

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**200677Orig1s000**

**CHEMISTRY REVIEW(S)**



### CMC Memo to File

To:	NDA 200-677
Date	14 Dec 2012
Applicant	Novartis Pharmaceuticals Corporation
Drug:	Signifor® (pasireotide) solution for injection
Subject	Overall Quality Recommendation
Reviewer	Dr. Olen Stephens

Pursuant the overall “acceptable” recommendation given on 14-Dec-2012 for the manufacturing facilities by the Office of Compliance, CMC recommends that NDA application 200-677 be approved. All labeling changes have been communicated to the applicant through the clinical project manager. There are no pending CMC review deficiencies.

**FDA CDER EES  
ESTABLISHMENT EVALUATION REQUEST  
DETAIL REPORT**

<b>Application:</b>	NDA 200677/000	<b>Action Goal:</b>	
<b>Stamp Date:</b>	21-JUN-2011	<b>District Goal:</b>	18-OCT-2012
<b>Regulatory:</b>	17-DEC-2012		
<b>Applicant:</b>	NOVARTIS PHARMS 1 HEALTH PLAZA BLDG 405 2006 EAST HANOVER, NJ 079361080	<b>Brand Name:</b>	SIGNIFOR (SOM230) (pasireotide) injectio
		<b>Estab. Name:</b>	
		<b>Generic Name:</b>	
<b>Priority:</b>	1	<b>Product Number; Dosage Form; Ingredient; Strengths</b>	
<b>Org. Code:</b>	510		001; SOLUTION, INJECTION; PASIREOTIDE; .3MG 002; SOLUTION, INJECTION; PASIREOTIDE; .6MG 003; SOLUTION, INJECTION; PASIREOTIDE; .9MG
<b>Application Comment:</b>	SEE ESTABLISHMENT INFO BELOW (on 21-JUN-2011 by K. SHARMA () 3017961270)		
<b>FDA Contacts:</b>	K. SHARMA	Project Manager	3017961270
	S. TRAN	Team Leader	3017961764

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<b>Overall Recommendation:</b>	ACCEPTABLE	on 14-DEC-2012	by M. STOCK	(HFD-320)	3017964753
	PENDING	on 21-FEB-2012	by EES_PROD		
	PENDING	on 22-JUN-2011	by EES_PROD		
	PENDING	on 22-JUN-2011	by EES_PROD		

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**FDA CDER EES  
ESTABLISHMENT EVALUATION REQUEST  
DETAIL REPORT**

**Establishment:** CFN: 9611204 FEI: 3007303963  
NOVARTIS PHARMA AG  
LICHTSRASSE 35  
BASEL, , SWITZERLAND

**DMF No:** **AADA:**

**Responsibilities:** DRUG SUBSTANCE RELEASE TESTER

**Establishment Comment:** DRUG SUBSTANCE QUALITY CONTROL (BACTERIAL ENDOTOXINS TEST AND MICROBIAL ENUMERATION TEST) (on 21-JUN-2011 by K. SHARMA (J) 3017961270)

**Profile:** CONTROL TESTING LABORATORY **OAI Status:** NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	22-JUN-2011				SHARMAKH
OC RECOMMENDATION	22-JUN-2011			ACCEPTABLE BASED ON PROFILE	INYARDA
REQUEST CANCELLED	22-AUG-2011			APPLICATION WITHDRAWN	EES_ADMIN
SUBMITTED TO OC	21-FEB-2012				SHARMAKH
SUBMITTED TO DO	22-FEB-2012	GMP Inspection			INYARDA
ASSIGNED INSPECTION TO IB	23-FEB-2012	GMP Inspection			PHILPYE
INSPECTION PERFORMED	23-FEB-2012				FACTS_EES
AUTOMATIC WITHHOLD STATUS ISSUED BY FACTS, DUE TO FIRM BEING OUT OF BUSINESS OR MERGED					
INSPECTION SCHEDULED	30-MAY-2012		19-JUL-2012		PHILPYE
DO RECOMMENDATION	03-DEC-2012			ACCEPTABLE BASED ON FILE REVIEW	PHILPYE
OC RECOMMENDATION	04-DEC-2012			ACCEPTABLE DISTRICT RECOMMENDATION	GODWINF

**FDA CDER EES  
ESTABLISHMENT EVALUATION REQUEST  
DETAIL REPORT**

**Establishment:** CFN: 9612715 FEI: 3002807776  
 NOVARTIS PHARMA AG  
 CORK  
 RINGASKIDDY, CORK, , IRELAND

**DMF No:** **AADA:**

**Responsibilities:** DRUG SUBSTANCE MANUFACTURER  
 DRUG SUBSTANCE STABILITY TESTER

**Establishment Comment:** DRUG SUBSTANCE MANUFACTURING QUALITY CONTROL (ALL TESTS, EXCEPT (b) (4)  
 (DCP/ICP.OES), ASSAY OF (b) (4) STABILITY TESTER (on 21-JUN-2011 by K. SHARMA () 3017961270)

**Profile:** NON-STERILE API BY CHEMICAL SYNTHESIS **OAI Status:** NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	22-JUN-2011				SHARMAKH
OC RECOMMENDATION	22-JUN-2011			ACCEPTABLE BASED ON PROFILE	INYARDA
REQUEST CANCELLED	22-AUG-2011				EES_ADMIN APPLICATION WITHDRAWN
SUBMITTED TO OC	21-FEB-2012				SHARMAKH
OC RECOMMENDATION	21-FEB-2012			ACCEPTABLE BASED ON PROFILE	INYARDA

**FDA CDER EES  
ESTABLISHMENT EVALUATION REQUEST  
DETAIL REPORT**

**Establishment:** CFN: 9692043 FEI: 3002653483  
 NOVARTIS PHARMA STEIN AG  
 SCHAFFHAUSERSTRASSE 101  
 STEIN, , SWITZERLAND

**DMF No:** AADA:

**Responsibilities:** FINISHED DOSAGE LABELER  
 FINISHED DOSAGE MANUFACTURER  
 FINISHED DOSAGE OTHER TESTER  
 FINISHED DOSAGE PACKAGER  
 FINISHED DOSAGE STABILITY TESTER

**Establishment Comment:** DRUG PRODUCT MANUFACTURING, QUALITY CONTROL, STABILTY, PACKAGING AND LABELING (on 21-JUN-2011 by K. SHARMA () 3017961270)

**Profile:** (b) (4) OAI Status: NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	22-JUN-2011				SHARMAKH
SUBMITTED TO DO	22-JUN-2011	10-Day Letter			INYARDA
DO RECOMMENDATION	23-JUN-2011			ACCEPTABLE BASED ON FILE REVIEW	PHILPYE
OC RECOMMENDATION	26-JUN-2011			ACCEPTABLE DISTRICT RECOMMENDATION	SMITHDE
REQUEST CANCELLED	22-AUG-2011				EES_ADMIN APPLICATION WITHDRAWN
SUBMITTED TO OC	21-FEB-2012				SHARMAKH
SUBMITTED TO DO	22-FEB-2012	GMP Inspection			INYARDA
PDUFA = 17-DEC-2012; LAST EI FOR THIS SITE = 02-MAR-2010.					
ASSIGNED INSPECTION TO IB	23-FEB-2012	GMP Inspection			PHILPYE
INSPECTION SCHEDULED	09-MAY-2012		21-JUN-2012		PHILPYE
DO RECOMMENDATION	13-DEC-2012			ACCEPTABLE INSPECTION	PHILPYE
PLEASE SEE NOTE ABOUT FIRM NAME POTENTIAL DISCREPANCY					
OC RECOMMENDATION	14-DEC-2012			ACCEPTABLE DISTRICT RECOMMENDATION	STOCKM

**FDA CDER EES  
ESTABLISHMENT EVALUATION REQUEST  
DETAIL REPORT**

**Establishment:** CFN: 9614433 FEI: 3002807773  
 NOVARTIS PHARMANALYTICA SA  
 VIA SERFINO BLESTRA 31  
 LOCARNO, , SWITZERLAND

**DMF No:** AADA:

**Responsibilities:** FINISHED DOSAGE STABILITY TESTER

**Establishment Comment:** DRUG PRODUCT STABILITY TESTER (on 21-JUN-2011 by K. SHARMA () 3017961270)

**Profile:** CONTROL TESTING LABORATORY **OAI Status:** NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	22-JUN-2011				SHARMAKH
SUBMITTED TO DO	22-JUN-2011	GMP Inspection			INYARDA
ASSIGNED INSPECTION TO IB	23-JUN-2011	GMP Inspection			PHILPYE
REQUEST CANCELLED	22-AUG-2011				EES_ADMIN APPLICATION WITHDRAWN
SUBMITTED TO OC	21-FEB-2012				SHARMAKH
OC RECOMMENDATION	22-FEB-2012			ACCEPTABLE BASED ON PROFILE	INYARDA

FDA CDER EES  
ESTABLISHMENT EVALUATION REQUEST  
DETAIL REPORT

Establishment: CFN: [REDACTED] FEI: [REDACTED] (b) (4)

DMF No: [REDACTED] AADA:

Responsibilities: DRUG SUBSTANCE RELEASE TESTER

Establishment Comment: DRUG SUBSTANCE QUALITY CONTROL [REDACTED] (b) (4) DCP/ICP-OES), [REDACTED] (b) (4)  
(b) (4) (on 21-JUN-2011 by K. SHARMA (J 3017961270))

Profile: CONTROL TESTING LABORATORY OAI Status: NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	22-JUN-2011				SHARMAKH
OC RECOMMENDATION	22-JUN-2011			ACCEPTABLE BASED ON PROFILE	INYARDA
REQUEST CANCELLED	22-AUG-2011				EES_ADMIN APPLICATION WITHDRAWN
SUBMITTED TO OC	21-FEB-2012				SHARMAKH
OC RECOMMENDATION	22-FEB-2012			ACCEPTABLE BASED ON PROFILE	INYARDA

NDA 21-856

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HFD-/Division File

HFD-510

HFD-510/J. Johnson

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Olen Stephens, Ph.D.  
Chemistry Reviewer

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Ali Al-Hakim, Ph.D.  
Branch VII Chief, ONDQA

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/s/  
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OLEN M STEPHENS

12/14/2012

CMC recommendation: approval

ALI H AL HAKIM

12/14/2012

# **NDA 200-677**

**Signifor<sup>®</sup>**  
**(pasireotide) solution for injection**

**Novartis Pharmaceuticals Corporation**

**Olen M. Stephens**  
**Pre-Marketing Division III for the**  
**Division of Metabolic and Endocrinology Products**

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# Chemistry Review Data Sheet

1. NDA 200-677

2. REVIEW #: 1

3. REVIEW DATE: 16-Oct-2012

4. REVIEWER: Olen M. Stephens

5. PREVIOUS DOCUMENTS:

Previous Documents

Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Document Date

Original Submission (0000)

21-Jun-2011

Resubmission (0004)

17-Feb-2012

Amendment (0017)

25-Jul-2012

7. NAME & ADDRESS OF APPLICANT:

Name: Novartis Pharmaceutical Corporation

Address: One Health Plaza  
East Hanover, NJ 07936-1080

Representative: Leslie Bennett, Sr. Associate Director, DRA

Telephone: 862-778-6364

8. DRUG PRODUCT NAME/CODE/TYPE:

## Chemistry Review Data Sheet

- a) Proprietary Name: Signifor®  
b) Non-Proprietary Name (USAN): pasireotide  
c) Code Name/#: SOM230

9. LEGAL BASIS FOR SUBMISSION: 505 (b)(1)

10. PHARMACOL. CATEGORY: Somatostatin receptor (sst1, sst2, sst3, and sst5) agonist

11. DOSAGE FORM: Solution for injection

12. STRENGTH/POTENCY: 0.3 mg/mL, 0.6 mg/mL, and 0.9 mg/mL (1 mL in ampoules)

13. ROUTE OF ADMINISTRATION: Subcutaneous

14. Rx/OTC DISPENSED:  Rx  OTC

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

SPOTS product – Form Completed

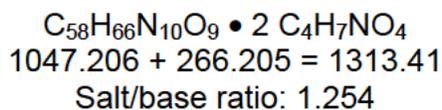
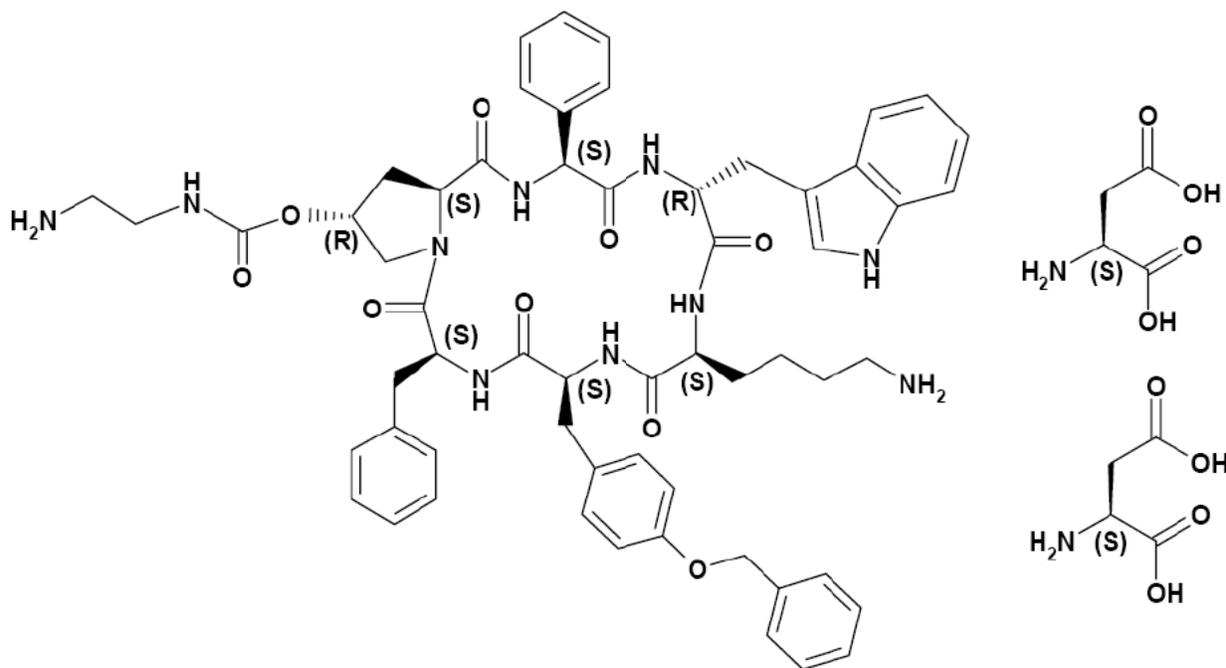
Not a SPOTS product

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

Pasireotide diaspartate

Chemical name: (2-Aminoethyl)carbamic acid (2R,5S,8S,11S,14R,17S,19aS)-11-(4-aminobutyl)-5-benzyl-8-(4-benzyloxybenzyl)-14-(1H-indol-3-ylmethyl)-4,7,10,13,16,19-hexaazocyclooctadecahydro-3a,6,9,12,15,18-hexaazacyclopentacyclooctadecen-2-yl ester, di[(S)-2-aminosuccinic acid] salt

## Chemistry Review Data Sheet



## 17. RELATED/SUPPORTING DOCUMENTS:

## A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	1 mL Type I glass ampoule	4, 3	Adequate N/A		LoA: 26-Sep-2011 Adequate
	II		1 mL Type I glass ampoule	4	Adequate N/A		
	II		1 mL Type I glass ampoule	4	Adequate N/A		

<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

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

Chemistry Review Data Sheet

- 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:**

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
Cross Referenced IND	(b) (4)	Active; no current hold
Cross Referenced IND	IND 68,635	Active; no current hold
Cross Referenced IND	(b) (4)	Active; no current hold
Cross Referenced IND	(b) (4)	Active; no current hold

18. STATUS:

**ONDC:**

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
<b>EES</b>	<b>Pending</b>		
Pharm/Tox	Approval	4-Oct-12	Miyun Tsai-Turton
Biopharm	Approval	10-Oct-12	Houda Mahayni
Microbiology	Approval	3-Jul-12	Bryan Riley

# The Chemistry Review for NDA 200-677

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

From a CMC review perspective, the NDA is recommended for approval. There are no pending CMC deficiencies to resolve.

The overall recommendation is still pending from the Office of Compliance for GMP inspections. The CMC recommendation does not include cGMP findings.

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

None

### II. Summary of Chemistry Assessments

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

Pasireotide (SOM230), a new chemical entity, is a somatostatin analogue. Like natural somatostatin and other somatostatin analogues (SSA), pasireotide exerts its pharmacological activity via binding to somatostatin receptors (sst). Pasireotide (SOM230) solution for injection contains pasireotide diaspertate as the active drug substance. The drug substance is a somatostatin analogue. It is a novel cyclohexapeptide containing (b) (4)

Pasireotide diaspertate has been formulated as 0.3 mg/1 ml, 0.6 mg/1 ml and 0.9 mg/1 ml solution for injection in ampoules. It is an immediate-release dosage form for subcutaneous administration and used for the treatment of Cushing's disease.

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

SIGNIFOR is a somatostatin analog indicated for the treatment of patients with Cushing's disease who require medical therapeutic intervention. Initial doses of 0.9 mg/mL and 0.6 mg/mL are recommended for patients depending on their level of hepatic impairment. SIGNIFOR should not be used in patients with severe hepatic impairment.

## Executive Summary Section

SIGNIFOR is administered subcutaneously by self-injection and is supplied as a sterile solution in a single-dose, 1 mL colorless glass ampoule containing pasireotide in 0.3 mg/mL, 0.6 mg/mL, or 0.9 mg/mL strengths for subcutaneous injection. SIGNIFOR ampoules are packaged in a box of 60 ampoules, arranged in 10 packs of 6 ampoules each. Store at 25° C (77°F); excursions permitted to 15°-30°C (59°-86°F), protect from light. A 24 month shelf life is granted for all dose strengths.

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

Chemistry, Manufacturing and Controls deficiencies for the drug substance and drug product have been adequately addressed. There are no CMC deficiencies, but an overall recommendation from Office of Compliance is outstanding.

**III. Administrative****A. Reviewer's Signature  
[electronic]****B. Endorsement Block**

ChemistName/Date: Same date as draft review  
ChemistryTeamLeaderName/Date  
ProjectManagerName/Date

**C. CC Block**

82 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/  
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OLEN M STEPHENS

10/16/2012

From the CMC point of view, the NDA is recommended for approval. There are no pending CMC deficiencies to resolve.

The overall recommendation is still pending from the Office of Compliance for GMP inspections. The CMC recommendation does not include cGMP findings.

ALI H AL HAKIM

10/16/2012

## PRODUCT QUALITY - BIOPHARMACEUTICS FILING REVIEW

<b>NDA Number</b>	200-677
<b>Submission Date</b>	February 17, 2012
<b>Product name, generic name of the active</b>	Signifor® (Pasireotide)
<b>Dosage form and strength</b>	Injection (0.3 mg/mL, 0.6 mg/mL, and 0.9 mg/mL)
<b>Applicant</b>	Novartis
<b>Clinical Division</b>	DMEP
<b>Type of Submission</b>	New Drug Application
<b>Biopharmaceutics Reviewer</b>	Houda Mahayni, Ph.D.
<b>Biopharmaceutics Supervisory Lead (acting)</b>	Angelica Dorantes, Ph.D.

The following parameters for the ONDQA's Product Quality-Biopharmaceutics filing checklist are necessary in order to initiate a full biopharmaceutics review (i.e., complete enough to review but may have deficiencies).

<b>ONDQA-BIOPHARMACEUTICS</b>				
<b>A. INITIAL OVERVIEW OF THE NDA APPLICATION FOR FILING</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
1.	Does the application contain dissolution data?		x	No in-vitro dissolution studies were performed because Pasireotide is formulated as an aqueous solution for s.c. administration via the parenteral route.
2.	Is the dissolution test part of the DP specifications?		x	
3.	Does the application contain the dissolution method development report?		x	
4.	Is there a validation package for the analytical method and dissolution methodology?		x	
5.	Does the application include a biowaiver request?	x		0.6 mg/mL and 0.9 mg/mL are dosage strengths included in the clinical trial. However, the 0.3 mg/mL strength was not included in the clinical trial. Therefore, a biowaiver request for the 0.3 mg/mL is implied.
6.	Does the application include a IVIVC model?		x	
7.	Is information such as BCS classification mentioned, and supportive data provided?		x	
8.	Is information on mixing the product with foods or liquids included?		x	Pasireotide s.c. is administered via the parenteral route. Therefore, a food effect is not expected to occur.

## PRODUCT QUALITY - BIOPHARMACEUTICS FILING REVIEW

9.	Is there any <i>in vivo</i> BA or BE information in the submission?	x		<p>The Applicant stated that results from pre-clinical studies demonstrated a complete absolute bioavailability of pasireotide s.c. as compared to pasireotide i.v. in rats and monkey. Therefore, the absolute bioavailability of pasireotide is expected to be complete following s.c. administration in humans.</p> <p>The composition of product used in the pivotal study is identical to the intended market with the exception of the primary packaging. Therefore, the applicant did not perform a BE study.</p>
<b>B. FILING CONCLUSION</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
10.	<b>IS THE BIOPHARMACEUTICS SECTIONS OF THE APPLICATION FILEABLE?</b>	x		
11.	Is the NDA fileable from the product quality-biopharmaceutics perspective? If the NDA is not fileable, state the reasons and provide <b>filing</b> comments to be sent to the Applicant.	x		Not Applicable
12.	Is the NDA fileable from the biopharmaceutics perspective? If the NDA is not fileable, state the reasons and provide <b>filing</b> comments to be sent to the Applicant.	x		Fileable
13.	Are there any <b>potential review</b> issues to be forwarded to the Applicant for the 74-day letter?		x	No comments for the applicant

*{See appended electronic signature page}*

Houda Mahayi, Ph.D.  
Biopharmaceutics Reviewer  
Office of New Drug Quality Assessment

04/09/12  
Date

*{See appended electronic signature page}*

Angelica Dorantes, Ph.D.  
Biopharmaceutics Supervisory Lead (acting)  
Office of New Drug Quality Assessment

04/09/12  
Date

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/s/  
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HOUDA MAHAYNI  
04/09/2012

ANGELICA DORANTES  
04/09/2012



### CMC Memo to File

Date	26 Aug 2011
NDA#	68,635
Sponsor:	Novartis Pharmaceutical Corporation
Drug:	Signifor® (pasireotide) injection
Reviewer	Dr. Olen Stephens

In the original treatment IND 68,635 (submitted 27-Jul-2011), the IND referenced NDA 200-677 for necessary CMC information. On 19-Aug-2011, Novartis submitted amendment 0002 to the NDA (copied below in the Appendix), alerting the review team of emerging stability data that was not submitted in the original submission. In this letter, Novartis reported the observation of (b) (4) particulates discovered in historical and intended commercial drug product batches for the to-be-marketed presentation of pre-filled syringes. A teleconference with Novartis was conducted on 19-Aug-2011 to seek clarity as to the prevalence of this trend with regards the number of syringes that had particulates, the number, size, identity & origin of the particulates, and time of on-set for particulate formation. These questions were not fully answered during the teleconference and Novartis acknowledged that a root cause analysis is ongoing. Pending the results of the analysis, the current application would be amended to reflect the findings of the root cause analysis. Novartis mentioned several possible approaches that would require different degrees of amendments including changes to the container closure configuration or other manufacturing process changes. Ultimately, Novartis withdrew NDA 200-677 (19-Aug-2011).

Note that the product quality concerns identified in NDA amendment 0002 and in the 19-Aug-2011 teleconference do not extend to treatment IND 68,635 because a different container closure system is used for the clinical trial. As stated in the letter below (Amendment 0002; 19-Aug-2011), “all completed and ongoing clinical studies with the pasireotide solution for injection submitted to the INDs (b) (4) and 68,635) were and are being conducted with the ampoule form of the drug product.” Note that specifications for this drug product (pasireotide solution in ampoules) are tested for visible and sub-visible particles as per USP <788>; (b) (4) particulates observed for the pre-filled syringes of NDA 200-677 have not been observed in the ampoules. Though the root cause analysis is ongoing, Novartis believes the source of the particulates observed in the pre-filled syringes originate from (b) (4). Since there is (b) (4) in the ampoule, one would not expect to see particulates from this origin.

Therefore, the silicon-based particulates observed in the pre-filled syringes do not appear to be a concern for the proposed ampoule container closure system in the treatment IND (27-Jul-2011). Pursuant an overall acceptable recommendation by the Office of Compliance regarding the manufacturing and testing facilities, the CMC recommendation is that it is reasonably safe to initiate the clinical trial.

(b) (4)

APPENDIX:



Leslie Bennett, RAC (US, EU)  
Sr. Associate Director  
Drug Regulatory Affairs

Novartis Pharmaceuticals  
Corporation  
One Health Plaza, Bldg 105  
East Hanover, NJ 07936-1080

Tel: 862-778-6364  
Fax: 973-781-5217  
leslie.bennett@novartis.com

August 18, 2011

Mary Parks, M.D.  
Director  
Division of Metabolism and Endocrinology Products  
Office of Drug Evaluation II  
Food and Drug Administration  
Document Control Room  
Center for Drug Evaluation and Research  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

**NDA 200677**  
**SIGNIFOR® (pasireotide) injection**  
**AMENDMENT TO PENDING NDA**

Dear Dr. Parks,

Reference is made to the above-cited NDA currently under review. This NDA was submitted on June 21, 2011 seeking approval of pasireotide solution for injection in pre-filled syringes (PFS) for the treatment of Cushing's disease patients. The NDA contained complete information on the efficacy, safety, chemistry (drug substance and drug product), clinical pharmacology and pre-clinical studies for this product. This letter is to inform you of a quality issue that was recently discovered in the ongoing stability testing program.

The chemistry information provided in the NDA included long-term stability (3 years) results from a protocol submitted to the Agency on June 28, 2004 (SN006). Those data were generated with the registration stability batches of the PFS drug product manufactured at (b) (4) and the results fully supported the shelf-life and storage conditions claimed for the product in the NDA. Also provided in the NDA was information on the validation batches manufactured at the intended launch site (Novartis Stein, Switzerland), including a commitment to follow the long-term stability on those batches. As described in the Post-Approval Stability Protocol and Stability Commitment (Module 3.2.P.8.2 Section 6), information on long term stability would be submitted via annual report.

During the stability testing, translucent, "flake like" visible particles were found in one batch of the (b) (4) dosage strength, a strength not intended for launch. The stability specification for the test "appearance of the solution" requires the solution to be "clear and colorless" by visual examination. Upon this finding, the stability commitment batches (0.3mg and 0.9mg) were re-examined and particles were found in some syringes across all dosage strengths. Preliminary results from a thorough ongoing root cause analysis (RCA) showed that the particles are composed mainly of (b) (4) (b) (4)

Additionally, the RCA suggests according to the current status of the investigation that the (b) (4) (b) (4) is a major contributor to the generation of the particles.

As per the data submitted in the NDA, for the 3 years testing of the registration stability batches, all batches complied with all the set specifications, including those for "appearance of the solution" and "particulate matter" which fulfill the USP and Pharm. Eur requirements. Of note, the (b) (4) used in registration stability were subject to a different (b) (4) (b) (4) than at Stein (b) (4). Nonetheless, because of the findings with the stability commitment batches, we examined samples of the registration stability batches, now stored for 7 years. It is important to note

that the drug product shelf-life claimed in the NDA is only 2 years. In those samples, similar particles were seen but in smaller quantities. The composition of the particles detected in the registration stability batches is also silicon-based. The RCA is also trying to elucidate whether the particles seen in the registration batches are due simply to an expected "ageing" phenomenon, considering that the re-examination took place after the samples were stored for 7 years i.e. 5 years beyond the claimed shelf-life.

Novartis is evaluating several options to guarantee the quality of the product. Among the options under consideration is the registration of the ampoule version of the drug product. The ampoule form was the clinical presentation used for the clinical development program of the s.c. formulation, including the Phase 3 study B2305. Available batches of the ampoules were subjected to a thorough investigation and no particles were detected. These findings further corroborate the preliminary results of the RCA for the PFS, as no [REDACTED] (b)(4) of the ampoules.

Novartis would like to reinforce that all completed and ongoing clinical studies with the pasireotide solution for injection submitted to the INDs [REDACTED] (b)(4) 68,635) were and are being conducted with the ampoule form of the drug product. Therefore, the quality issue recently uncovered with the PFS did not put patients at risk nor impact the conduct or the results of those trials.

Novartis is seeking to open a dialogue with the Agency on this matter. The ongoing thorough RCA will guide the modifications to the drug product quality module. Novartis is nearing completion of its investigation and intends to request a meeting with the Agency to discuss a proposal on the path forward in the very near future. We are happy to discuss this while we are diligently pursuing this investigation and evaluating this situation. If you have any questions or need additional information, I can be reached directly at (862) 778-6364, by cell at [REDACTED] (b)(6) by fax at (973) 781-5217, or by email at leslie.bennett@novartis.com. Alternatively, you may contact Lynne McGrath, Vice President, NA Head Drug Regulatory Affairs at (862) 778-5139 or by email at lynne.mcgrath@novartis.com.

Sincerely,

*-Leslie Ann Bennett-*

Leslie Ann Bennett, RAC (US, EU)  
Senior Associate Director, Drug Regulatory Affairs

HFD-/Division File  
HFD-510  
HFD-510/

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Olen Stephens, Ph.D.  
Chemistry Reviewer

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Ali Al-Hakim, Ph.D.  
Branch VII Chief, ONDQA

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/s/  
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OLEN M STEPHENS  
08/26/2011

ALI H AL HAKIM  
08/26/2011

Initial Quality/CMC Assessment  
ONDQA

**Division of Metabolism and Endocrinology Products**

**NDA:** 200677

**Applicant:** Novartis Pharmaceuticals Corp.

**Stamp Date:** 21-JUN-2011

**PDUFA Date:** 20-APR-2012

**Proposed Proprietary Name:** Signifor

**Established Name:** Pasireotide

**Dosage form and strength:** Solution for injection  
0.3, 0.6, 0.9 mg/mL (free base)

**Route of Administration:** Subcutaneous injection

**Indications:** Cushing's disease

**CMC Lead:** Su (Suong) Tran, ONDQA

**ONDQA Fileability:** Yes

Are there comments for the 74-day letter? Yes.

- FDA does not routinely designate official names of drugs. Apply for a U.S. Adopted Name for your drug substance (reference is made to the U.S. Pharmacopeia Dictionary for details) and advise us of the progress of your application.
- Confirm that there was no major manufacturing change associated with the drug substance manufacturing transfer from (b) (4)
- In section 3.2.P.2, regarding the qualification of the proposed (b) (4), you state that no leachable was found greater than the detection limit of (b) (4) (later changed to (b) (4) with an optimized test method). Provide information in support of the detection limit being an appropriate safety threshold.
- Provide the location in the NDA of the information on the functionality testing of the assembled pre-filled syringe, which should cover attributes such as plunger release force and travel force.
- The primary stability batches submitted in the NDA are Y0670704, Y0690704, Y0710804, Y0730704, Y0750704, and Y0770804, all packaged in the (b) (4) syringes. In section 3.2.P.8.1 you indicate that these batches were manufactured at (b) (4) and in

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section 3.2.P.5.4 the same batches were manufactured at (b) (4). Clarify the manufacturing site of the primary stability batches and provide information (e.g., process, equipment) to compare the manufacturing site of the stability batches to the commercial manufacturing site.

- In section 3.2.P.8.2 you indicate that three production scale batches of the 0.3 mg/mL and 0.9 mg/mL strengths were manufactured in (b) (4) 2009, each batch packaged in the proposed commercial pre-filled syringes from (b) (4). Confirm that these production scale batches were manufactured at the commercial site Novartis Stein. You also state that these batches were placed on stability studies. Explain why stability data from these batches are not included in the NDA.
- Considering the increasing trend in degradation and decreasing trend in assay results observed in the primary stability batches when stored at 25 °C/60% RH and 30 °C/70% or 75% RH, we advise you to label the product for long-term storage under refrigerated conditions based on the better stability profile at 5 °C.

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<b>CONSULTS/ CMC RELATED REVIEWS</b>	<b>COMMENT</b>
CBER	<i>Not applicable</i>
CDRH	<i>Not applicable. The injectable solution is packaged in a pre-filled single-use glass syringe.</i>
EA	The categorical exclusion claim will be assessed by Primary Reviewer.
Compliance (OMPQ)	EER was sent to Compliance by ONDQA PM (K. Sharma) on 22-JUN-2011.
Methods Validation	<i>Validation may be requested of FDA labs after test methods are finalized.</i>
Microbiology	Review of sterility assurance.
OBP	<i>Not applicable</i>
ONDQA Biopharm	<i>Review of the biowaiver request (glass vial vs. pre-filled syringe).</i>
OSE	<i>Labeling consult request will be sent as part of DMEP's request.</i>
Pharm/Tox	<i>Not applicable (Impurities/degradants limits are within FDA's qualification threshold for (b)(4) impurities and ICH's qualification threshold specific to the maximum daily dose.)</i>
QbD	<i>Not applicable</i>

This is an electronic NDA, filed as a 505(b)(1) application, with the supporting IND 68635.

The drug substance is pasireotide diaspertate: New Molecular Entity (NME), synthetic cyclohexapeptide (molecular weight 1313) produced by (b)(4) and somatostatin analogue.

The drug product is an immediate-release solution for SC injection in the dosage strengths of 0.3, 0.6, 0.9 mg/mL (free base). The product will be packaged in pre-filled single-use glass syringes. The product is light-sensitive and will be stored at room temperature.

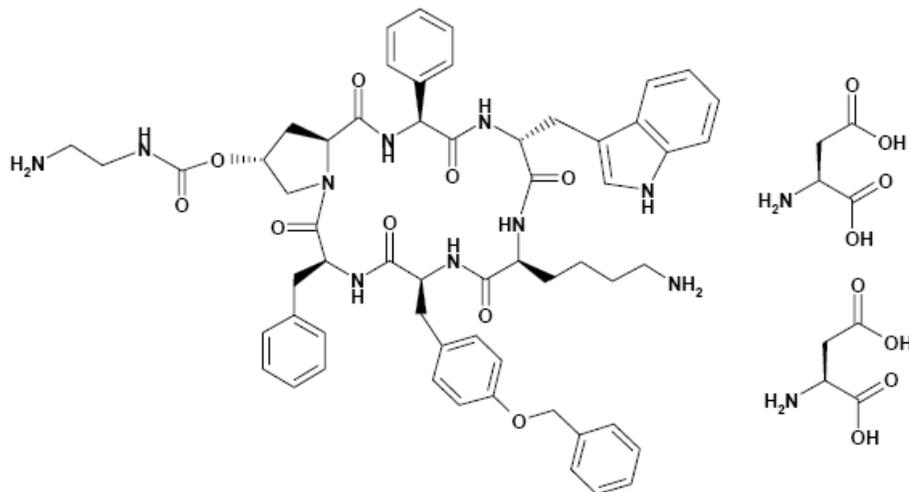
**Maximum daily dose is 1.8 mg pasireotide.**

Initial Quality/CMC Assessment  
ONDQA

Has all information requested during the IND phases, and at the pre-NDA meetings been included?  
Yes.

**Drug substance:**

**1.2.1 Structural formula**



**1.2.2 Molecular formula**

$C_{58}H_{66}N_{10}O_9 \cdot 2 C_4H_7NO_4$

**1.2.3 Relative molecular mass**

$1047.206 + 266.205 = 1313.41$

Salt/base ratio: 1.254

**1.1.1 International non-proprietary name modified (INN<sup>m</sup>)**

Pasireotide diaspартate

**1.1.2 National approved names (USAN, BAN, JAN)**

Not yet established

**1.1.3 Systematic chemical names**

**1.1.3.1 Chemical name**

(2-Aminoethyl)carbamic acid (2R,5S,8S,11S,14R,17S,19aS)-11-(4-aminobutyl)-5-benzyl-8-(4-benzyloxybenzyl)-14-(1H-indol-3-ylmethyl)-4,7,10,13,16,19-hexaoxo-17-phenyloctadecahydro-3a,6,9,12,15,18-hexaazacyclopentacyclooctadecen-2-yl ester, di[(S)-2-aminosuccinic acid] salt

**1.1.3.2 CAS name (9CI)**

Cyclo[(2S)-2-phenylglycyl-D-tryptophyl-L-lysyl-O-(phenylmethyl)-L-tyrosyl-L-phenylalanyl-(4R)-4-[[[(2-aminoethyl)amino]carbonyl]oxy]-L-prolyl] L-aspartate

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Initial Quality/CMC Assessment  
ONDQA

**PRODUCT QUALITY**  
**FILING REVIEW FOR NDA (ONDQA)**

<b>NDA Number: 200677</b>	<b>Established/Proper Name: pasireotide</b>
<b>Applicant: Novartis</b>	<b>Stamp Date: 21-JUN-2011</b>

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. GENERAL				
	Parameter	Yes	No	Comment
1.	Is the CMC section organized adequately?	x		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	x		
3.	Are all the pages in the CMC section legible?	x		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	x		
B. facilities*				
	Parameter	Yes	No	Comment
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	x		
6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? <b>This question is not applicable for synthesized API.</b>			
7.	Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list: <ul style="list-style-type: none"> <li>• Name of facility,</li> <li>• Full address of facility including street, city, state, country</li> <li>• FEI number for facility (if previously registered with FDA)</li> <li>• Full name and title, telephone, fax number and email for on-site contact person.</li> <li>• Is the manufacturing responsibility and function identified for each facility?, and</li> <li>• DMF number (if applicable)</li> </ul>	x		
8.	Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: <ul style="list-style-type: none"> <li>• Name of facility,</li> <li>• Full address of facility including street, city, state, country</li> <li>• FEI number for facility (if previously registered with FDA)</li> <li>• Full name and title, telephone, fax number and email for on-site contact person.</li> <li>• Is the manufacturing responsibility and function identified for each facility?, and</li> <li>• DMF number (if applicable)</li> </ul>	x		

## Initial Quality/CMC Assessment ONDQA

9.	<p>Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> <li>• Name of facility,</li> <li>• Full address of facility including street, city, state, country</li> <li>• FEI number for facility (if previously registered with FDA)</li> <li>• Full name and title, telephone, fax number and email for on-site contact person.</li> <li>• Is the manufacturing responsibility and function identified for each facility?, and</li> <li>• DMF number (if applicable)</li> </ul>	x		
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	x		

\* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.

<b>C. ENVIRONMENTAL ASSESSMENT</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
11.	Has an environmental assessment report or categorical exclusion been provided?	x		
<b>D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
12.	Has an environmental assessment report or categorical exclusion been provided?	x		
13.	Does the section contain a description of the DS manufacturing process?	X		
14.	Does the section contain identification and controls of critical steps and intermediates of the DS?	X		
15.	Does the section contain information regarding the characterization of the DS?	X		
16.	Does the section contain controls for the DS?	X		
17.	Has stability data and analysis been provided for the drug substance?	X		
18.	Does the application contain Quality by Design (QbD) information regarding the DS?		x	
19.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		x	

Initial Quality/CMC Assessment  
ONDQA

E. DRUG PRODUCT (DP)				
	Parameter	Yes	No	Comment
20.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	x		
21.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	x		
22.	Is there a batch production record and a proposed master batch record?	x		
23.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	x		
24.	Have any biowaivers been requested?			See Biopharm filing memo
25.	Does the section contain description of to-be-marketed container/closure system and presentations)?	x		
26.	Does the section contain controls of the final drug product?	x		
27.	Has stability data and analysis been provided to support the requested expiration date?	x		Review issue: whether data and analysis are adequate to support expiry
28.	Does the application contain Quality by Design (QbD) information regarding the DP?		x	
29.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		x	
F. methods validation (Mv)				
	Parameter	Yes	No	Comment
30.	Is there a methods validation package?	x		
G. microbiology				
	Parameter	Yes	No	Comment
31.	If appropriate, is a separate microbiological section included assuring sterility of the drug product?			See Microbiology filing memo
H. master files (DMF/MAF)				
	Parameter	Yes	No	Comment
32.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	x		
I. Labeling				
	Parameter	Yes	No	Comment
33.	Has the draft package insert been provided?	x		
34.	Have the immediate container and carton labels been provided?	x		
J. filing conclusion				
	Parameter	Yes	No	Comment
35.	IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?	x		
36.	If the NDA is not fileable from the product quality perspective, state the reasons and provide filing comments to be sent to the Applicant.			
37.	Are there any potential review issues to be forwarded to the Applicant for the 74-day letter?	X		See the first page of this review.

*{See appended electronic signature page}*

Su (Suong) Tran

CMC Lead, Office of New Drug Quality Assessment

*{See appended electronic signature page}*

Ali Al Hakim

Branch Chief, Office of New Drug Quality Assessment

Date *{see appended electronic signature page}*

Date *{see appended electronic signature page}*

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/s/  
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SUONG T TRAN  
08/09/2011

ALI H AL HAKIM  
08/09/2011

## PRODUCT QUALITY MICROBIOLOGY FILING CHECKLIST

**NDA Number:** 200-677/N-000

**Applicant:** Novartis

**Letter Date:** 21 June 2011

**Drug Name:** Signifor® (Pasireotide) **NDA Type:** 505(b)(1)

**Stamp Date:** 21 June 2011

The following are necessary to initiate a review of the NDA application:

	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comments</b>
1	Is the product quality microbiology information described in the NDA and organized in a manner to allow substantive review to begin? Is it legible, indexed, and/or paginated adequately?	<b>X</b>		
2	Has the applicant submitted an overall description of the manufacturing processes and microbiological controls used in the manufacture of the drug product?	<b>X</b>		
3	Has the applicant submitted protocols and results of validation studies concerning microbiological control processes used in the manufacture of the drug product?	<b>X</b>		
4	Are any study reports or published articles in a foreign language? If yes, has the translated version been included in the submission for review?		<b>X</b>	
5	Has the applicant submitted preservative effectiveness studies (if applicable) and container-closure integrity studies?	<b>X</b>		(b) (4)
6	Has the applicant submitted microbiological specifications for the drug product and a description of the test methods?	<b>X</b>		
7	Has the applicant submitted the results of analytical method verification studies?	<b>X</b>		
8	Has the applicant submitted all special/critical studies/data requested during pre-submission meetings and/or discussions?			Not applicable.
9	Is this NDA fileable? If not, then describe why.	<b>X</b>		

Additional Comments: None.

\_\_\_\_\_  
John W. Metcalfe, Ph.D.

\_\_\_\_\_  
Date

\_\_\_\_\_  
Bryan S. Riley, Ph.D.

\_\_\_\_\_  
Date

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/s/  
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JOHN W METCALFE  
07/11/2011

BRYAN S RILEY  
07/12/2011  
I concur.