

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**207027Orig1s000**

**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 21, 2015  
**Requesting Office or Division:** Division of Hematology Products (DHP)  
**Application Type and Number:** NDA 207027  
**Product Name and Strength:** Promacta (Eltrombopag) for Oral Suspension  
**Submission Date:** August 21, 2015  
**Applicant/Sponsor Name:** GSK  
**OSE RCM #:** 2015-492-1  
**DMEPA Team Leader:** Yelena Maslov, Pharm.D.

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#### 1 PURPOSE OF MEMO

Division of Hematology Products requested that we review the revised container (b) (4) label (Appendix A) to determine if it is 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 CONCLUSIONS

The revised container (b) (4) label is acceptable from a medication error perspective.

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<sup>1</sup> Rutledge, M. Label and Labeling Review for Promacta (NDA 207027). 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); 2015 July 14. 23 p. OSE RCM No.: 2015-492.

APPENDIX A. (b) (4) LABEL SUBMITTED VIA EMAIL ON AUGUST 21, 2015



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/s/  
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YELENA L MASLOV  
08/21/2015

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**MEMORANDUM**  
**REVIEW OF REVISED 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 20, 2015  
**Requesting Office or Division:** Division of Hematology Products (DHP)  
**Application Type and Number:** NDA 207027  
**Product Name and Strength:** Promacta (eltrombopag) (b) (4) for Oral Suspension, 25 mg  
**Applicant/Sponsor Name:** GlaxoSmithKline  
**OSE RCM #:** 2015-492  
**DMEPA Primary Reviewer:** Michelle Rutledge, PharmD  
**DMEPA Team Leader:** Yelena Maslov, PharmD

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**1 PURPOSE OF MEMO**

This memorandum responds to a request from the Division of Hematology Products (DHP) to evaluate the revised proposed instructions for use and prescribing information labeling for Promacta (eltrombopag) for areas of vulnerability that can lead to medication errors from the use of partial dosing (12.5 mg) for the Promacta (b) (4) for Oral Suspension formulation.<sup>1</sup>

**2 CONCLUSIONS & RECOMMENDATIONS**

Typical doses of Promacta can range between 25 mg (1-packet), 50 mg (2-packets), or 75 mg (3-packets) and these doses will be given by administering the entire 20 mL volume from an oral syringe. Administration of the product by this method was tested in human factor (HF) studies that we evaluated in review, OSE RCM# 2015-492<sup>1</sup>.

However, for patients of East Asian ancestry with immune idiopathic thrombocytopenia (ITP) and hepatic impairment (child-Pugh Class A, B, C) where initiating Promacta at a reduced dose once daily is a consideration and dose adjustments based on platelet count results in patients

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<sup>1</sup> Rutledge, M. Promacta Labeling and Human Factors Results Review. 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); 2015JUL14. 4-5 p. OSE RCM No.: 2015-492.

with chronic immune thrombocytopenia, partial dosing of Promacta is indicated. A partial dose of 12.5 mg of the Promacta for Oral Suspension can be achieved by administering a partial volume from a 20-mL syringe (10-mL of 25mg (1-packet), which equals the partial 12.5 mg dose) versus delivering all of the medicine in the syringe for other doses. We considered whether an additional human factor (HF) study would be needed to ensure patients can administer 12.5 mg partial dose. However, based on conversation with the clinical team, they informed us that patients/caregivers administered partial doses from the oral syringes successfully in clinical studies. Therefore, we conclude that additional HF studies are not required at this time.

Additionally, our review of the proposed revised labeling identified areas of needed improvement to ensure the safe use of the product. Below are our recommendations which have been agreed upon by the team and these proposed changes have been implemented.

## **2.2 RECOMMENDATIONS**

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

**a. Prescribing Information, Section 2.4 Administration – Preparation of the Oral Suspension**

1. This Section contains incomplete instructions for use and thus is confusing and misleading. We recommend to provide reference to the Instructions for Use and have complete information regarding preparation and administration in the IFU. Alternatively, you can consider providing complete and comprehensive instructions for use in Section 2.4 as well.

**b. Instructions for Use**

1. Add information after, “12.5 mg dose (1 packet)” in Step 4 reiterating to the patient that a different administration volume is needed, such as Note: Please see specific instructions for 12.5 mg dose.
2. Add information after, “to the 10-mL mark on the syringe” in Step 9 reiterating to the patient that this specific information only applies to the 12.5 mg partial dose.

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/s/  
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MICHELLE K RUTLEDGE  
08/21/2015

YELENA L MASLOV  
08/21/2015

## PMR/PMC Development Template: Product Quality (CMC)

This template should be completed by the review chemist (ONDP) or biologist (OBP) and included for *each* type of CMC PMR/PMC in the Action Package. See #4 for a list of CMC PMR/PMC types

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NDA/BLA #                      NDA 207027  
Product Name:                      Promacta (eltrombopag) for oral suspension

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PMC #2 Description:              Conduct in-use stability studies using a crushed tablet and the powder for oral suspension in foods or drinks that do not contain polyvalent cations (e.g. applesauce, juice, etc.)

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PMC Schedule Milestones:	Final Protocol Submission:	<u>12/2015</u>
	Study/Trial Completion:	<u>04/2016</u>
	Final Report Submission:	<u>06/2016</u>

- **ADD MORE AS NEEDED USING THE SAME TABULAR FORMAT FOR EACH PMC.**
- **INCLUDE DESCRIPTIONS AND MILESTONES IN THE TABLE ABOVE FOR ALL CMC/OBP NON-REPORTABLE PMCS FOR WHICH THE FOLLOWING ANSWERS WILL BE IDENTICAL. USE A SEPARATE TEMPLATE FOR EACH PMR/PMC FOR WHICH THE ANSWERS TO THE FOLLOWING QUESTIONS DIFFER.**
- **DO NOT USE THIS FORM IF ANY STUDIES WILL BE REQUIRED UNDER FDAAA OR WILL BE PUBLICALLY REPORTABLE**

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check reason below and describe.

- Need for drug (unmet need/life-threatening condition)
- Long-term data needed (e.g., stability data)
- Only feasible to conduct post-approval
- Improvements to methods
- Theoretical concern
- Manufacturing process analysis
- Other

Promacta is labeled to be taken on an empty stomach. Young children may be more compliant with dosage administration if the product is mixed with soft food.

2. Describe the particular review issue and the goal of the study.



PMC# 2: Since there is a significant food effect in foods containing polyvalent cations, the current labeling states that Promacta should be taken on an empty stomach (1 hour before or 2 hours after a meal). Young children require more frequent feedings than adults. Non-compliance with fasting recommendations could lead to reduced drug exposure and ineffective therapy. Since this product will be taken by young children, mixing in soft foods may allow better compliance.

3. [OMIT – for PMRs only]

4. What type of study is agreed upon (describe and check type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- Dissolution testing
- Assay
- Sterility
- Potency
- Product delivery
- Drug substance characterization
- Intermediates characterization
- Impurity characterization
- Reformulation
- Manufacturing process issues
- Other – new strength

Describe the agreed-upon study:

The applicant will conduct in-use stability studies using a crushed tablet and the powder for oral suspension in foods or drinks that do not contain polyvalent cations (e.g. applesauce, juice, etc.) to determine the stability of the drug substance in these media.

5. To be completed by ONDP/OBP Manager:

- Does the study meet criteria for PMCs?
- Are the objectives clear from the description of the PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

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**PMR/PMC Development Coordinator:**

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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(signature line for BLAs only)

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/s/  
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MARA B MILLER  
08/19/2015

OLEN M STEPHENS  
08/19/2015

**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: August 13, 2015

To: Ann Farrell, MD  
Director  
**Division of Hematology Products (DHP)**

Robert Kane, MD  
Deputy Director for Safety  
**Division of Hematology Products (DHP)**

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

Barbara Fuller, RN, MSN, CWOCN  
Team Leader, Patient Labeling  
**Division of Medical Policy Programs (DMPP)**

From: Nathan Caulk, MS, BSN, RN  
Patient Labeling Reviewer  
**Division of Medical Policy Programs (DMPP)**

James Dvorsky, PharmD  
Regulatory Reviewer  
**Office of Prescription Drug Promotion (OPDP)**

Subject: Review of Patient Labeling: Medication Guide (MG) and  
Instructions for Use (IFU)

Drug Name (established name): PROMACTA (eltrombopag)

Dosage Form and Route: for oral suspension

Application Type/Number: NDA 207027

Applicant: Novartis

## 1 INTRODUCTION

On February 24, 2015, Novartis submitted for the Agency's review a New Drug Application (NDA) 207027 for PROMACTA (eltrombopag) for oral suspension. This submission proposes a new dosage formulation and a proposed indication to include patients 1 year and older:

PROMACTA (eltrombopag) is indicated for the treatment of thrombocytopenia in **adult and pediatric patients 1 year and older** with chronic immune (idiopathic) thrombocytopenia (ITP) who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy.

PROMACTA (eltrombopag) tablets was originally approved on November 20, 2008 for the treatment of thrombocytopenia in patients with chronic immune (idiopathic) thrombocytopenia (ITP) who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy.

- On November 16, 2012, PROMACTA (eltrombopag) tablets was approved for the treatment of thrombocytopenia in patients with chronic hepatitis C to allow the initiation and maintenance of interferon-based therapy.
- On August, 26, 2014 PROMACTA (eltrombopag) tablets was approved for the treatment of patients with severe aplastic anemia who have had an insufficient response to immunosuppressive therapy.
- On June 11, 2015 PROMACTA (eltrombopag) tablets was approved for the inclusion of pediatric patients ages 6 years and older as part of the current approved indication for the treatment of thrombocytopenia in adult patients with chronic immune (idiopathic) thrombocytopenia (ITP) who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Hematology Products (DHP) on April 1, 2015, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) and Instructions for Use (IFU) for PROMACTA (eltrombopag) for oral suspension.

DMPP conferred with the Division of Medication Error, Prevention, and Analysis (DMEPA) and a separate DMEPA review of the IFU was completed July 14, 2015.

## 2 MATERIAL REVIEWED

- Draft PROMACTA (eltrombopag) for oral suspension MG and IFU received on February 24, 2015, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on August 4, 2015.
- Draft PROMACTA (eltrombopag) for oral suspension Prescribing Information (PI) received on February 24, 2015, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on August 4, 2015.

## 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. In our review of the MG and IFU the target reading level is at or below an 8<sup>th</sup> grade 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 APFont to make medical information more accessible for patients with vision loss. We have reformatted the MG and IFU document using the Arial font, size 10.

In our collaborative review of the MG and IFU we have:

- simplified wording and clarified concepts where possible
- ensured that the MG and IFU is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG and IFU is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG and IFU meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

#### **4 CONCLUSIONS**

The MG and IFU are 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 and IFU 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 and IFU.

Please let us know if you have any questions.

16 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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NATHAN P CAULK  
08/13/2015

JAMES S DVORSKY  
08/13/2015

BARBARA A FULLER  
08/13/2015

LASHAWN M GRIFFITHS  
08/13/2015

## PMR/PMC Development Template: Product Quality (CMC)

This template should be completed by the review chemist (ONDP) or biologist (OBP) and included for *each* type of CMC PMR/PMC in the Action Package. See #4 for a list of CMC PMR/PMC types

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NDA/BLA #                      NDA 207027  
Product Name:                      Promacta (eltrombopag) for oral suspension

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PMC #1 Description:              Develop a 12.5 mg strength to provide for an additional dosing for patients needing less than the current lowest dose option of 25 mg

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PMC Schedule Milestones:	Development Plan Submission:	<u>12/2015</u>
	Development Study Completion:	<u>12/2017</u>
	Final Report Submission:	<u>03/2018</u>

- **ADD MORE AS NEEDED USING THE SAME TABULAR FORMAT FOR EACH PMC.**
- **INCLUDE DESCRIPTIONS AND MILESTONES IN THE TABLE ABOVE FOR ALL CMC/OBP NON-REPORTABLE PMCS FOR WHICH THE FOLLOWING ANSWERS WILL BE IDENTICAL. USE A SEPARATE TEMPLATE FOR EACH PMR/PMC FOR WHICH THE ANSWERS TO THE FOLLOWING QUESTIONS DIFFER.**
- **DO NOT USE THIS FORM IF ANY STUDIES WILL BE REQUIRED UNDER FDAAA OR WILL BE PUBLICALLY REPORTABLE**

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check reason below and describe.

- Need for drug (unmet need/life-threatening condition)
- Long-term data needed (e.g., stability data)
- Only feasible to conduct post-approval
- Improvements to methods
- Theoretical concern
- Manufacturing process analysis
- Other

A PMC is recommended since a dose reduction can be achieved using one-half the dose of the proposed 25 mg strength, following reconstitution.

2. Describe the particular review issue and the goal of the study.

PMC# 1: A 12.5 mg strength is needed in the event a dose reduction or incremental dose adjustments of 12.5mg are required. There is a concern that caregivers would use a portion of the reconstituted 25 mg stickpack and store the remaining product for later administration the following day, to avoid wasting the prepared suspension. A genotoxic impurity (b) (4) forms above the level of threshold of toxicological concern (TTC) (b) (4) following reconstitution of the powder in the stickpack. To avoid the potential for storing the reconstituted drug product and ingestion of a product with genotoxic impurities, a lower strength is needed. The development of a 12.5 mg strength would avoid the need to waste half of the prepared product.

3. [OMIT – for PMRs only]
4. What type of study is agreed upon (describe and check type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- Dissolution testing
- Assay
- Sterility
- Potency
- Product delivery
- Drug substance characterization
- Intermediates characterization
- Impurity characterization
- Reformulation
- Manufacturing process issues




Other – new strength


Describe the agreed-upon study:

The applicant will develop a 12.5 mg dosage presentation to allow dose reduction or incremental dose adjustments. The development of this dosage form will include the following studies:

(b) (4)



The current proposed timelines and milestones take into account the need to complete all of the activities outlined above. (b) (4)



5. To be completed by ONDP/OBP Manager:

- Does the study meet criteria for PMCs?
- Are the objectives clear from the description of the PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

---

**PMR/PMC Development Coordinator:**

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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(signature line for BLAs only)

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

**\*\*\*Pre-decisional Agency Information\*\*\***

**Memorandum**

**Date:** 8/5/2015

**To:** Kimberly Scott, Regulatory Project Manager  
Division of Hematology Products

**From:** James Dvorsky, Regulatory Reviewer  
Office of Prescription Drug Promotion

**Through:** Katie Davis, Team Leader  
Office of Prescription Drug Promotion

**Subject:** Comments on draft labeling (Package Insert) for NDA 207027  
Promacta (eltrombopag) for oral suspension

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In response to your labeling consult request on March 30, 2015, we have reviewed the draft Package Insert for Promacta and do not have any comments at this time. This review is based upon the August 4, 2015, version of the label.

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/s/  
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JAMES S DVORSKY  
08/05/2015



## DEPARTMENT OF HEALTH & HUMAN SERVICES

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Food and Drug Administration  
10903 New Hampshire Avenue  
Document Mail Center  
Silver Spring, MD 20993-0002

**Date:** July 10, 2015

**From:** Janice Polacek, RN, BSN, CRNI  
Lead Reviewer  
CDRH/ODE/GHDB

**To:** Kimberly Scott, RN, BSN, OCN  
Regulatory Health Project Manager  
Division of Hematology Products  
Office of Hematology and Oncology Products  
CDER

**CC:** Janice Brown  
OMPT/CDER/OPQ

**Subject:** CDRH Consult-Device Review  
NDA 207027/ICC1500117  
Eltrombopag/Promacta Powder for Oral Suspension 25mg

**Recommendation:** NDA Approval for consideration of the Device Constituent –Adapta-Cap, Oral dosing syringe and 40 cc reconstitution bottle.

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### **I. Recommendation:**

The device consultant has performed a design review of submission materials intended to support the safety and functionality of the of the device constituent parts of the subject combination product. This review covered device design and functionality of the final finished assembled device, as well as individual components. This review did not cover manufacturing or sterility (non-sterile product) of the device constituents. The review did not cover any aspect of the drug product or primary container closure. The review of submission documentation by CDRH/ODE found that the device is made up of three components made by two different manufacturers. These components are purchased in bulk and packaged in an ISO Class  $\text{B}_4$  environment and assembled by the sponsor.

Essential performance elements of the device were considered to be:

- Component compatibility and resistance to separation
- Dose accuracy of the syringe
- Freedom from leakage
- Force required to attach and detach system components
- Functionality after aging and shipping
- Biocompatibility of the components
- Review of Instructions of Use.

**Review of the information provided by the sponsor found sufficient documentation and evidence of performance of the device constituent part of the combination product to recommend approval.**

**II. Consult Purpose:**

The Center for Drug Evaluation and Research (CDER) has requested a device specific review from the Center for Devices and Radiological Health (CDRH), regarding NDA207027. The device constituent part of this combination product consists of a reusable 40 cc mixing bottle with lid and cap and a reusable oral 20 cc syringe. These device components are used to reconstitute and deliver Eltrombopag for the treatment of chronic immune (idiopathic) thrombocytopenia (ITP) in children one year and older. The drug has been previously approved in a pill formulation.

**III. Review Summary**

Consultants

(b) (4)

Review Content Covered

Functionality of the Adapta-Cap™, HDPE bottle and 20 cc oral dosing syringe  
Biocompatibility of the Adapta-Cap™, HDPE bottle and 20 cc oral dosing syringe  
Shipping and aging of the final finished device  
Directions for use as it relates to the device  
Cleaning instructions of the device  
Labeling and instructions for use

Review Content Not Covered

Review of the drug product  
Manufacture of the drug product  
Stability of the drug product after aging  
Shipping of the final drug product device combination  
Manufacture of the device constituent parts of the combination product  
Review of the primary container closure-drug product interactions (toxicology)  
Human factors validation

**IV. Documents Reviewed**

NDA207027, Serial 0000  
Quality Information Amendment Response to FDA Comments dated 27 March 2015 (received 4/20/2015)  
Quality Information Amendment Response to FDA Comments dated 20 May 2015 (received 5/22/2015)  
Quality Information Amendment Response to FDA Comments dated 27 May 2015 (received 5/29/2015)  
DMF # (b) (4) page 81  
DMF # (b) (4) page 45  
Human Factor study #14063 (email on 5/15/2015)  
Draft labeling-Instructions for use.

**V. Device Review**

Indications for Use (proposed)

*Eltrombopag Powder for Oral Suspension is indicated for the treatment of thrombocytopenia in adult and pediatric patients 1 year and older with chronic immune (idiopathic) thrombocytopenia (ITP) who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy*

The NDA holder is has approval of for patient populations 6 years and up and is now seeking approval for the pediatric population 1 year to 5 years old.

Dosage and Administration

Eltrombopag Powder for Oral Suspension (referred to as Eltrombopag PfOS), 25 mg/day to maximum dose of 75mg/day.

Following reconstitution, the product should be administered immediately, or within 30 minutes of reconstitution when stored at 15 to 30°C (59 to 86°F)

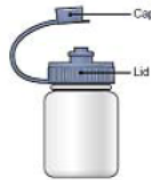
According to the sponsor, Eltrombopag FfOS has been developed for the youngest age group of the pediatric population and patients who cannot swallow. Eltrombopag is packaged into heat sealed foil laminated stickpacks. The content of the stickpack is reconstituted with water and is intended to be dosed immediately, within 30 minutes of reconstitution. Reconstitution of the drug product necessitates the need for the reusable mixing bottle with lid and cap and the oral dosing syringe, which are the subject of this review.

DEVICE DESCRIPTION

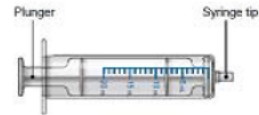
PROMACTA powder for oral suspension (30 foil packets)



Reusable mixing bottle with lid and cap (1)



Reusable oral syringe (1)



The sponsor states that the oral dosing syringe and threaded (Adapta-Cap™) are standard items from the supplier's (b) (4) products catalogue. The reusable mixing bottle is sourced from the supplier using GSK owned design. The table below lists the manufacturer for all components used for this device. The sponsor states that the ancillary component suppliers are assessed through regular audits to assure conformance to GMP and GlaxoSmithKline quality policies. Testing is performed by the NDA holder upon receipt of the components to confirm suitability for intended use. [Information located in 3.2.P.7]

Ancillary Component Manufacturers

Component	Manufacturer	Address	DMF No.	Reference to DMF access letter
HDPE Bottle	(b) (4)	(b) (4)	(b) (4)	m1.4.2
HDPE Bottle				m1.4.2
HDPE (b) (4)				m1.4.2
Dosing Syringe				--
Bottle Closure				--
(b) (4)				

The oral dosing syringe and threaded bottle closure with syringe port capability are registered by the component manufacture with the FDA’s Medical Device database under product code (b) (4). In accordance with the governing Device Directive 820, these components are categorized as class I cGMP exempt medical devices.

Eltrombopag PfOS is packaged into a heat-sealed foil laminate stickpacks. The review of the primary container closure will be done by CDER. This review will cover the reusable mixing bottle with lid and cap and the reusable oral syringe.

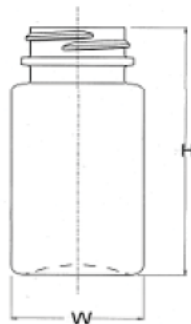
Eltrombopag Powder for Oral Suspension (PfOS) is reconstituted with water prior to administration. To facilitate the reconstitution procedure [detailed in P.2.2. Pharmaceutical Development], a 40 cc HDPE reconstitution bottle and a 20 mL oral dosing syringe are provided. In addition, a threaded closure with syringe-port capability is included to reduce the risk of spillage and facilitate dosing pediatric patients with an oral syringe.

2.3.1. HDPE Bottle

Test	Test Method	Specification
Identity Test	IR	Concordant with reference A representative IR spectrum is presented in Figure 4.
Visual inspection	Visual examination	Absence of critical defects
Dimensional inspection	(b) (4)	Complies with critical limits

Figure 3 Representative Drawing of the HDPE Bottle

40 cc HDPE Bottle	Nominal Dimension (mm)
Height (H)	55.1
Diameter (W)	39.7

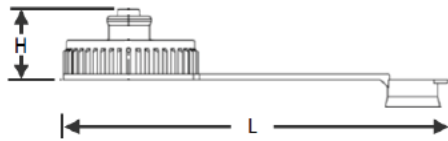


2.3.3. Threaded Closure with Syringe Port

Test	Test Method	Specification
Identity Test	IR	Concordant with reference
Visual inspection	Visual examination	Absence of critical defects
Dimensional inspection	(b) (4) Functional examination	Complies with acceptance criteria

Figure 6 Representative Drawing of the Threaded Bottle Closure with Syringe Port

Threaded Bottle Closure with Syringe	Nominal Dimension (mm)
Closure height (H)	19.1
Closure length (L)	100.3



2.3.2. Dosing Syringe

Test	Test Method	Specification
Visual inspection	Visual examination	Absence of critical defects
Dimensional inspection	(b) (4) Functional examination	Complies with acceptance criteria

Figure 5 Representative Drawing of the Dosing Syringe

Dosing Syringe	Nominal Dimension (mm)
Barrel diameter (A)	(b) (4)
Barrel length (B)	(b) (4)



Reviewer Comment:

The reusable bottle, Adapta-Cap™, and dosing syringe are an appropriate size and fitment and are expected to be physically compatible to achieve reconstitution and delivery of this drug product.

STERILITY

The ancillary components are provided non-sterile from suppliers that have been audited and approved by GlaxoSmithKline.

Reviewer comments to sponsor IR (question 5) from 3/27/2015:

*Please provide a description of the level of cleanliness associated with production and packaging of the final finished device product as well as mitigations present to ensure that the final finished product is not supplied in an unsafe or undesirable manner due to contamination.*

In response to the above IR, the sponsor stated that the components are supplied (b) (4)



(b) (4)

A new reusable bottle, Adapta-cap™ and 20 ml syringe is provided with each box of 30 stickpacks.  
**This is an acceptable answer**

BIOCOMPATIBILITY

Located in NDA 207027 [3.2.P.2.4 Container closure system development] the sponsor provides the following information about the selection of the ancillary components of this combination product

- Reconstitution bottle made from high density Polyethylene (HDPE) (b) (4)
- Selected due to robust nature and inherent low risk of extractable and leachable concern
- The 40 cc round bottle (b) (4)
- The threaded closure with syringe-port capability made from (b) (4)
- The 20 cc dosing syringe has 1 ml graduation markings to facilitate accurate dispensing of reconstitution (b) (4)
- Risk assessment was conducted and found the product contact materials to be a very low risk for leachables.

Materials of Construction for Dosing Components

Bottle	High Density Polyethylene (HDPE), white colorant
Closure	(b) (4)
Dosing Syringe Barrel Plunger	(b) (4)

For the ancillary components, the sponsor’s risk assessment (provided in response to 3/27/15 IR questions) concluded the risk from potential leachables to be low; this conclusion is (b) (4) referenced below.

**Bottle** High density polyethylene, 21 CFR 177.1520  
 The bottle has also been tested and shown to comply with the requirements of USP <661>.

**Closure** (b) (4)

**Dosing Syringe Barrel,** (b) (4)

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

Elements of the risk analysis documentation submitted to support safety of system components are excerpted below:

**Summary of Risk Assessment for Ancillary Components including Definition of Failure Modes Considered and Risk Mitigation Activities**

Risk Item Number	Potential Risk Area (Device part)	Potential Leachable Pathway	Potential Failure Effect	Risk Mitigation Activities	Overall Risk Assessment Categorisation
1	Bottle	Substances migrating from product contact side of bottle into aqueous formulation during product reconstitution step.	Exposure to a patient of these leachables by consumption of drug formulation	Compliance with CFR, low probability of migration	Low
2	Bottle	Substances migrating from mold release agents of bottle into aqueous formulation during product reconstitution step.	Exposure to a patient of these leachables by consumption of drug formulation	Confirmed absence of mold release agent	Low
3	Closure	Substances migrating from closure into aqueous formulation during product reconstitution step.	Exposure to a patient of these leachables by consumption of drug formulation	Compliance with CFR, low probability of migration	Low
4	Closure	Substances migrating from mold release agents of closure into aqueous formulation during product reconstitution step.	Exposure to a patient of these leachables by consumption of drug formulation	Confirmed absence of mold release agent	Low
5	Syringe Barrel	Substances migrating from barrel into aqueous formulation during product reconstitution step.	Exposure to a patient of these leachables by consumption of drug formulation	Low Severity, Low Probability	Low
6	Syringe Barrel	Substances migrating from mold release agents of closure into aqueous formulation during product reconstitution step.	Exposure to a patient of these leachables by consumption of drug formulation	Confirmed absence of mold release agent	Low
7	Syringe Barrel	Leaching of (b) (4) into formulation.	Exposure to a patient of these leachables by consumption of drug formulation	Oral Consumption of (b) (4) considered to be low risk	Low

**Summary of Risk Assessment for Ancillary Components including  
Definition of Failure Modes Considered and Risk Mitigation Activities  
(Continued)**

Risk Item Number	Potential Risk Area (Device part)	Potential Leachable Pathway	Potential Failure Effect	Risk Mitigation Activities	Overall Risk Assessment Categorisation
8	Syringe Plunger	Substances migrating from barrel into aqueous formulation during product reconstitution step.	Exposure to a patient of these leachables by consumption of drug formulation	Low Severity, Low Probability	Low
9	Syringe Plunger	Substances migrating from mold release agents of bottle cap into aqueous formulation during product reconstitution step.	Exposure to a patient of these leachables by consumption of drug formulation	Confirmed absence of mold release agent	Low
10	Syringe Plunger (b) (4)	Substances migrating from (b) (4) into aqueous formulation during product reconstitution step.	Exposure to a patient of these leachables by consumption of drug formulation	Low Severity, Low Probability	Low
11	Syringe Plunger (b) (4)	Substances migrating from mold release agents of (b) (4) into aqueous formulation during product reconstitution step.	Exposure to a patient of these leachables by consumption of drug formulation	Low Severity, Low Probability	Low
12	Syringe Plunger (b) (4)	Leaching of (b) (4) and ingredients from (b) (4) into formulation.	Exposure to a patient of these leachables by consumption of drug formulation	Oral Consumption of (b) (4) considered to be low risk	Low
13	Syringe Plunger (b) (4)	Leaching of (b) (4) from (b) (4) into drug formulation	Exposure to a patient of these leachables by consumption of drug formulation	Low Severity, Low Probability	Low
14	Syringe Ink	Substances derived from Solvent system of Ink Migrate through syringe into drug formulation	Exposure to a patient of these leachables by consumption of drug formulation	Declarations of compliance include ink meeting Toy Safety regulations DIN EN 71 & ASTM F963-95 (including migration of toxic substances)	Low
15	Syringe Ink	Substances derived from pigments of Ink Migrate through syringe into drug formulation	Exposure to a patient of these leachables by consumption of drug formulation	Declarations of compliance include ink meeting Toy Safety regulations DIN EN 71 & ASTM F963-95 (including migration of toxic substances)	Low

**Reviewers comments to sponsor IR (question 2) from 3/27/2015:**

*Provide information which supports that all materials present within the final finished device components are biocompatible and free from unacceptable toxicological risk in the context of their intended use.*

In response to the above IR, the sponsor provided materials of construction for the dosing components as well as CFR compliance certificates to demonstrate suitability of the materials used to manufacture the device constituents. The sponsor further states that an evaluation of potential leachables from the device components was conducted and a risk assessment was carried out to highlight areas for extractable profiling. The sponsor states that the product contact materials were found to be very low risk for leachables. The sponsor will be asked to provide that report. **Further information requested on 5/20/2015.**

**Reviewer comments to sponsor IR (question1) from 5/20/2015:**

*Please provide the leachable evaluation and risk assessment conducted for the ancillary components. A leachables evaluation is critical to evaluate the safety of this device when used with children.*

In response to the above IR, the sponsor provided results of an failure modes and effects analysis (

FMEA) conducted to identify leachables exposure from product contact components. Both the primary and ancillary components were assessed. [See risk assessment in tables above]

Eltrombopag PfOS is considered to be (b) (4) with the foil laminate (stickpack) for the (b) (4) (b) (4) and thus this contact material was assigned the highest risk score in the failure modes. (Not part of this review) The ancillary components are only in direct contact with the Eltrombopag FfOS for 30 minutes or less, thus are considered to be low risk for potential leachables and because the materials of construction used to manufacture the ancillary components with the indirect food additives regulations referenced. The sponsor was asked to provide test reports for USP <661>.

**Further information requested.**

Reviewer response to sponsor IR (question 1) from 5/27/2015:

*Please provide the test results used to evaluate for the ancillary components per USP<661>.*

Test reports for USP <661> were provided by the sponsor for the HDPE bottle from both suppliers used. These results are reported as passing.

The Adapta-cap and oral dosing syringe information was considered by the sponsor to be proprietary to the component supplier (b) (4). The sponsor provided the DMF locations and provided a letter of reference to retrieve this information. Test reports for the Adapta-cap (b) (4) the syringe were located in the DMFs and are reported as passing.

Per the biocompatibility consultant, the sponsor provided USP<661> test results, from which the results were considered safe. (b) (4)

Additionally, the reconstitution bottle and syringe are to be thoroughly rinsed and dried between uses, leaving no residual drug build up on the device and syringe, therefore the product is considered acceptable for use with the labeled patient population.

The sponsor has provided CFR certificates of compliance to appropriate (b) (4) regulations and passing test results for USP<661>. The drug product has (b) (4) with the device constituent. The sponsor evaluated the potential leachables and extractables and conducted a risk assessment which found the product contact materials to be a very low risk for leachables. The product is intended to be dosed immediately, within 30 minutes of reconstitution, and this is clearly stated in the Instructions for Use.

In consideration of: statements of compliance with relevant material sections of the CFR, the testing records of USP<661> provided by the sponsor, the risk assessment provided, and the duration and nature of contact between the drug product and the device elements, the reviewer finds this section acceptable.

**I find the sponsor's response acceptable.**

PERFORMANCE TESTING

In order to assess if this device will perform as intended the sponsor was asked to provide information to support the safety and performance of the device.

*The device constituent of the combination product must perform as intended. The components must fit together as to avoid leakage. The syringe must fit into the syringe port. In the case of a dosage different than that in increments of 25 mg, the graduated scale of the syringe must be accurate.*

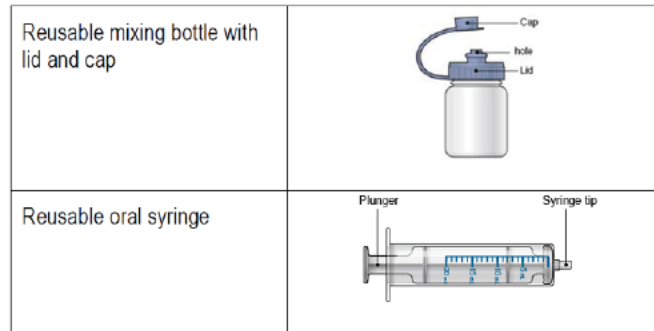
The applicant states that the ancillary bottle is purchased against a specification and quality agreement

between GlaxoSmithKline and the supplier, and that testing is performed on receipt of materials until the supplier reliability has been established.

The ability to reconstitute and accurately deliver the required dose, limiting a caregiver's exposure and to prevent spillage should also be considered when evaluating the device constituents.

On March 27 the sponsor was sent questions pertaining to the performance of this device. The questions are listed in their entirety at the end of this memo.

**Images of the Mixing Bottle Assembly and Oral Dosing Syringe**



The drug product is provided in a stick pack and must be reconstituted in order to be administered.

The caregiver must prepare the drug product as follows:

- Gently shake the bottle with the cap and lid attached, back and forth for at least 20 seconds to mix the water with the powder (i.e., mixing).
- Withdraw the medication from the inverted bottle using the syringe provided.



(b) (4)

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SHIPPING

The sponsor states that a formal shipping and handling study was performed in accordance with ASTM D1463-09 to simulate the effects of the distribution cycle for the commercial packaged product.

Reviewer comments to sponsor IR (question 4) from 3/27/2015:

*Please provide information which demonstrates that the device constituent parts of the product are capable of meeting their intended use after being subject to shipping and handling conditions.*

One hundred percent visual inspection of the stickpacks and the dosing components was performed pre- and post-testing. No physical damage to the stickpacks or the dosing components was observed; minor carton denting typical of the drop test was observed. This supports the capability of the commercial packaged product to meet its intended use after being subjected to normal shipping and handling conditions.

The sponsor states in their response that the bulk components are shipped from suppliers to the GSK facility under normal shipping and handling conditions and received and released for GMP. The recovery results that were provided in the performance section of this memo (answer to question 1c. demonstrate that the device performs as intended after shipping and handling).

**I accept the sponsor's response.**



Reviewer comments to sponsor IR (question 3) from 3/27/2015:

*Please provide information which demonstrates that the device is capable of meeting their intended use after a time period equal to or greater than the packaged drug product expiration date.*

The sponsor provided dose accuracy testing using a single stickpack and three stickpacks, utilizing the 20



ml reconstitution (b) (4). This testing was done using components three years after their manufacturing date which is greater than the proposed 24 month shelf life of the packaged drug product. The device performed as intended for a period greater than the proposed shelf life.

**I accept the sponsor's response.**

#### Human Factors

- The submission also includes instructions for use that detail the reconstitution process for Eltrombopag PfOS. 20 cc of drinking water is withdrawn and placed in the open mixing bottle.
- Packets of medication are added to the 20 cc water, the lid is screwed on tightly making sure that the cap is pushed onto lid.
- The medication is then agitated to reconstitute the powdered medication.
- The 20cc syringe is inserted in to the syringe port and the reconstituted medication is withdrawn and administered to the child.
- (b) (4)
- The mixing bottle, cap/lid and syringe are then rinsed with running water and allowed to air dry.

#### Reviewer Comment:

The sponsor conducted a human factors study to evaluate the ability of a parent or caregiver to perform the critical tasks needed to prepare, measure and administer the prescribed dose of the drug product. The subjects were given the IFU and all equipment necessary to prepare measure and administer the dose of medication. The subjects were not given a demonstration, but were given an opportunity to independently review the information and familiarize themselves with the products much like they would if they were at home about to prepare a dose of the product for a child for the first time, with no provider in the room and without guidance or instruction from the study team. (b) (4)

(b) (4)

Given that this is a prescription medication for pediatric patients, parents and caregivers would have several resources such as a healthcare provider, pharmacist, doctors nurse from whom they could receive guidance and hands on training. In clinical practice, caregivers would be given instruction from the prescribing clinician and lab values would be monitored. Any lab values not expected would result in a review of medication administration.

The reviewer agrees with this rationale.

The results of the Human Factors study Validation study support the intended IFU. [Information provided by the sponsor via email 5/15/2015]

#### LABELING/DIRECTIONS FOR USE

#### Reviewer Comment:

The sponsor provided draft patient Instructions for Use, including illustrations, a step by step procedure for mixing the drug product. Directions for reconstitution of 1 to 3 packets of drug product, procedure for administration of drug product to the child, along with appropriate cleaning of the device are included. The sponsor has included appropriate warnings and precautions within the instructions for use.

**Labeling is acceptable.**

## VI. Record of Interactive Review Questions

The following questions were sent to the NDA holder on in March 27, 2015 and responses received to all questions on April 20, 2015 and are discussed within this memorandum.

1. The Agency is unable to locate information that verifies the device constituent parts of the product can perform as intended. The following list includes specific system attributes for which no associated verification information was found within the submission. Please note that this list may not include all relevant elements of device constituent part performance.
  - a. Physical retention of device components and resistance to separation during use.
  - b. Accuracy of the syringe and any graduated markings to deliver the required medication dose.
  - c. Allowance for transfer, mixing and delivery of the medication dose.
  - d. Force required attaching and detaching system components (cap/lid from bottle)
  - e. Freedom from system leakage.
2. The Agency is unable to locate information regarding the suitability of materials used to manufacture the device constituent parts of the system. Please provide information which supports that all materials present within the final finished device components are biocompatible and free from unacceptable toxicological risk the context of their intended use under the subject NDA.
3. The Agency is unable to locate information which demonstrates that the device constituent parts are capable of meeting their intended use after a time period equal to or greater than the packaged drug product expiration date.
4. The Agency is unable to locate information which demonstrates that the device constituent parts of the product are capable of meeting their intended use after being subjected to shipping and handling conditions.
5. Based on your description of the ancillary components, it appears that you are providing these devices as non-sterile. Please provide a description of the level of cleanliness associated with production and packaging of the final finished device product as well as mitigations present to ensure that the final finished product is not supplied in an unsafe or undesirable manner due to contamination

The following IR questions were sent to the NDA holder on May 20, 2015 and response received on May 21, 2015 and are discussed within this memorandum.

1. In NDA207027 3.2.P.2.4 Pharmaceutical Development, you state that an evaluation of potential leachables from the product contact ancillary components was conducted and a risk assessment was carried out to highlight areas for extractable profiling. You further state that the risk assessment found the product contact materials to be very low risk for leachable. The data for this evaluation could not be located. Please provide the leachable evaluation and risk assessment conducted for the ancillary components. A leachables evaluation is critical to evaluate the safety of this device when used with children.






2. In NDA207027 Labeling instructions cleaning instruction state “Rinse the mixing bottle, lid, syringe and plunger under running water and air dry”. I could not locate any performance testing done to evaluate [REDACTED] (b) (4). Please provide results of testing demonstrating performance after 30 uses per the directions for use. Assuring that the ancillary components perform as intended is critical for accurate dosing of this medication.

The following IR question sent to the NDA holder on May 27, 2015 and response received on May 29, 2015 and is discussed within the risk assessment section of this memo.

1. In NDA207027 3.2.P.2.4 Pharmaceutical Development, you state that an evaluation of potential leachables from the product contact ancillary components was conducted and a risk assessment was carried out to highlight areas for extractable profiling. On May 21, 2015, you provided a risk assessment in the form of a FMEA. You further state that the bottle has been tested and shown to comply with the requirements of USP<661>. Please provide the test results used to evaluate for the ancillary components per USP<661>. A leachables evaluation is critical to evaluate the safety of this device when used with children.

The sponsor was sent the following IR on June 29, 2015.

1. On May 29, 2015 you were asked to provide test results per USP <661> for the product ancillary components for NDA207027. You stated in your response that the dosing syringe and bottle closure test results are located in [REDACTED] (b) (4) DMF. You provided the DMF number and the page number (DMF # [REDACTED] (b) (4) page 81 and DMF# [REDACTED] (b) (4) page 45) as well as the letters of authorizations for those DMF files. Please provide the volume number for the DMF files for the dosing syringe and bottle closure.

Digital Signature Concurrence Table	
Reviewer Sign-Off	 Janice L. Polacek -S 2015.07.12 19:53:04 -04'00'
Team Lead	 Ryan J. Mcgowan -S <small>Digitally signed by Ryan J. Mcgowan -S            DN: c=US, o=U.S. Government, ou=HHS,            ou=FDA, ou=People,            0.9.2342.19200300.100.1.1=2000352462,            cn=Ryan J. Mcgowan -S            Date: 2015.07.13 06:58:57 -04'00'</small>
Branch Chief Sign-Off	 Richard C. Chapman -S 2015.07.13 08:59:07 -04'00'

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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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KIMBERLY L SCOTT

07/29/2015

CDRH consult review being entered into DARRTS for, CMC Team Lead, Janice Brown.

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## **LABEL AND LABELING AND HUMAN FACTORS 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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**Date of This Review:** July 14, 2015  
**Requesting Office or Division:** Division of Hematology Products (DHP)  
**Application Type and Number:** NDA 207027  
**Product Name and Strength:** Promacta (eltrombopag) (b)(4) for Oral Suspension, 25 mg  
**Product Type:** Single Ingredient  
**Rx or OTC:** Rx  
**Applicant/Sponsor Name:** GlaxoSmithKline  
**Submission Dates:** February 24, 2015 and May 27, 2015  
**OSE RCM #:** 2015-492  
**DMEPA Primary Reviewer:** Michelle Rutledge, PharmD  
**DMEPA Team Leader:** Yelena Maslov, PharmD

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## 1 REASON FOR REVIEW

This review evaluates the results of the human factor study as well as proposed container label, carton labeling, instructions for use, and prescribing information labeling for Promacta (eltrombopag) for areas of vulnerability that could lead to medication errors. The applicant is proposing to market a powder for oral suspension formulation indicated for the treatment of thrombocytopenia in adult and pediatric patients 1 year and older with chronic immune (idiopathic) thrombocytopenia (ITP) who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy.

## 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>Material Reviewed</b>	<b>Appendix Section (for Methods and Results)</b>
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B - N/A
Human Factors Study	C
ISMP Newsletters	D - N/A
FDA Adverse Event Reporting System (FAERS)*	E - N/A
Other	F - N/A
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 postmarket safety surveillance.

## 3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

### *Human Factors*

The Human Factors study results appear to demonstrate that the product can be used safely and effectively provided patients receive training and read the instructions for use (IFU) prior to product preparation.

### *Methodology*

DMEPA finds the proposed methodology (e.g., objective, population, number of participants, critical tasks, etc.) to be acceptable from the medication error perspective (See Appendix X for more details regarding methodology).

### *Results*

There were 15 failures occurring with 10 participants total as follows:

- Wrong number of stickpacks (n=2)
- Wrong technique in preparation (n=1)
- Wrong technique in “administration” of medication (n=2)
- Failing to Rinse the mixing bottle and administer after rinsing (n=10)

See additional details below regarding each type of error as follows:

- Wrong number of stickpacks (n=2): Two participants did not use all the correct amount of stickpacks for the dose by emptying fewer stickpacks than the full prescribed dose into the mixing bottle. This would result in clinically significant underdose. This error can be mitigated by revising the Dosage and Administration Section and Patient Counseling Section of the prescribing information (PI) to include information for health care providers regarding training their patients on how to prepare the product correctly with specific attention to how many stickpacks should be used. Additionally, we recommend that the IFU contains prominent information regarding the fact that a person may need to use more than one stickpack to ensure they administer the prescribed dose.
- Wrong technique in preparation of Promacta suspension (n=1): One participant drew an undetermined amount of water into the cup and emptied one stickpack into the water. Then withdraw 20 mLs out of the cup and put that mixture into the mixing water. The participant threw away the remaining mixture from the cup into the sink. However, the participant did not read or refer to IFU before preparation procedure. Thus, it is important that healthcare professionals educate patients specifically regarding how to correctly prepare the product and refer patients to the IFU as instructions for use of this product are not intuitive and require manipulation.
- One participant used the wrong technique in the administration process by not using the syringe to give the dose (n=1). The participant started drawing medicine up into syringe, then pushed medicine back into bottle, opened cap/lid and poured medicine into cup directly from bottle. The subject described concern of spilling the product due to the pressure needed to hold the syringe. Based on this error, DMEPA sent an IR response to the Sponsor on June 30, 2015 to clarify whether any harm would result if this were to occur in actual use. In the IR response on July 1, 2015, Novartis explained that this error would not result in patient harm as patient would receive the entire dose. Thus, no additional mitigation steps are needed at this time.
- One subject (n=1) drew the correct amount, but did not administer the product to the “baby” because they did not think their task was to do so. Thus, it appears to be an artifact of the study as the participant did perform preparation of Promacta suspension correctly. Thus, no additional mitigation steps are needed at this time.

• 

***Labels and labeling***

We reviewed the proposed label and labeling and identified the following areas of vulnerability to errors:

- Need for additional clarification in administration instructions for the Dosage and Administration and Patient Counseling of the Prescribing Information and IFU

Therefore, we conclude that the proposed labeling can be improved to promote the safe use of the product in regards to inclusion of clarifying statements for administration on labeling.

## **4 CONCLUSION & RECOMMENDATIONS**

### **4.1 RECOMMENDATIONS FOR THE DIVISION**

#### **A. Dosage and Administration Section (Section 2) and Patient Counseling (Section 17) of Prescribing Information**

1. We recommend adding language regarding training patients on how to use the product correctly at the prescribed dose to assist with the safe use of this product, such as, “Prior to use of this product, ensure patients or caregivers receive training on proper dosing, preparation and administration of the product.”

### **4.2 RECOMMENDATIONS FOR GSK**

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

#### **A. Instructions for Use**

1. We recommend revising the language regarding the correct number of packets per dose and to make that information more prominent as human factors study demonstrate that patients may use an incorrect number of packets to mix a dose. Consider stating the following information in bolded font in Step 4 immediately after statement “Take only the prescribed number of packets for one dose out of the kit”. “You may need to use more than one packet to prepare the entire dose.”

If you have further questions or need clarifications, please contact Sarah Harris, OSE Project Manager, at 240-402-4774.

**APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED**

**APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION**

Table 2 presents relevant product information for Promacta that GSK submitted on February 24, 2015 and May 27, 2015.

<b>Table 2. Relevant Product Information for Promacta</b>	
<b>Initial Approval Date</b>	November 20, 2008
<b>Active Ingredient</b>	Eltrombopag
<b>Indication</b>	<p><u>Thrombocytopenia in Patients with Chronic ITP</u>                      Treatment of thrombocytopenia in <i>adult and pediatric patients 1 year and older</i> with chronic immune (idiopathic) thrombocytopenia (ITP) who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy. [Proposed]</p> <p><u>Thrombocytopenia in Patients with Hepatitis C Infection</u>                      Treatment of thrombocytopenia in patients with chronic hepatitis C to allow the initiation and maintenance of interferon-based therapy.</p> <p><u>Severe Aplastic Anemia</u>                      Treatment of patients with severe aplastic anemia who have had an insufficient response to immunosuppressive therapy.</p>
<b>Route of Administration</b>	Oral
<b>Dosage Form</b>	<ul style="list-style-type: none"> <li>• Tablets</li> <li>• <i>Powder for Oral Suspension [Proposed]</i></li> </ul>
<b>Strength</b>	<ul style="list-style-type: none"> <li>• 12.5 mg, 25 mg, 50 mg, 75 mg, 100 mg tablets</li> <li>• <i>25 mg Powder for Oral Suspension unit-dose packets [Proposed]</i></li> </ul>
<b>Dose and Frequency</b>	<ul style="list-style-type: none"> <li>• Take on an empty stomach (1 hour before or 2 hours after a meal).</li> <li>• <i>Take PROMACTA at least 2 hours before or 4 hours after</i> other medications, foods, or supplements containing polyvalent cations (e.g., iron, calcium, aluminum, magnesium, selenium, and zinc). [Proposed]</li> <li>• <u>Chronic ITP</u>: Initiate PROMACTA at 50 mg once daily for</li> </ul>



	<p>most <i>adult and pediatric</i> patients <b>6 years and older and at 25 mg once daily for most pediatric patients aged 1 to 5 years</b>. Reduce initial dose in patients with hepatic impairment and/or patients of East Asian ancestry. Adjust to maintain platelet count greater than or equal to <math>50 \times 10^9/L</math>. Do not exceed 75 mg per day. [Proposed]</p> <ul style="list-style-type: none"> <li>• <u>Chronic Hepatitis C-associated Thrombocytopenia</u>: Initiate PROMACTA at 25 mg once daily for all patients. Adjust to achieve target platelet count required to initiate antiviral therapy. Do not exceed a daily dose of 100 mg.</li> <li>• <u>Severe Aplastic Anemia</u>: Initiate PROMACTA at 50 mg once daily for most patients. Reduce initial dose in patients with hepatic impairment or patients of East Asian ancestry. Adjust to maintain platelet count greater than <math>50 \times 10^9/L</math>. Do not exceed 150 mg per day.</li> </ul>
<b>How Supplied</b>	<ul style="list-style-type: none"> <li>• 12.5 mg, 25 mg, 50 mg, 75 mg, or 100 mg tablets, bottles of 30</li> <li>• <b>25 mg Powder for Oral Suspension unit-dose packets, co-packaged in a kit with a 40-cc reconstitution vessel, an oral dosing syringe, and a threaded closure with syringe-port capability. Each kit contains 30 packets. [Proposed]</b></li> </ul>
<b>Storage</b>	<p>Room temperature between 20°C and 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F)</p> <p><b><i>Powder for Oral Suspension – Following reconstitution, the product should be administered immediately but may be stored for a maximum period of 30 minutes between 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [Proposed]</i></b></p>

## APPENDIX C. HUMAN FACTORS STUDY

### C.1 Study Design

#### Objectives:

The primary objective of this study was to evaluate the parent or caregiver's ability to follow the steps in the Instructions for Use (IFU) to prepare, measure and administer a dose of the product.

#### The five critical use steps that were measured included:

1. Add water into mixing bottle (IFU Steps 1,2,3)
2. Empty full dose (prescribed number of stickpacks) into mixing bottle (IFU Steps 4,5,6)
3. Mix/shake powder/water mixture in mixing bottle (IFU Step 7)
4. Administer full dose – Fill syringe completely (IFU Steps 8,9,10)
5. (b) (4)

Three additional areas of potential difficulty/confusion were also evaluated during the study:

1. Whether the subject spilled or dropped the materials or medication.
2. Whether any clean-up steps were taken if there was a spill.
3. If any subjects had to begin again.

A post-use interview was conducted to evaluate the reasons for any incorrect results, as well as any areas of confusion or difficulty with the process or the IFU.

#### Methodology:

The study took place in a non-clinical setting.

Upon arrival onsite, the subject read and signed a Confidentiality/Non-Disclosure Agreement (CDA). Subjects then reviewed and completed an Informed Consent Form (ICF). To determine health literacy, an interviewer administered the Rapid Estimate of Adult Literacy in Medicine (REALM)<sup>4</sup> test.

The study was comprised of a simulated use test, followed by a post-use interview. Subjects were first presented with the IFU and the test materials. All subjects were then given materials for the study to include a carton containing 5 stickpacks (from which they prepared an assigned dose of 1, 2 or 3 stickpacks), a mixing bottle, an adapta-cap and lid, and a syringe, along with a pair of scissors, 2 empty cups, and access to drinking water. The interviewer, using a scripted statement, described the purpose of the study and gave a usage scenario that involved having the subject imagine their child has just been prescribed this product and to proceed as they normally would to prepare for and administer a dose. Subjects were then given an opportunity to independently review the information and familiarize themselves with the product as if they were at home about to prepare a dose of the product for a child for the first time, with no one in the room and without guidance or instruction from the study team.

Once the subject finished reviewing the information, the product demonstration was conducted. The subject was randomized to an assigned dose (1, 2 or 3 stickpacks). The subject was then asked to demonstrate the preparation and administration steps; placebo and not active drug product was administered to a cup to simulate dosing.

The interviewer left the room and moved behind the 1-way mirror with the trained observer to assess the subject's actions relating to the critical usage steps, and the degree of difficulty and number of attempts made in the performance of these steps. These observations were then documented on an objective Observer's Checklist to evaluate whether each critical step was completed correctly or incorrectly based on the instruction in the IFU.

Following the subject's completion of the demonstration, the interviewer returned to the room and conducted a post-use interview that included a discussion on any steps that were performed incorrectly and delved into the reasons for the action taken. Additional qualitative questions were asked to ascertain if there were areas of difficulty or confusion with the process itself or with the IFU.

### **User Population:**

The user population groups were selected based on the anticipated user groups for pediatric dosing. General Population of Parents and Caregivers, Ages 20 and Older (N=30)

- Subgroup 1: Normal Literacy Parents and Caregivers, Ages 20+ (n=15)
  - o Subgroup 1A: Normal Literacy Parents and Caregivers, 20-50 years of age (n=7-8)
  - o Subgroup 1B: Normal Literacy Parents and Caregivers, >51 years of age (n=7-8)
- Subgroup 2: Low Literacy Parents and Caregivers, Ages 20+ (n=15)

User profile characteristics were gathered and reported for exploratory purposes for visual (corrected vision using glasses or contacts, glaucoma or cataracts) and dexterity (arthritis, left-handed, right-handed) characteristics.

### **Number of Subjects (planned and analyzed):**

Study Participants: Untrained

Planned: Approximately 30 subjects were to have been enrolled at 1 research site in 1 pre-designated cohort, with approximately 15 subjects having tested as low literate.

Analyzed: 32 subjects were enrolled and 32 subjects completed:

General Population of Parents and Caregivers, Ages 20 and Older (**N=32**)

- Subgroup 1: Normal Literacy Parents and Caregivers, Ages 20+ (n=17)
  - o Subgroup 1A: Normal Literacy Parents and Caregivers, 20-50 years of age (n=9)
  - o Subgroup 1B: Normal Literacy Parents and Caregivers, >51 years of age (n=8)
- Subgroup 2: Low Literacy Parents and Caregivers, Ages 20+ (n=15)

### **User Interface:**

The subject was given the following materials:

1. Carton: A white carton was provided to represent the intended commercial pack.
2. Stickpacks: Five (5) individual stickpacks were provided to represent the 30 stickpacks that may typically be included in the commercial prescription.
3. Bottle: One (1) mixing bottle was provided.
4. Adapta-cap and Lid: One (1) adapta-cap and attached lid (for use on the mixing bottle) was provided separately.
5. Syringe: One (1) syringe with mL markings was provided for use.
6. Empty cups: Two (2) empty cups were provided for the subject to use – one to fill with water and one to simulate the child’s mouth for administration of the dose.
7. Scissors: One (1) pair of scissors was provided for the subject to use to cut open the stickpacks.
8. Sink: Subjects had access to a working sink that provided drinking water.
9. Instructions for Use Leaflet: The latest version of the intended commercial IFU was included to provide clear instruction of use. It was folded to represent the final commercial IFU.

## C.2 Results

### Human Factors Results and Tabulations of Individual Subject Data

#### Observed Critical Usage Steps

There were 5 critical usage steps that were established for this human factors study. The results were moderate, with 68.8% of all subjects completing all critical steps correctly. Normal literacy subjects scored higher (88.2%) as compared to low literacy subjects (46.7%).

Two of the five critical steps (Add water into mixing bottle; Mix/shake powder/water mixture in mixing bottle) were demonstrated correctly by all subjects. mixture in mixing bottle) were demonstrated correctly by all subjects.

[Table 10](#) shows results for each step individually and for cumulative ‘All Steps Correct’. Number and percentage of correct and incorrect subjects are shown, with the overall correct score (Total Correct + Mitigation) presented first, along with the 94% exact confidence interval. Correct scores based on the IFU (Correctly Without Mitigation) and correct scores that were not completed technically perfect but have been mitigated based on no or limited impact on safety risk or efficacy (Correctly With Mitigation) are shown separately beneath the overall correct score.

**Table 10: Results for Critical Steps with Mitigation - Total**

Critical Usage Step	Total (N=32)		All
	n(%)	(95%CI)	
<b>Steps Correct</b>			
• <b>Total Correct + Mitigation</b>	<b>22 (68.8)</b>	<b>(49.99, 83.88)</b>	
1. Add water into mixing bottle ( <i>Checklist Step 1a</i> )			

<ul style="list-style-type: none"> <li>• <b>Total Correct + Mitigation</b></li> <li>○ <i>Correctly Without Mitigation</i></li> <li>○ <i>Correctly With Mitigation</i></li> </ul>	<b>32 (100.0)</b> 27 (84.4) 5 (15.6)	<b>(89.11, 100.00)</b>
<ul style="list-style-type: none"> <li>• Incorrect</li> </ul>	0 (0.0)	
<hr/>		
2. Empty full dose (prescribed number of stickpacks) into mixing bottle ( <i>Checklist Step 2a_1</i> )		
<ul style="list-style-type: none"> <li>• <b>Total Correct + Mitigation</b></li> <li>○ <i>Correctly Without Mitigation</i></li> <li>○ <i>Correctly With Mitigation</i></li> </ul>	<b>29 (90.6)</b> 24 (75.0) 5 (15.6)	<b>(74.98, 98.02)</b>
<ul style="list-style-type: none"> <li>• Incorrect</li> </ul>	3 (9.4)	
<hr/>		
3. Mix/shake powder/water mixture in mixing bottle ( <i>Checklist Step 4a</i> )		
<ul style="list-style-type: none"> <li>• <b>Total Correct + Mitigation</b></li> <li>○ <i>Correctly Without Mitigation</i></li> <li>○ <i>Correctly With Mitigation</i></li> </ul>	<b>32 (100.0)</b> 32 (100.0) 0 (0.0)	<b>(89.11, 100.00)</b>
<ul style="list-style-type: none"> <li>• Incorrect</li> </ul>	0 (0.0)	
<hr/>		
4. Administer full dose – Fill syringe completely ( <i>Checklist Step 5a</i> )		
<ul style="list-style-type: none"> <li>• <b>Total Correct + Mitigation</b></li> <li>○ <i>Correctly Without Mitigation</i></li> <li>○ <i>Correctly With Mitigation</i></li> </ul>	<b>27 (84.4)</b> 24 (75.0) 3 (9.4)	<b>(67.21, 94.74)</b>
<ul style="list-style-type: none"> <li>• Incorrect</li> </ul>	5 (15.6)	

(b) (4)

A review of the three steps that had at least one subject score as ‘Incorrect’ identified the following issues:

**Critical Usage Step 2 - Empty full dose (prescribed number of stickpacks) into mixing bottle (*Checklist Step 2a\_1*):** Three subjects did not empty the full dose of the prescribed number of stickpacks correctly into the mixing bottle.

- Subjects 01-003 (Subgroup 1; NL) and 01-024 (Subgroup 2; LL) emptied fewer stickpacks than the full prescribed dose into the mixing bottle. Upon follow-up questioning, subjects mentioned not remembering to check the dosing card, and assuming that information would have been on the box like a typical prescription.

- Subject 01-022 (Subgroup 2; LL) emptied 1 stickpack into the cup of water, then drew 20mL out of the cup and put that mixture into the mixing bottle (leaving the remaining powder/water mixture in the cup). The subject then emptied the remaining powder/water mixture out of the cup into the sink. Upon follow-up, the subject mentioned being confused and trying to complete the demonstration without referencing the instructions, but recognizing they had made a mistake.

**Critical Usage Step 4 – Administer full dose – Fill syringe completely (*Checklist Step 5a*):** Five subjects did not correctly simulate fully administering the dose (b) (4)

- 01-028 (Subgroup 2; LL) - Only about 10-15mL of dose was pulled out with syringe and then administered, instead of 20mL. At follow-up, the subject acknowledged seeing that the IFU said to pull out 20mL and was trying to do so. The subject described trying to pull the rest out, after not being able to get it all out with the first draw.
- 01-022 (Subgroup 2; LL) – Drew correct amount into syringe but stopped and did not administer into the cup. When asked why – the subject mentioned just not thinking about putting it into the cup.
- 01-019 (Subgroup 2; LL) - Started drawing medicine up into syringe, then pushed medicine back into bottle, opened cap/lid and poured medicine into cup directly from bottle. At follow-up, the subject mentioned concern about spilling, due to the pressure needed to hold the plunger/syringe trying to pull the syringe off the bottle.
- 01-003 (Subgroup 1; NL) and 01-024 (Subgroup 2; LL) – An incorrect number of stickpacks were emptied into the bottle at the start, so a full dose could not be administered.

(b) (4)

When reviewing the critical step performance by Subgroup ([Table 11](#)), scores were very high for normal literacy subjects, ranging from 88% - 100%. Scores for low literacy subjects ranged from 47% - 100%, with these subjects having the most difficulty with (b) (4). When breaking down Subgroup 1 further by age, all subjects (100%) in Subgroup 1a (Normal Literacy Parents/Guardians, Ages 20-50) completed all steps correctly (See [Appendix 15.1](#)).

**Table 11: Results for Critical Steps with Mitigation by Subgroup**

**Table 11: Results for Critical Steps with Mitigation by Subgroup**

Critical Usage Step	Subgroup 1: Normal Literacy Parents/Guardians (N=17)		Subgroup 2: Low Literacy Parents/Guardians (N=15)	
	n (%)	(95% CI)	n (%)	(95% CI)
	<b>All Steps Correct</b>			
• <b>Total Correct + Mitigation</b>	<b>15 (88.2)</b>	<b>(63.56, 98.54)</b>	<b>7 (46.7)</b>	<b>(21.27, 73.41)</b>
1. Add water into mixing bottle ( <i>Checklist Step 1a</i> )				
• <b>Total Correct + Mitigation</b>	<b>17 (100.0)</b>	<b>(80.49, 100.00)</b>	<b>15 (100.0)</b>	<b>(78.20, 100.00)</b>
○ Correctly Without Mitigation	17 (100.0)		10 (66.7)	
○ Correctly With Mitigation	0 (0.0)		5 (33.3)	
○ Incorrect	0 (0.0)		0 (0.0)	
2. Empty full dose (prescribed number of stickpacks) into mixing bottle ( <i>Checklist Step 2a_1</i> )				
• <b>Total Correct + Mitigation</b>	<b>16 (94.1)</b>	<b>(71.31, 99.85)</b>	<b>13 (86.7)</b>	<b>(59.54, 98.34)</b>
○ Correctly Without Mitigation	16 (94.1)		8 (53.3)	



Critical Usage Step	Subgroup 1: Normal Literacy Parents/Guardians (N=17)		Subgroup 2: Low Literacy Parents/Guardians (N=15)	
	n (%)	(95% CI)	n (%)	(95% CI)
○ Correctly With Mitigation	0 (0.0)		5 (33.3)	
○ Incorrect	1 (5.9)		2 (13.3)	
3. Mix/shake powder/water mixture in mixing bottle ( <i>Checklist Step 4a</i> )				
• <b>Total Correct + Mitigation</b>	<b>17 (100.0)</b>	<b>(80.49, 100.00)</b>	<b>15 (100.0)</b>	<b>(78.20, 100.00)</b>
○ Correctly Without Mitigation	17 (100.0)		15 (100.0)	
○ Correctly With Mitigation	0 (0.0)		0 (0.0)	
○ Incorrect	0 (0.0)		0 (0.0)	
4. Administer full dose – Fill syringe completely ( <i>Checklist Step 5a</i> )				
• <b>Total Correct + Mitigation</b>	<b>16 (94.1)</b>	<b>(71.31, 99.85)</b>	<b>11 (73.3)</b>	<b>(44.90, 92.21)</b>
○ Correctly Without Mitigation	15 (88.2)		9 (60.0)	
○ Correctly With Mitigation	1 (5.9)		2 (13.3)	
○ Incorrect	1 (5.9)		4 (26.7)	

(b) (4)

### Additional Analyses

All subjects but one made only one attempt to complete the simulation. One subject initially emptied one stickpack into the cup of water, realized their mistake, and dumped out the contents of the cup into the sink. The subject then re-filled the cup with fresh water, and proceeded to complete the simulated use demonstration. No subjects spilled more than a trace amount of powder during the simulation.

All subjects were asked to describe their experience preparing and administering a dose of the medicine. More than half of subjects responded that it was easy to prepare (62.5%, n=20) and easy to give/administer (56.3%, n=18). However, just over one quarter of subjects (28.1%, n=9) felt there were too many steps to get correct and the process was too tedious. A subset of subjects also mentioned being nervous about spilling (12.5%, n=4) (b) (4)

All subjects were asked whether anything was confusing. More than half of subjects responded that it was not confusing (62.5%, n=20). (b) (4)

Similarly, 18.8% of subjects (n=6) felt it should be more clear to complete all steps, (b) (4)

## SAFETY EVALUATION

### Adverse Events



patients will be monitored therapeutically by platelet counts and any deviations from the expected therapeutic effects will be assessed by the healthcare provider. In totality, the results from this Human Factors Validation study support the use of the proposed IFU.

## **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>1</sup> along with postmarket medication error data, we reviewed the following Promacta labels and labeling submitted by GSK on February 24, 2015 and May 27, 2015.

- Packet Container label
- Outer Carton labeling
- Inner Carton Labeling
- Instructions for Use
- Prescribing Information labeling (not listed)

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

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

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

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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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MICHELLE K RUTLEDGE  
07/14/2015

YELENA L MASLOV  
07/14/2015

# REGULATORY PROJECT MANAGER PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW OF THE PRESCRIBING INFORMATION

**Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements**

**Application:** NDA 207027

**Application Type:** New NDA

**Name of Drug/Dosage Form:** PROMACTA (eltrombopag) powder for oral suspension, 25mg

**Applicant:** Novartis Pharmaceuticals Corp

**Receipt Date:** February 24, 2015

**Goal Date:** August 24, 2015

## 1. Regulatory History and Applicant's Main Proposals

This NDA provides for a new dosage form of Promacta (powder for oral suspension) and provides for a new indication "thrombocytopenia in adult and pediatric patients 1 year and older with chronic immune (idiopathic) thrombocytopenia (ITP) who have had insufficient response to corticosteroids, immunoglobulins, or splenectomy."

## 2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

## 3. Conclusions/Recommendations

No SRPI format deficiencies were identified in the review of this PI.

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## Appendix

The Selected Requirement of Prescribing Information (SRPI) is a 42-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

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## Highlights

See Appendix A for a sample tool illustrating the format for the Highlights.

## Selected Requirements of Prescribing Information

### HIGHLIGHTS GENERAL FORMAT

- YES** 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

**Comment:**

- YES** 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. **Instructions to complete this item:** If the length of the HL is one-half page or less, select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select “NO” unless a waiver has been granted.

**Comment:** *The PI used for this NDA is the same PI used for previously approved NDA 022291 for which a waiver has previously been granted.*

- YES** 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.

**Comment:**

- YES** 4. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.

**Comment:**

- YES** 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.

**Comment:**

- YES** 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

**Comment:**

- YES** 7. Section headings must be presented in the following order in HL:

Section	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required
• Product Title	Required
• Initial U.S. Approval	Required
• Boxed Warning	Required if a BOXED WARNING is in the FPI
• Recent Major Changes	Required for only certain changes to PI*
• Indications and Usage	Required
• Dosage and Administration	Required
• Dosage Forms and Strengths	Required
• Contraindications	Required (if no contraindications must state “None.”)
• Warnings and Precautions	Not required by regulation, but should be present
• Adverse Reactions	Required
• Drug Interactions	Optional
• Use in Specific Populations	Optional

## Selected Requirements of Prescribing Information

• Patient Counseling Information Statement	Required
• Revision Date	Required

\* RMC only applies to the BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS sections.

### Comment:

## HIGHLIGHTS DETAILS

### Highlights Heading

- YES** 8. At the beginning of HL, the following heading must be **bolded** and should appear in all UPPER CASE letters: “**HIGHLIGHTS OF PRESCRIBING INFORMATION**”.

### Comment:

### Highlights Limitation Statement

- YES** 9. The **bolded** HL Limitation Statement must include the following verbatim statement: “**These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).**” The name of drug product should appear in UPPER CASE letters.

### Comment:

### Product Title in Highlights

- YES** 10. Product title must be **bolded**.

### Comment:

### Initial U.S. Approval in Highlights

- YES** 11. Initial U.S. Approval in HL must be **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit year**.

### Comment:

### Boxed Warning (BW) in Highlights

- YES** 12. All text in the BW must be **bolded**.

### Comment:

- YES** 13. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”). The BW heading should be centered.

### Comment:

- YES** 14. The BW must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” This statement should be centered immediately beneath the heading and appear in *italics*.

### Comment:

- YES** 15. The BW must be limited in length to 20 lines (this includes white space but does not include the BW heading and the statement “*See full prescribing information for complete boxed warning.*”).



## Selected Requirements of Prescribing Information

### Comment:

#### Recent Major Changes (RMC) in Highlights

- YES** 16. RMC pertains to only the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in FPI.

### Comment:

- YES** 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section's identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, "Warnings and Precautions, Acute Liver Failure (5.1) --- 9/2013".

### Comment:

- YES** 18. The RMC must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment: *At the time of action, old RMCs will be removed.*

#### Indications and Usage in Highlights

- YES** 19. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: "(Product) is a (name of established pharmacologic class) indicated for (indication)".

### Comment:

#### Dosage Forms and Strengths in Highlights

- NO** 20. For a product that has several dosage forms (e.g., capsules, tablets, and injection), bulleted subheadings or tabular presentations of information should be used under the Dosage Forms and Strengths heading.

### Comment:

#### Contraindications in Highlights

- YES** 21. All contraindications listed in the FPI must also be listed in HL or must include the statement "None" if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.

### Comment:

#### Adverse Reactions in Highlights

- YES** 22. For drug products other than vaccines, the verbatim **bolded** statement must be present: "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**".

### Comment:

#### Patient Counseling Information Statement in Highlights

## Selected Requirements of Prescribing Information

**YES** 23. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product **has** FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide**”

*Comment:*

### Revision Date in Highlights

**YES** 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., “**Revised: 9/2013**”).

*Comment:*

## Selected Requirements of Prescribing Information

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### Contents: Table of Contents (TOC)

See Appendix A for a sample tool illustrating the format for the Table of Contents.

- YES** 25. The TOC should be in a two-column format.  
*Comment:*
- YES** 26. The following heading must appear at the beginning of the TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”. This heading should be in all UPPER CASE letters and **bolded**.  
*Comment:*
- YES** 27. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.  
*Comment:*
- YES** 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.  
*Comment:*
- YES** 29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].  
*Comment:*
- YES** 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.  
*Comment:*
- YES** 31. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “FULL PRESCRIBING INFORMATION: CONTENTS” must be followed by an asterisk and the following statement must appear at the end of TOC: “\*Sections or subsections omitted from the full prescribing information are not listed.”  
*Comment:*

## Selected Requirements of Prescribing Information

### Full Prescribing Information (FPI)

#### FULL PRESCRIBING INFORMATION: GENERAL FORMAT

- YES** 32. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below (section and subsection headings should be in UPPER CASE and title case, respectively). If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

<b>BOXED WARNING</b>
<b>1 INDICATIONS AND USAGE</b>
<b>2 DOSAGE AND ADMINISTRATION</b>
<b>3 DOSAGE FORMS AND STRENGTHS</b>
<b>4 CONTRAINDICATIONS</b>
<b>5 WARNINGS AND PRECAUTIONS</b>
<b>6 ADVERSE REACTIONS</b>
<b>7 DRUG INTERACTIONS</b>
<b>8 USE IN SPECIFIC POPULATIONS</b>
<b>8.1 Pregnancy</b>
<b>8.2 Labor and Delivery</b>
<b>8.3 Nursing Mothers</b>
<b>8.4 Pediatric Use</b>
<b>8.5 Geriatric Use</b>
<b>9 DRUG ABUSE AND DEPENDENCE</b>
<b>9.1 Controlled Substance</b>
<b>9.2 Abuse</b>
<b>9.3 Dependence</b>
<b>10 OVERDOSAGE</b>
<b>11 DESCRIPTION</b>
<b>12 CLINICAL PHARMACOLOGY</b>
<b>12.1 Mechanism of Action</b>
<b>12.2 Pharmacodynamics</b>
<b>12.3 Pharmacokinetics</b>
<b>12.4 Microbiology (by guidance)</b>
<b>12.5 Pharmacogenomics (by guidance)</b>
<b>13 NONCLINICAL TOXICOLOGY</b>
<b>13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility</b>
<b>13.2 Animal Toxicology and/or Pharmacology</b>
<b>14 CLINICAL STUDIES</b>
<b>15 REFERENCES</b>
<b>16 HOW SUPPLIED/STORAGE AND HANDLING</b>
<b>17 PATIENT COUNSELING INFORMATION</b>

**Comment:**

- YES** 33. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, “[*see Warnings and Precautions (5.2)*]” or “[*see Warnings and Precautions (5.2)*]”.

**Comment:**

## Selected Requirements of Prescribing Information

- YES** 34. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

*Comment:*

### FULL PRESCRIBING INFORMATION DETAILS

#### FPI Heading

- YES** 35. The following heading must be **bolded** and appear at the beginning of the FPI: “**FULL PRESCRIBING INFORMATION**”. This heading should be in UPPER CASE.

*Comment:*

#### BOXED WARNING Section in the FPI

- YES** 36. In the BW, all text should be **bolded**.

*Comment:*

- YES** 37. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”).

*Comment:*

#### CONTRAINDICATIONS Section in the FPI

- YES** 38. If no Contraindications are known, this section must state “None.”

*Comment:*

#### ADVERSE REACTIONS Section in the FPI

- YES** 39. When clinical trials adverse reactions data are included (typically in the “Clinical Trials Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.”

*Comment:*

- N/A** 40. When postmarketing adverse reaction data are included (typically in the “Postmarketing Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

*Comment:*

#### PATIENT COUNSELING INFORMATION Section in the FPI

- YES** 41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and

## Selected Requirements of Prescribing Information

include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

**Comment:**

- YES** 42. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

**Comment:**

# Selected Requirements of Prescribing Information

## Appendix A: Format of the Highlights and Table of Contents

### HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use [DRUG NAME] safely and effectively. See full prescribing information for [DRUG NAME].

[DRUG NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol]  
Initial U.S. Approval: [year]

**WARNING: [SUBJECT OF WARNING]**

*See full prescribing information for complete boxed warning.*

- [text]
- [text]

### RECENT MAJOR CHANGES

[section (X.X)] [m/year]  
[section (X.X)] [m/year]

### INDICATIONS AND USAGE

[DRUG NAME] is a [name of pharmacologic class] indicated for [text]

### DOSAGE AND ADMINISTRATION

- [text]
- [text]

### DOSAGE FORMS AND STRENGTHS

[text]

### CONTRAINDICATIONS

- [text]
- [text]

### WARNINGS AND PRECAUTIONS

- [text]
- [text]

### ADVERSE REACTIONS

Most common adverse reactions (incidence > x%) are [text].

To report SUSPECTED ADVERSE REACTIONS, contact [name of manufacturer] at [phone #] or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

### DRUG INTERACTIONS

- [text]
- [text]

### USE IN SPECIFIC POPULATIONS

- [text]
- [text]

See 17 for PATIENT COUNSELING INFORMATION [and FDA-approved patient labeling OR and Medication Guide].

Revised: [m/year]

### FULL PRESCRIBING INFORMATION: CONTENTS\*

WARNING: [SUBJECT OF WARNING]

#### 1 INDICATIONS AND USAGE

#### 2 DOSAGE AND ADMINISTRATION

2.1 [text]

2.2 [text]

#### 3 DOSAGE FORMS AND STRENGTHS

#### 4 CONTRAINDICATIONS

#### 5 WARNINGS AND PRECAUTIONS

5.1 [text]

5.2 [text]

#### 6 ADVERSE REACTIONS

6.1 [text]

6.2 [text]

#### 7 DRUG INTERACTIONS

7.1 [text]

7.2 [text]

#### 8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Labor and Delivery

8.3 Nursing Mothers

8.4 Pediatric Use

8.5 Geriatric Use

#### 9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

9.2 Abuse

9.3 Dependence

#### 10 OVERDOSAGE

#### 11 DESCRIPTION

#### 12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.2 Pharmacodynamics

12.3 Pharmacokinetics

12.4 Microbiology

12.5 Pharmacogenomics

#### 13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

13.2 Animal Toxicology and/or Pharmacology

#### 14 CLINICAL STUDIES

14.1 [text]

14.2 [text]

#### 15 REFERENCES

#### 16 HOW SUPPLIED/STORAGE AND HANDLING

#### 17 PATIENT COUNSELING INFORMATION

\*Sections or subsections omitted from the full prescribing information are not listed.

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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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KIMBERLY L SCOTT  
05/08/2015

MARA B MILLER  
05/08/2015



## RPM FILING REVIEW

(Including Memo of Filing Meeting)

**To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]**

Application Information		
NDA # 207027 BLA#	NDA Supplement #: S- BLA Supplement #: S-	Efficacy Supplement Category: <input type="checkbox"/> New Indication (SE1) <input type="checkbox"/> New Dosing Regimen (SE2) <input type="checkbox"/> New Route Of Administration (SE3) <input type="checkbox"/> Comparative Efficacy Claim (SE4) <input type="checkbox"/> New Patient Population (SE5) <input type="checkbox"/> Rx To OTC Switch (SE6) <input type="checkbox"/> Accelerated Approval Confirmatory Study (SE7) <input type="checkbox"/> Animal Rule Confirmatory Study (SE7) <input type="checkbox"/> Labeling Change With Clinical Data (SE8) <input type="checkbox"/> Manufacturing Change With Clinical Data (SE9) <input type="checkbox"/> Pediatric
Proprietary Name: PROMACTA Established/Proper Name: eltrombopag Dosage Form: Powder for oral suspension Strengths: 25mg		
Applicant: Novartis Pharmaceuticals Corporation Agent for Applicant (if applicable):		
Date of Application: February 24, 2015 Date of Receipt: February 24, 2015 Date clock started after UN:		
PDUFA/BsUFA Goal Date: August 24, 2015		Action Goal Date (if different):
Filing Date: April 25, 2015		Date of Filing Meeting: March 25, 2015
Chemical Classification (original NDAs only) : <input type="checkbox"/> Type 1- New Molecular Entity (NME); NME and New Combination <input type="checkbox"/> Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination <input checked="" type="checkbox"/> Type 3- New Dosage Form <input type="checkbox"/> Type 4- New Combination <input type="checkbox"/> Type 5- New Formulation or New Manufacturer <input type="checkbox"/> Type 7- Drug Already Marketed without Approved NDA <input type="checkbox"/> Type 8- Partial Rx to OTC Switch		
Proposed indication(s)/Proposed change(s): New formulation for pediatrics one years old or greater with chronic idiopathic thrombocytopenia		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:		<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:</i> <a href="http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499">http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499</a>		

Type of BLA	<input type="checkbox"/> 351(a) <input type="checkbox"/> 351(k)
<b><i>If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team</i></b>	
Review Classification:	<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority
<b><i>The application will be a priority review if:</i></b>	<input checked="" type="checkbox"/> Pediatric WR
<ul style="list-style-type: none"> <li><i>A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH)</i></li> <li><i>The product is a Qualified Infectious Disease Product (QIDP)</i></li> <li><i>A Tropical Disease Priority Review Voucher was submitted</i></li> <li><i>A Pediatric Rare Disease Priority Review Voucher was submitted</i></li> </ul>	<input type="checkbox"/> QIDP <input type="checkbox"/> Tropical Disease Priority Review Voucher <input type="checkbox"/> Pediatric Rare Disease Priority Review Voucher
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>
Part 3 Combination Product? <input checked="" type="checkbox"/>	<input checked="" type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)
<b><i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i></b>	

<input type="checkbox"/> Fast Track Designation <input type="checkbox"/> Breakthrough Therapy Designation <i>(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)</i> <input type="checkbox"/> Rolling Review <input checked="" type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <ul style="list-style-type: none"> <li><input type="checkbox"/> FDAAA [505(o)]</li> <li><input type="checkbox"/> PREA deferred pediatric studies (FDCA Section 505B)</li> <li><input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41)</li> <li><input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)</li> </ul>
Other:	

Collaborative Review Division (if OTC product):

List referenced IND Number(s):  
IND 063293

Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA/BsUFA and Action Goal dates correct in tracking system?  <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Are the established/proper and applicant names correct in tracking system?  <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

<i>to the supporting IND(s) if not already entered into tracking system.</i>				
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? <i>Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:</i> <a href="http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm">http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm</a> <i>If no, ask the document room staff to make the appropriate entries.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>Application Integrity Policy</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at:</i> <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a> <i>If yes, explain in comment column.</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<b>If affected by AIP, has OC/OMPQ been notified of the submission? If yes, date notified:</b>	<input type="checkbox"/>	<input type="checkbox"/>		
<b>User Fees</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<u>User Fee Status</u> <i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i>	Payment for this application ( <i>check daily email from <a href="mailto:UserFeeAR@fda.hhs.gov">UserFeeAR@fda.hhs.gov</a></i> ): <input type="checkbox"/> Paid <input checked="" type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required			
<i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i>	Payment of other user fees: <input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears			
<u>User Fee Bundling Policy</u> <i>Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:</i> <a href="http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf">http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf</a>	Has the user fee bundling policy been appropriately applied? <i>If no, or you are not sure, consult the User Fee Staff.</i> <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No			
<b>505(b)(2) (NDAs/NDA Efficacy Supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is the application a 505(b)(2) NDA? ( <i>Check the 356h form,</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		

cover letter, and annotated labeling). <b>If yes</b> , answer the bulleted questions below:					
• Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?		<input type="checkbox"/>	<input type="checkbox"/>		
• Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].		<input type="checkbox"/>	<input type="checkbox"/>		
• Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?		<input type="checkbox"/>	<input type="checkbox"/>		
<i>If you answered yes to any of the above bulleted questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs for advice.</i>					
• Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)?		<input type="checkbox"/>	<input type="checkbox"/>		
<i>Check the Electronic Orange Book at: <a href="http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm">http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</a></i>					
<b>If yes</b> , please list below:					
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration		
<i>If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i>					
<b>Exclusivity</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>	
Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug Designations and Approvals list at: <a href="http://www.accessdata.fda.gov/scripts/opdlisting/opd/index.cfm">http://www.accessdata.fda.gov/scripts/opdlisting/opd/index.cfm</a></i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>			
<b>If another product has orphan exclusivity</b> , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>		
<i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>					
<b>NDAs/NDA efficacy supplements only:</b> Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<b>If yes</b> , # years requested:					



<i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>				
<b>NDAs only:</b> Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<b>If yes, did the applicant:</b> (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?  <i>If yes, contact the Orange Book Staff (CDER-Orange Book Staff).</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>BLAs only:</b> Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act?  <i>If yes, notify Marlene Schultz-DePalo, OBP Biosimilars RPM</i>  <i>Note: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

Format and Content				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic)  <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
<b>If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?</b>				
<b>Overall Format/Content</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<b>If electronic submission, does it follow the eCTD guidance?</b> <sup>1</sup> <b>If not, explain (e.g., waiver granted).</b>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>Index:</b> Does the submission contain an accurate comprehensive index?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Is the submission complete as required under 21 CFR 314.50 (NDAs/NDA efficacy supplements) or under 21 CFR 601.2 (BLAs/BLA efficacy supplements) including:	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

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<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

<input type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input type="checkbox"/> pagination <input type="checkbox"/> navigable hyperlinks (electronic submissions only)				
<b>If no, explain.</b>				
<b>BLAs only:</b> Companion application received if a shared or divided manufacturing arrangement?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<b>If yes, BLA #</b>				
<b>Forms and Certifications</b>				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397/3792), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
<b>Application Form</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>Patent Information (NDAs/NDA efficacy supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>Financial Disclosure</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
<b>Clinical Trials Database</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is form FDA 3674 included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i>				

<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				
<b>Debarment Certification</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a correctly worded Debarment Certification included with authorized signature?  <i>Certification is not required for supplements if submitted in the original application; If foreign applicant, <b>both</b> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i>  <i>Note: Debarment Certification should use wording in FD&amp;C Act Section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>Field Copy Certification (NDAs/NDA efficacy supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<b>For paper submissions only:</b> Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?  <i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i>  <i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<b>Controlled Substance/Product with Abuse Potential</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?  <i>If yes, date consult sent to the Controlled Substance Staff:</i>  <u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<b>Pediatrics</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<b><u>PREA</u></b> Does the application trigger PREA?  <i>If yes, notify <a href="mailto:PeRC@fda.hhs.gov">PeRC@fda.hhs.gov</a> to schedule required PeRC meeting<sup>2</sup></i>  <i>Note: NDAs/BLAs/efficacy supplements for new active ingredients</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		Product has orphan designation for this indication

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027829.htm>

Version: 3/20/2014

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<i>(including new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver &amp; deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i>				
<b>If the application triggers PREA, is there an agreed Initial Pediatric Study Plan (iPSP)?</b>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<i>If no, may be an RTF issue - contact DPMH for advice.</i>				
<b>If required by the agreed iPSP, are the pediatric studies outlined in the agreed iPSP completed and included in the application?</b>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<i>If no, may be an RTF issue - contact DPMH for advice.</i>				
<b><u>BPCA:</u></b>				Meeting is June 2, 2015
Is this submission a complete response to a pediatric Written Request?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)<sup>3</sup></i>				
<b>Proprietary Name</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a proposed proprietary name submitted?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>				
<b>REMS</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a REMS submitted?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>				
<b>Prescription Labeling</b>	<input type="checkbox"/> <b>Not applicable</b>			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input checked="" type="checkbox"/> Instructions for Use (IFU) <input checked="" type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is Electronic Content of Labeling (COL) submitted in SPL format?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If no, request applicant to submit SPL before the filing date.</i>				

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027837.htm>

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Is the PI submitted in PLR format? <sup>4</sup>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<b>If PI not submitted in PLR format</b> , was a waiver or deferral requested before the application was received or in the submission? <b>If requested before application was submitted</b> , what is the status of the request?  <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<b>For applications submitted on or after June 30, 2015:</b> Is the PI submitted in PLLR format? <sup>5</sup>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<b>If PI not submitted in PLLR format</b> , was a waiver or deferral requested before the application was received or in the submission? <b>If requested before application was submitted</b> , what is the status of the request?  <i>If no waiver or deferral, request applicant to submit labeling in PLR/PLLR format before the filing date.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Consulted DMPP/Patient Labeling
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>OTC Labeling</b>	<input checked="" type="checkbox"/> <b>Not Applicable</b>			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is electronic content of labeling (COL) submitted?  <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>		
Are annotated specifications submitted for all stock keeping units (SKUs)?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

<i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<i>If no, request in 74-day letter.</i>				
All labeling/packaging sent to OSE/DMEPA?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>Other Consults</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	CDRH
<i>If yes, specify consult(s) and date(s) sent: March 11, 2015</i>				
<b>Meeting Minutes/SPAs</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
End-of Phase 2 meeting(s)? <b>Date(s):</b>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<i>If yes, distribute minutes before filing meeting</i>				
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? <b>Date(s):</b>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		Preliminary meeting comments sent, but meeting was cancelled
<i>If yes, distribute minutes before filing meeting</i>				
Any Special Protocol Assessments (SPAs)? <b>Date(s):</b>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<i>If yes, distribute letter and/or relevant minutes before filing meeting</i>				

ATTACHMENT

**MEMO OF FILING MEETING**

**DATE:** 3/25/2015

**BACKGROUND:** NDA 207027 provides for a new dosage form of Promacta (powder for oral suspension) and provides for an expanded indication of the previously approved indication for thrombocytopenia: “thrombocytopenia in adult and pediatric patients 1 year and older with chronic immune (idiopathic) thrombocytopenia (ITP) who have had insufficient response to corticosteroids, immunoglobulins, or splenectomy.”

**REVIEW TEAM:**

<b>Discipline/Organization</b>	<b>Names</b>		<b>Present at filing meeting? (Y or N)</b>
Regulatory Project Management	RPM:	KIMBERLY SCOTT	Y
	CPMS/TL:	THERESA CARIOTI	Y
Cross-Discipline Team Leader (CDTL)	JANICE BROWN		Y
Division Director/Deputy	ANN T. FARRELL		Y
Office Director/Deputy	RICHARD PAZDUR		N
Clinical	Reviewer:	LORI EHRLICH	Y
	TL:	VIRGINIA KWITKOWSKI	Y
Social Scientist Review ( <i>for OTC products</i> )	Reviewer:	N/A	
	TL:	N/A	
OTC Labeling Review ( <i>for OTC products</i> )	Reviewer:	N/A	
	TL:	N/A	
Clinical Microbiology ( <i>for antimicrobial products</i> )	Reviewer:	N/A	
	TL:	N/A	
Clinical Pharmacology	Reviewer:	Jee Eun Lee	Y
	TL:	Nitin Mehrota	Y
Biostatistics	Reviewer:	Chia-Wen Ko	

	TL:	Lei Nie	
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Chris Sheth	N
	TL:	Pedro DelValle	Y
Statistics (carcinogenicity)	Reviewer:	N/A	
	TL:	N/A	
Immunogenicity (assay/assay validation) <i>(for protein/peptide products only)</i>	Reviewer:	N/A	
	TL:	N/A	
Product Quality (CMC)	Reviewer:	Danuta Gromek-Woods	Y
	TL:	Janice Brown	Y
Biopharmaceutics	Reviewer:	Banu Zolnik	N
	TL:	Okpo Eradiri	
Quality Microbiology	Reviewer:	Johnathan Swoboda	N
	TL:	N/A	
CMC Labeling Review	Reviewer:	N/A	
	TL:	N/A	
Facility Review/Inspection	Reviewer:	N/A	
	TL:	N/A	
OSE/DMEPA (proprietary name, carton/container labels)) Medication Error Reviewer	Reviewer:	Michelle Rutledge	Y
	TL:	Yelena Maslov	Y
OSE/DRISK (REMS)	Reviewer:	N/A	
	TL:	N/A	
OC/OSI/DSC/PMSB (REMS)	Reviewer:	N/A	
	TL:	N/A	

Bioresearch Monitoring (OSI)	Reviewer:	N/A	
	TL:	N/A	
Controlled Substance Staff (CSS)	Reviewer:	N/A	
	TL:	N/A	
Other reviewers/disciplines CDRH	Reviewer:	Janice Polacek	Y
	TL:	Brian McGowan	Y
OPDP	Reviewer: James Dvorsky Team Lead: Brantley Dorch		
DPV	SE: Lynda McCulley TL: Peter Diak		
OTR	Arzu Selen		Y

**FILING MEETING DISCUSSION:**

<p><b>GENERAL</b></p> <ul style="list-style-type: none"> <li>• 505(b)(2) filing issues: <ul style="list-style-type: none"> <li>○ Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</li> <li>○ Did the applicant provide a scientific “bridge” demonstrating the relationship between the proposed product and the referenced product(s)/published literature?</li> </ul> </li> </ul> <p>Describe the scientific bridge (e.g., BA/BE studies):</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO  <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>• Per reviewers, are all parts in English or English translation?</li> </ul> <p><b>If no, explain:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>• Electronic Submission comments</li> </ul> <p><b>List comments:</b> cross-referencing NDA 022291 in module 3.2.S</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> No comments
<p><b>CLINICAL</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE

<b>Comments:</b>	<input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>Clinical study site(s) inspections(s) needed?</li> </ul> <p><b>If no, explain:</b></p>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Advisory Committee Meeting needed?</li> </ul> <p><b>Comments:</b></p> <p><i>If no, for an NME NDA or original BLA, include the reason. For example:</i></p> <ul style="list-style-type: none"> <li><i>this drug/biologic is not the first in its class</i></li> <li><i>the clinical study design was acceptable</i></li> <li><i>the application did not raise significant safety or efficacy issues</i></li> <li><i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i></li> </ul>	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined  Reason:
<ul style="list-style-type: none"> <li>If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?</li> </ul> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>CONTROLLED SUBSTANCE STAFF</b></p> <ul style="list-style-type: none"> <li>Abuse Liability/Potential</li> </ul> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<p><b>CLINICAL MICROBIOLOGY</b></p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<p><b>CLINICAL PHARMACOLOGY</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>Clinical pharmacology study site(s) inspections(s) needed?</li> </ul>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO

<p><b>BIostatistics</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><b>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</b></p> <p><b>Comments:</b> no studies to review</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><b>IMMUNOGENICITY (protein/peptide products only)</b></p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><b>PRODUCT QUALITY (CMC)</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><b>New Molecular Entity (NDAs only)</b></p> <ul style="list-style-type: none"> <li>Is the product an NME?</li> </ul>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p><b><u>Environmental Assessment</u></b></p> <ul style="list-style-type: none"> <li>Categorical exclusion for environmental assessment (EA) requested.</li> </ul> <p><b>If no</b>, was a complete EA submitted?</p> <p><b>If EA submitted</b>, consulted to EA officer (OPS)?</p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b><u>Quality Microbiology</u></b></p> <ul style="list-style-type: none"> <li>Was the Microbiology Team consulted for validation of sterilization?</li> </ul>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<p><b>Comments:</b> microbiology was consult but not for sterilization but to look at microbial control of a non-sterile product.</p>	
<p><b><u>Facility Inspection</u></b></p> <ul style="list-style-type: none"> <li>• Establishment(s) ready for inspection?</li> <li>▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ?</li> </ul> <p><b>Comments:</b> Completed by OPQ</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><b><u>Facility/Microbiology Review (BLAs only)</u></b></p> <p><b>Comments:</b></p>	<p><input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><b><u>CMC Labeling Review</u></b></p> <p><b>Comments:</b></p>	<p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><b>APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)</b></p> <ul style="list-style-type: none"> <li>• Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application?</li> <li>• If so, were the late submission components all submitted within 30 days?</li> </ul>	<p><input checked="" type="checkbox"/> N/A</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<ul style="list-style-type: none"> <li>• What late submission components, if any, arrived after 30 days?</li> </ul>	<p>.</p>



<ul style="list-style-type: none"> <li>Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?  Missing parts in Module 3 section 2.S, but submitted</li> </ul>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Is a comprehensive and readily located list of all clinical sites included or referenced in the application?</li> </ul>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?</li> </ul>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<b>REGULATORY PROJECT MANAGEMENT</b>	
<b>Signatory Authority:</b> Ann Farrell, MD  <b>Date of Mid-Cycle Meeting</b> (for NME NDAs/BLAs in “the Program” PDUFA V):  <b>21<sup>st</sup> Century Review Milestones (see attached)</b> (listing review milestones in this document is optional):  <b>Comments:</b>	
<b>REGULATORY CONCLUSIONS/DEFICIENCIES</b>	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing.  <u>Review Issues:</u>  <input checked="" type="checkbox"/> No review issues have been identified for the 74-day letter.  <input type="checkbox"/> Review issues have been identified for the 74-day letter. – <u>Review Classification:</u>  <input type="checkbox"/> Standard Review  <input checked="" type="checkbox"/> Priority Review
<b>ACTIONS ITEMS</b>	
<input checked="" type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, orphan drug).
<input type="checkbox"/>	If RTF, notify everyone who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by

	Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	351(k) BLA/supplement: If filed, send filing notification letter on day 60
<input checked="" type="checkbox"/>	If priority review: <ul style="list-style-type: none"> <li>• notify sponsor in writing by day 60 (see CST for choices)-</li> <li>• notify OMPQ (so facility inspections can be scheduled earlier)</li> </ul>
<input type="checkbox"/>	Send review issues/no review issues by day 74
<input checked="" type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	Update the PDUFA V DARRTS page (for applications in the Program)
<input type="checkbox"/>	Other

annual review of template by OND ADRAs completed: September 2014

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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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KIMBERLY L SCOTT  
04/28/2015

MARA B MILLER  
04/29/2015