interval**

There were no clinically relevant changes in PR or QRS.

## 6 APPENDIX

### 6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

|                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                   |
|--------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Therapeutic dose         | <p>Include maximum proposed clinical dosing regimen.</p> <p>500 mg APF530 (10mg granisetron) administered subcutaneously (SC) once per seven days</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                                                                                                                                                                                                                   |
| Maximum tolerated dose   | <p>Include if studied or NOAEL dose</p> <p>Not studied</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                                                                                                                                                                                                                   |
| Principal adverse events | <p>Include most common adverse events; dose limiting adverse events</p> <p>Healthy male volunteers: single dose 1000 mg APF530 ( 20 mg granisetron) : no serious adverse events</p> <p>Chemo patients: single dose 750 mg APF530 (15 mg granisetron): no <u>drug related serious adverse event</u></p> <p>In Phase 3 trial APF530 500 mg dose (10 mg granisetron) most common <u>related adverse events</u>: constipation 4.5%<br/>headache 2.7%</p> <p>Most <u>common injection site reaction adverse events</u> Phase 3 study 250 mg APF530 (5 mg granisetron) vs. 500 mg APF530 (10 mg granisetron):</p> <p>Injection site bruising: 16.8% vs. 18.6%</p> <p>Injection site erythema: 9.0% vs. 11.2%</p> <p>Injection site nodule: 5.3% vs. 11.2%</p> <p>Injection site pain: 4.7% vs. 8.2%</p> <p>Injection site hemorrhage: 4.7% vs. 3.8%</p> |                                                                                                                                                                                                                                   |
| Maximum dose tested      | Single Dose                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | <p>Specify dose</p> <p>Healthy volunteers: 1000 mg APF 530 (20 mg granisetron):</p> <p>Chemo patients: 750 mg APF530 (15mg granisetron):</p>                                                                                      |
|                          | Multiple Dose                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | <p>Specify dosing interval and duration</p> <p>Phase 3 study 250 mg APF530 (5mg granisetron) vs. 500 mg APF530 (10 mg granisetron): Dosing interval once/seven days; Patients dosed from one to four cycles in Phase 3 study.</p> |

|                                                                                                                                                                                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                                                                                                                                                                                                                                                                                                                         |                  |                      |                          |      |                      |      |     |     |      |      |      |      |     |   |      |      |     |      |     |    |      |      |     |      |      |    |      |      |     |      |                  |                  |                          |      |           |      |     |   |      |      |       |      |     |    |      |      |        |      |     |    |      |      |        |      |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------|----------------------|--------------------------|------|----------------------|------|-----|-----|------|------|------|------|-----|---|------|------|-----|------|-----|----|------|------|-----|------|------|----|------|------|-----|------|------------------|------------------|--------------------------|------|-----------|------|-----|---|------|------|-------|------|-----|----|------|------|--------|------|-----|----|------|------|--------|------|
| Exposures Achieved at Maximum Tested Dose<br><br>AUC data (ng·hr/mL) presented as mean ± standard deviation with relative standard deviation in parenthesis for the time course studied. | Single Dose                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | Mean (%CV) C <sub>max</sub> and AUC<br><br>Healthy Volunteers: 1000 mg APF530 (20 mg granisetron)<br><br>Mean C <sub>max</sub> 18.1 ± 8.57 (47.3%)<br><br>Mean AUC 0-168 = 658 ± 219 (33.3%)<br><br>Chemo patients: 750 mg APF530 (15 mg granisetron)<br><br>Mean C <sub>max</sub> 29.8 ± 17.47 (58.6%)<br><br>Mean AUC 0-168 = 2148.4 ± 1206.6 (56.2%) |                  |                      |                          |      |                      |      |     |     |      |      |      |      |     |   |      |      |     |      |     |    |      |      |     |      |      |    |      |      |     |      |                  |                  |                          |      |           |      |     |   |      |      |       |      |     |    |      |      |        |      |     |    |      |      |        |      |
|                                                                                                                                                                                          | Multiple Dose                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | Mean (%CV) C <sub>max</sub> and AUC<br><br>No PK collected after 1 <sup>st</sup> cycle                                                                                                                                                                                                                                                                  |                  |                      |                          |      |                      |      |     |     |      |      |      |      |     |   |      |      |     |      |     |    |      |      |     |      |      |    |      |      |     |      |                  |                  |                          |      |           |      |     |   |      |      |       |      |     |    |      |      |        |      |     |    |      |      |        |      |
| Range of linear PK                                                                                                                                                                       | Specify dosing regimen<br><br>Healthy volunteers dosed with APF530<br><table><tr><td>APF530 dose (mg)</td><td>granisetron (mg)</td><td>C<sub>max</sub> (ng/mL)</td><td>%RSD</td><td>AUC 0-168 (ng·hr/mL)</td><td>%RSD</td></tr><tr><td>125</td><td>2.5</td><td>2.04</td><td>60.8</td><td>60.4</td><td>75.2</td></tr><tr><td>250</td><td>5</td><td>4.17</td><td>59.2</td><td>131</td><td>75.3</td></tr><tr><td>500</td><td>10</td><td>10.6</td><td>74.6</td><td>343</td><td>80.2</td></tr><tr><td>1000</td><td>20</td><td>18.1</td><td>47.3</td><td>658</td><td>33.3</td></tr></table><br><br>Chemo patients dosed with APF530<br><table><tr><td>APF530 dose (mg)</td><td>granisetron (mg)</td><td>C<sub>max</sub> (ng/mL)</td><td>%RSD</td><td>AUC 0-168</td><td>%RSD</td></tr><tr><td>250</td><td>5</td><td>11.6</td><td>58.9</td><td>740.3</td><td>97.5</td></tr><tr><td>500</td><td>10</td><td>17.8</td><td>72.5</td><td>1385.1</td><td>97.3</td></tr><tr><td>750</td><td>15</td><td>29.8</td><td>58.6</td><td>2148.4</td><td>56.2</td></tr></table> |                                                                                                                                                                                                                                                                                                                                                         | APF530 dose (mg) | granisetron (mg)     | C <sub>max</sub> (ng/mL) | %RSD | AUC 0-168 (ng·hr/mL) | %RSD | 125 | 2.5 | 2.04 | 60.8 | 60.4 | 75.2 | 250 | 5 | 4.17 | 59.2 | 131 | 75.3 | 500 | 10 | 10.6 | 74.6 | 343 | 80.2 | 1000 | 20 | 18.1 | 47.3 | 658 | 33.3 | APF530 dose (mg) | granisetron (mg) | C <sub>max</sub> (ng/mL) | %RSD | AUC 0-168 | %RSD | 250 | 5 | 11.6 | 58.9 | 740.3 | 97.5 | 500 | 10 | 17.8 | 72.5 | 1385.1 | 97.3 | 750 | 15 | 29.8 | 58.6 | 2148.4 | 56.2 |
| APF530 dose (mg)                                                                                                                                                                         | granisetron (mg)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | C <sub>max</sub> (ng/mL)                                                                                                                                                                                                                                                                                                                                | %RSD             | AUC 0-168 (ng·hr/mL) | %RSD                     |      |                      |      |     |     |      |      |      |      |     |   |      |      |     |      |     |    |      |      |     |      |      |    |      |      |     |      |                  |                  |                          |      |           |      |     |   |      |      |       |      |     |    |      |      |        |      |     |    |      |      |        |      |
| 125                                                                                                                                                                                      | 2.5                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | 2.04                                                                                                                                                                                                                                                                                                                                                    | 60.8             | 60.4                 | 75.2                     |      |                      |      |     |     |      |      |      |      |     |   |      |      |     |      |     |    |      |      |     |      |      |    |      |      |     |      |                  |                  |                          |      |           |      |     |   |      |      |       |      |     |    |      |      |        |      |     |    |      |      |        |      |
| 250                                                                                                                                                                                      | 5                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | 4.17                                                                                                                                                                                                                                                                                                                                                    | 59.2             | 131                  | 75.3                     |      |                      |      |     |     |      |      |      |      |     |   |      |      |     |      |     |    |      |      |     |      |      |    |      |      |     |      |                  |                  |                          |      |           |      |     |   |      |      |       |      |     |    |      |      |        |      |     |    |      |      |        |      |
| 500                                                                                                                                                                                      | 10                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | 10.6                                                                                                                                                                                                                                                                                                                                                    | 74.6             | 343                  | 80.2                     |      |                      |      |     |     |      |      |      |      |     |   |      |      |     |      |     |    |      |      |     |      |      |    |      |      |     |      |                  |                  |                          |      |           |      |     |   |      |      |       |      |     |    |      |      |        |      |     |    |      |      |        |      |
| 1000                                                                                                                                                                                     | 20                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | 18.1                                                                                                                                                                                                                                                                                                                                                    | 47.3             | 658                  | 33.3                     |      |                      |      |     |     |      |      |      |      |     |   |      |      |     |      |     |    |      |      |     |      |      |    |      |      |     |      |                  |                  |                          |      |           |      |     |   |      |      |       |      |     |    |      |      |        |      |     |    |      |      |        |      |
| APF530 dose (mg)                                                                                                                                                                         | granisetron (mg)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | C <sub>max</sub> (ng/mL)                                                                                                                                                                                                                                                                                                                                | %RSD             | AUC 0-168            | %RSD                     |      |                      |      |     |     |      |      |      |      |     |   |      |      |     |      |     |    |      |      |     |      |      |    |      |      |     |      |                  |                  |                          |      |           |      |     |   |      |      |       |      |     |    |      |      |        |      |     |    |      |      |        |      |
| 250                                                                                                                                                                                      | 5                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | 11.6                                                                                                                                                                                                                                                                                                                                                    | 58.9             | 740.3                | 97.5                     |      |                      |      |     |     |      |      |      |      |     |   |      |      |     |      |     |    |      |      |     |      |      |    |      |      |     |      |                  |                  |                          |      |           |      |     |   |      |      |       |      |     |    |      |      |        |      |     |    |      |      |        |      |
| 500                                                                                                                                                                                      | 10                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | 17.8                                                                                                                                                                                                                                                                                                                                                    | 72.5             | 1385.1               | 97.3                     |      |                      |      |     |     |      |      |      |      |     |   |      |      |     |      |     |    |      |      |     |      |      |    |      |      |     |      |                  |                  |                          |      |           |      |     |   |      |      |       |      |     |    |      |      |        |      |     |    |      |      |        |      |
| 750                                                                                                                                                                                      | 15                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | 29.8                                                                                                                                                                                                                                                                                                                                                    | 58.6             | 2148.4               | 56.2                     |      |                      |      |     |     |      |      |      |      |     |   |      |      |     |      |     |    |      |      |     |      |      |    |      |      |     |      |                  |                  |                          |      |           |      |     |   |      |      |       |      |     |    |      |      |        |      |     |    |      |      |        |      |
| Accumulation at steady state                                                                                                                                                             | Mean (%CV); specify dosing regimen<br><br>Not studied with APF530                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                                                         |                  |                      |                          |      |                      |      |     |     |      |      |      |      |     |   |      |      |     |      |     |    |      |      |     |      |      |    |      |      |     |      |                  |                  |                          |      |           |      |     |   |      |      |       |      |     |    |      |      |        |      |     |    |      |      |        |      |
| Metabolites                                                                                                                                                                              | Include listing of all metabolites and activity<br><br>Not studied with APF530, however, granisetron metabolism involves N-demethylation and aromatic ring oxidation followed by conjugation.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                                                                                                                                                                                                                                                                                                                                         |                  |                      |                          |      |                      |      |     |     |      |      |      |      |     |   |      |      |     |      |     |    |      |      |     |      |      |    |      |      |     |      |                  |                  |                          |      |           |      |     |   |      |      |       |      |     |    |      |      |        |      |     |    |      |      |        |      |

|              |                                   |                                                                                                                                                                                                                                                                                                                                                                                                                             |
|--------------|-----------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Absorption   | Absolute/Relative Bioavailability | <p>Mean (%CV)</p> <p>In healthy subjects, complete absolute bioavailability was demonstrated for a dose 500 mg APF530 (10 mg granisetron) to range between 68% to 186%. Presented as a least squares mean ratio and 95% confidence interval was determined to be 131% (84.4% - 203%).</p>                                                                                                                                   |
|              | T <sub>max</sub>                  | <p>• Median (range) for parent</p> <p>In chemo patients for a dose of 500 mg APF530 (10 mg granisetron) the median T<sub>max</sub> for granisetron was observed to be 22.9 hours with a range of 6-118 hours.</p> <p>• Median (range) for metabolites</p> <p>Not studied with APF530</p>                                                                                                                                    |
| Distribution | Vd/F or Vd                        | <p>Mean (%CV)</p> <p>In chemo patients, for a dose of 500 mg APF530 (10 mg granisetron) the mean apparent volume of distribution (Vd/F) was determined to be 943,758 mL with a percent relative standard deviation of 104%</p>                                                                                                                                                                                              |
|              | % bound                           | <p>Mean (%CV)</p> <p>Not studied with APF530, however, granisetron plasma protein binding is approximately 65% and granisetron distributes freely between plasma and red blood cells</p>                                                                                                                                                                                                                                    |
| Elimination  | Route                             | <p>• Primary route; percent dose eliminated</p> <p>Not studied with APF530; however, clearance is predominantly by hepatic metabolism as seen in the healthy volunteers, approximately 12% of the administered dose is eliminated unchanged in the urine in 48 hours. The remainder of the dose is excreted as metabolites, 49% in the urine and 34% in the feces.</p> <p>• Other routes</p> <p>Not studied with APF530</p> |
|              | Terminal t <sub>1/2</sub>         | <p>• Mean (%CV) for parent</p> <p>• Mean (%CV) for metabolites</p> <p>In chemo patients, for a dose of 500 mg APF530 (10 mg granisetron) the elimination half life was determined to be 28.8 hours with a percent relative standard deviation of 39%.</p>                                                                                                                                                                   |
|              | CL/F or CL                        | <p>Mean (%CV)</p> <p>In chemo patients, mean apparent total clearance CL<sub>tot</sub>/F for a dose of 500 mg APF530 (10 mg</p>                                                                                                                                                                                                                                                                                             |

|                                                                                                                                                                                                                                                                              |                                       |                                                                                                                                                                                                                                                                                                                                                                                                             |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                                                                                                                                                                                                                                              |                                       | granisetron) was determined to be 27,499 mL/hr with a percent relative standard deviation of 127%.                                                                                                                                                                                                                                                                                                          |
| <b>Intrinsic Factors</b><br><br><b>Cancer Patients</b><br><br>Comparisons shown for APF530 500 mg dose (10 mg of granisetron)<br><br>AUC data (ng·hr/mL) presented as mean ± standard deviation with relative standard deviation in parenthesis for the time course studied. | <b>Age</b>                            | Specify mean changes in C <sub>max</sub> and AUC<br><br>Under 65 Mean C <sub>24hr</sub> 15.8ng/mL<br>(min: 0.514 ng/mL, max: 85.9 ng/mL)<br><br>AUC 0-120 = 921.5 ± 764.8 (83%)<br>AUC 0-168 = 1156.7 ± 1162.2 (100.5%)<br><br>Over 65 Mean C <sub>24hr</sub> 19.6ng/mL<br>(min: 2.22 ng/mL, max: 35.2 ng/mL)<br><br>AUC 0-120 = 1383.8 ± 679.6 (49.1%)<br>AUC 0-168 = 1121.6 ± 1012.1 (90.2%)              |
|                                                                                                                                                                                                                                                                              | <b>Sex</b>                            | Specify mean changes in C <sub>max</sub> and AUC<br><br>Females Mean C <sub>24hr</sub> 17.3ng/mL<br>(min: 0.514 ng/mL, max: 85.9 ng/mL)<br><br>AUC 0-120 = 1082.2 ± 755.3 (69.8%)<br>AUC 0-168 = 1131.2 ± 1132.2 (100.1%)<br><br>Males Mean C <sub>24hr</sub> 15.1ng/mL<br>(min: 2.21 ng/mL, max: 35.2 ng/mL)<br><br>AUC 0-120 = 1075.2 ± 807.0 (75.1%)<br>AUC 0-168 = 1367.4 ± 1288.0 (94.2%)              |
|                                                                                                                                                                                                                                                                              | <b>Race</b>                           | Specify mean changes in C <sub>max</sub> and AUC<br><br>Caucasians Mean C <sub>24hr</sub> 16.6ng/mL<br>(min: 0.864 ng/mL, max: 85.9 ng/mL)<br><br>AUC 0-120 = 1073.3 ± 746.6 (69.6%)<br>AUC 0-168 = 1113.9 ± 1151.3 (103.4%)<br><br>Non-Caucasians Mean C <sub>24hr</sub> 17.9ng/mL<br>(min: 0.514 ng/mL, max: 41.9 ng/mL)<br><br>AUC 0-120 = 1094.7 ± 825.3 (75.4%)<br>AUC 0-168 = 1413.8 ± 1111.3 (78.6%) |
|                                                                                                                                                                                                                                                                              | <b>Hepatic &amp; Renal Impairment</b> | Specify mean changes in C <sub>max</sub> and AUC<br><br>Not studied with APF530, however in patients with hepatic impairment due to neoplastic liver involvement, total plasma clearance following a single 40 mcg/kg intravenous dose of granisetron hydrochloride was approximately halved compared to patients without hepatic impairment. Given the wide variability in                                 |

|                                                                                                                                                                                                                                                                       |                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                                                                                                                                                                                                                                       |                                                                                                                                                                              | <p>pharmacokinetic parameters of granisetron and the good tolerance of doses well above the recommended dose, dose adjustment in patients with hepatic functional impairment is not necessary.</p> <p>Total clearance of granisetron was not affected in patients with severe renal failure who received a single 40 mcg/kg intravenous dose of granisetron hydrochloride.</p>                                                                                                               |
| <p><b>Extrinsic Factors</b></p> <p>Cancer Patients Comparisons shown for APF530 500 mg dose (10 mg of granisetron)</p> <p>AUC data (ng·hr/mL) presented as mean ± standard deviation with relative standard deviation in parenthesis for the time course studied.</p> | <b>Drug interactions</b>                                                                                                                                                     | <p>Include listing of studied DDI studies with mean changes in C<sub>max</sub> and AUC</p> <p>Anthracycline Used in Chemotherapy Mean C<sub>24hr</sub> 15.9 ng/mL (min: 2.21 ng/mL max: 76.4 ng/mL)</p> <p>AUC 0-120 = 861.7 ± 591.2 (68.6%)<br/>AUC 0-168 = 956.2 ± 1015.7 (106.2%)</p> <p>Anthracycline Not used in Chemotherapy Mean C<sub>24hr</sub> 17.1 ng/mL (min: 0.514 ng/mL max: 85.9 ng/mL)</p> <p>AUC 0-120 = 1167.4 ± 811.9 (69.6%)<br/>AUC 0-168 = 1228.9 ± 1181.6 (96.2%)</p> |
|                                                                                                                                                                                                                                                                       | <b>Food Effects</b>                                                                                                                                                          | <p>Specify mean changes in C<sub>max</sub> and AUC and meal type (i.e., high-fat, standard, low-fat)</p> <p>Not available</p>                                                                                                                                                                                                                                                                                                                                                                |
| <b>Expected High Clinical Exposure Scenario</b>                                                                                                                                                                                                                       | <p>Describe worst case scenario and expected fold-change in C<sub>max</sub> and AUC. The increase in exposure should be covered by the supra-therapeutic dose. See below</p> |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |

## 6.2 (CLIN) TABLE OF STUDY ASSESSMENTS

Copy from protocol/study report

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/s/  
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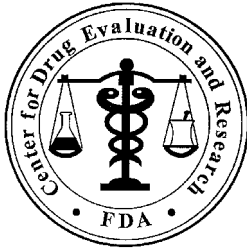
JANICE B BRODSKY  
12/21/2012

QIANYU DANG  
12/21/2012

JEE E LEE  
12/21/2012

KEVIN M KRUDYS  
01/02/2013

NORMAN L STOCKBRIDGE  
01/02/2013



**Department of Health and Human Services**  
**Public Health Service**  
**Food and Drug Administration**  
**Center for Drug Evaluation and Research**  
**Office of Surveillance and Epidemiology**

Date: March 4, 2010

To: Donna Griebel, MD, Director  
Division of Gastroenterology Products

Through: Kristina C. Arnwine, PharmD, Team Leader  
Denise Toyer, PharmD, Deputy Director  
Division of Medication Error Prevention and Analysis

From: Tselaine Jones Smith, PharmD, Safety Evaluator  
Division of Medication Error Prevention and Analysis

Subject: Labeling Review

Drug Name(s): Sustol (Granisetron) Extended-Release for Injection, 10 mg

Application Type/Number: NDA 022445

Sponsor: A.P. Pharma

OSE RCM #: 2009-1392

## **1 INTRODUCTION**

This review is written in response to a request from the Division of Gastroenterology Products (DGP) for a review of the syringe label, carton labeling, package insert labeling and 'kit insert' labeling for Sustol (Granisetron (b) (4)) from a medication error perspective.

## **2 CONCLUSION**

We acknowledge receipt of your July 20, 2009, consult request for the proposed product labeling (syringe label, carton labeling, package insert labeling and 'kit insert' labeling) for Sustol. DMEPA notes the outcome of the Team Meeting on January 25, 2010, during which DGP determined that final labeling negotiations would not be initiated during the current review cycle and that a Complete Response letter would be issued. Therefore, DMEPA will provide comments regarding labeling for this application during the subsequent review cycle. DMEPA requests that DGP submit a new consult request for the labeling and proprietary name upon receipt of the Applicant's complete response to the deficiencies.

We would be willing to meet with the Division for further discussion, if needed. Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have questions or need clarifications, please contact OSE Project Manager, Nitin Patel, at 301-796-5412.

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

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/s/

TSELAIN E JONES SMITH  
03/04/2010

KRISTINA C ARNWINE  
03/04/2010

DENISE P TOYER  
03/04/2010

**M E M O R A N D U M**

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

---

**CLINICAL INSPECTION SUMMARY**

DATE:

TO: Todd Phillips, Regulatory Project Manager  
Karyn Berry, Medical Officer  
Division of Gastrointestinal Drug Products

FROM: Khairy W. Malek, M.D.  
Good Clinical Practice Branch 2  
Division of Scientific Investigations

THROUGH: Tejashri Purohit-Sheth, M.D.  
Branch Chief  
Good Clinical Practice Branch 2  
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections.

NDA or BLA: 22-445

APPLICANT: A.P. Pharma, Inc.

DRUG: Sustol TM (granisetron)

NME: No

THERAPEUTIC CLASSIFICATION: Standard

INDICATIONS: Prevention of acute-onset and delayed-onset chemotherapy-  
Induced nausea and vomiting

CONSULTATION REQUEST DATE: September 24, 2009

DIVISION ACTION GOAL DATE: March 18, 2010

PDUFA DATE: March 18, 2010

CIS Goal Date: February 5, 2010

## I. BACKGROUND:

Granisetron is an approved anti-nauseant and antiemetic drug for the prevention of chemotherapy-induced; radiation induced; and post-operative nausea and vomiting. The new application is a new formulation for a sustained delivery of the drug, for the prevention of acute and delayed chemotherapy-induced nausea and vomiting (CINV). One pivotal study was submitted in support of this application:

Protocol: # and Title: C2006-01 “A Pivotal Phase 3 Observer-Blind, Randomized Clinical Trial of the Efficacy and Safety of APF530 Compared to “Aloxi” for the Prevention of Acute-Onset and Delayed-Onset Chemotherapy-Induced Nausea and Vomiting Following the Administration of Either Moderately or Highly Emetogenic Chemotherapy Regimens”.

Efficacy Primary Endpoints:

1. Complete response (CR) defined as “No emetic episodes and no use of rescue medication” during the acute phase (0-24 hours) following the administration of chemotherapy in Treatment Cycle 1.
2. CR during the delayed-onset phase (24-120 hours) following the administration of chemotherapy in Treatment Cycle 1. CR will be measured in 24-hour increments up to 120 hours.

Two clinical sites were inspected in support of this application: Site 003 (Dr. Gabrail) and Site 007 (Dr. Charu).

## II. RESULTS (by Site):

| Name of CI, IRB, or Sponsor Location                                                     | Protocol #: and # of Subjects: | Inspection Date    | Final Classification |
|------------------------------------------------------------------------------------------|--------------------------------|--------------------|----------------------|
| Nashat Gabrail, M.D.<br>4875 Highbee Ave. NW<br>Canton, OH 44718<br>Site # 003           | C2006-01<br>85 subjects        | 12/1-<br>12/17/09  | VAI                  |
| Veena Charu, M.D.<br>1801 W Romneya Dr.,<br>Suite 203<br>Anaheim, CA 92801<br>Site # 007 | C2006-01<br>78 subjects        | 11/23-<br>11/30/09 | NAI                  |

### Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

Pending = Preliminary classification based on information in 483 or preliminary

communication with the field; EIR has not been received from the field and complete review of EIR is pending.

**1. Site # 003-Nashat Gabrail, M.D.**

Gabrail Cancer Center, 4875 Highbee Avenue NW, Canton OH 44718

- a. What was inspected: At this site 86 subjects were randomized and 75 subjects completed the study. There were 5 deaths; 2 lost to follow-up and 3 were withdrawn.

The field investigator reviewed the records of 20 subjects completely plus the records of another 20 subjects for inclusion/exclusion criteria, AEs and comparison of the CRFs to the sponsor's data listings. There was substantial correspondence between source documents and the CRFs and sponsor listing provided. There was no limitation to the inspection.

b. General observations/commentary:

The inspection revealed an important protocol violation in that the first 49 subjects were given additional "Solu-Medrol" injections. The CI defended his action as that was the standard of care in his practice and that he was unaware of the protocol restriction till the monitor brought this subject to his attention. Two other subjects, # 67 & 79 received anti-emetics and Subject #66 received lorazepam, a protocol prohibited drug.

c. Assessment of data integrity:

Although the study, in general, appears to have been conducted adequately, the finding that the first 49 subjects were given additional Solu-Medrol injections represents a protocol violation for a large number of subjects. Whether this finding is considered clinically significant, is deferred to the review division. Depending on whether this is considered clinically significant, the review division may choose to exclude these subjects in their analyses. The remaining subjects' data (about 35) can be used in support of the NDA indication, and perhaps the data from the 49 subjects as well, depending on the review division's determination of the clinical significance of the finding and the impact in the evaluation of safety and efficacy.

**2. Site 007-Veena Charu, M. D.**

PCMI Inc., 1801 West Romney Drive, Suite 203, Anaheim CA 82801

a. What was inspected:

At this site 78 were enrolled into the study; sixty eight (68) subjects completed the study. An audit of all the 78 subjects' records and comparison of source documentation to case report forms (CRFs) and data listings were conducted. There was no limitation to the inspection.

b. General Observations/Commentary:

The study appears to have been conducted adequately at this site. The inspection revealed no violations of federal regulations and a Form FDA-483 was not issued.

c. Assessment of data integrity:

The data from this site can be used in support of the NDA indication.

#### **IV. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS**

Two clinical investigators, Dr. Gabrail and Dr. Charu, were inspected in support of this application. Apart from the subjects who received protocol un-approved medications mentioned above at Dr. Gabrail's site, the data from the remaining subjects at Dr. Gabrail's site and the data from Dr. Charu's site can be used in support of the NDA indication. Depending on the review division's determination of the clinical significance of the finding at Dr. Gabrail's site described above and the impact of this finding in the evaluation of safety and efficacy, the data from these subjects may also be considered in support of the NDA.

{See appended electronic signature page}

Khairy Malek, M.D.  
Good Clinical Practice Branch II  
Division of Scientific Investigations

#### **CONCURRENCE:**

{See appended electronic signature page}

Tejashri Purohit-Sheth, M.D.  
Branch Chief  
Good Clinical Practice Branch II  
Division of Scientific Investigations

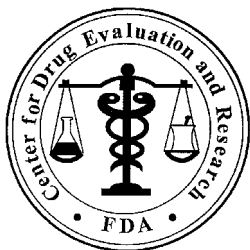
| Application<br>Type/Number | Submission<br>Type/Number | Submitter Name | Product Name |
|----------------------------|---------------------------|----------------|--------------|
| NDA-22445                  | ORIG-1                    | AP PHARMA INC  | APF530       |

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/s/

KHAIRY W MALEK  
02/22/2010

TEJASHRI S PUROHIT-SHETH  
02/22/2010



**Department of Health and Human Services**  
**Public Health Service**  
**Food and Drug Administration**  
**Center for Drug Evaluation and Research**  
**Office of Surveillance and Epidemiology**

Date: February 22, 2010

To: Donna Griebel, MD, Director  
Division of Gastroenterology Products

Through: Kristina C. Arnwine, PharmD, Team Leader  
Denise Toyer, PharmD, Deputy Director  
Carol Holquist, RPh, Director  
Division of Medication Error Prevention and Analysis

From: Tselaine Jones Smith, PharmD, Safety Evaluator  
Division of Medication Error Prevention and Analysis

Subject: Product Design Review

Drug Name: Sustol (Granisetron) Extended-release Injection  
10 mg per single-use syringe

Application Type/Number: NDA # 022445

Applicant: AP Pharma

OSE RCM #: 2009-1329

## CONTENTS

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| INTRODUCTION .....               | 3 |
| 1    METHODS AND MATERIALS ..... | 3 |
| 2    COMMENTS .....              | 3 |

## INTRODUCTION

This review responds to a request from the Division of Gastroenterology Products for the Division of Medication Error Prevention and Analysis to summarize the medication error concerns regarding the proposed product design of Sustol (Granisetrol (b) (4)). These concerns were forwarded to the Division in an email on December 8, 2009. Subsequently, the concerns were communicated to the Applicant in an Information Request letter dated December 15, 2009.

## 1 METHODS AND MATERIALS

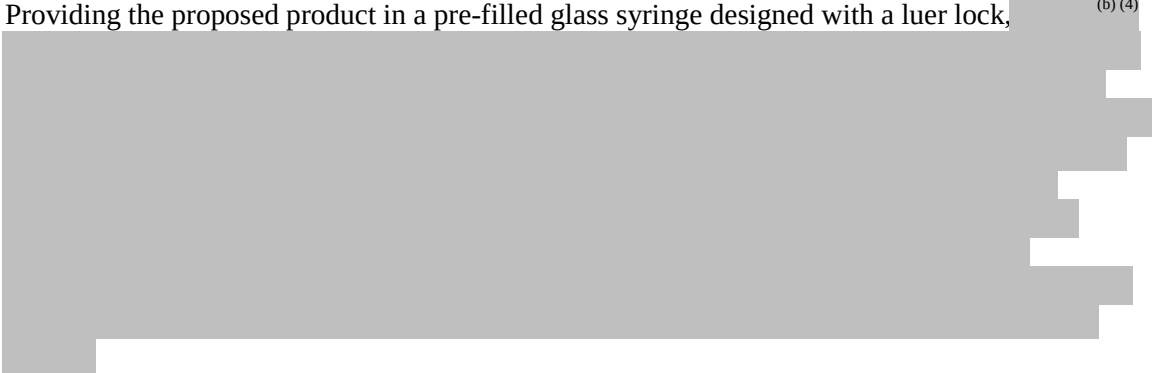
The Division of Medication Error Prevention and Analysis (DMEPA) used Failure Mode and Effects Analysis (FMEA)<sup>1</sup> in our evaluation of the product design of the Sustol kit submitted September 15, 2009.

## 2 COMMENTS

DMEPA's review of the proposed product design for Sustol (Granisetrol (b) (4)) identified several potential sources of medication error specifically with respect to product preparation, wrong route of administration, and overdose.

### 1. Product design may lead to wrong route of administration and overdose

Sustol is recommended for subcutaneous administration. However, most products within the same class of drugs, antiemetic 5HT<sub>3</sub> receptor antagonists, are administered orally or intravenously. Since this will be the first granisetrol product administered by a different route, confirmation bias with pre-existing products may lead to wrong route of administration errors as healthcare practitioners will be familiar with granisetrol injection being administered intravenously. Additionally, features of the product design can also contribute to errors leading to administration of granisetrol via the wrong route leading to overdose.

- a. Providing the proposed product in a pre-filled glass syringe designed with a luer lock, (b) (4)  

- b. In the December 2, 2009 teleconference, the Applicant stated if the needle were attached to the luer-lock, it would be difficult to administer the product from the pre-filled glass syringe. The Applicant stated due to the syringe's diameter and the viscosity of the product there would have to be a significant amount of force applied to the plunger in order to expel the contents. However, we attached the syringe to the luer lock on the glass syringe and found that we were able to expel the product through the needle with minimal force applied to the plunger.
- c. This product requires (b) (4)  
. Thus, the proposed process is inconsistent with the usual practice for

---

<sup>1</sup> Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

preparation and administration of products packaged in pre-filled syringes and can lead to preparation and administration errors. During the teleconference FDA inquired whether or not [REDACTED] (b) (4). From a microbiology and medication error perspective, supplying this product in a single syringe [REDACTED] (b) (4)

- d. Providing the product in a pre-filled syringe along [REDACTED] (b) (4)

2. [REDACTED] (b) (4) Needle of Subcutaneous Injection

3. In the December 2, 2009 teleconference, the Applicant stated that usability studies were completed. Provide the protocol used in the usability studies. In addition, provide the raw data and summary of the study findings along with revisions that were made to the product design, packaging, labels and labeling based on the study results.

4. [REDACTED] (b) (4)

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have questions or need clarifications, please contact OSE Project Manager, Nitin Patel at 301-796-5412.

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

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/s/

TSELAINE E JONES SMITH  
02/22/2010

KRISTINA C ARNWINE  
02/22/2010

CAROL A HOLQUIST on behalf of DENISE P TOYER  
02/22/2010

CAROL A HOLQUIST  
02/22/2010

**MEMORANDUM**  
**DEPARTMENT OF HEALTH AND HUMAN SERVICES**  
**FOOD AND DRUG ADMINISTRATION**  
**CENTER FOR DRUG EVALUATION AND RESEARCH**  
**CONTROLLED SUBSTANCE STAFF**

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**Date:** February 22, 2010

**To:** Donna Griebel, M.D., Director  
Division of Gastroenterology Products

**Through:** Michael Klein, Ph.D., Director  
Silvia Calderon, Ph.D., Team Leader  
Controlled Substance Staff

**From:** Katherine Bonson, Ph.D., Pharmacologist  
Controlled Substance Staff

**Subject:** NDA Review  
Labeling Recommendations  
NDA 22-445  
Sustol (granisetron injection), 10 mg/0.4 ml single-use glass syringe  
Indication: (b) (4)  
Sponsor: A.P. Pharma, Inc.

**Summary:**

Granisetron was first approved by FDA in 1994 under the tradename Kytril as a treatment for nausea and vomiting associated with cancer chemotherapy and radiation-therapy. Three formulations of granisetron (oral tablets, oral solution and intravenous solution) are currently approved. None of the labels for these products include Section 9.0 "Drug Abuse and Dependence" and none include any information on abuse potential or physical dependence.

In the present submission, Sustol (granisetron injection; NDA 22-445) (b) (4). The proposed dose is a single 10 mg subcutaneous dose administered ~30 minutes before the start of a single-day chemotherapy. The Sponsor submitted no information on abuse potential or physical dependence in the NDA and excluded Section 9.0 "Drug Abuse and Dependence" from the proposed drug label.

In this document, CSS describes information reviewed regarding the abuse potential of granisetron and proposes the inclusion of Section 9.0 Drug Abuse and Dependence of the drug label.

### **Label Text Recommendation**

\* Based on the evaluation of available data (see Summary of Information Reviewed below), CSS proposes the following label text revision for Section 9.0 Drug Abuse and Dependence:

#### *9.0 Drug Abuse and Dependence*

##### *9.1 Controlled Substance Class*

Granisetron is not a controlled substance.

##### *9.2 Abuse*

There are no signals in epidemiological databases or in the scientific and medical literature that suggest granisetron has abuse potential compared to other antiemetic drugs. However, granisetron has not been prospectively evaluated for abuse potential. Thus, it is not possible to predict the extent to which a CNS-active drug will be misused, diverted and/or abused.

##### *9.3 Dependence*

There are no signals in epidemiological databases or in the scientific and medical literature that suggest granisetron produces physical dependence. However, granisetron has not been prospectively evaluated for physical dependence. Thus, it is not possible to predict the extent to which a CNS-active drug will produce physical or psychiatric symptoms upon discontinuation.

### **Summary of Information Reviewed**

In order to prepare an accurate drug label for Section 9.0 Drug Abuse and Dependence, CSS reviewed abuse-related data submitted in the NDA, epidemiological data, and information available in the scientific and medical literature.

#### *Abuse-Related Data in the NDA Submission*

The Sponsor submitted no abuse-related data in the NDA submission. A review of the clinical adverse events (AEs) show very few CNS-related AEs. Of those listed, the predominant AE was headache (2.8% incidence), with other CNS AEs reported with an incidence of < 1% (dizziness, anxiety and restlessness). In the absence of a euphoria-related AE signal, these CNS AEs do not indicate that granisetron has abuse potential.

The NDA also did not include any information related to the evaluation of physical dependence. The proposed drug label, and previously approved drug labels for marketed

granisetron drug products, do not include information about physical dependence, including information about withdrawal.

The medical officer in the Division of Gastroenterology Products, Dr. Karyn Berry, confirmed in several conversations during the course of her NDA review that this NDA submission for granisetron did not show any signals from clinical trials that were indicative of abuse potential or physical dependence.

### *Epidemiological Data*

Epidemiological surveys can provide important indicators of whether a drug is being misused or abused by the general population. Information about granisetron is available in the Drug Abuse Warning Network (DAWN), a national public health surveillance system sponsored by SAMHSA that monitors drug-related emergency department (ED) visits for the Nation and for selected metropolitan areas.

DAWN relies on a national sample of general, non-Federal hospitals operating 24-hour EDs. DAWN is designed to obtain information on all drug-related ED visits, regardless of the motive for using the drug. DAWN captures data on all drugs: illicit drugs, prescription and over-the-counter pharmaceuticals, dietary supplements, nonpharmaceutical inhalants, alcohol when it is combined with another drug and, for patients under age 21, ED visits where alcohol is the only substance.

One measure provided by DAWN is that of nonmedical use of a pharmaceutical (NMUP), which represents drug-related ED visits that involve taking more than the prescribed dose of a prescription pharmaceutical or more than the recommended dose of an OTC pharmaceutical or supplement; taking a pharmaceutical prescribed for another individual; deliberate poisoning with a pharmaceutical by another person; and documented misuse or abuse of a prescription or OTC pharmaceutical or dietary supplement. NMUP may involve pharmaceuticals alone or pharmaceuticals in combination with illicit drugs or alcohol.

Data in DAWN's "National Estimates of Drug-Related Emergency Department Visits, 2004-2008" were analyzed to determine the number of NMUP related to use of any "antiemetic/antivertigo agent". This category of drugs includes 5HT3 receptor antagonist antiemetics (such as marketed granisetron drug products), phenothiazine antiemetics, anticholinergic antiemetics and miscellaneous antiemetics. Out of the subclasses of drugs in this category, the number of ED visits in which 5HT3 receptor antagonist antiemetics, phenothiazine antiemetics or miscellaneous antiemetics were mentioned were so low that the data for each drug class produced either an estimate with a relative standard error greater than 50%, or a count or estimate less than 30. Thus, the data were suppressed for these three drug subclasses. In contrast, data from the fourth subclass of "antiemetic/antivertigo agents", the anticholinergic antiemetics, accounted for nearly 90% of the ED mentions for this class of drugs. Anticholinergic drugs are not recognized as drugs of abuse and none are scheduled under the Controlled Substances Act.

Thus, the epidemiological data from DAWN suggest that granisetron does not have abuse potential, similar to that of other non-scheduled antiemetic/antivertigo agents.

*Evidence of Abuse Potential of Granisetron in the Scientific and Medical Literature*

CSS conducted a PubMed search of the scientific and medical literature regarding the abuse potential of granisetron. Specifically, a search was conducted to determine the availability of papers responsive to both “granisetron” and such terms as “abuse”, “addiction”, “euphoria”, “reward”, “reinforcement”, “dependence”, “self-administration”, “discrimination” and “withdrawal”.

This search did not reveal any evidence from case reports in humans or abuse-related studies in animals or humans that granisetron has abuse potential.

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

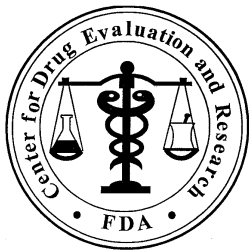
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/s/

KATHERINE R BONSON  
02/22/2010

SILVIA N CALDERON  
02/22/2010

MICHAEL KLEIN  
02/22/2010



**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology**

Date: February 12, 2010

To: Donna Griebel, MD, Director  
**Division of Gastroenterology Products (DGP)**

Through: Mary Willy, PhD, Deputy Director  
**Division of Risk management (DRISK)**

From: Sharon R. Mills, BSN, RN, CCRP  
Senior Patient Labeling Reviewer, Acting Team Leader  
Steve L. Morin, RN, BSN, OCN  
Patient Labeling Reviewer  
**Division of Risk Management**

Subject: Memo to File re: DRISK Review of Patient Labeling (Patient Package Insert)

Drug Name(s): Sustol (granisetron) Subcutaneous Injection

Application Type/Number: NDA 22-445

Applicant/sponsor: AP Pharma INC.

OSE RCM #: 2009-1334

The Division of Gastroenterology Products (DGP) requested that the Division of Risk Management review proposed patient labeling for New Drug Application (NDA) 22-445 submitted by AP Pharma INC for Sustol (granisetron) Subcutaneous Injection.

DGP does not plan to address labeling at this time. Therefore, we will defer our review of the Patient Package Insert until such time as the review division plans to address labeling. Please send us a new consult request at that time. This memo serves to close-out the consult request for Sustol (granisetron) Subcutaneous Injection.

Please let us know if you have any questions.

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

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/s/

STEVE L MORIN  
02/12/2010  
DRISK Deferral Memo

MARY E WILLY  
02/14/2010

**MEMORANDUM**

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

**DATE:** January 28, 2010

**TO:** File

**FROM:** Todd Phillips, Regulatory Project Manager

**SUBJECT:** CDRH/ODE/DAGID Consult Review in Support of Review of NDA 022445

**APPLICATION/DRUG:** NDA 022445/granisetron injection, subcutaneous

On December 8, 2009, The Division of Gastroenterology Products sent a request for consultation to the Office of Device Evaluation/Division of Anesthesiology, General Hospital, Infection Control, and Dental Devices (ODE/DAGID). The attached review is included in this application for ease of reference.

Attachment: CDRH/ODE/DAGID Review of NDA 022445



DEPARTMENT OF HEALTH AND HUMAN SERVICES

MEMORANDUM

Food and Drug Administration  
Center for Devices and  
Radiological Health  
Office of Device Evaluation  
White Oak Building 66  
10903 New Hampshire Avenue  
Silver Spring, MD 20993

**Date:** January 12, 2010  
**From:** Weihong Gu  
General Hospital Devices Branch, DAGID, ODE, CDRH  
**To:** Todd D Phillips  
CDER/OND/ODE3/DGP  
**Subject:** Drug product APF530

Device Sponsor: A.P. Pharma, Inc.  
Device Name: Drug product APF530

**1. Background**

A.P. Pharma utilizes (b) (4) syringe barrel with luer tip as the primary closure system for drug product APF530. The product is viscous in nature and presents unique challenges to the drug delivery system utilized to administer the product to subjects / patients. The APF530 drug product is presently administered to subjects / patients. (b) (4)

**2. Devices**

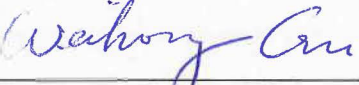
- (b) (4)
- 
- 
- 

*Reviewer's Note: In the submission we found above devices used in the Drug product APF530. However it is not clear to identify which needle will be used in the system. The sponsor needs to clearly indicate all of the devices used in the Drug product APF530 system. If the device has been approved by FDA please list the 510(K) number as well. They also need to provide the description of each device used in the system.*

**3. Materials**

The sponsor has presented the product description of device (b) (4) (b) (4)

8. You did not provide the biocompatibility test for all of the devices. These are body contact devices. Please provide Agency with the biocompatibility test protocols, pass/fail criteria and test results for all of the devices used in the system. Please provide the list of the FDA recognized standards are cited as well. We recommend the biocompatibility test should be followed by ISO 10993 serial or its equivalent.
9. We can not find the performance bench testing information for all of the devices in the submission. Please provide/indicate verification tests protocols, pass/fail criteria and test results to demonstrate all of the system devices meet the design requirements. For example the test of stiffness, resistance to breakage, resistance to corrosion, leak, and hub retention force testing for the (b) (4) needle; the test of leak, injection force, dose accuracy delivery etc, for (b) (4) syringe.

  
Weihong Gu

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

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/s/

TODD D PHILLIPS  
01/28/2010

**FOOD AND DRUG ADMINISTRATION  
Center for Drug Evaluation and Research  
Division of Drug Marketing, Advertising, and Communications**

**\*\*\*\*Pre-decisional Agency Information\*\*\*\***

**Memorandum**

**Date:** January 25, 2010

**To:** Todd Phillips, Regulatory Project Manager  
Division of Gastroenterology Products (DGP)

**From:** Shefali Doshi, Regulatory Review Officer  
Kathleen Klemm, Regulatory Review Officer  
Division of Drug Marketing, Advertising, and Communications (DDMAC)

**CC:** Robert Dean, DTC Group Leader  
Lisa Hubbard, Professional Group Leader  
DDMAC

**Subject:** NDA 22-445

DDMAC labeling comments for Granisetron subcutaneous injection

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We acknowledge receipt of your July 20, 2009, consult request for the proposed product labeling (Package Insert (PI), Patient Package Insert (PPI) and Carton and Container Labeling) for Granisetron subcutaneous injection, NDA 22-445. DDMAC notes the outcome of the Team Meeting on January 25, 2010, during which DGP determined that final labeling negotiations would not be initiated during the current review cycle and that a Complete Response letter would be issued. Therefore, DDMAC will provide comments regarding labeling for this application during a subsequent review cycle. DDMAC requests that DGP submit a new consult request during the subsequent review cycle.

Thank you for the opportunity to comment on these proposed materials.

If you have any questions regarding the PPI, please contact Shefali Doshi at 301.796.1780 or Shefali.Doshi@fda.hhs.gov. If you have any questions regarding the PI or Carton and Container Labeling, please contact Katie Klemm at 301.796.3946 or Kathleen.Klemm@fda.hhs.gov.

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

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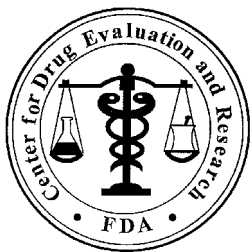
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KATHLEEN KLEMM  
01/25/2010



**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology**

Date: October 30, 2009

To: Deveonne Hamilton-Stokes  
Safety Evaluator  
Division of Medication Error Prevention and Analysis (DMEPA)  
Office of Surveillance and Epidemiology

Thru: Laura Governale, Pharm.D., MBA  
Drug Use Data Analyst Team Leader  
Division of Epidemiology  
Office of Surveillance and Epidemiology

From: Patty Greene, Pharm.D.  
Drug Use Data Analyst  
Division of Epidemiology  
Office of Surveillance and Epidemiology

Subject: Extent of use for Sosol<sup>®</sup> (sulfisoxazole) – potential confusion with  
“Sustol” trade name review

Drug Name(s): “Sustol” (secondary name)  
(granisetron) subcutaneous injection 10mg

Application Type/Number: NDA 22-445

Submission Number:

Applicant/sponsor: A.P. Pharma, Inc.

OSE RCM #: 2009-1600

## 1 INTRODUCTION

The Division of Medication Error Prevention and Analysis (DMEPA) is conducting a trade name review for “Sustol” (granisetron) subcutaneous injection, a serotonin 5HT<sub>3</sub> receptor antagonist indicated for the prevention of chemotherapy-induced nausea and vomiting. In support of that assessment, usage data on a similarly named product, oral Sosol<sup>®</sup> (sulfisoxazole) tablet, was requested to evaluate the frequency of dispensing for that product as a potential for trade name confusion for years 2003 through 2008. Oral Sosol<sup>®</sup> (sulfisoxazole) tablets manufactured by MK Laboratories are no longer marketed in the United States.

## 2 METHODS AND MATERIAL

### 2.1 DATA SOURCES

Proprietary drug use databases licensed by the Agency were used to conduct this analysis. Outpatient use was measured using SDI, Vector One<sup>®</sup>: National (VONA) – see Appendix for full database description. From this data source, nationally projected estimates of the numbers of total (new and refill) prescriptions were obtained for sulfisoxazole products.

In addition, dispensed *new* prescriptions characterized as Prescribed New Prescriptions (PNRx), Dispensed as Written (DAW), Filled by Other Generic (FBOG), and Filled by Other Brand (FBOB) were obtained for sulfisoxazole products. These parameters are part of SDI’s substitution data, which tracks how a product was originally prescribed by a physician in addition to how a pharmacist ultimately dispenses it.

Prescribed New Prescription (PNRx): The number of times a product was prescribed; applies to newly written prescriptions (not refills). Equals DAW + FBOG + FBOB.

Dispensed As Written (DAW): Prescription dispensed by the pharmacist as it is written by the physician.

Filled By Other Generic (FBOG): Prescribed prescriptions for a generic product that was filled by a generic product.

Filled By Other Brand (FBOB): A generic product is prescribed and filled with a branded generic product.

## 3 DATA

During years 2003 through 2008, there were no dispensed prescriptions for oral Sosol<sup>®</sup> tablets. For year 2008, approximately (b) (4) total prescriptions (new and refill) were dispensed through outpatient retail pharmacies for sulfisoxazole products. Of the total prescriptions dispensed in year 2008, (b) (4) were filled as the generic product (**Table 1**).

Table 1. Total number of dispensed prescriptions for Sulfisoxazole oral tablets from U.S. outpatient retail pharmacies, Years 2003 - 2008

|               | 2003    |       | 2004 |       | 2005 |       | 2006 |       | 2007 |       | 2008 |       |
|---------------|---------|-------|------|-------|------|-------|------|-------|------|-------|------|-------|
|               | TRxs    | Share | TRxs | Share | TRxs | Share | TRxs | Share | TRxs | Share | TRxs | Share |
|               | N       | %     | N    | %     | N    | %     | N    | %     | N    | %     | N    | %     |
| Grand Total   | (b) (4) |       |      |       |      |       |      |       |      |       |      |       |
| Sulfisoxazole |         |       |      |       |      |       |      |       |      |       |      |       |
| Gulfasin      |         |       |      |       |      |       |      |       |      |       |      |       |

Source: SDI Vector One<sup>®</sup>: National, Data Extracted October-2009. File: VONA 2009-1600 Sustol Tradename TRx 10-26-09.xls

We further examined dispensed *new* prescriptions for sulfisoxazole products to ascertain how a product was originally prescribed by a physician and, subsequently, how a pharmacist ultimately dispensed it. Table 2 below shows the number of dispensed *new* prescriptions for oral sulfisoxazole products for years 2003 through 2008.

Table 2. Projected number of new prescriptions written for sulfisoxazole products from U.S. outpatient retail pharmacies, Years 2003 - 2008

|                      | 2003    |       | 2004  |       | 2005  |       | 2006  |       | 2007  |       | 2008  |       |
|----------------------|---------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|
|                      | PNRXs   | Share | PNRXs | Share | PNRXs | Share | PNRXs | Share | PNRXs | Share | PNRXs | Share |
|                      | N       | %     | N     | %     | N     | %     | N     | %     | N     | %     | N     | %     |
| TOTAL MARKET         | (b) (4) |       |       |       |       |       |       |       |       |       |       |       |
| Sulfisoxazole Syst   |         |       |       |       |       |       |       |       |       |       |       |       |
| Filled By Other Gen. |         |       |       |       |       |       |       |       |       |       |       |       |
| Gulfasin             |         |       |       |       |       |       |       |       |       |       |       |       |
| Disp. As Written     |         |       |       |       |       |       |       |       |       |       |       |       |
| Gantrisin Systemic   |         |       |       |       |       |       |       |       |       |       |       |       |
| Filled By Other Gen. |         |       |       |       |       |       |       |       |       |       |       |       |

Source: SDI Vector One®: National, Data Extracted October-2009. File: VONA 2009-1600 Sustol Tradename PNRx 10-26-09.xls

During year 2008, 80 new prescriptions were written for sulfisoxazole, of which (b) (4) were dispensed as written for the branded product.

#### 4 CONCLUSIONS

For the review period, no dispensed prescriptions for oral Sosol<sup>®</sup> tablets were identified in databases available to FDA.

## 5 APPENDIX

### ***SDI Vector One®: National (VONA)***

SDI's VONA measures retail dispensing of prescriptions or the frequency with which drugs move out of retail pharmacies into the hands of consumers via formal prescriptions. Information on the physician specialty, the patient's age and gender, and estimates for the numbers of patients that are continuing or new to therapy are available.

The Vector One® database integrates prescription activity from a variety of sources including national retail chains, mass merchandisers, mail order pharmacies, pharmacy benefits managers and their data systems, and provider groups. Vector One® receives over 2.0 billion prescription claims per year, representing over 160 million unique patients. Since 2002 Vector One® has captured information on over 8 billion prescriptions representing 200 million unique patients.

Prescriptions are captured from a sample of approximately 59,000 pharmacies throughout the US. The pharmacies in the data base account for nearly all retail pharmacies and represent nearly half of retail prescriptions dispensed nationwide. SDI receives all prescriptions from approximately one-third of the stores and a significant sample of prescriptions from the remaining stores.

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/s/  
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PATTY A GREENE  
10/30/2009

LAURA A GOVERNALE  
10/30/2009