CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203255Orig1s000

CHEMISTRY REVIEW(S)

NDA 203-255

SIGNIFOR® LAR 20mg, 40mg, 60mg (Pasireotide) for injectable suspension

Novartis Pharmaceuticals Corporation

Ravindra Kasliwal, Ph.D.

Milagros Salazar, Ph.D.

ONDQA/ DNDQA III/ Branch VII

for

Division of Metabolism and Endocrine Products

Table of Contents

CMC Review Data Sheet

1. NDA 203-255

2. REVIEW # 1

3. REVIEW DATE: 11-AUG-2014

4. REVIEWERs: Ravindra Kasliwal, Ph.D. (drug substance) and Milagros Salazar, Ph.D.(drug product).

5. PREVIOUS DOCUMENTS: None

Previous Documents	Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	15-NOV-2013
Amendment SD-15	12-JUN-2014
Amendment SD-16	30-JUN-2014
Amendment SD-17	11-JUL-2014

7. NAME & ADDRESS OF APPLICANT:

Name:	Novartis Pharmaceutical Corporation
Address:	One Health Plaza, Bldg. 105 East Hanover, NJ 07936
Representative:	Rose Gao, M.S. Director, Drug Regulatory Affairs Email: rose.gao@novartis.com
Telephone:	862-778-6795 Fax: 973-781-5217

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: SIGNIFOR® LAR
b) Non-Proprietary Name: Pasireotide
c) Code Name/#: SOM230
d) Chem. Type/Submission Priority:
- Chem. Type: 2 (New salt), 3 (New formulation)
- Submission Priority: Standard

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

10. PHARMACOL. CATEGORY: somatostatin analog, a cyclohexapeptide

11. DOSAGE FORM: [redacted] (b) (4) Powder for Injectable Suspension, Kit (Long-acting release, depot injection)

12. STRENGTH/POTENCY: 20 mg, 40 mg and 60 mg

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

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

Chemical Name:

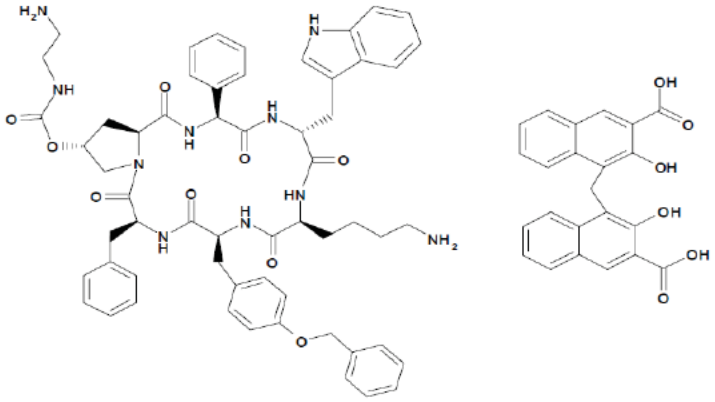
(2-Aminoethyl)carbamic acid (2R,5S,8S,11S,14R,17S,19aS)-11-(4-aminobutyl)-5-benzyl-8-(4- benzyloxybenzyl)-14-(1H-indol-3-ylmethyl)-4,7,10,13,16,19-hexaoxo-17-phenyloctadecahydro-3a,6,9,12,15,18-hexaazacyclopentacyclooctadecen-2-yl ester pamoic acid salt

Other names: INNM: Pasireotide pamoate USAN: Pasireotide (for the base)

Company/Lab Codes: SOM230C, SOM230-BFA, SOM230-BFA.001, SOM230-BFA.001(pamoate), SOM230 pamoate

CAS registry no.: 396091-79-5

Structural Formula:



Molecular Formula: $C_{58}H_{66}N_{10}O_9 \bullet C_{23}H_{16}O_6$

Relative Molecular Mass: 1047.21 + 388.37 = 1435.58

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENT
6895	II	Novartis Pharma AG	Excipient-DP powder Poly(D,L-lactide-co-glycolide) (50-60: 40-50) star polymer	1, 4	Active 3/26/87 Adequate	08-05-2014 Xavier Ysern, Ph.D.	LoA 23-Sep-2013
(b) (4)	IV	(b) (4)		1, 4	Active 1/30/2006 Adequate	08-08-2014 Xavier Ysern,Ph.D.	LoA 15-Dec-2011
	III			1, 4	Active 12/28/95 Adequate	Last review 12-Jul-2004 Joel Hathaway, PhD	LoA 4-Dec-2012
	III			1	Active 10/2/87 Adequate	11-Apr-2014 Milagros Salazar, PhD	LoA 20-Nov-2012
	III			1, 4	Active 5/12/97 Adequate	Last review 15-Jul-2003 Chien-Hua Niu, PhD (cmc) 31-Oct-2010 Denise Miller, PhD (micro)	LoA 6-Aug-2013
	V			1, 4	Active 1/23/97 Adequate	Last review 15-Aug-2013 Steffen/ Kiester/ Arigo/Dexter (micro)	LoA 6-Aug-2013
	III			1	Active 7/30/81 Adequate	11-Apr-2014 Milagros Salazar, PhD	LoA 6-Aug-2013

[1] 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

6 – DMF not available

7 – Other (explain under "Comments")

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

B. Other Documents for support or reference:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION – Status
IND	74,642	pasireotide LAR formulation for the treatment of acromegaly and Cushing's disease - Active
[redacted]		(b) (4)
IND	68,635	pasireotide s.c. formulation for the treatment of Cushing's disease and acromegaly - Active
510(k)	K963583	Vial adapter- Mixject dispensing pin/detachable vial holder Medimop Medical Projects Ltd - Active 7-Oct-1996
510(k)	K012736	Kendall Monoject safety needle hypodermic needle Sharps injury prevention (consisting of needle, safety shield and protective cap) Covidien LLC (Tyco Healthcare) - Active 25-Oct-2001
CDER	ORPHAN-92886	Orphan Drug Designation
NDA	19-668	Cardura® (Doxazosin mesylate) Tablet Pzifer Inc. - AP 11/02/1990
NDA	21-008	Sandostatin® LAR (Octreotide acetate) Depot Novartis - AP 11/25/1998
NDA	200-677	Signifor® (Pasiretide diaspartate) Solution, Injection Novartis - AP 12/14/2012

18. STATUS - **ONDQA:**

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		Jennifer Clark, Ph.D.
Clinical	N/A		Smita B. Abraham
Clin.Pharm.	N/A		Sang M. Chung
EES	Pending		PM OND: Jennifer Johnson PM ONDQA: Priyanka Kumar
Pharm./Tox.	Approvable	1-Aug-2014	Miyun Tsai-Turton, Ph.D.
Biopharmaceutics	Pending		John Duan, Ph.D.
LNC	Non-proprietary name For Signifor® LAR (pasireotide) for injectable suspension -		
Methods Validation	Revalidation of analytical methods by the Agency laboratories is not recommended		
DMEPA* Marketing and Advertising** OSE/ OMEPRM DRISK***	Proprietary name Signifor LAR – granted Recommendation for PI, container and carton labels	22-Jan-2014 28-Mar-2014	Tingting N Gao, Pharm D. Yelena L Maslov, Pharm.D Terrolyn Thomas, Ph.D.
Environmental Assessment	Claim of categorical exclusion - granted. (part of this review)		Milagros Salazar, Ph.D.
Microbiology	Pending		Vinayak Pawar, Ph.D.
CDRH consult 510(k)	Pending		Keith Marin, Ph.D.

* DMEPA: Division of Medication Error Prevention and Analysis
** Marketing and Advertising (formerly DDMAC)
*** OSE /Office of Medication Error, Prevention and Risk Management / Div. of Risk Management

The CMC Review for NDA 203-255

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Based on the adequacy of the information provided for the chemistry, manufacturing and controls, CMC , this application is recommended for approval, after completion of the following:

At this time, acceptability of the pre-filled syringe consult from CDRH, microbiology, biopharmaceutics, and the OC overall acceptance recommendation are still pending. Therefore, a final quality recommendation is pending.

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

None.

II. Summary of CMC Assessments

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

(1) Drug Substance

The active ingredient, pasireotide pamoate, is a cyclic hexapeptide containing (b) (4) (b) (4) The drug substance, pasireotide, contains 7 chiral centers, but by the route of synthesis there is only one stereoisomer.

Pasireotide pamoate is white to yellowish powder, (b) (4) The drug substance must be stored (b) (4) The drug substance under the storage conditions has a retest period of (b) (4). The impurities such as related substances, residual solvents, heavy metals, possible genotoxic/carcinogenic chemicals and other contaminants are adequately controlled.

Pasireotide has been previously approved as a diaspartate salt, which has a very high water solubility, and was used in a solution for injection product (NDA 200677). In this NDA the applicant intends to use the pamoate salt, which is very poorly soluble in water and incorporated in a depot (long acting release) formulation for intramuscular injection.

(2) Drug Product – Signifor® LAR Powder for injectable suspension

Pasireotide (SOM230) powder for suspension for injection, is a long acting release dosage form for parenteral (intramuscular) administration. It is a slightly yellowish to yellowish powder in a 6mL Type 1 brownish glass vial, consisting of drug loaded poly(D,L-lactide-co-glycolide) microparticles to be suspended in an aqueous diluent or vehicle prior to injection.

The drug product has a kit presentation consisting of:

1 glass 6mL vial of (b) (4) Signifor® LAR (pasireotide) 20mg, 40mg or 60mg Powder for injectable suspension
1 glass 3mL syringe pre-filled syringe with 2mL diluent
1 plunger rod of polypropylene, white
1 vial adapter of transparent polycarbonate
1 20G, 40mm (1 ½") stainless steel safety injection needle

Composition of Signifor® LAR, VIAL

Ingredients	Theoretical amount (mg) per strength			Function	Reference to standards
	20mg	40mg	60mg		
Drug substance					
SOM230 pamoate	27.420[1]	54.840[1]	82.260[1]	Active ingredient	Novartis
Excipients					
Poly(D,L-lactide-co-glycolide) (50-60:40-50) [2]	26.290	52.580	78.870	(b) (4)	Novartis
Poly(D,L-lactide-co-glycolide) (50:50) [3]	26.290	52.580	78.870		Novartis

The drug substance, pasireotide pamoate, is uniformly dis within the microparticles (b) (4)

The drug loading of the microparticles is 250 mg pasireotide free base per g of microparticles and formulated as (b) (4) powder. All dosage strengths (20mg, 40mg and 60mg) (b) (4) differ only in the amount of powder filled in the vials

The aqueous diluent provided for suspension of the microparticles prior to administration is a clear, colorless to slightly yellow or slightly brown solution. The diluent is presented in pre-filled 3mL Type 1 glass syringes colorless glass, with two grey rubber stoppers, finger grip, hub and cap. The vehicle is made of standard pharmacopoeial excipients in common use in parenteral solutions.

Composition of Diluent for injectable suspension, Pre-filled syringe

Ingredient	Composition in mg/ml	Composition in mg/syringe	Function
Mannitol	45.0	90.0	(b) (4)
(b) (4)	7.0	14.0	
Carboxymethylcellulose sodium			
(b) (4)	q.s.	q.s.	
Poloxamer 188	2.0	4.0	
Water for injections / (b) (4)	ad 1.0ml	ad 2.0ml	

The manufacturing [redacted]

[redacted]

The applicant identifies in-process controls performed throughout the manufacturing operations. The NDA provides controls for critical steps [redacted]

The NDA provides master batch record and records for executed production batches of SOM230 bulk powder (one), SOM230 vial (one 20mg and one 60 mg), Diluent product (one).

The [redacted] batches used in clinical development have been derived from [redacted] batches, all manufactured at the manufacturing site of Novartis Pharma AG, Basel.

Novartis Pharma AG, Basel, Switzerland is the proposed commercial manufacturing site for SOM230 Bulk for injectable suspension and [redacted].

(b) (4)

The quality control of the non-compendial ingredients (b) (4) used in the formulation of SOM 230 powder for injectable suspension are provided in the NDA and also referenced to the respective DMFs.

The drug products (SOM230 powder vial and Diluent pre-filled syringe) are controlled by the set of **release and shelf life specifications** listed in the NDA and summarized as follows:

Signifor® LAR (Pasireotide/SOM230) Powder for injectable suspension, 6 mL vial includes tests required for the dosage form and formulation characteristics such as appearance, pH, BET, sterility, drug burst (first (b) (4) hours), drug release (dissolution), suspendability, uniformity of deliverable dose. The product specific tests include identification, particle size, molecular mass of polymer and assay and degradation/related products.

Diluent for injectable suspension of Signifor® LAR includes testing for appearance (container), appearance solution (color, clarity), pH, viscosity, extractable volume particulate matter, bacterial endotoxins, sterility, tightness of containers and break out and sliding force.

The product and process controls, manufacturing data together with the developmental studies, where optimization of formulation components, conditions and targeted process parameters were established, are adequate to yield consistency in the manufacture of a product that complies with pre-established specifications to support its intended use as a long acting release dosage form with the intended identity, quality, purity and strength.

The expiration times proposed for the drug products are supported by real time stability studies and are are granted as listed below:

SOM230 Bulk Powder: (b) (4) (based on 3 batches of full commercial scale meeting all specifications at all time points from (b) (4)).

SOM230 20 mg, 40mg and 60 mg Powder VIALS: 36 months at 5°C/ambient (based on bracketing 3 batches of SOM230 20 mg Powder vials and 3 batches of SOM230 80 mg Powder vials from commercial site and commercial packaging and scale meeting requirements at all time-points for 0 to 36 months at 5°C/ambient. In addition of supporting stability data for 2 batches of an intermediate 60 mg strength with specifications when tested from 0 to 24 months at 5°C/ambient).

SOM230 20 mg, 40 and 60 mg Injectable Suspension**: to be used immediately after reconstitution** (based on stability of the 2 batches of SOM230 20 mg and 2 batches of SOM230 80 mg Injectable Suspension as tested at 3 hours after reconstitution and stored at 25°C/60% Relative.Humidity, RH.

Diluent in pre-filled syringes**: 60 months** at 5°C/ambient (based on stability data for 3 batches of the diluent for injectable suspension in pre-filled syringes stored for 60 months long term, 5°C/ambient, and accelerated conditions, 25°C/60% RH.

The CMC review team performed risk assessment on the product attributes that can impact product quality and concluded the risk to the overall product quality is low. See table below for an executive summary of the risk assessment for Signifor® LAR injectable suspension.

NDA 203-255 for Drug Product Pasireotide® LAR Powder for Injectable Suspension						
From Initial Quality Assessment				Review Assessment		
	Product Attribute/ CQA	Factors that can impact the CQA	Risk Ranking*	Risk Mitigation approach in control strategy	Risk Evaluation	Life Cycle consideration/ Comments**
API	Assay	• Impurities (b) (4) • Salt content • Storage, container closure • Raw materials • Process parameters • Site	L	(b) (4)	Acceptable	(b) (4)
	(b) (4) Content	• Raw Materials • Method of Manufacture • Raw material and Process	L		Acceptable	

		parameters		(b) (4)		(b) (4)
	Stability	• Salt content (b) (4) • Storage conditions • Container Closure	L		Acceptable	
	Physical Attributes / Stability	• Method of manufacture • Salt content (b) (4) • Storage	M		Acceptable. A change in particle size of solid material is not expected during storage.	
Sterility		• Formulation • Container closure • Process parameters • Scale/equipment • Site	H		Acceptable	
Endotoxin Pyrogen		• Formulation • Container closure • Process parameters • Scale/equipment • Site	M		Acceptable	
Assay, Stability		• Formulation • Container closure • Process parameters • Scale/equipment • Site	L		Acceptable	
Physical Stability (powder)		• Formulation • Container closure • Process parameters • Scale/equipment • Site	M		Acceptable	
Uniformity of dose (fill volume)		• Formulation • Container closure • Process parameters • Scale/equipment • Site	L		Acceptable	
Osmolality		• Formulation • Container closure • Process parameters • Scale/equipment • Site	L		Acceptable	
Particulate matter		• Formulation • Container closure • Process parameters • Scale/equipment • Site	M		Acceptable	
Leachable/		• Formulation		Control specs		

Extractables	• Container closure • Process parameters • Scale/equipment • Site	L	(b) (4)	Acceptable
Reconstitution time	• Formulation • Container closure • Process parameters • Scale/equipment • Site	Release L Stability M		Acceptable
In vitro release	• Formulation • Container closure • Process parameters • Scale/equipment • Site	H		Acceptable
(b) (4)	• Formulation • Container closure • Process parameters • Scale/equipment • Site	L		Acceptable
Appearance (b) (4) powder)	• Formulation • Container closure • Process parameters • Scale/equipment • Site	Release M Stability M		Acceptable

(b) (4)

(b) (4)

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

Signifor® LAR (pasireotide) for injectable suspension , 20, 40 or 60 mg is available as a kit product and is a long acting depot formulation for intramuscular (i.m.) administration once a month for the treatment of patients with acromegaly (b) (4) It has pharmacological properties mimicking those of the natural hormone somatostatin.

Signifor® LAR powder is to be reconstituted with an aqueous diluent solution, provided as part of the kit, prior to i.m. injection. Signifor® LAR is not to be diluted or mix with other products.

The recommended dose of Signifor® LAR Injectable suspension is 40 mg (initial dose) once every 4 weeks (28 days).

Signifor® LAR drug product kit is be stored at refrigerated temperatures between 2°C–8°C (36°F–46°F) until the time of use. Then the kit needs to remain at room temperature for a minimum of 30 minutes before reconstitution, but should not exceed 24 hours at room temperature. After reconstitution, the drug suspension must be administered immediately.

The shelf life for the drug product kit stored at between 2°C–8°C (36°F–46°F) is 36 months. The product should not be frozen.

C. Basis for Approvability or Not-Approval Recommendation

The application is recommended for approval from the chemistry, manufacturing and controls point of view under section 505(b)(1) of the Act, based on the information and data presented in this submission supporting the identity, purity, strength and quality of the drug product. The information on the quality of the drug substance and drug product has been adequately provided and there are no pending CMC issues.

At this time, the quality final recommendation is pending the recommendation from CDRH for the acceptability of the pre-filled syringe used for the diluent. In addition, OC/OMPQ has not issued an overall recommendation for the inspection and cGMP status of all manufacturing and control facilities listed in the NDA. Microbiology and Biopharmaceutics reviews are pending but the two disciplines recommend approval as of the wrap-up meeting 8/11/14.

III. Administrative

A. Reviewer's Signature:
Ravi Kasliwal, Ph.D., Reviewer, ONDQA-Div. III/Branch VII
Milagros Salazar, Ph.D., Reviewer, ONDQA-Div. III/Branch VII

B. Endorsement Block:

Danae Christodoulou, Ph.D., Acting Branch Chief, ONDQA-Div. III/Branch VII

C. CC Block: entered electronically in DARRTS

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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.

/s/

MILAGROS SALAZAR DRIVER
08/11/2014
CMC recommendation: Approvable.

RAVINDRA K KASLIWAL
08/11/2014
Reviewed drug substance section, including the API risk assessment.

DANAE D CHRISTODOULOU
08/11/2014
I concur with the reviewers' conclusions and recommendations

IQA and Filing Review Cover Sheet

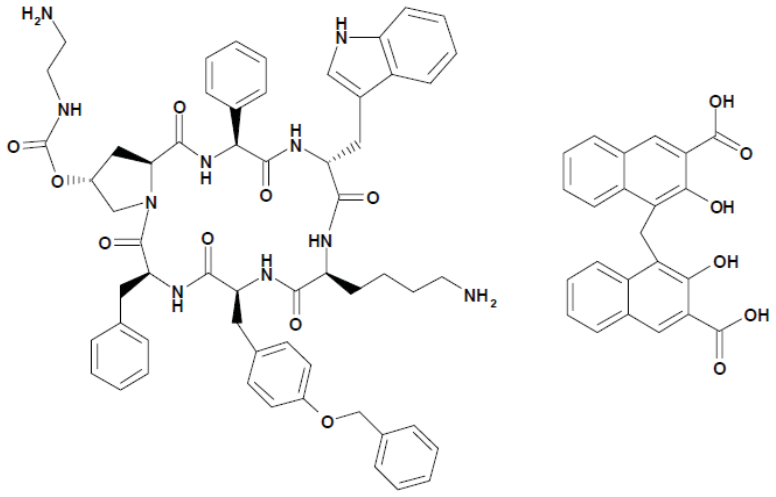
1. NEW DRUG APPLICATION NUMBER: 203255
2. DATES AND GOALS:

Letter Date: 15-NOV-2013	Submission Received Date : 15-NOV-2013
PDUFA Goal Date: 15-SEP-2014 (standard) (NDA is NOT in "The Program")	

3. PRODUCT PROPERTIES:

Trade or Proprietary Name:	Proposed: Signifor LAR
Established or Non-Proprietary Name (USAN):	Pasireotide
Dosage Form:	Powder for reconstitution in co-packaged diluent as injectable suspension
Route of Administration	Intramuscular injection
Strength/Potency	20 mg, 40 mg, and 60 mg
Rx/OTC Dispensed:	Rx

4. INDICATION: Treatment of acromegaly
5. DRUG SUBSTANCE STRUCTURAL FORMULA:



1.2.2 Molecular formula

$C_{58}H_{66}N_{10}O_9 \cdot C_{23}H_{16}O_6$

1.2.3 Relative molecular mass

1047.21 + 388.37 = 1435.58

6. NAME OF APPLICANT (as indicated on Form 356h): Novartis Pharmaceuticals

7. SUBMISSION PROPERTIES:

Review Priority (select one)	Standard
Submission Classification (Chemical Classification Code)	2
Application Type	505(b)(1)
Breakthrough Therapy	No
Responsible Organization (Clinical Division)	Division of Metabolism and Endocrinology Products CMC Lead: Suong (Su) Tran

8. CONSULTS:

CONSULT	YES	NO	COMMENTS:
Biometrics		x	
Clinical Pharmacology		x	
Establishment Evaluation Request (EER)	x		To be sent by ONDQA-PM
Pharmacology/Toxicology		x	
Methods Validation			To be determined by Primary Reviewer
Environmental Assessment			Categorical exclusion request to be reviewed by Primary Reviewer
CDRH	x		Review of syringe (b) (4) and syringe-vial adapter
Other			

Overall Filing Conclusions and Recommendations

CMC:

Is the Product Quality Section of the application fileable from a CMC perspective?
Yes

Are there potential CMC review issues to be forwarded to the Applicant with the 74-Day letter?
No

Biopharmaceutics: **(see the attached Biopharmaceutics filing review at the end)**

Is the Product Quality Section of the application fileable from a Biopharmaceutics perspective?
Yes

Are there potential Biopharmaceutics review issues to be forwarded to the Applicant with

the 74-Day letter? Yes
Biopharmaceutics Comments for 74-Day Letter: • Your proposed dissolution acceptance criteria are not adequate. (b) (4) The range of the acceptance criteria at any dissolution time point should be ± 10% deviation from the mean dissolution profile obtained from the clinical/bioavailability lots. Modify the proposed dissolution acceptance criteria according to this principle. Provide the dissolution data of the available batches, including the dissolution values for individual unit, the mean, the standard deviation (or CV%) and the plot. • It is stated that the purposes to perform IVIVC investigation (b) (4) . However, the information for IVIVC to (b) (4) was not submitted. Provide detailed IVIVC report, including the datasets for the in vitro, in vivo and the correlations in SAS transport format. Submit the (b) (4) • (b) (4)

Microbiology:

Is the Product Quality Section of the application fileable from a Microbiology perspective?	
Yes	See Microbiology Filing Review in DARRTS for details and for any potential Microbiology review issues.
Microbiology Filing Issues: See Microbiology Filing Review for details and for any potential Microbiology review issues.	

ONDQA Initial Quality Assessment (IQA) and Filing Review
For new NDAs

Summary of Initial Quality Assessment

Does the submission contain any of the following elements?			
Nanotechnology	QbD Elements	PET	Other, please explain

Is a team review recommended?	Team review: CMC drug substance and product, biopharmaceutics, microbiology

Summary of Critical Issues and Complexities

Previous quality-related meeting between FDA and the sponsor:

From FDA's letter dated 06-DEC-2007:

1. The stability protocol is acceptable with a premise that the packaging process of [redacted] (b) (4)
2. Revise the stability testing specifications listed in Table 5-1 to include a test for in vitro drug release and a test for pH on stability. Testing for in vitro drug release should also be part of product release specifications.
3. Revise the protocol for stability testing of the suspension (Section 7.2.3) to provide for semi-annual testing and to include two batches each for 20-mg and 80-mg strengths. Also include particle size testing of the suspension.
4. Revise your statistical evaluation plan to indicate that all stability-indicating quality attributes will be analyzed and adequate justification will be provided for pooling of the batch data, if pooling is done.
5. [redacted] (b) (4)

From FDA's letter dated 28-FEB-2008:

1. In testing for suspension stability (Section 7.2.3), you seem to have inadvertently omitted drug burst testing (refer to Test group 3 in Table 5-1), which was in the original protocol submitted on November 7, 2007. Please correct this omission and include this test in the stability study for the suspension.

Drug Substance. (see the copied specifications at the end of this review)

Reference is made by the applicant to the approved NDA 200677 for pasireotide diaspartate. The two NDAs have the same applicant, [redacted] The drug substance of this new NDA 203255 is the pamoate salt of pasireotide (USAN), a small synthetic cyclohexapeptide. The compound is amorphous and hygroscopic. The [redacted] The manufacture is [redacted]

The drug substance specification includes standard attributes for a small synthetic peptide (copied at the end of this review) and it is based on the approved drug substance specification for the diaspartate salt of NDA 200677. Each specification has a salt-specific test and acceptance criteria for the content of the counter-ion. Chirality is controlled by specific optical rotation. The proposed limits on impurities comply with the Eur. Ph.'s reporting, identification, and qualification thresholds for synthetic peptides, which agree with CDER's current thinking and consistency with other peptide applications. As noted earlier in the review, this drug substance is [redacted] The particle size distribution and specific surface area are critical attributes for the drug product's extended release performance, and the reviewer will evaluate the associated test methods and acceptance criteria based on all available data from the clinical batches.

The primary container closure system is a [redacted] The drug substance is stored at the [redacted]. Primary stability data include three primary batches, 831046 C0002 (used in one clinical batch), 831046 C0003, and 831046 C0004, produced by the current manufacturing process, at the commercial sites (including the commercial [redacted] site), and packaged in the commercial container closure system, with [redacted]. The NDA also includes photostability and stress stability data, and supportive stability data from batches manufactured at pilot sites. The reviewer should note the strange terminology used to designate the stability batches: the "commitment" data should be evaluated as primary, and the "registration" data should be evaluated as supportive.

Drug Product

SIGNIFOR LAR is available in a vial containing the sterile drug product powder, which, when mixed with sterile diluent, becomes a suspension given as an intramuscular injection once every 4 weeks.

Each vial contains:

	20 mg	40 mg	60 mg
Pasireotide pamoate	27.420 mg*	54.840 mg*	82.260 mg*
Poly(D,L-lactide-co-glycolide) [50-60:40-50]	26.290 mg	52.580 mg	78.870 mg
Poly(D,L-lactide-co-glycolide) [50:50]	26.290 mg	52.580 mg	78.870 mg
*Corresponds to 20 mg, 40 mg and 60 mg of pasireotide base respectively. Note: The overfill which permits the delivery of the labeled dose from the vial is not included.			

Each diluent pre-filled syringe contains:

Mannitol	90.0 mg
Carboxymethylcellulose sodium	14.0 mg
Poloxamer 188	4.0 mg
Water for injections	add to 2.0 ml
Note: The overfill which permits the delivery of the labeled volume of the diluent from the syringe is not included.	

The composition of the drug product and co-packaged diluent is copied at the end of this review. There is no novel excipient. There are two non-compendial excipients in the drug product: poly(D,L-lactide-co-glycolide) (50:50) liner copolymer and poly(D,L-lactide-co-glycolide) (50-60:40-50) star polymer. These excipients are common in extended release products, with the (b) (4) applicant's approved NDA 21008 Sandostatin LAR, and reference is also made to DMF 6895 for the CMC information on this material. (b) (4) reference is made to DMF (b) (4). The reviewer will evaluate the specifications of these noncompendial excipients with the focus on impurities and attributes that are important to the performance of the product, such as the molecular weight distribution and the mole ratio of glycolide and D,L-lactide.

The drug product has an overfill of (b) (4)% per vial for all three dosage strengths. The applicant states that the overfill is necessary to compensate for losses in the vial, syringe, vial adapter, and needle, which will be confirmed by the reviewer.

Comparability of the product used in the clinical studies, stability studies, and commercial product: Formulation 2b was used in all clinical studies and will be used for the commercial product. Clinical and stability batches were manufactured at pilot-scale or higher, at the commercial sites (b) (4)

The drug product manufacture consists of: (b) (4) . Stability data are provide in support of the

storage of the product bulk powder (prior to [redacted] (b) (4)) for [redacted] (b) (4).

The drug product specification includes attributes standard for this type of dosage form (powder for reconstitution as suspension). The ONDQA Biopharm review will cover drug burst, drug release, and the associated IVIVC study report. The Microbiology review will cover container closure integrity, bacterial endotoxins, and sterility. The dosage-form-specific attributes to be evaluated by the CMC reviewer will include particle size distribution, molecular mass of the polymer, suspendability, and uniformity of the deliverable dose, in addition to the attributes common to all drug products. Limits on degradants are within the applicable ICH thresholds for identification and qualification.

The drug product is packaged in a 6-mL Type I glass vial with rubber stopper, each with a referenced DMF. The applicant indicates that the stability batches were packaged in the commercial packaging system. A study report on potential leachables is provided in the NDA. The reviewer will check the information in the DMFs for applicable compendial testing of these materials.

A sufficient amount of stability data are submitted for the NDA filing: all primary stability batches are within the commercial vial batch size range, produced at the commercial site by the commercial process, and packaged in the commercial container closure system. [redacted] (b) (4) the stability report in the NDA includes this 80 mg strength and the 20 mg strength (three batches each strength) to bracket the intermediate 40 mg and 60 mg, since all strengths differ only by the fill amount per vial. For these six batches, 36-month data are provided for the long-term storage at 5 °C, 12-month at 25 °C/60% RH and 30 °C/75% RH, and 6-month at 40 °C/75% RH. In addition, two stability batches of the 60 mg strength have up to 24-month at 5 °C as bridging data. Other stability reports include photostability and freeze/thaw cycle. There is no in-use stability data because the product is labeled for immediate use when reconstituted.

FILING REVIEW CHECKLIST

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*				
*	**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.**			
	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? **This question is not applicable for synthesized API.**			n/a

	Parameter	**Yes**	**No**	**Comment**
7.	Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	x		
8.	Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	x		

	Parameter	Yes	No	Comment
9.	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: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	x		
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	x		

C. ENVIRONMENTAL ASSESMENT				
	Parameter	**Yes**	**No**	**Comment**
11.	Has an environmental assessment or claim of categorical exclusion been provided?	x		

D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	**Yes**	**No**	**Comment**
12.	Does the section contain a description of the DS manufacturing process?	x		
13.	Does the section contain identification and controls of critical steps and intermediates of the DS	x		
14.	Does the section contain information regarding the characterization of the DS?	x		
15.	Does the section contain controls for the DS?	x		
16.	Has stability data and analysis been provided for the drug substance?	x		
17.	Does the application contain Quality by Design (QbD) information regarding the DS?		x	
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		x	

E. DRUG PRODUCT (DP)				
	Parameter	**Yes**	**No**	**Comment**
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	x		
20.	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		
21.	Is there a batch production record and a proposed master batch record?	x		
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	x		
23.	Have any biowaivers been requested?		x	
24.	Does the section contain description of to-be-marketed container/closure system and presentations?	x		
25.	Does the section contain controls of the final drug product?	x		
26.	Has stability data and analysis been provided to support the requested expiration date?	x		
27.	Does the application contain Quality by Design (QbD) information regarding the DP?		x	
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		x	

F. METHODS VALIDATION (MV)				
	Parameter	**Yes**	**No**	**Comment**
29.	Is there a methods validation package?	x		

G. MICROBIOLOGY				
	Parameter	**Yes**	**No**	**Comment**

30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product	x		

H. MASTER FILES (DMF/MAF)				
	Parameter	**Yes**	**No**	**Comment**
31.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	x		

DMF #	TYPE	HOLDER	ITEM REFERENCED	LOA DATE	COMMENTS
6895	IV	Novartis	Poly(D,L-lactide-co-glycolide) (50-60:40-50)	23-SEP-2013	
(b) (4)	IV	(b) (4)		15-DEC-2011	
	III			04-DEC-2012	
	III			20-NOV-2012	
	III			06-AUG-2013	
	III			06-AUG-2013	

I. LABELING				
	Parameter	**Yes**	**No**	**Comment**
32.	Has the draft package insert been provided?	x		
33.	Have the immediate container and carton labels been provided?	x		

See appended electronic signature page}

Appendix 1. Composition of Drug Product

Table 1-2 Declared content of one vial of SOM230 20mg, 40mg and 60mg Powder for suspension for injection

Ingredients	Theoretical amount (mg) per strength			Function	Reference to standards
	20mg	40mg	60mg		
Drug substance					
SOM230 pamoate	27.420[1]	54.840[1]	82.260[1]	Active ingredient	Novartis
Excipients					
Poly(D,L-lactide-co-glycolide) (50-60:40-50)[2]	26.290	52.580	78.870	(b) (4)	Novartis
Poly(D,L-lactide-co-glycolide) (50:50)[3]	26.290	52.580	78.870		Novartis
	-	-	-		
(b) (4)	--	--	--		Ph. Eur./ NF
	--	--	--		Ph. Eur./ NF
	--	--	--		Ph. Eur./ NF
	--	--	--		Ph. Eur./ NF
	--	--	--		Ph. Eur./ USP
	--	--	--		Ph. Eur./ NF
	q.s.	q.s.	q.s.		Ph. Eur./ NF
Theoretical fill weight[5]	**80.00**[5]	**160.00**[5]	**240.00**[5]		

[1] Corresponding to 20mg, 40mg and 60mg of SOM230 base (active moiety), respectively. The salt/base ratio is (b) (4)

(b) (4)

[5] Note: Each vial contains a (b) (4) overfill (20mg, 40mg, 60mg strengths), which is not included in the table.

(b) (4)

Table 1-1 Declared content of the syringe of vehicle, 2ml solution[1]

Ingredient	Composition in mg/ml	Composition in mg/syringe	Function	Reference to standards
Mannitol	45.0	90.0	(b) (4)	Ph. Eur., USP
(b) (4) Carboxymethylcellulose sodium	7.0	14.0		Ph. Eur., USP
(b) (4)	q.s.	q.s.		Ph. Eur., USP
Poloxamer 188	2.0	4.0		Ph. Eur., NF
Water for injections / (b) (4)	ad 1.0ml	ad 2.0ml		Ph. Eur., USP

[1] The (b) (4) overfill which permits the delivery of the labeled volume of the vehicle from the syringe is not included in this table.

Appendix 2. Drug Product Specification

Table 5-1 Specifications for SOM230 20mg, 40mg and 60mg Powder for suspension for injection

Title of test, Principle	Requirements	Test performed for: Batch release	Test performed for: Stability studies
Appearance of the vial by visual inspection	20mg: 6 ml brownish glass vial with grey closure and grey flip-off cap 40mg: 6 ml brownish glass vial with grey closure and red flip-off cap 60mg: 6 ml brownish glass vial with grey closure and orange flip-off cap	+	–
Appearance of the constituted suspension by visual inspection	(b) (4) slightly yellowish to yellowish and homogeneous suspension	+	+
Appearance of the contents by visual inspection	Slightly yellowish to yellowish powder	+	+
Identification by TLC			
Pasireotide	Corresponds to the reference	+	–
Identification by reverse HPLC			
Pasireotide	Corresponds to the reference	+	–
pH value of the constituted suspension by potentiometry according to Ph. Eur. 2.2.3 or USP <791>	(b) (4)	+	–
Particle size by laser light diffraction (suspension cell) by Fraunhofer light diffraction	X90 ≤ (b) (4) µm X50 ≤ µm X10 ≥ µm	+	+
Molecular mass of the polymer by GPC	(b) (4) Da	+	+
Suspendability by visual inspection	The powder must be completely suspended in vehicle	+	+
	Withdrawal of suspension must be possible within one movement	+	+
	Injection of suspension must be possible within one movement	+	+
Drug burst, based on the declared content of pasireotide, by reverse HPLC After 24 h	Level 1: not more than (b) (4) % (for average and individual values) Level 2: not more than (b) (4) % (for average value) and not more than 2 individual values are > (b) (4) % and no individual value > (b) (4) %	+	+

Title of test, Principle	Requirements	Test performed for	
		Batch release	Stability studies
Tightness of container by dye intrusion (in a dye bath by applying vacuum and overpressure)	No container out of 40 containers tested shows visible blue discoloration of the content	–	+2)
Drug release, based on the content of free peptide, by reverse HPLC			
After 1 h	Not more than (b) (4)%	+	+
After 24 h	(b) (4)%	+	+
After 48 h	%	+	+
After 96 h	Not less than (b) (4) %	+	+
After 144 h	Not less than %	+	+
Uniformity of deliverable dose, based on the declared content of pasireotide, by reverse HPLC			
Single deliverable dose	(b) (4)%	+	–
Mean deliverable dose	%	+	–
Srel (n = 10)	Not more than (b) (4)%	+	–
(b) (4)	Not more than (b) (4) % (release)	+	–
	Not more than % (shelf-life)	–	+
Degradation products, based on the declared content of pasireotide, by reverse HPLC			
Specified (b) (4)	Not more than (b) (4) % (release)	+	–
	Not more than % shelf-life)	–	+
(b) (4)	Not more than % (release)	+	–
	Not more than % shelf-life)	–	+
	Not more than %	+	+
	Not more than %	+	+
Any unspecified degradation product	Not more than %	+	+
Total degradation products			
	Not more than (b) (4) % (release)	+	–
	Not more than % (shelf-life)	–	+
Bacterial endotoxins test (BET) by kinetic turbidimetric method in accordance with USP, JP and Ph. Eur., method C	Less than (b) (4) EU / mg powder for suspension for injection	+	+1)

Title of test, Principle	Requirements	Test performed for	
		Batch release	Stability studies
Sterility (b) (4) by (b) (4) in accordance with Ph. Eur./USP	No viable micro-organisms detectable	+	+2)
Sterility (b) (4) by (b) (4) in accordance with Ph. Eur./USP	No viable micro-organisms detectable	+	+2)
Uniformity of dosage units by content uniformity by reverse HPLC			
Pasireotide	Meets the requirements of Ph. Eur., USP and JP	+	–
Assay, based on the content of free peptide, by reverse HPLC			
Pasireotide	(b) (4) % (release)	+	–
	% (shelf-life)	–	+

1) Tested at the end of shelf-life 2) Tested annually

Appendix 3. Drug Substance Specification

Table 4-1 Specifications for Pasireotide pamoate

Title of Test, Principle	Requirements	Tests required		
		Batch Release	Re-test	Stability
Properties				
Appearance by visual examination	White to yellowish powder	+	+	+
Particle size by laser light diffraction	X_{90} (b) (4) µm X_{50} (b) (4) µm X_{10} (b) (4) µm	+	+	+1)
Specific Surface Area	Specific surface area (b) (4) m^2/g	+	+	+1)
Identification				
Identity by IR – Spectroscopy (b) (4)	Corresponds to reference	+	+	+
Identity by HPLC (b) (4)	Corresponds to reference	+	+	+
Purity				
Residual Solvents	Sum: (b) (4) % (b) (4)	+	-	-
Water (Karl-Fischer)	≤ (b) (4) %	+	+	+
Sulphated ash	≤ (b) (4) %	+	-	-
Specific optical rotation	(b) (4) degrees	+	+	+
Heavy metals (DCP/ICP-OES)	Sum (b) (4) ≤ (b) (4) ppm (b) (4) each (b) (4) each	+	-	-
Impurities by ion chromatography	(b) (4) ≤ (b) (4) %	+	-	-
Impurities by ion chromatography	(b) (4) ppm	+	-	-

Title of Test, Principle	Requirements	Tests required		
		Batch Release	Re-test	Stability
Clarity of the Solution	Clear	+	+	+
Colour of the solution	Not more intensely coloured than (b) (4)	+	+	+
Related Substances by HPLC (RP)	Sum (b) (4) % (b) (4) Unspecified sum ≤ (b) (4) % Unspecified each ≤ (b) (4) %	+	+	+
Assay				
(b) (4) analysis	Proportions of (b) (4) (b) (4)	+	-	-
Assay of salt forming agent	(Calculated as pamoic acid on an anhydrous basis)	+	-	-
Assay by HPLC (RP)	(b) (4) (Calculated as m/m% free peptide/free peptide on anhydrous basis)	+	+	+
Microbiology				
Microbial enumeration tests (MET)	Total aerobic microbial count: ≤ (b) (4) cfu/g Total yeasts and moulds count: ≤ (b) (4) cfu/g	+	1)	2)
Bacterial endotoxins tests (BET) (Turbidimetric technique)	< (b) (4) EU(IU)/mg substance tested	+	1)	2)

+ = Mandatory
- = Not performed
1) = Optional test
2) = Selected stability timepoints only

ONDQA - BIOPHARMACEUTICS
Initial Product Quality Assessment and Filing Review

NDA Number	203-255
Submission Date	November 15, 2013
Product name, generic name of the active	Signifor LAR (pasireotide pamoate) Injection
Dosage form and strength	Powder for Injection, 20, 40, and 60 mg
Applicant	Novartis
Clinical Division	Division of Metabolism and Endocrine Drug Products
Type of Submission	Original NDA 505(b)(1)
Biopharmaceutics Primary Reviewer	John Duan, Ph.D.
Biopharmaceutics Team Leader	Tapash Ghosh, Ph.D.

BIOPHARMACEUTICS INITIAL ASSESSMENT

Biopharmaceutics Summary

NDA 203-255 Pasireotide Powder for suspension for injection submitted on 11/15/2013 is proposed for the indication of the treatment of acromegaly. It is a long acting release dosage form for intramuscular administration.

The following dissolution method and acceptance criterion were proposed, including (b) (4) :

(b) (4) :

Apparatus:	USP II (paddle) Add about 1 g of glass beads (1 mm diameter, as used with USP apparatus 4) to each vessel
Rotation Speed:	50 ± 2 rpm
Test medium	pH 2 with cetyltrimethylammonium bromide CTAB (0.2%)
Volume:	500 ml
Temperature:	45 ± 0.5°C
Acceptance criterion:	(b) (4)

(b) (4) , based on t

Container:	(b) (4)
Rotation Speed:	
Test medium:	

ONDQA - BIOPHARMACEUTICS
Initial Product Quality Assessment and Filing Review

Volume: (b) (4)
Temperature:

Acceptance criterion: after (b) (4) h:
Level 1: not more than (b) (4) % (for average and individual values)
Level 2: not more than % (for average value) and not more than 2 individual values are > % and no individual value > (b) (4) %

These acceptance criteria are not fully justified, especially for the (b) (4). The range is as high as (b) (4) % at (b) (4) hours. The justifications with dissolution data at release and for stability should be provided.

An effort (b) (4) in vitro/in vivo correlation (IVIVC) for SOM230 Powder for suspension for injection was made by the Applicant. (b) (4)

(b) (4)

(b) (4) However, details of the IVIVC are not provided. Although there is no intention to apply for a biowaiver at current time, it may help to justify the proposed dissolution acceptance criteria. Therefore, the detailed IVIVC analyses should be provided.

(b) (4)

Figure: Drug product burst in function of drug substance PSD in clinical batches (drug substance X10, X50 and X90 in different colors)

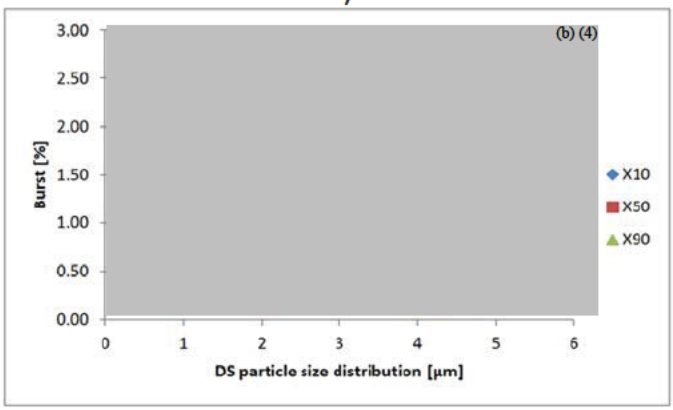
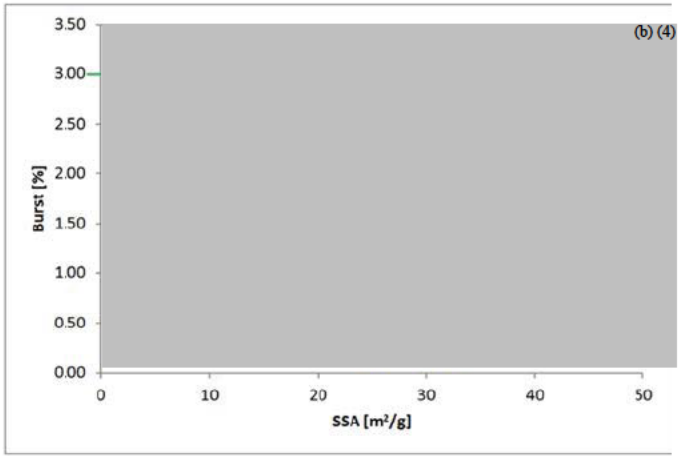


Figure: Drug product burst in function of drug substance SSA in clinical supply batches



Critical Review Issues

Critical review issues identified during filing are as follows.

- IVIVC study and its applicability.
- Suitability of the proposed dissolution method and acceptance criterion. All dissolution data available should be provided.
- Justification of the proposed range for particle size distribution (PSD) and specific surface area (SSA).

Comments for Day 74-Letter

The following comments should be conveyed to the Applicant:

- Your proposed dissolution acceptance criteria are not adequate. The so-called (b) (4) The range of the acceptance criteria at any dissolution time point should be ± 10% deviation from the mean dissolution profile obtained from the clinical/bioavailability lots. Modify the proposed dissolution acceptance criteria according to this principle. Provide the dissolution data of the available batches, including

the dissolution values for individual unit, the mean, the standard deviation (or CV%) and the plot.

- It is stated that the purposes to perform IVIVC investigation (b) (4) . However, the information for IVIVC to (b) (4) was not submitted. Provide detailed IVIVC report, including the datasets for the in vitro, in vivo and the correlations in SAS transport format. Submit the justifications (b) (4)
- (b) (4)

ONDQA - BIOPHARMACEUTICS
Initial Product Quality Assessment and Filing Review

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).

ONDQA-BIOPHARMACEUTICS **A. INITIAL** OVERVIEW OF THE NDA APPLICATION FOR FILING				
	PARAMETER	**YES**	**NO**	**COMMENT**
1.	Does the application contain dissolution data?	X		3.2.P.2.2, 3.2.P.5.3
2.	Is the dissolution test part of the DP specifications?	X		3.2.P.5.1
3.	Does the application contain the dissolution method development report?	X		3.2.P.2.2
4.	Is there a validation package for the analytical method and dissolution methodology?	X		3.2.P.5.3
5.	Does the application include a biowaiver request?		X	
6.	Does the application include an IVIVC model?	X		The model details have not been provided.
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	
9.	Is there any in *vivo* BA or BE information in the submission?	X		
10.	Is there a modified-release claim? If yes, address the following: a.) Is there information submitted to support the claim in accordance with 320.25(f)? b.) Is there information on the potential for alcohol-induced dose dumping?	X X	 X	 It is an injection

ONDQA - BIOPHARMACEUTICS
Initial Product Quality Assessment and Filing Review

B. FILING CONCLUSION				
	Parameter	**Yes**	**No**	**Comment**
11.	**IS THE BIOPHARMACEUTICS SECTIONS OF THE APPLICATION FILEABLE?**	X		
12.	If the NDA is not fileable from the product quality-biopharmaceutics perspective, state the reasons and provide **filing** comments to be sent to the Applicant.			Not applicable.
13.	Are there any **potential review** issues to be forwarded to the Applicant for the 74-day letter?	X		Please convey the Applicant in the 74-Day letter the comments listed in pages 3-4 of this filing review.

Administrative Block: *{See appended electronic signature page}*

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SUONG T TRAN
01/06/2014

TAPASH K GHOSH
01/06/2014

DANAE D CHRISTODOULOU
01/06/2014