

# CENTER FOR DRUG EVALUATION AND RESEARCH

## Approval Package for:

*APPLICATION NUMBER:*

**ANDA 201835**

**Name:** Methylprednisolone Acetate Injectable Suspension,  
USP(40 mg/1mL and 80 mg/1mL)

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**Sponsor:** Sagent Pharmaceuticals Inc.

**Approval Date:** June 27, 2018

# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*  
**ANDA201835Orig1s000**  
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**CENTER FOR DRUG EVALUATION AND RESEARCH**

*APPLICATION NUMBER:*  
**ANDA 201835**

**CHEMISTRY REVIEWS**

All fields are acceptable.

**ANDA 201-835**

**Methylprednisolone Acetate Injectable Suspension, USP  
(40 mg/1mL and 80 mg/1mL)**

**Sagent Pharmaceuticals Inc.**

**Rosario D'Costa  
Chemistry Division I**

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# Chemistry Review Data Sheet

1. ANDA # 201-835
2. REVIEW #: 3A
3. REVIEW DATE: 01/05/18/06/13/18
4. REVIEWER: Rosario D'Costa

## 5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Amendment:	July 29, 2016
Amendment:	December 13, 2011
Amendment:	October 07, 2010
Original (Application received)	August 13, 2010
Acceptable for Filing:	August 16, 2010

## 6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Amendment:	April 18, 2018
Amendment:	March 29, 2018
Amendment:	December 14, 2017

## 7. NAME & ADDRESS OF APPLICANT:

Name: Sagent Pharmaceuticals Inc.  
Address: 1901 N. Roselle Road, Suite 700  
Achaumburg, IL 60195  
Representative: Kalpesh Shroff

## Chemistry Review Data Sheet

Telephone: (b) (6)  
Facsimile: 847 908-1601

8. DRUG PRODUCT NAME/CODE/TYPE: Methylprednisolone Acetate Injectable Suspension, USP

9. LEGAL BASIS FOR SUBMISSION: FFD & CA

The basis for proposed ANDA for Methylprednisolone Acetate Injectable Suspension, USP 40mg/1mL and 80mg/1mL is the approved reference listed drug, Depo-Medrol®, held by Pharmacia & Upjohn (Pfizer) and the subject of NDA #011757 approved prior to January 01, 1982.

Paragraph II Certification: Sagent hereby certifies that in its opinion and to the best of its knowledge there are no listed patents in the current edition of Orange Book concerning Methylprednisolone Acetate Injectable Suspension, USP that claim the listed drug referred to in this application or that claim a use of this listed drug.

This certification is made in accordance with Section 505 (j) (2) (A) (vii) (II) of the FFD & CA and pursuant to 21 CFR 314.94 (a)(12)(i)(A)(2).

There is no unexpired exclusivity for the reference listed drug.

10. PHARMACOL. CATEGORY: Ant-Inflammatory.

11. DOSAGE FORM: Injectable Suspension

12. STRENGTH/POTENCY: 40mg/mL and 80mg/mL

13. ROUTE OF ADMINISTRATION: Intramuscular

14. Rx/OTC DISPENSED:  Rx  OTC

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

SPOTS product – Form Completed

Not a SPOTS product



## Chemistry Review Data Sheet

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

**What are the nomenclature, molecular structure, molecular formula, and molecular weight?**

Generic Name: Methylprednisolone Acetate

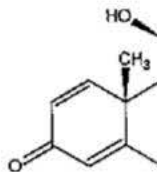
Chemical Name: Pregna-1,4-diene-3,20-dione, 21-(acetyloxy)-11,17-dihydroxy-6-methyl-(6 $\alpha$ ,11 $\beta$ ) OR 11 $\beta$ , 17, 21-Trihydroxy-6 $\alpha$ -methylpregna-1,4-diene-3,20-dione 21 acetate OR 11 $\beta$ , 17-Dihydroxy-6 $\alpha$ -methyl-3,20-dioxopregna-1,4-dien-21-ylacetate

Molecular Formula: C<sub>24</sub>H<sub>32</sub>O<sub>6</sub>

Molecular weight: 416.51

CAS registry number(s): 53-36-1

Anti-inflammatory



## 17. RELATED/SUPPORTING DOCUMENTS: None

## A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	(b) (4)	3	* Adequate	06/12/18	Y. Peng
	III			4			
	III			4			
	III			4			

N.A. = Not Available; \* Adequate with a comment.

<sup>1</sup> Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF



Chemistry Review Data Sheet

- 3 – Reviewed previously and no revision since last review
- 4 – Sufficient information in application
- 5 – Authority to reference not granted
- 6 – DMF not available
- 7 – Other (explain under "Comments")

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

**B. Other Documents: None**

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:      CMC Approvable

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	Acceptable	04/04/18	
EES	Acceptable	05/11/18	
Methods Validation	N/A		
Labeling	Acceptable	06/02/18	
Bioequivalence	Acceptable	04/02/18	
EA	Categorical Exclusion Requested (Acceptable)	02/28/11	
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt.  Yes     No    If no, explain reason(s) below:

# The Chemistry Review for ANDA 201-835

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

The chemistry section is adequate in areas of manufacturing and controls and is therefore recommended for “approvable”.

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

N/A

### II. Summary of Chemistry Assessments

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

The drug substance Methylprednisolone Acetate sterile is a white or almost white crystalline powder, practically insoluble in water, sparingly soluble in acetone and in alcohol and slightly soluble in ether. The drug substance and its impurities are characterized using the standard analytical techniques of FT-IR,  $^1\text{H}$ ,  $^{13}\text{C}$  NMR, MS, etc.

The drug product Methylprednisolone Acetate Injectable Suspension, USP 40mg/mL and 80mg/mL contains Methylprednisolone Acetate as an active ingredient and is based on the reference listed drug Depo-Medrol<sup>®</sup>. The pH of the drug product injectable suspension is between 3.5 and 7.0. It is used as an anti-inflammatory drug. The Methylprednisolone Acetate Injectable Suspension USP is available in multi-dose glass vials (40mg/1mL filled in 5mL and 10mL glass vials and 80mg/1mL in 5mL glass vials) as a sterile suspension for intramuscular administration.

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

The recommended dose for adults is up to 120mg or as prescribed by the physician.

#### C. Basis for Approvability or Not-Approval Recommendation

The “approvable” recommendation is based on adequate chemistry and manufacturing controls.

Labeling is acceptable.

Bioequivalence is acceptable.

Microbiology is acceptable.

EER is acceptable.



Chemistry Assessment

**What are the physicochemical properties including physical description, pKa, polymorphism, aqueous solubility (as function of pH), hygroscopicity, melting points, and partition coefficient?**

**Physicochemical Properties:**

The drug substance Methylprednisolone Acetate sterile is a white or almost white crystalline powder, practically insoluble in water, sparingly soluble in acetone and in alcohol and slightly soluble in ether. It exists in polymorphic forms (b) (4). (b) (4) The form used by the applicant shows the same pattern as the USP reference standard LG-2. The physicochemical characteristics such as melting point (205<sup>o</sup> to 208<sup>o</sup>C), aqueous solubility as a function of pH (mass solubility = 0.015g/L at pH 1 to 9), pKa = 12.41 ± 0.70 and partition co-efficient (Log P = 2.792 ± 0.584 @ 25<sup>o</sup>C; calculated using (b) (4) (b) (4) were included in the Amendment dated December 11, 2011.

**2.3.S.2 Manufacturer**

**Who manufactures the drug substance?**

(b) (4)

**How do the manufacturing processes and controls ensure consistent production of the drug substance?**

The complete manufacturing process is described in DMF (b) (4). Please refer to the DMF for a description of the drug substance manufacturing process, control of materials, in-process controls leading to the drug substance, etc.

Reviewer's Comments: (b) (4)  
(b) (4). The Drug Master File (b) (4) is adequate as of June 12, 2018.

**Deficiency: The DMF (b) (4) for Methylprednisolone Acetate has been reviewed and found to be inadequate. The DMF holder, (b) (4) has been notified of any deficiencies. The Agency will work with the DMF holder to resolve any issues if the DMF**

holder responses in a timely manner. Please be aware that the quality review of the sANDA cannot be fully completed until all DMF deficiencies are adequately resolved. Please consult with your DMF holder and provide the updated relevant drug substance sections (e.g., impurities, method validation/verification) for further Agency's evaluation.

The Drug Master File (b) (4) was reviewed and found to be adequate.

(b) (4)

(b) (4)

(b) (4) The information was extracted from the Drug Master File (b) (4) which was reviewed and found to be adequate with a comment. Also, please refer to Amendments dated April 18, 2018 and March 29, 2018. The response is acceptable.

### 2.3.S.3 Characterization

**How was the drug substance structure elucidated and characterized?**

#### Proof of Structure

Please refer to DMF No (b) (4) for information regarding the Methylprednisolone structure, based upon spectroscopy and analytical testing.

**How were the possible impurities identified and characterized?**

(b) (4)

Reviewer's Comments: The firm provided the required information on the physical and chemical properties of the drug substance. For additional information, please refer to the Drug Master File (b) (4) which is current as of June 12, 2018.

#### 2.3.S.4 Control of Drug Substance

**What is the drug substance specification? Does it include all the critical drug substance attributes that affect the manufacturing and quality of the drug product?**

The active ingredient sterile Methylprednisolone Acetate, USP is fully characterized in accordance with the current USP monograph requirements. (b) (4)

(b) (4)



(b) (4)

(b) (4) The test results meet the acceptance criteria.

Reviewer's Comments: The drug substance is adequately characterized per the proposed tests and specifications. (b) (4)

(b) (4)

#### Analytical Procedures:

**For each test in the specification, is the analytical method(s) suitable for its intended use and, if necessary, validated? What is the justification for the acceptance criterion?**

The analytical methods (USP) utilized for determination of Methylprednisolone Acetate and impurities in the drug substance were reviewed and found to be suitable for their intended purposes. Please refer to Reviews #1 and 2 for validation data.  
The drug substance is a compendia item and justification for the acceptance criteria is based on the current USP monograph requirements.

Reviewer's Comments: The analytical methods (USP) utilized for determination of Methylprednisolone Acetate and impurities in the drug substance were reviewed and found to be suitable for their intended purposes.

#### 2.3.S.5 Reference Standards and Materials

**How were the primary reference standards certified?**

A reference standard is available from USP. A working standard was prepared by analyzing a batch sample and qualifying it against a reference standard obtained from USP (Section 2.3.S.5; See also DMF (b) (4).

#### 2.3.S.6 Container Closure System

**What container closure system is used for packaging and storage of the drug substance?**

For information regarding the container/closure system please refer to DMF (b) (4).

#### 2.3.S.7 Stability

**What drug substance stability studies support the retest or expiration date and storage conditions for the drug substance?**

Please refer to DMF (b) (4) for a description of the drug substance stability program, study reports and conclusion.

Reviewer's Comments: For Methylprednisolone Acetate, the firm provided sufficient information on the manufacture, identification and characterization, packaging and stability of the drug substance. For more information, please refer to the Drug Master File (b) (4).

**2.3.P DRUG PRODUCT**

**2.3.P.1 Description and Composition of the Drug Product**

**What are the components and composition of the final product? What is the function(s) of each excipient?**

The finished drug product, Methylprednisolone Acetate Injectable Suspension, USP (40mg/mL and 80mg/mL) is an off-white colored sterile aqueous suspension for intramuscular administration. (b) (4)

(b) (4)

The list of ingredients, their pharmaceutical functions and amount per unit basis are presented in the following table:

Ingredients	Methylprednisolone Acetate Injectable Suspension	
	40mg/mL	80mg/mL
* Methylprednisolone Acetate, USP (active)	40.00	80mg
Polyethylene Glycol 3350, NF (b) (4)	(b) (4)	
Polysorbate 80 NF (b) (4)		
Sodium chloride, USP (b) (4)		
Monobasic sodium phosphate, NF (b) (4)		
Dibasic sodium phosphate, NF (b) (4)		
Benzyl alcohol, NF (b) (4)		
Sodium hydroxide, NF (b) (4)		
Hydrochloric acid (b) (4)		
(b) (4)		

\* Based on 100% assay.

**Do any excipients exceed the IIG limit for this route of administration?**

No. (b) (4)  
(b) (4)

**Do the differences between this formulation and the RLD present potential concerns with respect to therapeutic equivalence?**

No. The proposed generic formulation and the RLD contain the standard excipients consistent with the design of the parenteral dosage form. It has the same excipients as the innovator's product.

A comparison of the ingredients in the two formulations is presented in the following table:



Reference Listed Drug	Proposed Generic Drug Product	Function
Polyethylene Glycol 3350	Polyethylene Glycol 3350	(b) (4)
Polysorbate 80	Polysorbate 80	
Sodium chloride	Sodium chloride	
Monobasic sodium phosphate	Monobasic sodium phosphate	
Dibasic sodium phosphate	Dibasic sodium phosphate	
Benzyl alcohol	Benzyl alcohol	
Sodium hydroxide	Sodium hydroxide	
Hydrochloric acid	Hydrochloric acid	

Therefore there are no potential concerns with respect to therapeutic equivalence as the two formulations are similar.

### 2.3.P.2 Pharmaceutical Development

The basis of Sagent Pharmaceuticals Inc. proposed abbreviated new drug application [ANDA] for Methylprednisolone Acetate Injectable Suspension, USP (Multi-dose vials) is the approved reference listed drug [RLD] Depo-Medrol® (Methylprednisolone Acetate Injectable Suspension, USP). The generic drug product should contain the same ingredients, be sterile and pharmaceutically equivalent to the reference listed drug.

#### 2.3.P.2.1 Components of the Drug Product

##### 2.3.P.2.1.1 Drug Substance

Which properties or physical chemical characteristics of the drug substance affect drug product development, manufacture, or performance?



##### 2.3.P.2.1.2 Excipients

**What evidence supports compatibility between the excipients and the drug substance?**

The drug product Methylprednisolone Acetate Injectable Suspension, USP contains the same excipients as that in the RLD. The firm conducted compatibility studies between the drug substance and the excipients for 6 weeks during the product development. The presented data shows the API to be compatible with the excipients used in the drug product formulation.

**2.3.P.2.2 Drug Product**

(b) (4)



### 2.3.P.8.2 Stability Studies Supporting Proposed Shelf Life and Storage Conditions

#### What drug product stability studies support the proposed shelf life and storage conditions?

For stability studies, the drug product samples were stored under accelerated and controlled room temperature stability conditions (Table). The samples were stored in inverted and upright positions.

Batch Strength & Lot Number	Accelerated Stability and Test Intervals	Room Temperature and Test Intervals
40mg/mL; 7002910 (5mL vial); 7002909 (10mL vial)	40°C ± 2°C/75% ± 5%RH; 0, 1, 2 and 3 months	25°C ± 2°C/60% ± 5%RH; 0, 3, 6, 9, 12, 18, 24 and 36 months
80mg/mL; 7002912 (5mL vial)	40°C ± 2°C/75% ± 5%RH; 0, 1, 2 and 3 months	25°C ± 2°C/60% ± 5%RH; 0, 3, 6, 9, 12, 18, 24 and 36 months

The firm provided 24 months controlled room temperature stability data for the drug product packaged in the proposed container/closure system. The presented test data meets the acceptance criteria.

Reviewer's Comments: The stability data for the finished drug product meets the acceptance criteria.

#### What is the post-approval stability protocol?



In the post-approval stability protocol, the firm commits to place the first three commercial production batches of Methylprednisolone Acetate Injectable Suspension, USP in the marketed container/closure system on stability ( $25^{\circ}\text{C} \pm 2^{\circ}\text{C}/60\% \pm 5\% \text{RH}$ ) and tested at intervals of 0, 3, 6, 9, 12, 18, 24 months and 36 months until the desired expiration date is reached. Yearly thereafter, a minimum of one production lot in the marketed container/closure system will be added to the long-term stability program. The stability results will be reported to the Agency in the annual report.

Furthermore, the firm commits that if any commercial production lot that fails to meet the acceptance criteria of stability specifications or falls out of specifications, the Agency shall be informed and appropriate actions shall be taken as deemed necessary including product recall where applicable. Any significant chemical, physical, or other deterioration which results in the distributed product acquiring non-compliant characteristics will be reported to FDA as a "Field Alert Report" [21 CFR 314.81].

For additional information regarding the post-approval stability protocol refer to Module 3.2.8.2.

### III. Administrative

#### A. Reviewer's Signature

#### B. Endorsement Block

Chemist Name/Date: RD'Costa, Ph.D./01/05/18/06/13/18

Chemistry TeamLeader Name/Date: Paul Schwartz, Ph.D.

ProjectManagerName/Date: Gbenga Okubadejo, PM, /

M:\MyDocuments\201835.REV03A.doc

**Chemistry Review:** CMC Approvable

#### C. CC Block

ANDA

ANDA DUP

DIV FILE

Field Copy



Rosario  
D Costa

Digitally signed by Rosario D Costa  
Date: 6/14/2018 12:39:50PM  
GUID: 508da701000286f57180bf234c81727f



Andrew  
Langowski

Digitally signed by Andrew Langowski  
Date: 6/14/2018 03:06:41PM  
GUID: 508da701000287558957cdcc92d0a088



**Q1 ANDA Amendment  
QUALITY ASSESSMENT**



**Recommendation:**

**ANDA: Not Approvable**

**ANDA 201835-ORIG-1-AMEND-14**

**Amendment Review**

<b>Drug Name/Dosage Form</b>	Methylprednisolone Acetate Injectable Suspension, USP
<b>Strength</b>	40 mg/mL and 80 mg/mL
<b>Reviewer(s)</b>	Neeraj Chopra
<b>Applicant</b>	Sagent Pharmaceuticals, Inc.

<b>SUBMISSION(S) REVIEWED</b>	<b>DOCUMENT DATE</b>
Quality Response	12/14/2017

**DMFs:**

<b>DMF #</b>	<b>TYPE</b>	<b>HOLDER</b>	<b>ITEM REFERENCED</b>	<b>STATUS<sup>1</sup></b>	<b>DATE REVIEW COMPLETED</b>	<b>COMMENTS</b>
(b) (4)	Type II	(b) (4)	(b) (4)	1	3/7/2018 by Yuefeng (Simon) Peng	Inadequate

<sup>1</sup> Adequate, Adequate with Information Request, Deficient, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

The ANDA submission was last reviewed by Rosario D’Costa, dated 5/18/2017 and found inadequate due to the inadequate DMF.

In response to the complete response letter dated 6/5/2017, applicant submitted the DMF response and risk assessment report for the elemental impurities as per ICH Q3D.

Recent review of the DMF (b) (4) for the drug substance, Methylprednisolone Acetate, by Yuefeng (Simon) Peng dated 3/7/2018 is found to be inadequate.

As requested by the Agency applicant performed the risk assessment of the elemental impurities as per ICH Q3D on the drug substance, (b) (4)

(b) (4)



Neeraj  
Chopra

Digitally signed by Neeraj Chopra  
Date: 3/12/2018 11:44:59AM  
GUID: 53b30d470000e31e1fb44c3474268878



Andrew  
Langowski

Digitally signed by Andrew Langowski  
Date: 3/12/2018 12:09:38PM  
GUID: 508da701000287558957cdcc92d0a088



**Not Approvable – Major Deficiency**

**ANDA 201-835**

**Methylprednisolone Acetate Injectable Suspension, USP  
(40 mg/1mL and 80 mg/1mL)**

**Sagent Pharmaceuticals Inc.**

**Rosario D'Costa  
Chemistry Division I**

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C. CC Block .....	
<b>Chemistry Assessment .....</b>	<b>7</b>
<b>Chemistry Comments .....</b>	<b>36</b>

# Chemistry Review Data Sheet

1. ANDA # 201-835
2. REVIEW #: 2
3. REVIEW DATE: 02/11/14
4. REVIEWER: Rosario D'Costa

## 5. PREVIOUS DOCUMENTS:

Previous Documents

Amendment:  
Original (Application received)  
Acceptable for Filing:

Document Date

October 07, 2010  
August 13, 2010  
August 16, 2010

## 6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Amendment:

Document Date

December 13, 2011

## 7. NAME & ADDRESS OF APPLICANT:

Name: Sagent Pharmaceuticals Inc.  
Address: 1901 N. Roselle Road, Suite 700  
Achaumburg, IL 60195  
Representative: Kalpesh Shroff  
Telephone: (b) (6)  
Facsimile: 847 908-1601

## Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE: Methylprednisolone Acetate Injectable Suspension, USP

9. LEGAL BASIS FOR SUBMISSION: FFD & CA

The basis for proposed ANDA for Methylprednisolone Acetate Injectable Suspension, USP 40mg/1mL and 80mg/1mL is the approved reference listed drug, Depo-Medrol®, held by Pharmacia & Upjohn (Pfizer) and the subject of NDA #011757 approved prior to January 01, 1982.

Paragraph II Certification: Sagent hereby certifies that in its opinion and to the best of its knowledge there are no listed patents in the current edition of Orange Book concerning Methylprednisolone Acetate Injectable Suspension, USP that claim the listed drug referred to in this application or that claim a use of this listed drug.

This certification is made in accordance with Section 505 (j) (2) (A) (vii) (II) of the FFD & CA and pursuant to 21 CFR 314.94 (a)(12)(i)(A)(2).

There is no unexpired exclusivity for the reference listed drug.

10. PHARMACOL. CATEGORY: Ant-Inflammatory.

11. DOSAGE FORM: Injectable Suspension

12. STRENGTH/POTENCY: 40mg/mL and 80mg/mL

13. ROUTE OF ADMINISTRATION: Intramuscular

14. Rx/OTC DISPENSED:  Rx  OTC

15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\):](#)

SPOTS product – Form Completed

Not a SPOTS product



## Chemistry Review Data Sheet

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

**What are the nomenclature, molecular structure, molecular formula, and molecular weight?**

Generic Name: Methylprednisolone Acetate

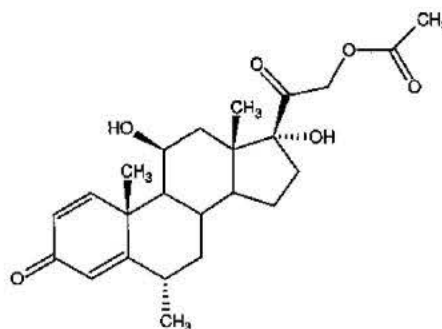
Chemical Name: Pregna-1,4-diene-3,20-dione, 21-(acetyloxy)-11,17-dihydroxy-6-methyl-(6 $\alpha$ ,11 $\beta$ ) **OR** 11 $\beta$ , 17, 21-Trihydroxy-6 $\alpha$ -methylpregna-1,4-diene-3,20-dione 21 acetate **OR** 11 $\beta$ , 17-Dihydroxy-6 $\alpha$ -methyl-3,20-dioxopregna-1,4-dien-21-ylacetate

Molecular Formula: C<sub>24</sub>H<sub>32</sub>O<sub>6</sub>

Molecular weight: 416.51

CAS registry number(s): 53-36-1

Anti-inflammatory



## 17. RELATED/SUPPORTING DOCUMENTS: None

## A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	(b) (4)	3	Adequate	02/11/14	Bhattacharya, Nandini
	III			4			
	III			4			
	III			4			

N A = Not Available

<sup>1</sup> Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 –Type 1 DMF

## Chemistry Review Data Sheet

- 3 – Reviewed previously and no revision since last review
- 4 – Sufficient information in application
- 5 – Authority to reference not granted
- 6 – DMF not available
- 7 – Other (explain under "Comments")

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

**B. Other Documents: None**

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS: CMC not Approvable

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	Acceptable	02/11/14	Bhattacharya, Nandini
EES	Pending		
Methods Validation	N/A		
Labeling	Acceptable	12/11/13	Liu, Theresa
Bioequivalence	Acceptable	08/06/13	Babaa, Nabeel
EA	Categorical Exclusion Requested (Acceptable)	02/28/11	
Radiopharmaceutical	N/A		

## 19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt.  Yes  No If no, explain reason(s) below:

# The Chemistry Review for ANDA 201-835

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

The chemistry section is inadequate in areas of manufacturing and controls and is therefore recommended for “non-approvable”.

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

N/A

### II. Summary of Chemistry Assessments

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

The drug substance Methylprednisolone Acetate sterile is a white or almost white crystalline powder, practically insoluble in water, sparingly soluble in acetone and in alcohol and slightly soluble in ether. The drug substance and its impurities are characterized using the standard analytical techniques of FT-IR,  $^1\text{H}$ ,  $^{13}\text{C}$  NMR, MS, etc.

The drug product Methylprednisolone Acetate Injectable Suspension, USP 40mg/mL and 80mg/mL contains Methylprednisolone Acetate as an active ingredient and is based on the reference listed drug Depo-Medrol<sup>®</sup>. The pH of the drug product injectable suspension is between 3.5 and 7.0. It is used as an anti-inflammatory drug. The Methylprednisolone Acetate Injectable Suspension USP is available in multi-dose glass vials (40mg/1mL filled in 5mL and 10mL glass vials and 80mg/1mL in 5mL glass vials) as a sterile suspension for intramuscular administration.

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

The recommended dose for adults is up to 120mg or as prescribed by the physician.

#### C. Basis for Approvability or Not-Approval Recommendation

The “non-approvable” recommendation is based on inadequate chemistry and manufacturing controls.

Labeling is acceptable.

Bioequivalence is acceptable.

Microbiology is acceptable.

EER is acceptable (Overall recommendation is pending).



## Chemistry Assessment

**What are the physicochemical properties including physical description, pKa, polymorphism, aqueous solubility (as function of pH), hygroscopicity, melting points, and partition coefficient?**

### **Physicochemical Properties:**

The drug substance Methylprednisolone Acetate sterile is a white or almost white crystalline powder, practically insoluble in water, sparingly soluble in acetone and in alcohol and slightly soluble in ether. It exists in polymorphic forms (b) (4).  
(b) (4) The form used by the applicant shows the same pattern as the USP reference standard LG-2.

**Deficiency: For the drug substance, the physicochemical characteristics such as melting point, aqueous solubility as a function of pH, partition co-efficient, etc. is missing from the document. Please address.**

As requested, the firm provided the physicochemical characteristics such as melting point (205<sup>0</sup> to 208<sup>0</sup>C), aqueous solubility as a function of pH (mass solubility = 0.015g/L at pH 1 to 9), pKa = 12.41 ± 0.70 and partition co-efficient (Log P = 2.792 ± 0.584 @ 25<sup>0</sup>C), etc. which was missing from the document (b) (4). The response is adequate.

### **2.3.S.2 Manufacturer**

**Who manufactures the drug substance?**

(b) (4)

**How do the manufacturing processes and controls ensure consistent production of the drug substance?**

The complete manufacturing process is described in DMF (b) (4). Please refer to the DMF for a description of the drug substance manufacturing process, control of materials, in-process controls leading to the drug substance, etc.

(b) (4)

### 2.3.S.3 Characterization

**How was the drug substance structure elucidated and characterized?**

#### **Proof of Structure**

Please refer to DMF No. (b) (4) for information regarding the Methylprednisolone structure, based upon spectroscopy and analytical testing.

(b) (4)

### 2.3.S.4 Control of Drug Substance

**What is the drug substance specification? Does it include all the critical drug substance attributes that affect the manufacturing and quality of the drug product?**

The active ingredient sterile Methylprednisolone Acetate, USP is fully characterized in accordance with the current USP monograph requirements. All the critical drug substance attributes that affect the manufacture and quality of the drug product such as identification, assay, purity, etc. are included in the drug substance specifications.

### **III. Administrative**

#### **A. Reviewer's Signature**

#### **B. Endorsement Block**

Chemist Name/Date: RD'Costa, Ph.D./02/19/14  
ChemistryTeamLeaderName/Date: ZSun for TL/02/19/14  
ProjectManagerName/Date: Mark Gonitzke, PM, /5/27/2014  
M:\MyDocuments\201835.REV02.doc

#### **C. CC Block**

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ANDA: 201-835

APPLICANT: Sagent Pharmaceuticals Inc.

DRUG PRODUCT: Methylprednisolone Acetate Injectable Suspension, USP 40 mg/mL and 80 mg/mL

The following deficiencies listed below may be delivered via the easily correctable deficiency method (10 day firm response expected) if the situation allows  YES  NO

A. The deficiencies presented below represent MAJOR deficiencies.:

1.

2.

3.

4.

(b) (4)

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comment in your response:

The firms referenced in your ANDA relative to the manufacturing and testing of the drug substance and the product must be in compliance with the cGMP's at the time of approval.

Sincerely yours,

*{See appended electronic signature page}*

Robert Iser  
Director  
Division of Chemistry IV

Office of Generic Drugs  
Center for Drug Evaluation and Research

-----  
**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/  
-----

ROSARIO D COSTA  
06/02/2014

MARK A GONITZKE  
06/02/2014

ZHIGANG SUN  
06/02/2014

NAIQI YA on behalf of ROBERT L ISER  
06/10/2014

**ANDA 201-835**

**Methylprednisolone Acetate Injectable Suspension, USP  
(40 mg/1mL and 80 mg/1mL)**

**Sagent Pharmaceuticals Inc.**

**Rosario D'Costa  
Chemistry Division I**



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# Chemistry Review Data Sheet

1. ANDA # 201-835
2. REVIEW #: 1
3. REVIEW DATE: 02/23/11
4. REVIEWER: Rosario D'Costa

## 5. PREVIOUS DOCUMENTS:

Previous Documents

None

Document Date

## 6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Amendment:

Original (Application received)

Acceptable for Filing:

Document Date

October 07, 2010

August 13, 2010

August 16, 2010

## 7. NAME & ADDRESS OF APPLICANT:

Name: Sagent Pharmaceuticals Inc.

Address: 1901 N. Roselle Road, Suite 700  
Achaumburg, IL 60195

Representative: Kalpesh Shroff

## Chemistry Review Data Sheet

Telephone: (b) (6)  
Facsimile: 847 908-1601

8. DRUG PRODUCT NAME/CODE/TYPE: Methylprednisolone Acetate Injectable Suspension, USP

9. LEGAL BASIS FOR SUBMISSION: FFD & CA

The basis for proposed ANDA for Methylprednisolone Acetate Injectable Suspension, USP 40mg/1mL and 80mg/1mL is the approved reference listed drug, Depo-Medrol®, held by Pharmacia & Upjohn (Pfizer) and the subject of NDA #011757 approved prior to January 01, 1982.

Paragraph II Certification: Sagent hereby certifies that in its opinion and to the best of its knowledge there are no listed patents in the current edition of Orange Book concerning Methylprednisolone Acetate Injectable Suspension, USP that claim the listed drug referred to in this application or that claim a use of this listed drug.

This certification is made in accordance with Section 505 (j) (2) (A) (vii) (II) of the FFD & CA and pursuant to 21 CFR 314.94 (a)(12)(i)(A)(2).

There is no unexpired exclusivity for the reference listed drug.

10. PHARMACOL. CATEGORY: Ant-Inflammatory.

11. DOSAGE FORM: Injectable Suspension

12. STRENGTH/POTENCY: 40mg/mL and 80mg/mL

13. ROUTE OF ADMINISTRATION: Intramuscular

14. Rx/OTC DISPENSED:  Rx  OTC

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

SPOTS product – Form Completed

Not a SPOTS product



## Chemistry Review Data Sheet

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

**What are the nomenclature, molecular structure, molecular formula, and molecular weight?**

Generic Name: Methylprednisolone Acetate

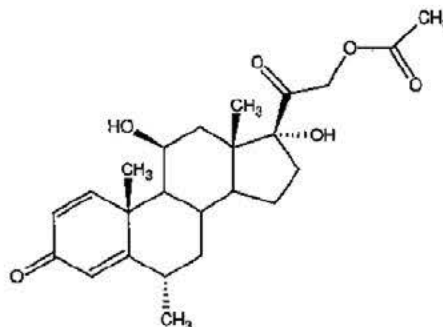
Chemical Name: Pregna-1,4-diene-3,20-dione, 21-(acetyloxy)-11,17-dihydroxy-6-methyl-(6 $\alpha$ ,11 $\beta$ ) **OR** 11 $\beta$ , 17, 21-Trihydroxy-6 $\alpha$ -methylpregna-1,4-diene-3,20-dione 21 acetate **OR** 11 $\beta$ , 17-Dihydroxy-6 $\alpha$ -methyl-3,20-dioxopregna-1,4-dien-21-ylacetate

Molecular Formula: C<sub>24</sub>H<sub>32</sub>O<sub>6</sub>

Molecular weight: 416.51

CAS registry number(s): 53-36-1

Anti-inflammatory



## 17. RELATED/SUPPORTING DOCUMENTS: None

## A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	(b) (4)	1	Inadequate	04/11/11	RD'Costa
	III			4			
	III			4			
	III			4			

N A = Not Available

<sup>1</sup> Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 –Type 1 DMF

Chemistry Review Data Sheet

- 3 – Reviewed previously and no revision since last review
- 4 – Sufficient information in application
- 5 – Authority to reference not granted
- 6 – DMF not available
- 7 – Other (explain under "Comments")

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

**B. Other Documents: None**

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:      Not Approvable

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	Deficiency	04/08/11	
EES	Pending		
Methods Validation	N/A		
Labeling	Pending		
Bioequivalence	Pending		
EA	Categorical Exclusion Requested (Acceptable)	02/28/11	
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt.  Yes     No    If no, explain reason(s) below:

# The Chemistry Review for ANDA 201-835

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

The chemistry section is inadequate in areas of manufacturing and controls and is therefore recommended for “non-approvable” .

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

N/A

### II. Summary of Chemistry Assessments

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

The drug substance Methylprednisolone Acetate sterile is a white or almost white crystalline powder, practically insoluble in water, sparingly soluble in acetone and in alcohol and slightly soluble in ether. The drug substance and its impurities are characterized using the standard analytical techniques of FT-IR, <sup>1</sup>H, <sup>13</sup>C NMR, MS, etc.

The drug product Methylprednisolone Acetate Injectable Suspension, USP 40mg/mL and 80mg/mL contains Methylprednisolone Acetate as an active ingredient and is based on the reference listed drug Depo-Medrol<sup>®</sup>. The pH of the drug product injectable suspension is between 3.5 and 7.0. It is used as an anti-inflammatory drug. The Methylprednisolone Acetate Injectable Suspension USP is available in multi-dose glass vials (40mg/1mL filled in 5mL and 10mL glass vials and 80mg/1mL in 5mL glass vials) as a sterile suspension for intramuscular administration.

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

The recommended dose for adults is up to 120mg or as prescribed by the physician.

#### C. Basis for Approvability or Not-Approval Recommendation

The “non-approvable” recommendation is based on inadequate chemistry and manufacturing controls.

Labeling; Microbiology and EER are pending.



## Chemistry Assessment

Chemistry Assessment

**What are the physicochemical properties including physical description, pKa, polymorphism, aqueous solubility (as function of pH), hygroscopicity, melting points, and partition coefficient?**

**Physicochemical Properties:**

The drug substance Methylprednisolone Acetate sterile is a white or almost white crystalline powder, practically insoluble in water, sparingly soluble in acetone and in alcohol and slightly soluble in ether. It exists in polymorphic forms (b) (4).  
(b) (4) The form used by the applicant shows the same pattern as the USP reference standard LG-2.

**Deficiency: For the drug substance, the physicochemical characteristics such as melting point, aqueous solubility as a function of pH, partition co-efficient, etc. is missing from the document. Please address.**

**2.3.S.2 Manufacturer**

**Who manufactures the drug substance?**

(b) (4)

**How do the manufacturing processes and controls ensure consistent production of the drug substance?**

The complete manufacturing process is described in DMF (b) (4). Please refer to the DMF for a description of the drug substance manufacturing process, control of materials, in-process controls leading to the drug substance, etc.

(b) (4)

## Chemistry Assessment

## 2.3.S.3 Characterization

**How was the drug substance structure elucidated and characterized?**

**Proof of Structure**

Please refer to DMF No. (b) (4) for full details regarding proof of the Methylprednisolone structure, based upon spectroscopy and analytical testing.

**How were the possible impurities identified and characterized?**

(b) (4)

**Deficiency: The Drug Master File # (b) (4) was reviewed and found to be inadequate. Please do not respond until the DMF holder has responded to the deficiencies cited in the review.**

## 2.3.S.4 Control of Drug Substance

**What is the drug substance specification? Does it include all the critical drug substance attributes that affect the manufacturing and quality of the drug product?**

## Chemistry Assessment

(b) (4)

**2.3.P.8.2 Stability Studies Supporting Proposed Shelf Life and Storage Conditions****What drug product stability studies support the proposed shelf life and storage conditions?**

For stability studies, the drug product samples were stored under accelerated and controlled room temperature stability conditions (Table). The samples were stored in inverted and upright conditions.

Batch Strength & Lot Number	Accelerated Stability and Test Intervals	Room Temperature and Test Intervals
40mg/mL; 7002910 (5mL vial); 7002909 (10mL vial)	40°C ± 2°C/75% ± 5%RH; 0, 1, 2 and 3 months	25°C ± 2°C/60% ± 5%RH; 0, 3, 6, 9, 12, 18, 24 and 36 months
80mg/mL; 7002912 (5mL vial)	40°C ± 2°C/75% ± 5%RH; 0, 1, 2 and 3 months	25°C ± 2°C/60% ± 5%RH; 0, 3, 6, 9, 12, 18, 24 and 36 months

The firm provided 3 months stability data for the drug product samples stored under accelerated and 12 months under stability data under controlled room temperature stability conditions. The presented stability data meets the proposed acceptance criteria. The analysis of the stability samples shows the (b) (4)

(b) (4) Based on the available stability data, trending to higher values is minimum as the test results fall below the proposed specifications. Based on the satisfactory accelerated stability data (3 months), a tentative 24 months expiration dating period is proposed, which will be confirmed by long term temperature stability data. This is acceptable to the Agency.

Reviewer's Comments: The test results for stability of the finished drug product for samples stored under accelerated and room temperature conditions meet the proposed acceptance criteria. The specifications for individual impurities meet the current USP monograph requirements.



## Chemistry Assessment

**What is the post-approval stability protocol?**

In the post-approval stability protocol, the firm commits to place the first three commercial production batches of Methylprednisolone Acetate Injectable Suspension, USP in the marketed container/closure system on stability ( $25^{\circ}\text{C} \pm 2^{\circ}\text{C}/60\% \pm 5\% \text{RH}$ ) and tested at intervals of 0, 3, 6, 9, 12, 18, 24 months and 36 months until the desired expiration date is reached. Yearly thereafter, a minimum of one production lot in the marketed container/closure system will be added to the long-term stability program. The stability results will be reported to the Agency in the annual report.

Furthermore, we commit that if any commercial production lot fails to meet the acceptance criteria of stability specifications or falls out of specifications, the Agency shall be informed and appropriate actions shall be taken.

Any significant chemical, physical, or other deterioration which results in the distributed product acquiring non-compliant characteristics will be reported to FDA as a "Field Alert Report" [21 CFR 314.81].

For additional details regarding the post-approval stability protocol refer to Module 3.2.8.2.

**Deficiency: In the post-approval stability commitment we note the following statement “any lot that falls out of specifications will be reported to the Agency and appropriate actions taken”. Please clarify what actions will be taken should a lot of the drug product fails the stability specifications.**

**III. Administrative****A. Reviewer’s Signature****B. Endorsement Block**

ChemistName/Date: RD’Costa, Ph.D./03/28/11

ChemistryTeamLeaderName/Date: AMueller PhD./03/28/11

ProjectManagerName/Date: Doan Dat, PM, /03/28/11

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**C. CC Block**

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**36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT**

ANDA: 201-835

APPLICANT: Sagent Pharmaceuticals, Inc.

DRUG PRODUCT: Methylprednisolone Acetate Injectable Suspension, USP 40 mg/mL & 80 mg/mL

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

1.

2.

3.

4.

5.

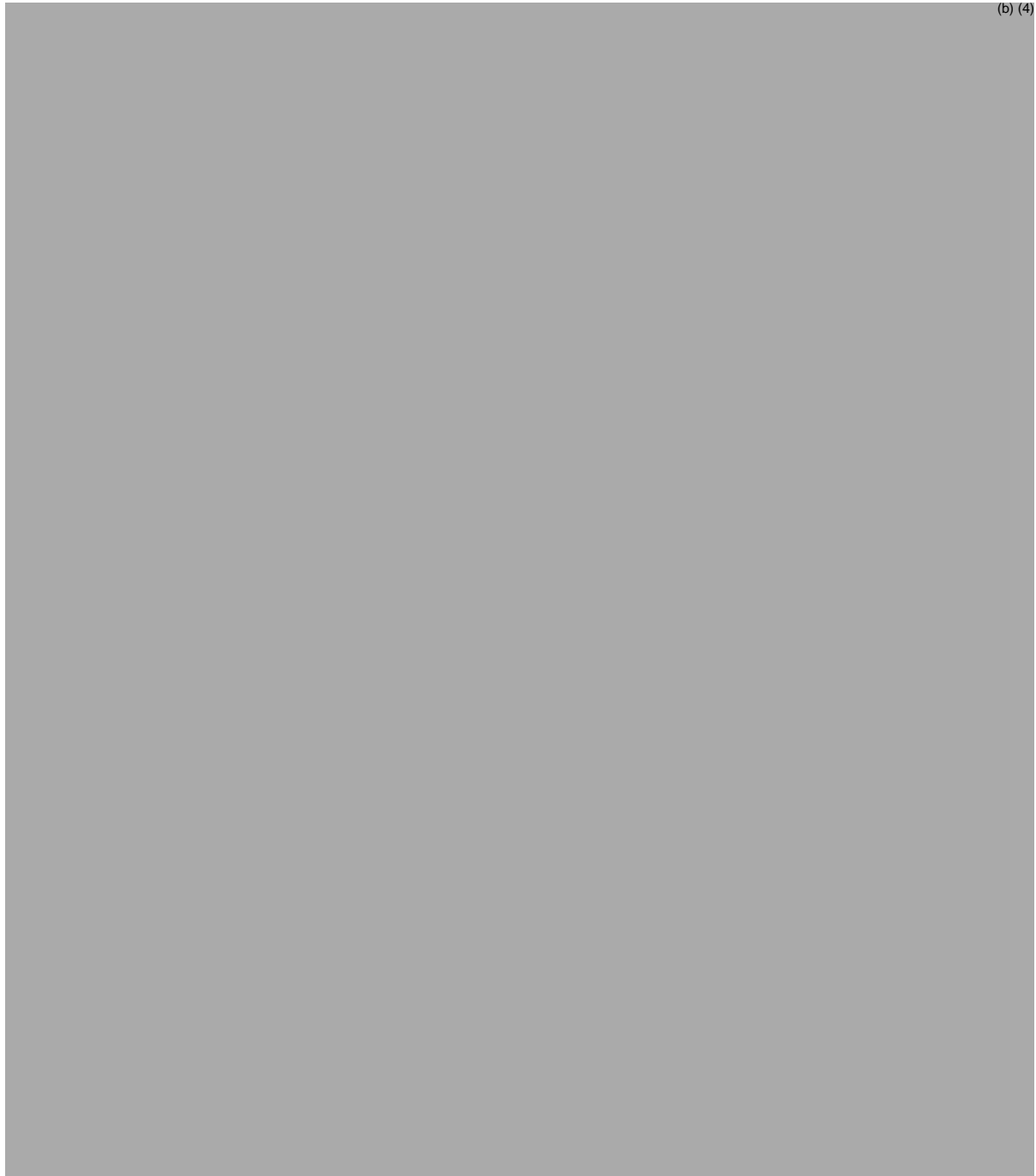
6.

7.

8.

9.

B.



(b) (4)



3.

4.

Sincerely yours,

*{See appended electronic signature page}*

Paul Schwartz, Ph.D.  
Acting Director  
Division of Chemistry I  
Office of Generic Drugs  
Center for Drug Evaluation and Research

**B. Endorsement Block**

ChemistName/Date: RD'Costa, Ph.D./03/28/11

ChemistryTeamLeaderName/Date: AMueller PhD./03/28/11

ProjectManagerName/Date: Doan Dat, PM, /03/28/11

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**C. CC Block**

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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/  
-----

ROSARIO F D COSTA  
05/24/2011

DAT T DOAN  
06/07/2011

ALBERT J MUELLER  
06/08/2011