

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

203441Orig1s000

CHEMISTRY REVIEW(S)

MEMORANDUM

Date: December 20, 2012

To: NDA 203441

From: Terrance Ocheltree, Ph.D., R.Ph.
Director
Division of New Drug Quality Assessment II
ONDQA

Subject: Tertiary review and Concurrence of ONDQA recommendation for NDA 203441, Gattex® teduglutide, for injection, 5 mg per vial (10 mg/mL after reconstituted). Teduglutide is a new molecular entity (NME).

Teduglutide in NDA 203441 is proposed for the treatment of adult patients with short bowel syndrome (SBS) and improvement of intestinal absorption of fluid and nutrients.

I have assessed the ONDQA reviews of NDA 203441 by Yichun Sun, Ph.D. and concur with the ONDQA recommendation of Approval. The initial ONDQA CMC review was entered into DARRTS on July 27, 2012, with a recommendation for a Complete Response due to an absence of a recommendation from the Office of Compliance on the manufacturing and testing sites, pending labeling issues and pending results for the methods validation consult. A methods validation consult was sent to the Division of Pharmaceutical Analysis (DPA), Office of Testing and Research. According to the Method Validation Report Summary entered into DARRTS by Michael Trehy, Ph.D. on November 21, 2012 the two HPLC methods were determined to be acceptable for quality control and regulatory purposes by Kallol Biswas, Ph.D. An ONDQA Biopharmaceutics review was not preformed due to the proposed dosage form. On December 14, 2012 the Office of Compliance entered an Overall Recommendation of "Acceptable" into EES after the applicant withdrew the (b) (4) drug substance manufacturing site from the application. A second CMC review was entered into DARRTS on December 14, 2012 updating the status of the recommendation from the Office of Compliance, resolution of labeling issues and acceptability of the methods.

Teduglutide for injection is supplied in a sterile, single-use 3-mL, USP Type I glass vial containing 5 mg of teduglutide as a white lyophilized powder in a 30-vial kit and a single-vial kit. The lyophilized powder is intended to be reconstituted with 0.5 mL of sterile Water for Injection (sWFI), USP, immediately before administration by subcutaneous injection. Each vial of teduglutide also contains 3.88 mg L-histidine, 15 mg mannitol, 0.644 mg monobasic sodium phosphate monohydrate, and 3.434 mg dibasic sodium phosphate heptahydrate. The sWFI is provided in a prefilled syringe. The product should be used within 3 hrs after reconstitution.

The drug substance, teduglutide is manufactured by (b) (4). A (b) (4) month retest date is recommended when the drug substance is stored at $-20^{\circ} \pm 5^{\circ}\text{C}$ or below.

The drug product, teduglutide for injection, is manufactured by Hospira, Inc, McPherson, KS. The Sterile Water for Injection (sWFI) prefilled syringes are manufactured by (b) (4)

The teduglutide and sWFI are co-packaged at (b) (4)

A 36 months expiration dating period for the product stored refrigerated at 2°C to 8°C (36°F and 46°F), prior to dispensing. Once dispensed to the patient the product may be stored at room temperature up to 25°C (77°F) (b) (4).

The drug product is packaged in two configurations, a single-vial kit and a 30-vial kit. The single vial kit comes as one package (single box) with the non-drug components included in the box. The 30-vial kit comes as two packages, one for the drug product vials and another for the non-drug components. The box containing the non-drug components is stored at room temperature. The box containing the drug product vials must be stored refrigerated until dispensed. The packaging configuration then requires the dispensing pharmacist to remove the drug vials from their outer container, add the drug vials to the larger box containing the non-drug components, add a use by date to the outer carton and then dispense the whole kit which will be stored at room temperature by the patient (b) (4)

The kits are as described below:

The product to be dispensed either a single-vial kit or a 30-vial kit. The single-vial kit is pre-assembled and ready to be used. It contains:

One-vial kit (NDC 68875-0101-4):

- One single-use vial of drug
- One disposable prefilled syringe containing 0.5 mL Sterile Water for Injection USP for reconstitution, with a separate needle (22G x 1½ in) to attach to the syringe
- One sterile disposable 1-mL syringe with needle (26G x 5/8 in) for dosing
- Four alcohol swabs

The 30-vial kit is to be assembled by a pharmacist with the following two cartons:

Carton of Drug (NDC 68875-0101-2):

- Thirty single-use vials of drug

Carton of Ancillary Supplies (NDC 68875-0101-3):

- Thirty disposable prefilled syringes containing 0.5 mL Sterile Water for Injection Thirty separate needles (22G x 1½ in) to attach to the syringes for reconstitution
- Thirty sterile disposable 1-mL syringes with needle (26G x 5/8 in)
- Sixty alcohol swabs

Reconstitution of the lyophilized drug with 0.5 mL of preservative-free Sterile Water for Injection, provided in a prefilled syringe, is required prior to subcutaneous administration of the drug. Reconstituted GATTEX is a sterile, clear, colorless to light straw-colored 10 mg/mL solution, which is essentially free from particulates. Upon reconstitution with the 0.5 mL Sterile Water for Injection provided in the prefilled syringe, a maximum of 0.38 mL of the reconstituted solution which contains 3.8 mg of teduglutide can be withdrawn from the vial for dosing.

The container carton labels for the two packaging configurations are not well designed. Valuable information is contained on the sides and bottom panels instead of the front (top) panel. Messages to the pharmacist related to storage and dispensing are not readily visible. Nor are instructions completely clear. For example, there is a place on the front label for the pharmacist to apply a (b) (4). However, these issues do not affect the approval decision for this application.

During the writing of this review it was also noted that the drug vials contained incorrect storage conditions. (b) (4)

(b) (4) This was initially justified by stating that having multiple storage conditions on the label may confuse the patient and that the patient was the person most likely to see the individual vials (due to them being packaged in a kit). After a discussion with relevant members of the review team, it was determined that the vials should be labeled according to the requirements for long term stability. The Applicant was contacted on December 19, 2012 to inform them of this necessary change and also to request that the front panels contain a storage condition statement directed to the patient. The vial label was updated to state "Prior to dispensing, store at 2°C to 8°C (36°F to 46°F). Do not freeze" on December 20, 2012. The following statement will be added to the outer cartons front panel: "Attention patients: Store at room temperature up to 25°C (77°F). Do not freeze." Section 16 HOW SUPPLIED/STORAGE AND HANDLING of the package insert will be revised to be consistent with the outer cartons.

I concur with the determination that the information as provided in the NDA is adequate to assure the identity, strength, purity, and quality of the drug product and support the recommended drug product shelf life as described above for the proposed commercial product when it is stored at controlled room temperature.

There is one ONDQA related Post Marketing Commitment (PMC). The PMC calls for: "Elemental Impurities specifications will be expanded to include limits and testing for all metals, as recommended in USP <232>." This is to be implemented by the Applicant by March 31, 2013.

I concur with the determination that the information as provided in the NDA is adequate to assure the identity, strength, purity, and quality of the drug product and support the recommended drug product shelf life as described above for the proposed commercial product when it is stored at controlled room temperature.

The secondary review of the CMC reviews was performed by Moo-Jhong Rhee, Ph.D.

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/s/

TERRANCE W OCHEL TREE
12/20/2012

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: December 14, 2012

From: Yichun Sun, Ph.D.
Review Chemist, ONDQA
Division of New Drug Quality Assessment II
ONDQA

Through: Moo-Jhong Rhee, Ph.D.
Chief, Branch IV
Division of New Drug Quality Assessment II
ONDQA

To: CMC Review #1 of NDA 203441

Subject: Final Recommendation

At the time when the CMC review #1 was written, there were three pending issues listed as follows:

- 1) The overall acceptable recommendation of **Establishment Evaluation** was still pending.
- 2) There were issues on the **Label/Labeling** that needed to be resolved.
- 3) Report of **Method Validation** from the Division of Pharmaceutical Analysis, Office of Testing and Research, CDER was still pending.

* Safety concern of (b) (4) (**Elemental Impurities**) was raised by the review team after the CMC review #1 was written.

Establishment Evaluation

After inspection, one of two the drug substance sites, (b) (4) is not acceptable due to GMP violations. A T-con was held with the NDA applicant on December 12, 2012 to discuss the options for the applicant to pursue. As there is another drug substance manufacture site (b) (4) for the NDA, the applicant decided to withdraw the unacceptable drug substance manufacture site during the T-con. An amendment to withdraw (b) (4) site was received on December 13, 2012.

On December 14, 2012, the Office of Compliance gave an overall **“Acceptable”** recommendation for all the facilities involved in the manufacture and test of the drug substance and drug product (**Attachment - 1**).

Evaluation of Label/Labeling

On November 9, 2012, the NDA applicant submitted an amendment providing the finalized mock up container and carton labels. Additionally, the applicant also agreed to all the CMC changes made to the package insert. All the labels/labeling issues are now **satisfactorily resolved**. The CMC sections of the final package insert, and mock up container and carton labels are attached (**Attachment - 2**).

HPLC Method Validation

On November 14, 2012, the report of method validation for the two HPLC methods used for quantitation of impurities in both drug substance and drug product in NDA 203441 was received. The two HPLC methods were **satisfactorily validated** by Dr. Kallol Biswas from the Division of Pharmaceutical Analysis, Office of Testing and Research, CDER (**Attachment - 3**).

*** Elemental Impurities**

The issue of safety concern of elemental impurities in the drug substance has been **satisfactorily resolved (Attachment - 4)**.

Recommendation:

All the previous pending issues are now satisfactorily resolved, and therefore, from the ONDQA’s perspective, this NDA is recommended for **APPROVAL**.

Attachment - 1 (Summary Report of Establishment Evaluation)

FDA CDER EES ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Application:	NDA 203441/000	Sponsor:	NPS PHARMS INC
Org. Code:	180		550 HILLS DR 3RD FL
Priority:	1		BEDMINSTER, NJ 07921
Stamp Date:	30-NOV-2011	Brand Name:	Gatex (teduglutide)
PDUFA Date:	30-DEC-2012	Estab. Name:	
Action Goal:		Generic Name:	
District Goal:	31-OCT-2012	Product Number; Dosage Form; Ingredient; Strengths	
			001: POWDER, FOR INJECTION SOLUTION, LYOPHILIZED; TEDUGLUTIDE; 10MG
FDA Contacts:	C. TRAN-ZWANETZ	Project Manager	(HFD-800) 3017963877
	Y. SUN	Review Chemist	3017961388
	M. KOWBLANSKY	Team Leader	3017961390

Overall Recommendation:	ACCEPTABLE	on 14-DEC-2012	by D. SMITH	(HFD-323)	3017965321
	PENDING	on 04-DEC-2012	by EES_PROD		
	PENDING	on 20-SEP-2012	by EES_PROD		
	PENDING	on 02-MAR-2012	by EES_PROD		
	WITHHOLD	on 02-MAR-2012	by EES_PROD		
	PENDING	on 02-MAR-2012	by EES_PROD		
	WITHHOLD	on 25-JAN-2012	by EES_PROD		
	PENDING	on 23-JAN-2012	by EES_PROD		
	PENDING	on 23-JAN-2012	by EES_PROD		
	PENDING	on 23-JAN-2012	by EES_PROD		

Establishment:	CFN:	FEI:	(b) (4)
			(b) (4)
DMF No:		AADA:	
Responsibilities:	DRUG SUBSTANCE MANUFACTURER		
			(b) (4)
Profile:		OAI Status:	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	20-JUL-2012		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		

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

Establishment:	CFN: 1925262	FEI: 1925262	
	HOSPIRA WORLDWIDE, INC		
DMF No:	MCPHERSON, , UNITED STATES 674609301		AADA:
Responsibilities:	FINISHED DOSAGE MANUFACTURER (b) (4)		
Profile:	(b) (4)		OAI Status: NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	23-MAR-2012		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		

Establishment:	CFN: (b) (4)	FEI: (b) (4)	
	(b) (4)		
DMF No:	(b) (4)		AADA:
Responsibilities:	(b) (4)		
Profile:	(b) (4)		OAI Status: NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	21-MAY-2012		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		

Establishment:	CFN: (b) (4)	FEI: (b) (4)	
	(b) (4)		
DMF No:	(b) (4)		AADA:
Responsibilities:	(b) (4)		
Profile:	(b) (4)		OAI Status: NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	30-JAN-2012		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		

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

Establishment:	CFN:	FEI:	(b) (4)
		(b) (4)	
DMF No:		AADA:	
Responsibilities:			
Profile:		OAI Status:	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	24-SEP-2012		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		
Profile:	(b) (4)	OAI Status:	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	24-SEP-2012		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		

Establishment:	CFN:	FEI:	(b) (4)
		(b) (4)	
DMF No:		AADA:	
Responsibilities:			
Profile:		OAI Status:	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	04-DEC-2012		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		

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

Establishment: CFN: FEI: (b) (4)
(b) (4)
DMF No: AADA:
Responsibilities:
Profile: OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 07-FEB-2012
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Establishment: CFN: FEI: (b) (4)
(b) (4)
DMF No: AADA:
Responsibilities:
Profile: OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 24-JAN-2012
Decision: ACCEPTABLE
Reason: BASED ON FILE REVIEW

Establishment: CFN: (b) (4) FEI: (b) (4)
(b) (4)
DMF No: AADA:
Responsibilities:
Profile: OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 24-JAN-2012
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

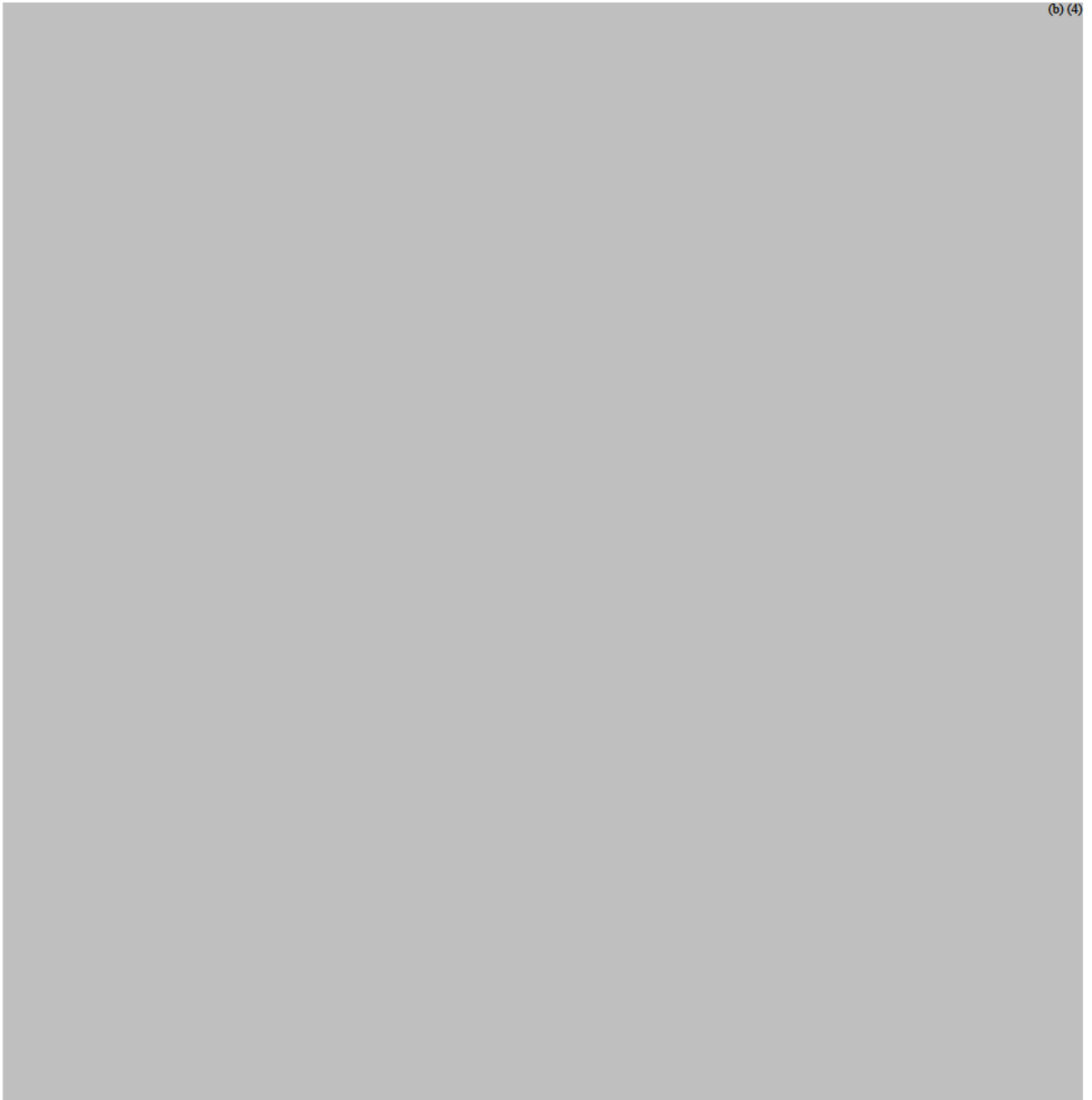
**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT**

Establishment: CFN: (b) (4) FEI: (b) (4)
(b) (4)
DMF No: AADA:
Responsibilities:
Profile: OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 04-DEC-2012
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

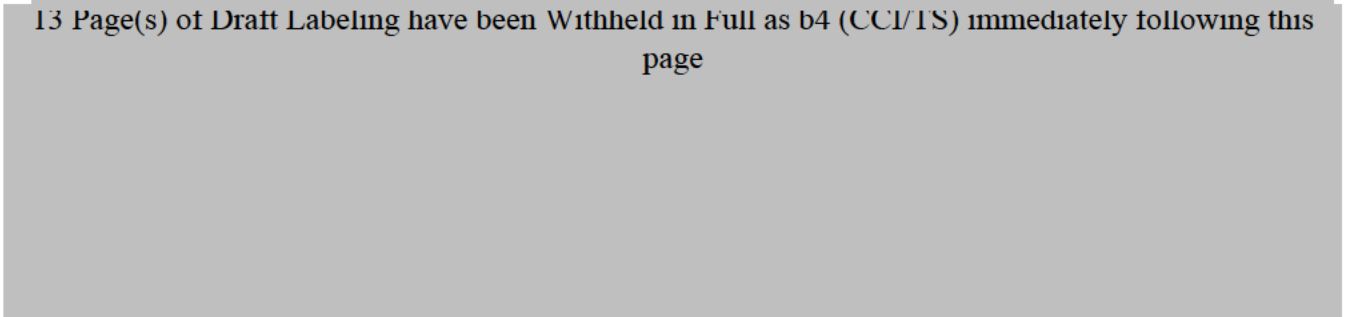
Establishment: CFN: FEI: (b) (4)
(b) (4)
DMF No: AADA:
Responsibilities:
Profile: OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 04-DEC-2012
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Attachment - 2 (CMC Sections of the Finalized Labeling and Labels)

(b) (4)



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



Attachment - 3 (Method Validation)

According to the method validation report provided by Dr. Kallol Biswas from the Division of Pharmaceutical Analysis, Office of Testing and Research, CDER, the HPLC method, (b) (4)



Therefore, it is concluded that the two HPLC methods used for quantitation of impurities in both drug substance and drug product in NDA 203441 are **satisfactorily validated and** acceptable to be used to ensure the purity of the drug substance and drug product in the NDA.

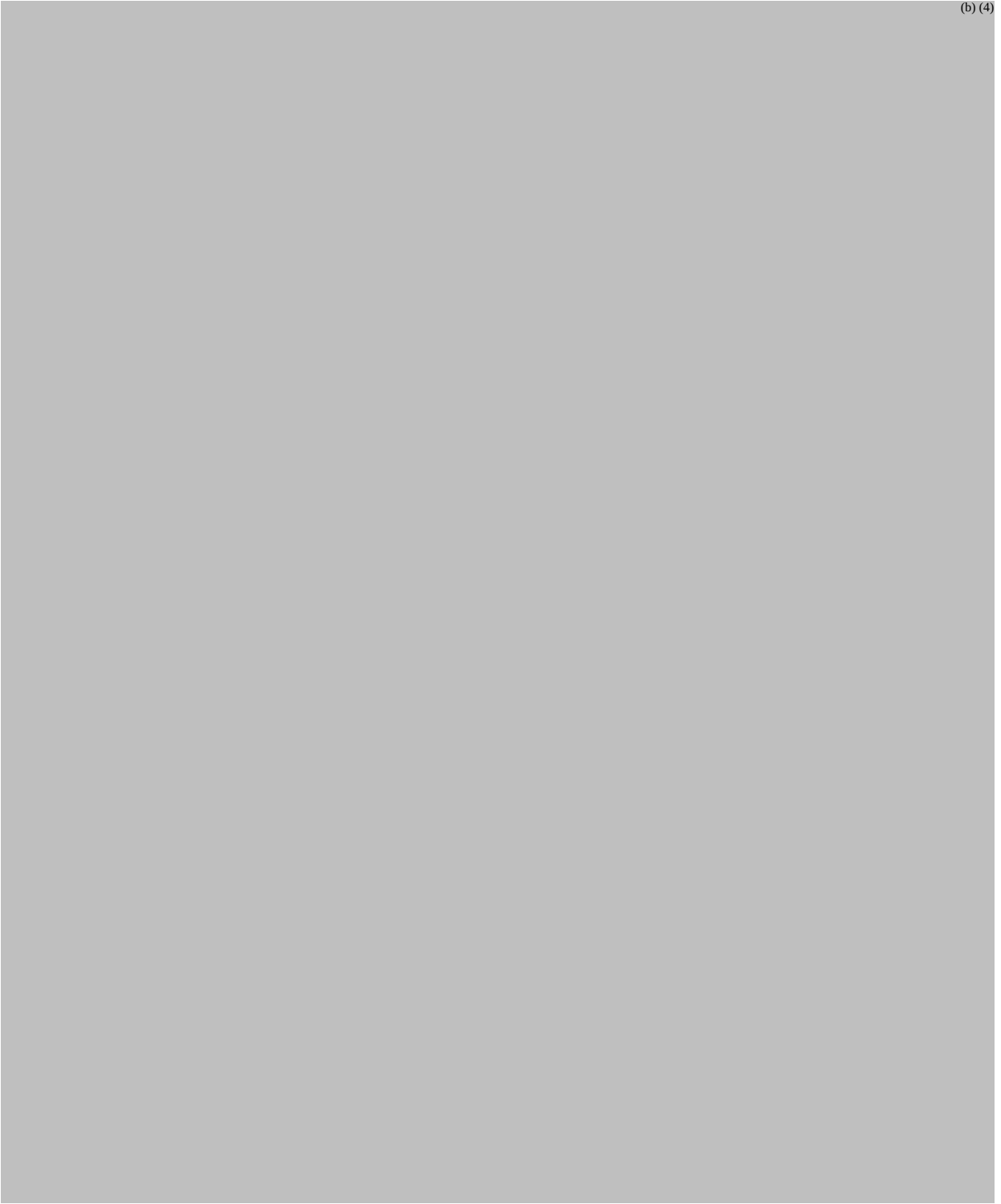
Attachment - 4 (Elemental Impurities)

Safety concern of (b) (4) was raised by the review team. Detailed information regarding this issue and its resolution are summarized as follows:

An IR letter dated May 15, 2012 was sent to request the NDA applicant to add a test method and an acceptance criterion for (b) (4) to the drug substance specification. In the responding amendment dated June 18, 2012, the applicant (NPS Pharmaceuticals) agreed to add a test method and acceptance criterion for (b) (4) to the drug substance specification. However, the applicant proposed to implement this change as a post approval commitment. FDA had accepted the proposal as a post approval commitment in June 2012.



(b) (4)





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/s/

YICHUN SUN
12/14/2012

MOO JHONG RHEE
12/14/2012
Chief, Branch IV

NDA 203-441

Gattex® (teduglutide [rDNA origin]) for injection

NPS Pharmaceuticals

Yichun Sun, Ph.D.

**Branch IV
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment**

**CMC REVIEW OF NDA 203-441
For the Division of Gastroenterology and Inborn Errors Products
(HFD-180)**

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Chemistry Review Data Sheet

1. NDA: 203-441
2. REVIEW #: 1
3. REVIEW DATE: 27-July-2012
4. REVIEWER: Yichun Sun, Ph.D.
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
IND 58,213	27-April-1999
EOP 2 meeting Memorandum (IND 58,213)	17-November-2003
Pre-NDA CMC meeting minutes	30-November-2010

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original	30-November-2011
Amendment	18-June-2012
Amendment	29-June-2012
Amendment	10-July-2012

7. NAME & ADDRESS OF APPLICANT:

Name: NPS Pharmaceuticals
Address: 550 Hills Drive, 3rd Floor
Bedminster, NJ 07921
Representative: Sandra C. Cottrell, MA, Ph.D.
Telephone: 908-450-5300

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Gattex
- b) Non-Proprietary Name (USAN): Teduglutide
- c) Code Name/# (ONDQA only): N/A
- d) Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: 1
- Submission Priority: Standard Review

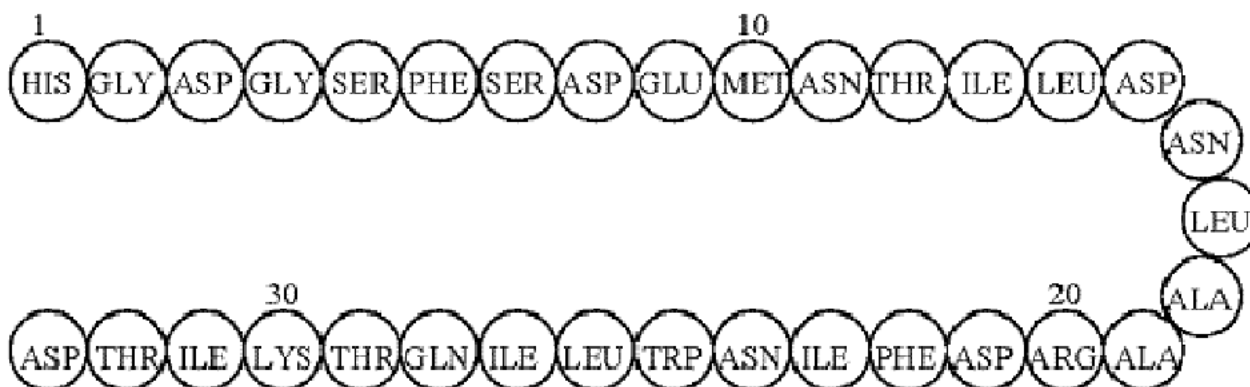
9. LEGAL BASIS FOR SUBMISSION: 505 (b)(1)
10. PHARMACOL. CATEGORY: Analogue of the human glucagon-like peptide-2
11. DOSAGE FORM: For injection
12. STRENGTH/POTENCY: 5 mg per vial (10 mg/mL after reconstituted)
13. ROUTE OF ADMINISTRATION: Subcutaneous injection
14. Rx/OTC DISPENSED: X Rx OTC
15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\):](#)

 X SPOTS product – Form Completed

 Not a SPOTS product

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

Teduglutide



Primary Sequence of Teduglutide

Empirical formula: $C_{164}H_{252}N_{44}O_{55}S$

Molecular weight: 3752 Daltons

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	(b) (4)	1	Adequate	7/26/12	NA
	II		(b) (4)	1	Adequate	7/26/12	NA
	III		(b) (4)	4	Adequate	NA	NA
	III		(b) (4)	3	Adequate	NA	NA
	III		(b) (4)	4	Adequate	NA	NA
	III		(b) (4)	4	Adequate	NA	NA
	III		(b) (4)	4	Adequate	NA	NA
	III		(b) (4)	1	Adequate	7/26/12	NA
	V		(b) (4)	3	Adequate	NA	NA
	V		(b) (4)	4	Adequate	NA	NA
			(b) (4)				

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: NA**18. STATUS:****ONDQA:**

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	----	----
EES	Pending	----	----
Pharm/Tox	N/A	----	----
Biopharm	N/A	----	----
LNC	N/A	----	----
Methods Validation	Pending	----	----
DMEPA	N/A	----	----
EA	Claim for Categorical Exclusion is granted.	See p.263	Y. Sun
Quality Microbiology	Approval	March 30, 2012	Bryan S. Riley, Ph.D.

Note: The request of methods validation consult was sent to the Division of Pharmaceutical Analysis (DPA), Office of Testing and Research on February 23, 2012. The results of method validation from DPA are pending. The NDA is recommended for approval without completion of the validation of the methods.

The Chemistry Review for NDA 203-441

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA has provided sufficient information to assure identity, strength, purity, and quality of the drug product.

However, the Office of Compliance has *not* made an overall 'acceptable' recommendation for the facilities involved in this application as of this review date.

The label/labeling issues have *not* been resolved yet.

Therefore, from the ONDQA perspective, this NDA is not recommended for approval in its present form per 21 CFR 314.125 (b)(6),(13) until all those remaining issues are satisfactorily resolved.

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

The applicant was requested to add a test method and an acceptance criterion for (b) (4) to the drug substance specification in the IR letter dated May 15, 2012.

The applicant agreed to add a test method and acceptance criterion for (b) (4) to the drug substance specification in the amendment dated June 18, 2012. The applicant is currently developing a suitable procedure for teduglutide drug substance and plans to test representative batches, establish acceptance criteria, and will subsequently add this test to the drug substance specification. The applicant proposes to implement this as a post approval commitment.

II. Summary of Chemistry Assessments

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

Drug Substance

The active ingredient used in Gattex (teduglutide [rDNA origin]) for injection, which is indicated for the treatment of adult patients with short bowel syndrome (SBS) and for improving intestinal absorption of fluid and nutrients, is teduglutide (rDNA origin). Teduglutide (rDNA origin) is a 33 amino acid glucagon-like peptide-2 (GLP-2) analog manufactured using a strain of *Escherichia coli* (*E. coli*) modified by recombinant DNA technology. (b) (4)

The manufacturing process of teduglutide includes the following steps:

(b) (4)

(b) (4)

Teduglutide drug substance is a clear, colorless to light straw colored liquid composed of teduglutide in aqueous buffer. (b) (4)

Drug Product

The drug product, Gattex (teduglutide [rDNA origin]) for injection, is proposed to be used to treat short bowel syndrome (SBS) and, to improve intestinal absorption of fluid and nutrients. Teduglutide for injection is supplied in a sterile, single-use 3-mL, USP Type I glass vial containing 5 mg of teduglutide as a white lyophilized powder. Each vial also contains 3.88 mg L-histidine, 15 mg mannitol, 0.644 mg monobasic sodium phosphate monohydrate, and 3.434 mg dibasic sodium phosphate heptahydrate. The lyophilized powder is intended to be reconstituted with 0.5 mL of sterile Water for Injection (sWFI), USP, which is provided in a prefilled syringe, immediately before administration by subcutaneous injection. The reconstituted drug product is a nominal 10 mg/mL, sterile, clear, colorless to light straw-colored solution. The reconstituted solution has a pH of approximately 7.4. Up to 0.38 mL of the reconstituted solution can be withdrawn using a co-packaged dosing syringe for subcutaneous injection. The drug product is manufactured using an aseptic process. The manufacture of teduglutide for injection is comprised of the following steps:

(b) (4)

(b) (4)

The identity, strength, purity and quality of the drug product are adequately controlled by the drug product specification. The proposed expiration dating period of 36 months is supported by the long-term stability data provided. The proposed storage time period and condition (b) (4) for the drug product by patients is also supported by the stability data. The results of in-use stability study of the reconstituted drug product demonstrated that the reconstituted drug product is stable for up to 24 hours at room temperature. The drug product would qualify for categorical exclusion from the preparation of an environmental assessment according to 21 CFR 25.31(b).

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

Gattex (teduglutide [rDNA origin]) for injection is a glucagon-like peptide-2 (GLP-2) analog indicated for:

- The treatment of adult patients with short bowel syndrome (SBS).
- Improvement of intestinal absorption of fluid and nutrients.

The recommended dose of Gattex is 0.05 mg/kg given subcutaneously once daily. It can not be used for intravenous or intramuscular injection. It is a single-use vial. The product should be used within 3 hrs after reconstitution.

C. Basis for Not-Approval Recommendation

21CFR 314.125(b)(13)

- No final recommendation from the Office of Compliance is available.

21CFR 314.125(b)(6)

- Label and labeling issues are not resolved. (see the **List of Deficiencies**, p. 265)

III. Administrative**A. Reviewer's Signature**

/s/ Y. Sun, Ph.D.

B. Endorsement Block

Yichun Sun, Ph.D.

Reviewer

Date

Marie Kowblansky, Ph.D.

Pharmaceutical Assessment lead

Date

Moo-Jhong Rhee, Ph.D.

Branch Chief

Date

Cathy Tran-Zwanetz, M.S.

Project Manager

Date

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/s/

YICHUN SUN
07/27/2012

MOO JHONG RHEE
07/30/2012
Chief, Branch IV

Initial Quality Assessment
Branch 3
Pre-Marketing Assessment Division 2

OND Division: Division of Gastroenterology and Inborn Error Products
NDA: 203-441
Applicant: NPS Pharmaceuticals
Stamp Date: 11/30/2011
Review Date: 12/28/2011
PDUFA Date: 9/30/2012
Filing Meeting: 1/4/2012
Proposed Trademark: GATTEX
Established Name: teduglutide [rDNA origin]
Dosage Form: powder for injection
Route of Administration: subcutaneous injection
Indication: short bowel syndrome

CMC Lead: Marie Kowblansky, PhD

	YES	NO
ONDQA Fileability:	☒	
Comments for 74-Day Letter		☒

A. Summary

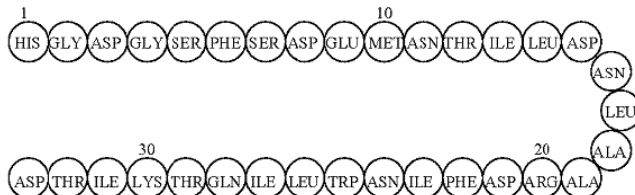
GATTEX® (teduglutide [rDNA origin]) powder for subcutaneous injection is intended for once daily administration in the treatment of short bowel syndrome, with a recommended dose of 0.05 mg/kg/day. This product, which has Orphan Drug designation, was developed under IND 58,213. It will be marketed in a single-use 3 mL glass vial containing 5 mg of teduglutide as a lyophilized powder for reconstitution with 0.5 mL sterile water for injection (sWFI) that will be copackaged in a single-use prefilled syringe. An additional disposable syringe (1 mL) for administration of the reconstituted solution will also be copackaged with the product. Because teduglutide is a new molecular entity, according to the Chemical Classification Code this is a Type 1 application and because of the co-packaged sWFI, Gattex has been classified as a combination product.

Drug Substance

Teduglutide is a 33-amino-acid peptide analog of naturally occurring human glucagon-like peptide-2 (GLP-2) produced recombinantly in *E. coli*. (b) (4)

Its chemical name and structural formula are:

L-histidyl-L-glycyl-L-aspartyl-L-glycyl-L-seryl-L-phenylalanyl-L-seryl-L-aspartyl-L-glutamyl-L-methionyl-L-asparaginyl-L-threonyl-L-isoleucyl-L-leucyl-L-aspartyl-L-asparaginyl-L-leucyl-L-alanyl-L-alanyl-L-arginyl-L-aspartyl-L-phenylalanyl-L-isoleucyl-L-asparaginyl-L-tryptophanyl-L-leucyl-L-isoleucyl-L-glutamyl-L-threonyl-L-lysyl-L-isoleucyl-L-threonyl-L-aspartic acid.



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In-use stability data are presented, demonstrating that the reconstituted product is stable for 24 hours at 25°C/60% RH, and thereby supporting the label claim that reconstituted product may be used for up to three hours following reconstitution.

Co-packaged Reconstitution Diluent: The reconstitution diluent is 0.5 mL of sterile Water for Injection (sWFI), USP, supplied in a prefilled, single-use 1-mL glass syringe. DMFs (b) (4) and (b) (4) are referenced for all information regarding the sWFI prefilled syringes.

The firm requests categorical exclusion from preparing an environmental assessment, with an estimate that the concentration of drug substance that would enter the aquatic environment would be approximately (b) (4), well below the 1 ppb that would trigger the requirement for submitting an environmental assessment.

Inspection requests for the facilities involved in the manufacture of the drug substance and drug product have been entered into EES. The only exception to this is the (b) (4) facility that manufactures and stores the master and working cell banks. The Office of Compliance has informed us that these types of facilities are normally not inspected. This issue has been presented to ONDQA upper management for a final judgment on this matter.

Established name: teduglutide, which is the USAN name for this drug substance.

Methods validation: The reviewer should determine which methods should be submitted to the FDA laboratories for validation.

The full CMC review of this NDA will be done by Yichun Sun, PhD.

B. Critical issues for review

The following issues will require closer scrutiny during the course of the review



C. Comments for 74-Day Letter -- None

D. Recommendation – From the CMC perspective this application is fileable

Marie Kowblansky, PhD
CMC Lead

1/10/2012
Date

Moo-Jhong Rhee, PhD
Branch Chief

FILING CHECKLIST

NDA Number: **Supplement Number and Type:** **Established/Proper Name:**

NDA 202-811 original linaclotide

Applicant: **Letter Date:** **Stamp Date:**

(b) (4) August 9, 2011 August 9, 2011

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?	√		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	√		
3.	Are all the pages in the CMC section legible?	√		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	√		

B. FACILITIES*				
	Parameter	Yes	No	Comment
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	√		
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.			Not applicable
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)	√		

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)	√		
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)	√		
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	√		

* 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.

C. ENVIRONMENTAL ASSESMENT				
	Parameter	Yes	No	Comment
11.	Has an environmental assessment report or categorical exclusion been provided?	√		Claim of categorical exclusion

D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	Yes	No	Comment
12.	Does the section contain a description of the DS manufacturing process?	√		
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?	√		
14.	Does the section contain information regarding the characterization of the DS?	√		
15.	Does the section contain controls for the DS?	√		
16.	Has stability data and analysis been provided for the drug substance?	√		
17.	Does the application contain Quality by Design (QbD) information regarding the DS?		√	Not a filing issue
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		√	Not a filing issue

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?	√		
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?	√		
21.	Is there a batch production record and a proposed master batch record?	√		
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	√		
23.	Have any biowaivers been requested?		√	
24.	Does the section contain description of to-be-marketed container/closure system and presentations)?	√		
25.	Does the section contain controls of the final drug product?	√		
26.	Has stability data and analysis been provided to support the requested expiration date?	√		
27.	Does the application contain Quality by Design (QbD) information regarding the DP?		√	Not a filing issue
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		√	Not a filing issue

F. METHODS VALIDATION (MV)				
	Parameter	Yes	No	Comment

29.	Is there a methods validation package?		√	Although no separate validation package has been submitted, there appears to be sufficient methods validation information in the body of the submission
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G. MICROBIOLOGY				
	Parameter	Yes	No	Comment
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product?		√	Not required

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?	√		

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

J. FILING CONCLUSION				
	Parameter	Yes	No	Comment
34.	IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?	√		
35.	If the NDA is not fileable from the product quality perspective, state the reasons and provide filing comments to be sent to the Applicant.			Not applicable
36.	Are there any potential review issues to be forwarded to the Applicant for the 74-day letter?		√	

{See appended electronic signature page}

Marie Kowblansky, Ph.D.
CMC Lead

{See appended electronic signature page}

Moo-Jhong Rhee, Ph.D.
Branch Chief
Division II
Office of New Drug Quality Assessment

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

/s/

MARIE KOWBLANSKY
01/12/2012

MOO JHONG RHEE
01/12/2012
Chief, Branch IV