CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204026Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

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

Risk Evaluation and Mitigation Strategies (REMS) Review Addendum

Date:	February 7, 2013
Reviewers:	Joyce Weaver, Pharm.D., Risk Management Analyst, Division of Risk Management (DRISK) Kate Oswell, M.A., Health Communications Analyst, DRISK
Team Leader	Cynthia LaCivita, Pharm.D., Team Leader, DRISK
Subject:	Addendum to DRISK reviews of January 4, 18, & 25, 2013 and February 4, 2013
Drug Name(s):	Pomalyst (pomalidomide)
Therapeutic Class:	Thalidomide analogue
Dosage and Route:	1mg, 2mg, 3mg and 4mg capsules
Application Type:	204026
Applicant/sponsor:	Celgene
OSE RCM #:	2012-923

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1 INTRODUCTION

This review, an addendum to the January 4, 18, and 25, 2013, and February 4, 2013 reviews, documents DRISK's evaluation of Celgene's amended Pomalyst REMS submission, received February 6, 2013. The February 7, 2013 submission responds to comments sent to the sponsor February 5 and 6, 2013.

2 MATERIALS REVIEWED

REMS, REMS materials, and REMS Supporting Document received February 6, 2013.

3 RESULT OF REVIEW

The sponsor has responded appropriately to the Agency comments.

4 CONCLUSION/RECOMMENDATION

The REMS received February 6, 2013 (attached) is acceptable. DRISK recommends approval of the REMS.

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/s/

JOYCE P WEAVER
02/07/2013

MARY E WILLY
02/07/2013
I concur

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management
Risk Evaluation and Mitigation Strategy (REMS) Review Addendum

Date:	February 3, 2013
Reviewer(s):	Cynthia LaCivita, Pharm.D., Team Leader Division of Risk Management (DRISK) Kate Oswell, M.A., Health Communications Analyst, DRISK Joyce Weaver, Pharm.D., Risk Management Analyst, DRISK
Subject:	Addendum to DRISK reviews dated January 4, 18, and 25, 2013; evaluation of the proposed REMS
Drug Name(s):	Pomalidomide
Therapeutic Class:	Immunomodulatory agent; thalidomide analogue
Dosage and Route:	1mg, 2 mg, 3 mg, and 4 mg capsules
Application Type/Number:	204026
Applicant/sponsor:	Celgene
OSE RCM #:	2012-923

*** This document contains proprietary and confidential information that should not be released to the public. ***

1 INTRODUCTION/BACKGROUND

This review, an addendum to the January 4, 18 and 25, 2013 reviews, documents DRISK's evaluation of Celgene's January 31, 2013 email submission of the amended proposed Pomalyst REMS.

The January 31, 2013 submission from Celgene is in response to DRISK's comments addressed in the January 25, 2012 review by Joyce Weaver.

2 MATERIALS REVIEWED

- REMS, REMS materials, and the REMS Supporting Document submitted by email on January 31, 2013.

3 RESULTS OF REVIEW

The following issues need to be addressed in the REMS, REMS materials, and the REMS Supporting Document

Below is a summary of edits and queries regarding the file "Pomalyst REMS Proposed Master File", also refer to the attached file withFDA edits in track changes.

i. REMS Document

Page 1, revise phone number to Celgene's number

Pages 4 and 5, minor changes in formatting

Pages 6 and 7, query about the source of the phone numbers used on these pages

ii. Landing Page for CelgeneRiskManagment.com

Pages 112 and 113, The following changes should be made to the first paragraph and the middle sections of the page. RevAssist and S.T.E.P.S. should be changed to Thalomid REMS (formerly known as S.T.E.P.S) and Revlimid REMS (formerly known as RevAssist) This change should be consist throughout the REMS materials (including Pharmacy Training slides) and REMS Supporting Document.

iii. Pomalyst REMS landing page

Pages 115-153, (b) (4)

iv. Pomalyst (pomalidomide) Pregnancy Exposure Registry

Page, 157, please edit to:

POMALYST (pomalidomide) is structurally related to (b) (4) –thalidomide and lenalidomide. Thalidomide is a known human teratogen with an active pharmaceutical ingredient that causes severe life-threatening birth defects. POMALYST was found to be teratogenic in a developmental study in

rats and rabbits. The teratogenic effect of POMALYST in humans cannot be ruled out.

The following are a part of the REMS, and should be attached to the REMS document:

- Celgene REMS Programs Pharmacy Training: Pomalyst REMS Program
- Emergency Contraception Brochure

REMS Supporting Document

Pages 42 and 43 – Revise the landing page of the website. The first paragraph and the middle sections of the page that identifies RevAssist and S.T.E.P.S. should be changed to Thalomid REMS (formerly known as S.T.E.P.S) and Revlimid REMS (formerly known as RevAssist)

Additional points of clarification are identified in FDA's track changes in the attached the REMS Supporting Document.

Pharmacy Training

Slide 4 - [redacted] (b) (4)

The attached files that contain edits and queries in track changes, the attached files should be sent to the sponsor.

1. "Pomalyst REMS Proposed Master File" which includes the REMS document, REMS materials and landing pages of the websites
2. REMS Supporting Document

The attached REMS, REMS materials, and REMS Supporting Document are acceptable providing Celgene makes the necessary changes identified in this review and by track changes in the attached documents.

The final submission of the amended REMS, REMS material should be submitted to the Agency as one document. The REMS Supporting Document and appendices should be submitted as a separate file.

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/s/

CYNTHIA L LACIVITA
02/03/2013

CLAUDIA B MANZO
02/04/2013
concur

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management
Risk Evaluation and Mitigation Strategy (REMS) Review Addendum

Date:	January 25, 2013
Reviewer(s):	Joyce Weaver, Pharm.D., Risk Management Analyst Division of Risk Management (DRISK)
	Kate Oswell, M.A., Health Communications Analyst, DRISK
Team Leader:	Cynthia LaCivita, Pharm.D., Team Leader DRISK
Subject:	Addendum to DRISK reviews dated January 4 and 18, 2013; evaluation of the proposed REMS
Drug Name(s):	Pomalidomide
Therapeutic Class:	Immunomodulatory agent; thalidomide analogue
Dosage and Route:	1mg, 2mg, 3mg, and 4mg capsules
Application Type/Number:	204026
Applicant/sponsor:	Celgene
OSE RCM #:	2012-923

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1 INTRODUCTION/BACKGROUND

This review, an addendum to the January 4 2013, and January 18, 2013 reviews, documents DRISK's evaluation of the email submission of January 21, 2013.

When the pomalidomide REMS and REMS materials were being reviewed for Agency clearance, the Office of Regulatory Policy (ORP) raised a question regarding the differences in terminology in the labeling and in the REMS; for example, the labeling had current Agency referring to females of reproductive potential, and embryo-fetal toxicity, while the REMS contained the terminology used previously, females of childbearing potential and teratogenicity. The Office of Regulatory Policy advised DRISK that the terminology in the REMS should be aligned to the labeling. Celgene was advised of the decision, and they informally resubmitted the REMS and materials January 21, 2013 aligning the terminology.

Additionally, Celgene agreed to a change in the name of the REMS from (b) (4) to Pomalyst REMS. The submission January 21 incorporates the new name of the REMS.

Based on experience with thalidomide and lenalidomide assessments, the DRISK Assessment team asked for changes in the REMS assessments.

2 MATERIALS REVIEWED

We reviewed the REMS, REMS materials, and the REMS Supporting Document submitted by email January 21, 2013.

3 RESULTS OF REVIEW

The REMS, REMS materials, and REMS Supporting Document showing necessary changes are attached. The changed REMS assessment plan was emailed to Celgene January 22, 2013. Discussion is ongoing with Celgene regarding the REMS Assessment plan.

3.1 REMS ASSESSMENT

Each REMS Assessment will include the following:

Each REMS assessment report must provide the following:

1. Pregnancies:

    a. Number of pregnancies reported during the REMS assessment reporting period and annually for each REMS reporting period.

    b. Outcome of each pregnancy

    c. Follow-up of outstanding pregnancy reports from previous assessment reporting period

d. Root cause analysis of each reported pregnancy

e. Link to most recent Periodic Safety Update Report (PSUR) that provides information on worldwide pregnancies. Discussion of any new information provided in the PSUR regarding pregnancy

f. [redacted] (b) (4)

2. Reporting on the restricted distribution program:

   a. Provide the number of pharmacies and physicians certified, and patients enrolled during the current REMS assessment reporting period and during each previous REMS assessment reporting period

   b. Patient demographics for the current REMS assessment reporting period and for previous REMS assessment reporting periods to include gender, age, diagnosis, females of reproductive potential (FRP)

   c. Number of female patients for whom pregnancy testing can be discontinued because menopause has been documented by follicle-stimulating hormone/luteinizing hormone (FSH/LH) levels during this REMS assessment reporting period and for previous REMS assessment reporting periods

3. Documentation of safe use conditions (via mandatory surveys)

   a. Flagged prescriptions/documentations of safe use of particular interest include those that have the potential of allowing pregnant patients access to the drug, and those that result in a delay or interruption of treatment. Provide the following, relative to flagged prescriptions/documentation of safe use:

      i. A list of identified flags, the reasons for the flags, and the actions taken to correct. Provide for the reporting period (by month); and summarize findings from each previous assessment report.

      ii. Provide the number and proportion of flagged prescriptions intended for an FRP due to lack of documentation of a negative

pregnancy test, positive pregnancy test, and/or a delay in obtaining a pregnancy test.

iii. Provide the number and proportion of flags that caused a delay in treatment initiation or a gap in therapy for patients. Provide the time to resolution of flags (mean, minimum, maximum) and include a graph of time to resolution versus numbers of prescriptions (or number of mandatory surveys conducted to document safe use conditions) for the reporting period and for each previous reporting period

4. An assessment of the extent to which the elements to assure safe use are meeting the goal or goals to mitigate a specific serious risk listed in the labeling of the drug, or whether the goal or goals such elements should be modified.

4 RECOMMENDATIONS FOR DHP

The attached revised REMS, REMS materials, and REMS Supporting Document should be sent to the sponsor. Please advise the sponsor that the REMS and REMS materials are still undergoing internal Agency clearance, and additional changes might be needed. Celgene should be advised to revise the Pharmacy Training materials (62-page document) in accordance with the revised REMS and REMS materials to reflect the changes in terminology, and submit it for Agency review. Additionally, Celgene should be advised to submit for Agency review the landing pages for the Celgene Risk Management and the Pomalyst REMS websites.

5 ATTACHMENTS

REMS, REMS materials, REMS Supporting Document.

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/s/

JOYCE P WEAVER
01/25/2013

CYNTHIA L LACIVITA
01/25/2013
concur

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management
Addendum Risk Evaluation and Mitigation Strategy (REMS) Review

Date:	January 18, 2013
Reviewer(s):	Cynthia LaCivita, Pharm.D., Team Leader Division of Risk Management (DRISK) Joyce Weaver, Pharm.D., Risk Management Analyst DRISK Kate Oswell, M.A., Health Communications Analyst DRISK
Subject:	Addendum to DRISK review dated January 4, 2013; the evaluation of the proposed REMS
Drug Name(s):	Pomalidomide
Therapeutic Class:	Immunomodulatory agent; thalidomide analogue
Dosage and Route:	1mg, 2mg, 3mg, and 4mg capsules
Application Type/Number:	204026
Applicant/sponsor:	Celgene
OSE RCM #:	2012-923

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1 INTRODUCTION

This addendum provides additional comments and recommendation to the DRISK review dated January 4, 2013 on Celgene's proposed Risk Evaluation and Mitigation Strategy (REMS) for pomalidomide. Celgene is seeking approval of pomalidomide to treat multiple myeloma.

1.1 REGULATORY HISTORY

The pomalidomide original IND 066188 was submitted on November 13, 2002. The Agency and the sponsor met on March 19, 2010, and February 15, 2011 to discuss the clinical and regulatory development plan for pomalidomide. A pre-NDA meeting was held on September 13, 2011, with a follow up meeting held on February 2, 2012. On April 10, 2012, the Applicant submitted NDA 204026 for accelerated approval.

2 MATERIALS REVIEWED

- Pomalidomide labeling submitted by Celgene via e-mail on January 18, 2013
- January 4, 2013 DRISK REMS review for Pomalidomide (NDA 204026) by Joyce Weaver

3 DISCUSSION

REMS

The REMS document, REMS materials were revised to align with changes in labeling and to address comments that were provided during the clearance process. The REMS document, REMS materials and REMS Supporting Document must align with product labeling. The REMS Supporting Document must be revised to align with the REMS. Comments to the sponsor are listed below.

Please contact DRISK when this submission is recieved.

Assessment Plan

The DRISK assessment team provided additional advice on information that should be included in the REMS assessment

The following REMS assessment plan was provided to DHP on January 17, 2013 via e-mail and should be incorporated into the approval letter.

Each Assessment report must provide an evaluation of the following:

1. Pregnancies

   a. Number of pregnancies reported during the assessment reporting period and annually for each reporting period

   b. Outcome of each pregnancy

   c. Follow-up of outstanding pregnancy reports from previous assessment reporting period

   d. Root cause analysis of each reported pregnancy

e. Link to most recent PSUR report on pregnancies worldwide; discussion of any new information provided in the PSUR regarding pregnancy

(b) (4)

2. Reporting on the restricted distribution program:

a. Registered pharmacies, physicians, and patients during the current reporting period and during each previous annual reporting period: new and ongoing

b. Patient demographics: for current reporting period and for previous reporting periods: gender, age diagnosis, females of reproductive potential (FRP)

(b) (4)

d. Number of female patients for whom pregnancy testing can be discontinued because menopause has been documented by FSH/LH levels

3. Documentation of safe use conditions (via "mandatory survey")

a. Listing of flags identified, reasons, and actions taken to correct: Provide by month for the reporting period; and summarize findings from each previous assessment report

b. Flagged prescriptions/documentations of safe use of particular interest include those that have the potential of allowing a pregnant patient access to the drug and those that result in a delay or interruption of treatment:

i. Number and proportion of flagged prescriptions intended for a patient who is a female of reproductive potential due to lack of documentation of negative pregnancy test; positive pregnancy test; delay in obtaining pregnancy test;

ii. Number and proportion of flags that caused a delay in treatment initiation or a gap in therapy for the patient; provide the time to resolution of flags (mean, minimum, maximum) and include a graph of time to resolution vs. numbers of prescriptions (or number of mandatory surveys conducted to document safe use conditions) for the reporting period and for each previous reporting period

4. An assessment of the extent to which the elements to assure safe use are meeting the goal or goals to mitigate a specific serious risk listed in the labeling of the drug, or whether the goal or goals such elements should be modified.

4 RECOMMENDATIONS

DRISK recommends DHP request that the sponsor amend their submission and submit a modified REMS proposal incorporating FDA edits as shown on the attached document.

Comments to the Sponsor

The REMS, REMS materials, the Celgene REMS program Pharmacy Training must align with labeling. Additionally the REMS Supporting Document must align with the REMS document.

Please note there may be additional changes as the REMS is currently undergoing clearance through the Agency.

Please refer to the edits in track changes found in attached REMS and REMS materials.

Submit your proposed REMS and other materials in MS Word format. It makes review of these materials more efficient and it is easier for the web posting staff to make the document 508 compliant. It is preferable that the entire REMS document and attached materials be in a single MS Word document. If certain documents such as enrollment forms are only in PDF format, they may be submitted as such, but the preference is to include as many as possible be in a single MS Word document.

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/s/

CYNTHIA L LACIVITA
01/22/2013

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management
Final Risk Evaluation and Mitigation Strategy (REMS) Review

Date:	January 4, 2013
Reviewer(s):	Joyce Weaver, Pharm.D., Risk Management Analyst Division of Risk Management (DRISK)
	Kate Oswell, M.A., Health Communications Analyst, DRISK
Team Leader:	Cynthia LaCivita, Pharm.D., Team Leader DRISK
Division Director	Claudia Manzo, Pharm.D, Director DRISK
Drug Name(s):	Pomalidomide
Therapeutic Class:	Immunomodulatory agent; thalidomide analogue
Dosage and Route:	1mg, 2mg, 3mg, and 4mg capsules
Application Type/Number:	204026
Applicant/sponsor:	Celgene
OSE RCM #:	2012-923

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CONTENTS

1 INTRODUCTION

This review documents DRISK's evaluation of the proposed Risk Evaluation and Mitigation Strategy (REMS) for pomalidomide. Celgene is seeking approval of pomalidomide to treat multiple myeloma.

1.1 BACKGROUND

Multiple myeloma— Multiple myeloma, a cancer of plasma cells in bone marrow, has an annual incidence in the US of about 4 to 5 per 100,000. Relapsed refractory multiple myeloma is an incurable and life-threatening disease. Disease treatment is characterized by multiple relapses.

Pomalidomide—Pomalidomide is immunomodulatory agent related to thalidomide. The indication proposed by the sponsor for pomalidomide is in combination with dexamethasone for patients with relapsed and refractory multiple myeloma who have received at least 2 prior regimens of established benefit, including both lenalidomide and bortezomib and have demonstrated disease progression on the last therapy. The median duration of treatment in the clinical trial was 22 weeks (range 0.3 to 70 weeks).

The safety profile for pomalidomide appears to be similar to the two other drugs in the same class, thalidomide and lenalidomide. The most common adverse events in clinical testing were neutropenia, fatigue, asthenia, thrombocytopenia, anemia, and constipation. The safety concern that requires institution of a REMS is teratogencity. The other members of the class, thalidomide and lenalidomide, are approved with REMS to mitigate the risk of teratogenicity.

The safety profile for pomalidomide is acceptable for the proposed indicated population and is similar to that of thalidomide and lenalidomide, provided that pregnancy can be avoided. Should a pregnancy occur in a woman receiving the drug, teratogenicity is highly likely. The risk of teratogenicity resulting from a male partner who is receiving the drug at the time of conception/onset of pregnancy is unknown.

1.2 REGULATORY HISTORY

The pomalidomide original IND 066188 was submitted on November 13, 2002. The Agency and the sponsor met on March 19, 2010, and February 15, 2011 to discuss the clinical and regulatory development plan for pomalidomide. A pre-NDA meeting was held on September 13, 2011, with a follow up meeting held on February 2, 2012. On April 10, 2012, the Applicant submitted NDA 204026 for accelerated approval.[1]

[1] Regulatory history excerpted from December 20, 2012 clinical review, by Dr. Saleh Ayache.

2 MATERIALS REVIEWED

2.1 DATA AND INFORMATION SOURCES

- Pomalidomide, REMS submissions, Celgene, April 12, 2012 and December 7, 2012.
- Concurrent pending REMS modifications for thalidomide and lenalidomide.
- NDA 204026 Clinical Review, December 20, 2012, Dr. Saleh Ayache.
- Meeting minutes of FDA and Celgene meeting September 27, 2011 to discuss a path forward to harmonize the REMS for thalidomide and lenalidomide.
- Meeting minutes of REMS Oversight Committee meetings May 14, 2012, September 14, 2012.
- DRISK Interim REMS review for 021880 and 020785, lenalidomide and thalidomide, October 5, 2012.

3 RESULTS OF REVIEW

3.1 CLINICAL DEVELOPMENT PROGRAM

The efficacy and safety of pomalidomide was evaluated in 305 patients with relapsed or refractory multiple myeloma who were randomized in the two Phase 2 trials.

The overall response rate (the combined total of patients who experienced complete remission or partial response) in the first trial was 29.2% with a median duration of 7.4 months among subjects who received pomalidomide plus low-dose dexamethasone, and an overall response of 7.4% (median duration not yet achieved) among subjects who received pomalidomide alone.

The overall response rate in the second trial was 34.9% with a median duration of response of 10.5 months among subjects who received intermittent pomalidomide plus dexamethasone, and 34.1% with a median duration of 7.3 months among subjects who received continuous pomalidomide plus dexamethasone.

The contribution of pomalidomide to the results observed with the combination therapy cannot be determined, because the effect of pomalidomide was not isolated in the trials.

Dr. Ayache summarized the safety findings as follows after receiving pomalidomide 4 mg orally administered daily for 21 days in 28-day cycle. The median duration of treatment per patient with pomalidomide was 5 cycles (range 1 to 17).

- There were 57 (19%) deaths within 30 days of the last dose in both trials.
- Two-third (67%) of patients experienced serious adverse events (SAE). Infection was the most common SAE.
- Sixteen percent discontinued treatment due to treatment emergent adverse events (TEAE).
- Eighty-nine percent of patients experienced a Grade 3 or Grade 4 TEAE. Neutropenia and pneumonia were the most common TEAEs.

- Safety issues in ≥ 20% of patients include myelosuppression, infections, neuropathy, dizziness, GI toxicity, and fatigue.
- The safety profile for pomalidomide is similar to thalidomide and lenalidomide.
- No new safety signals were detected in the analysis of 120-day safety update data.
- Review of the adverse events of special interest revealed:
    - The combination of POM+DEX is myelosuppressive and manifested as neutropenia, anemia and thrombocytopenia
    - Infection occurred in two-third of the patients. Pneumonia was the most common infection.
    - The incidence of hemorrhagic events occurred in one-quarter of the patients.
    - The majority of the hemorrhagic events were grade 2 or less and epistaxis was the most common hemorrhagic event.
    - Thromboembolic events occurred in 3% of the patients. Patients enrolled in the clinical trials were required to use prophylactic anticoagulation.
    - Approximately 17% of patients experienced neurologic adverse events and peripheral neuropathy was the most common neurologic AE. All neurologic events were grade 2 or less.
    - Renal events of Grade 3 or 4 occurred in 9-10% of patients and acute renal failure was the most common renal event.
    - Other common TEAEs are dizziness, asthenia and fatigue, pyrexia and confusional state.

4 FDA'S ASSESSMENT OF NEED FOR A REMS

Pomalidomide is an analogue of thalidomide, a known human teratogen and part of a class of drugs that are approved with REMS to mitigate the risk of teratogenicity. Possible birth defects include phocomelia, dysmelia, amelia, bone hypoplasticity, and other congenital defects affecting the ear, heart, or internal organs. There are no human data for pomalidomide; however, pomalidomide is believed to carry the same human teratogenicity risk based on structural similarity to thalidomide and nonclinical findings showing teratogenic effects. The teratogenicity risks for thalidomide and lenalidomide have been mitigated with REMS with elements to assure safe use (ETASU). It is appropriate to institute a REMS for pomalidomide that is consistent with the REMS for others in this class of drugs.

5 SPONSOR'S REMS PROPOSAL

(b) (4)

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6 DISCUSSION

The Agency has discussed internally and has discussed with Celgene the REMS appropriate for the marketing of pomalidomide. There is consensus within the Agency, and Celgene agrees, that the REMS for pomalidomide should be consistent with the REMS for thalidomide and lenalidomide. Celgene plans to incorporate the REMS for pomalidomide into a harmonized REMS for the class of drugs, including thalidomide and lenalidomide. The harmonization of the REMS into a system providing access to prescribers from a single internet access point, (b) (4)

7 CONCLUSIONS

The REMS submitted with the application, April 12, 2012, as revised December 7, 2012 and appended to this review, is acceptable providing the FDA-proposed edits are accepted by the sponsor.

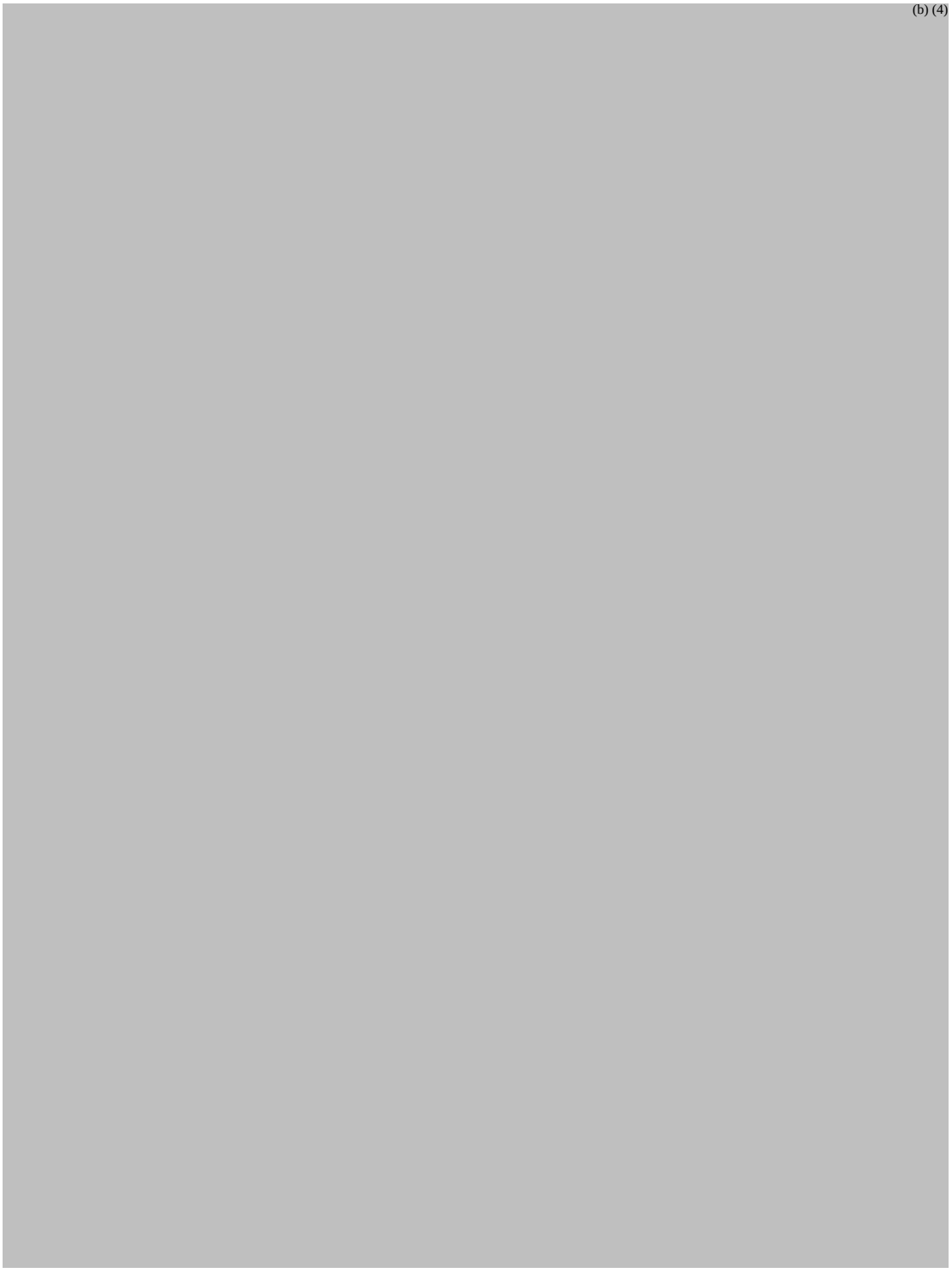
8 RECOMMENDATIONS FOR DHP

DRISK recommends DHP request the sponsor to submit a modified REMS proposal incorporating FDA edits as shown on the attached documents.

The following REMS assessment plan should be incorporated into the approval letter.

Each REMS Assessment will include the following:

(b) (4)



9 ATTACHMENTS

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JOYCE P WEAVER
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