

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

201917Orig1s000

CHEMISTRY REVIEW(S)



Chemistry Assessment Section

NDA 201-917

INCIVEK (telaprevir) Tablets

Vertex Pharmaceuticals, Inc.

Christopher Hough, Ph.D.

Bogdan Kurtyka, Ph.D.

George Lunn, Ph.D.

Lin Qi, Ph.D.

Division of Anti-Viral Products

REVIEW #: 2

REVIEW DATE: 20-May-2011



CHEMISTRY REVIEW TEMPLATE



Chemistry Assessment Section

SUBMISSIONS BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original	14-Jul-2010
Amendment	02-Sep-2010
Amendment	08-Oct-2010
Amendment	12-Dec-2010
Amendment	24-Jan-2010
Amendment	28-Mar-2011
Amendment	04-Apr-2011
Amendment	14-Apr-2011
Amendment	10-May-2011

NAME & ADDRESS OF APPLICANT:

Name: Vertex Pharmaceuticals Incorporated
Address: 130 Waverly Street
Cambridge, MA 02139
Representative: John F. Weet, Ph.D.
Vice-President, Regulatory Affairs
Telephone: 617 444 7789

DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: N/A
b) Non-Proprietary Name (USAN): Telaprevir
c) Code Name/# (ONDC only): VX-950
d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 1
 - Submission Priority: P

DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS LOA dated
(b) (4)	II	(b) (4)	(b) (4)	1	Adequate	Apr 25, 2011 (G.Lunn)	07/07/2010
	II			1	Adequate	May 11, 2011 (B.Kurtyka)	07/06/2010
	IV			1	Adequate	4/19/11	06/12/2009

Chemistry Assessment Section

(b) (4)		(b) (4)			(Reviewed by Lin Qi)	
	III		4			07/27/2009
	III		4			07/27/2009
	III		4			08/28/2009
	III		4			05/12/2010
	III		4			07/17/2009
	III		4			05/14/2010
	III		4			07/21/2009
	III		4			07/21/2009
	III		4			07/21/2009
	III		4			07/29/2009
	III		4			07/21/2009

¹ Action codes for DMF Table:
 1 – DMF Reviewed.
 4 – Sufficient information in application

1. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA has provided sufficient information to assure identity, strength, purity, and quality of the drug substance, (b) (4), and drug product. The labels and labeling have been finalized, and have adequate information as required. An Overall Recommendation of Acceptable has been made by the Office of Compliance. Appropriate

Chemistry Assessment Section

responses to information requests for DMF (b) (4) were received on March 28, 2011, and that DMF is now adequate and supports this NDA. Therefore, from the CMC perspective, this NDA is recommended for approval.

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

None

2. Summary of Chemistry Assessments**A. Description of the Drug Product(s) and Drug Substance(s)**

A Quality by Design approach has been used for the manufacture of telaprevir drug substance. Each step in the procedure has been evaluated and for each parameter a Normal Operating Range (NOR) and a Proven Acceptable Range (PAR) have been determined on the basis of experiments in which the parameter was varied. These experiments are described in detail and the NORs and PARs are acceptable. The critical/non-critical nature of each step was also assessed. The drug substance is manufactured following the process description together with the knowledge of the NOR and the PAR. Together this information is used to produce the manufacturing batch record. The NOR is given in the batch record and the PAR is available in the Process Support Document. As experience is gained the process can be adapted. Adequate specifications are provided for the starting materials, solvents, and reagents.

(b) (4)

An acceptable drug substance specification that has tests for appearance, identity, assay, impurities, (b) (4), heavy metals, and residue on ignition is provided. (b) (4)

(b) (4) The specified impurities have been qualified based on toxicological studies. The analytical methods are described at an acceptable level of detail and have been validated.

Satisfactory stability data obtained at 25°C/60% RH, 30°C/65% RH, and 40°C/75% RH for up to 24 months are provided for 9 batches. There are no out of specification results and no trends.

(b) (4)

(b) (4) . Two attributes critical to final product quality, particle size and bulk density, are tested for each batch according to the specification. Established specification limits assure proper safety,

Chemistry Assessment Section

bioavailability and efficacy of the final drug product. [REDACTED] (b) (4)

Telaprevir drug product is an immediate-release tablet for oral administration. Each tablet contains 375 mg of telaprevir drug substance, with a total target weight of 1 g. The tablet is capsule-shaped, film-coated purple and debossed with the characters “V 375” on one side. Each tablet contains as inactive ingredients colloidal silicon dioxide, croscarmellose sodium, dibasic calcium phosphate (anhydrous), hypromellose acetate succinate, microcrystalline cellulose, sodium lauryl sulfate, and sodium stearyl fumarate. In addition, [REDACTED] (b) (4) contains FD&C Red No. 40, FD&C Blue No. 2, polyethylene glycol [REDACTED] (b) (4) polyvinyl alcohol, talc, and titanium dioxide.

[REDACTED] (b) (4)

A QbD approach was applied to the drug product manufacturing process to define the NOR and PAR for material attributes and operating parameters of each unit operating process. Excipients were selected to provide a chemically and physically stable formulation with optimized performance. The applicant described in detail how some ranges were determined and how the process parameters were classified as critical, key, or non-critical by DoEs, process capability ratio (C_{pk}), stability models, and tablet lot histories. Detailed manufacturing process description and controls were provided in the master batch record.

A conventional specification, which includes tests for appearance, identity, assay, impurities, dosage uniformity by weight variation, physical form, dissolution, and [REDACTED] (b) (4), is provided for the tablet. As part of the control strategy, in-process controls/checks are established [REDACTED] (b) (4), including average tablet hardness (critical), average tablet weight, and average tablet thickness. The analytical methods are reasonably well described and have been validated.

The tablets are packaged in a 3 x 2-tablet [REDACTED] (b) (4) blister packs or a 168-count 400 cc high-density polyethylene (HDPE) in induction sealed bottle containing a desiccant. The blister packs are child resistant and are packaged in cartons containing a 1-week supply. Four weekly cartons are packed in a 28-day packer. The bottle is for institutional use and is not required to be child resistant. The bottle contains a 28-day supply for a single patient. Up to 24 months of stability data obtained at 25°C/60% RH are provided and a shelf life of 24 months is proposed for the tablets.

Telaprevir drug substance, [REDACTED] (b) (4), and drug product are manufactured in a number of facilities around the world. An Establishment Evaluation Request was submitted and an Overall Recommendation of Acceptable has been made.

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

Chemistry Assessment Section

INCIVEK is a HCV NS3-4A protease inhibitor indicated, in combination with peginterferon alfa and ribavirin, for the treatment of genotype 1 chronic hepatitis C in adult patients with compensated liver disease, including cirrhosis, who are treatment naïve or who have been previously treated, including prior null responders, partial responders, and relapsers.

Telaprevir tablets must not be administered as monotherapy and must only be prescribed with both peginterferon alfa and ribavirin. The recommended dose of INCIVEK tablets is 750 mg (two 375-mg tablets) taken orally 3 times a day (7-9 hours apart) with food. The total daily dose is 6 tablets (2250 mg).

C. Basis for Approvability or Not-Approval Recommendation

The applicant has provided sufficient information on raw material controls, manufacturing processes and process controls, and adequate specifications for assuring consistent product quality of the drug substance, [REDACTED] ^{(b) (4)}, and drug product. The NDA also has provided sufficient stability information on the drug product to assure strength, purity, and quality of the drug product during the expiration dating period.

CMC recommendations for the package insert, bottle, blister and carton labels were included in the labeling review process. Labels and labeling have now been finalized and include the required information.

Approval is recommended from the CMC perspective.

3. Review Of Common Technical Document-Quality (Ctd-Q) Module 1

A. Labeling & Package Insert

Chemistry Assessment Section

The following is a summary of the labeling review, and includes comments discussed as part of the multidisciplinary labeling review.

1

(b) (4)

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

Chemistry Assessment Section

Proprietary name, established name (font size, prominence)	Refer to DMEPA review.
Dosage strength	375 mg
Net quantity of dosage form	NA
“Rx only” displayed prominently on the main panel	included
Lot number and expiration date	included
Storage conditions	included
Bar code (21CFR 201.25)	included
NDC number (21 CFR 207.35(b)(3)(i))(Appear prominently in the top third of the principal display panel or it may appear as part of and contiguous to any bar-code symbol)	included
Manufacturer/distributor's name	included
Quantitative ingredient information (injectables)	NA
Statement of being sterile (if applicable)	NA
“See package insert for dosage information”	included
Special instructions (“Keep out of reach of children” is required for OTC in CFR. Optional for Rx drugs)	included

Evaluation: The container and carton labels are acceptable from a CMC perspective.

4. EES Report

EES Report as of 5/19/11.

Application:	NDA 201917/000	Action Goal:	
Stamp Date:	23-NOV-2010	District Goal:	
Regulatory:	23-MAY-2011		
Applicant:	VERTEX PHARMS 130 WAVERLY ST CAMBRIDGE, MA 021394242	Brand Name:	TELAPREVIR
		Estab. Name:	TELAPREVIR
		Generic Name:	
Priority:	14	Product Number; Dosage Form; Ingredient; Strengths	
Org. Code:	530		001; TABLET; TELAPREVIR; 375MG
Application Comment:	THIS IS A PRIORITY APPLICATION WITH A GOAL DATE OF MAY 23, 2011/ THIS IS A QSD APPLICATION. CONTACT ONQDA FOR REVIEWER PARTICIPATION IN THE INSPECTIONS. (on 05-DEC-2010 by D. HENRY () 301-796-4227)		
FDA Contacts:	D. HENRY	Project Manager	301-796-4227
	G. LUNN	Review Chemist	301-796-1701
	D. MATECKA	Team Leader	301-796-1415
<hr/>			
Overall Recommendation:	ACCEPTABLE	on 19-MAY-2011	by D. SMITH ()
<hr/>			

Chemistry Assessment Section

Establishment:  (b) (4)

DMF No:  AADA: 

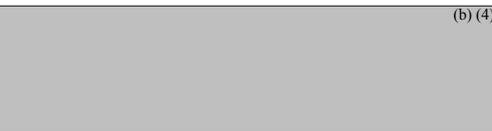
Responsibilities:  (b) (4)

Estab. Comment: 

Profile:  (b) (4)

OAI Status: NONE

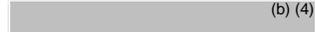
<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	05-DEC-2010				HENRYD
OC RECOMMENDATION	06-DEC-2010			ACCEPTABLE BASED ON PROFILE	INYARDA

Establishment:  (b) (4)

DMF No:  AADA: 

Responsibilities:  (b) (4)

Estab. Comment: 

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	05-DEC-2010				HENRYD
OC RECOMMENDATION	06-DEC-2010			ACCEPTABLE BASED ON PROFILE	INYARDA



CHEMISTRY REVIEW TEMPLATE



Chemistry Assessment Section

Establishment: [REDACTED] (b) (4)

DMF No: [REDACTED] ADA: [REDACTED]

Responsibilities: [REDACTED] (b) (4)

Estab. Comment: DMPQ FACILITY REVIEWER WOULD LIKE TO PARTICIPATE IN THIS SITE INSPECTION. PLEASE CONTACT VIBHAKAR SHAH. (on 22-DEC-2010 by C. CRUZ (HFD-323) 301-795-3254)
[REDACTED] (b) (4)

Profile: [REDACTED] (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	05-DEC-2010				HENRYD
SUBMITTED TO DO	06-DEC-2010	Product Specific			INYARDA
QBD ELEMENTS AS WELL AS NEW DOSAGE FORM FOR ESTABLISHMENT. REVIEWER WOULD LIKE TO PARTICIPATE ON INSPECTION.					
ASSIGNED INSPECTION TO IB	07-DEC-2010	Product Specific			PHILPYE
INSPECTION SCHEDULED	09-MAY-2011		29-APR-2011		IRIVERA
DO RECOMMENDATION	19-MAY-2011			ACCEPTABLE INSPECTION	PHILPYE
OC RECOMMENDATION	19-MAY-2011			ACCEPTABLE DISTRICT RECOMMENDATION	SMITHDE

Establishment: [REDACTED] (b) (4)

DMF No: [REDACTED] ADA: [REDACTED]

Responsibilities: [REDACTED] (b) (4)

Estab. Comment: [REDACTED] (b) (4)

Profile: [REDACTED] (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	05-DEC-2010				HENRYD
OC RECOMMENDATION	06-DEC-2010			ACCEPTABLE BASED ON PROFILE	INYARDA

Chemistry Assessment Section

Establishment: (b) (4)

DMF No: (b) (4) AADA:

Responsibilities: (b) (4)

Estab. Comment: DMPQ FACILITY REVIEWER WOULD LIKE TO PARTICIPATE IN THIS SITE INSPECTION. PLEASE CONTACT VIBHAKAR SHAH. (on 22-DEC-2010 by C. CRUZ (HFD-323) 301-796-3254)
THIS FACILITY UTILIZES QBD ELEMENTS (on 05-DEC-2010 by D. HENRY () 301-796-4227)

DMPQ FACILITY REVIEWER WOULD LIKE TO PARTICIPATE IN THIS SITE INSPECTION. PLEASE CONTACT VIBHAKAR SHAH. (on 22-DEC-2010 by C. CRUZ (HFD-323) 301-796-3254)

Profile: (b) (4) OAI Status: NONE
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	05-DEC-2010				HENRYD
SUBMITTED TO DO	06-DEC-2010	Product Specific			INYARDA
ASSIGNED INSPECTION TO IB	07-DEC-2010	Product Specific			PHILPYE
INSPECTION PERFORMED	10-DEC-2010		10-DEC-2010		JOSEPH.VANNELLI
<p>A pre-approval and cGMP inspection of an Active Pharmaceutical Ingredient (API) manufacturer was conducted per assignment request from CDER- HFD-320. The FACTS Assignment Number is 6321218 and Profile Class is (b) (4) Guidance from CP 7356.002F, Active Pharmaceutical Ingredient (API) Process Inspection; CP 7352.832, Pre-Approval Inspections/Investigations; and CP 7356.002, Drug Manufacturing Inspections, was used for the inspection. The API covered is (b) (4)</p> <p>The previous FDA drug inspection was for a Pre-Approval inspection of (b) (4) (b) (4). The inspection was completed on 11/09/07 and classified as VAI. There were four observations, pertaining to the laboratory, listed on the Inspectional Observations Form, FDA-483. During the current inspection I verified that all the deficiencies were corrected with the changes implemented.</p> <p>The current inspection included coverage of the firm's Quality and Laboratory Control Systems. The firm's Production, Materials, Packaging & Labeling, and Facilities & Equipment Systems were not covered in detail during the inspection. Documents and records relating to deviations, change control, quality investigations, corrective actions, training records, process and equipment validation, laboratory method validation and testing data were reviewed during the inspection.</p> <p>During this inspection it was found that the firm is operating in a state of control. There were no deviations placed on an FDA 483 form. The firm was not producing API (b) (4) during the inspection. No samples were collected and no refusals encountered during the inspection. Results of the inspection were faxed to DFI/International Operations and CDER/International Compliance on 12/10/2010.</p>					
ASSIGNED INSPECTION TO IB	21-JAN-2011	Product Specific			PHILPYE
INSPECTION PERFORMED	06-MAY-2011		06-MAY-2011		IRIVERA

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Chemistry Assessment Section

NO FD-483 ISSUED, FIRM IS ACCEPTABLE.

INSPECTION SCHEDULED	09-MAY-2011	06-MAY-2011	IRIVERA
DO RECOMMENDATION	19-MAY-2011	ACCEPTABLE INSPECTION	PHILPYE
OC RECOMMENDATION	19-MAY-2011	ACCEPTABLE DISTRICT RECOMMENDATION	SMITHOE
SUBMITTED TO OC	05-DEC-2010		HENRYD
SUBMITTED TO DO	06-DEC-2010	Product Specific	INYARDA
ASSIGNED INSPECTION TO IB	07-DEC-2010	Product Specific	PHILPYE
INSPECTION PERFORMED	10-DEC-2010	10-DEC-2010	JOSEPH.VANNELLI

AUTOMATIC WITHHOLD STATUS ISSUED BY FACTS, DUE TO FIRM BEING OUT OF BUSINESS OR MERGED A pre-approval and cGMP inspection of an Active Pharmaceutical Ingredient (API) manufacturer was conducted per assignment request from CDER- HFD-320. The FACTS Assignment Number is 6321218 and Profile Class is (b) (4) Guidance from CP 7356.002F, Active Pharmaceutical Ingredient (API) Process Inspection; CP 7352.832, Pre-Approval Inspections/Investigations; and CP 7356.002, Drug Manufacturing Inspections, was used for the inspection. The API covered is (b) (4)

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During this inspection it was found that the firm is operating in a state of control. There were no deviations placed on an FDA 483 form. The firm was not producing API, (b) (4) during the inspection. No samples were collected and no refusals encountered during the inspection. Results of the inspection were faxed to DFI/International Operations and CDER/International Compliance on 12/1

ASSIGNED INSPECTION TO IB	11-JAN-2011	Product Specific	PHILPYE
DECEMBER INSPECTION DID NOT COVER TABLETS			
INSPECTION PERFORMED	06-MAY-2011	06-MAY-2011	IRIVERA
NO FD-483 WAS ISSUED, FIRM IS ACCEPTABLE.			
INSPECTION SCHEDULED	09-MAY-2011	06-MAY-2011	IRIVERA
DO RECOMMENDATION	19-MAY-2011	ACCEPTABLE INSPECTION	PHILPYE
OC RECOMMENDATION	19-MAY-2011	ACCEPTABLE DISTRICT RECOMMENDATION	SMITHOE

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Chemistry Assessment Section

Establishment: (b) (4)

DMF No: **AADA:**

Responsibilities: (b) (4)

Estab. Comment: THE FACTS ASSIGNMENT # FOR THIS PAI IS 1248990, NOT 5651789. HAVE ASSIGNED A DUE DATE OF MARCH 15, 2011. (on 30-DEC-2010 by K. CULVER (HFR-CE4550) 502-425-0069)
 DMPQ FACILITY REVIEWER WOULD LIKE TO PARTICIPATE IN THIS SITE INSPECTION. PLEASE CONTACT VIBHAKAR SHAH. (on 22-DEC-2010 by C. CRUZ (HFD-323) 301-796-3254)
 THIS FACILITY UTILIZES QBD ELEMENTS (on 05-DEC-2010 by D. HENRY () 301-796-4227)

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	05-DEC-2010				HENRYD
SUBMITTED TO DO	07-DEC-2010	Product Specific			INYARDA
ASSIGNED INSPECTION TO IB	22-DEC-2010	Product Specific			KCULVER
INSPECTION PERFORMED	24-MAR-2011		24-MAR-2011		KCULVER
483 ISSUED FOR GENERLA GMP ISSUES FOR COMMERCIAL PRODUCTS AND 2 483 ITEMS FOR NDA 201917. GMP AND PAI PACS WILL BE VAL.					
DO RECOMMENDATION	29-APR-2011			ACCEPTABLE	KCULVER
PAI AND GMP ARE VAL. PROCESS VALIDATION WAS REVIEWED DURING PAI AND IT WAS OK.				INSPECTION	
OC RECOMMENDATION	29-APR-2011			ACCEPTABLE	INYARDA
				DISTRICT RECOMMENDATION	

Chemistry Assessment Section

Establishment: (b) (4)

DMF No: AADA:

Responsibilities: (b) (4)

Estab. Comment: DMPQ FACILITY REVIEWER WOULD LIKE TO PARTICIPATE IN THIS SITE INSPECTION. PLEASE CONTACT VIBHAKAR SHAH. (on 22-DEC-2010 by C. CRUZ (HFD-323) 301-796-3254)
THIS FACILITY UTILIZES QBD ELEMENTS (on 05-DEC-2010 by D. HENRY () 301-796-4227)

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	05-DEC-2010				HENRYD
SUBMITTED TO DO	06-DEC-2010	Product Specific			INYARDA
ASSIGNED INSPECTION TO IB	07-DEC-2010	Product Specific			PHILPYE
DO RECOMMENDATION	19-MAY-2011			ACCEPTABLE BASED ON FILE REVIEW INSPECTION	PHILPYE
OC RECOMMENDATION	19-MAY-2011			ACCEPTABLE DISTRICT RECOMMENDATION	SMITHDE

5. Signatures

Reviewers' Signatures

Christopher Hough, Ph.D. {Signed Electronically in DFS}
 Bogdan Kurtyka, Ph.D. {Signed Electronically in DFS}
 George Lunn, Ph.D. {Signed Electronically in DFS}
 Lin Qi, Ph.D. {Signed Electronically in DFS}

Endorsement Block

CMC-Lead: Stephen P. Miller, Ph.D. {Signed Electronically in DFS}

CC Block

Project Managers: Don Henry; Myung-Joo P. Hong

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

/s/

GEORGE LUNN

05/20/2011

Compliance has provided an overall recommendation of Acceptable and so this application is now recommended for approval from the CMC point of view.

LIN QI

05/20/2011

BOGDAN KURTYKA

05/20/2011

STEPHEN P MILLER

05/20/2011

I concur - this NDA is recommended for approval from the CMC perspective

NDA 201-917

INCIVEK (telaprevir) Tablets

Vertex Pharmaceuticals, Inc.

Christopher Hough, Ph.D.

Bogdan Kurtyka, Ph.D.

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Lin Qi, Ph.D.

Division of Anti-Viral Products

Table of Contents

Table of Contents	2
Chemistry Review Data Sheet.....	4
The Executive Summary	9
I. Recommendations	9
A. Recommendation and Conclusion on Approvability	9
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.....	9
II. Summary of Chemistry Assessments.....	9
A. Description of the Drug Product(s) and Drug Substance(s)	9
B. Description of How the Drug Product is Intended to be Used.....	11
C. Basis for Approvability or Not-Approval Recommendation.....	11
III. Administrative.....	12
A. Reviewer's Signature.....	12
B. Endorsement Block.....	12
C. CC Block	12
Chemistry Assessment	13
I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data.....	13
S DRUG SUBSTANCE [Telaprevir, (b) (4)].....	13
S.1 General Information [Telaprevir, (b) (4)].....	13
S.2 Manufacture [Telaprevir, (b) (4)].....	14
S.3 Characterization [Telaprevir, (b) (4)].....	55
S.4 Control of Drug Substance [Telaprevir, (b) (4)].....	60
S.5 Reference Standards or Materials [Telaprevir, (b) (4)].....	79
S.6 Container Closure System [Telaprevir, (b) (4)].....	80
S.7 Stability [Telaprevir, (b) (4)].....	80
P (b) (4).....	82
P.1 Description and Composition of the (b) (4).....	82
P.2 Pharmaceutical Development (b) (4).....	83
P.3 Manufacture (b) (4).....	91
P.4 Control of Excipients (b) (4).....	100
P.5 Control of Drug Product (b) (4).....	102
P.6 Reference Standards or Materials (b) (4).....	115
P.7 Container Closure System (b) (4).....	115
P.8 Stability (b) (4).....	116
P DRUG PRODUCT [INCIVEK (telaprevir) Tablets].....	119

P.1	Description and Composition of the Drug Product [INCIVEK (telaprevir) Tablets].....	119
P.2	Pharmaceutical Development [INCIVEK (telaprevir) Tablets].....	121
	Stage 1 - Target Product Profile.....	128
	Stage 2 - Critical Quality Attributes.....	128
	Stage 3 - Initial Risk Assessment.....	129
	Stage 4a – Telaprevir Tablet, 375 mg, Material Criticality Analysis.....	130
	Stage 4b – Tablet Process Criticality Analysis.....	133
P.3	Manufacture [INCIVEK (telaprevir) Tablets].....	161
P.4	Control of Excipients[INCIVEK (telaprevir) Tablets].....	171
P.5	Control of Drug Product [INCIVEK (telaprevir) Tablets].....	173
1.	Assay and Organic Impurities / Degradation Products-Tablet.....	173
2.	Determination of Physical Form-Tablet (Updated in Amendment Dated Dec 10, 2010).....	177
P.6	Reference Standards or Materials [INCIVEK (telaprevir) Tablets].....	187
P.7	Container Closure System [INCIVEK (telaprevir) Tablets].....	187
1.	Description Of Container Closure System For Telaprevir Tablet, 375 Mg.....	187
2.	Suitability of Container Closure Systems for Telaprevir Tablet, 375 Mg.....	188
3.	Quality Control of Container Closure Systems for Telaprevir Tablet, 375 Mg.....	189
P.8	Stability [INCIVEK (telaprevir) Tablets].....	191
	Primary Stability:.....	191
	Photostability:.....	194
	Other stability studies:.....	195
A	APPENDICES.....	197
R	REGIONAL INFORMATION.....	197
II.	Review Of Common Technical Document-Quality (Ctd-Q) Module 1.....	203
A.	Labeling & Package Insert.....	203
12	DESCRIPTION.....	204
16	HOW SUPPLIED/STORAGE AND HANDLING.....	205
B.	Environmental Assessment Or Claim Of Categorical Exclusion.....	210
III.	List Of Deficiencies To Be Communicated.....	211
IV.	EES Report.....	211

Chemistry Review Data Sheet

Chemistry Review Data Sheet

1. NDA 201-917

2. REVIEW #: 1

3. REVIEW DATE: 18-Apr-2011

4. REVIEWERS Christopher Hough, Ph.D.; Bogdan Kurtyka, Ph.D.; George Lunn, Ph.D.; Lin Qi, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents

None

Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Document Date

Original

14-Jul-2010

Amendment

02-Sep-2010

Amendment

08-Oct-2010

Amendment

12-Dec-2010

Amendment

24-Jan-2010

Amendment

28-Mar-2011

Amendment

04-Apr-2011

Amendment

14-Apr-2011

7. NAME & ADDRESS OF APPLICANT:

Chemistry Review Data Sheet

Name: Vertex Pharmaceuticals Incorporated
Address: 130 Waverly Street
Cambridge, MA 02139
Representative: John F. Weet, Ph.D.
Vice-President, Regulatory Affairs
Telephone: 617 444 7789

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: N/A
b) Non-Proprietary Name (USAN): Telaprevir
c) Code Name/# (ONDC only): VX-950
d) Chem. Type/Submission Priority (ONDC only):
• Chem. Type: 1
• Submission Priority: P

9. LEGAL BASIS FOR SUBMISSION:

10. PHARMACOL. CATEGORY: Anti-viral

11. DOSAGE FORM: Tablet

12. STRENGTH/POTENCY: 375 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: Rx OTC

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

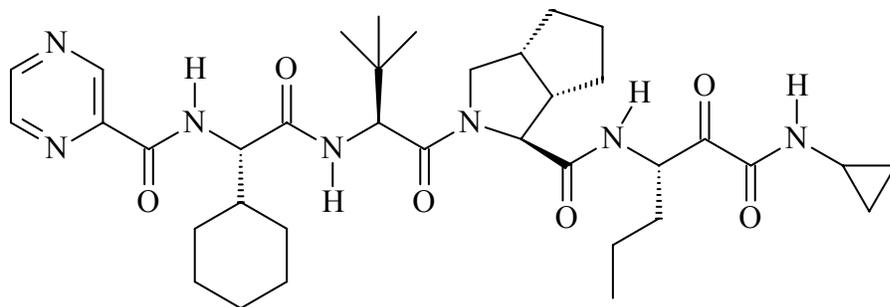
SPOTS product – Form Completed

Not a SPOTS product

Chemistry Review Data Sheet

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

(1S,3aR,6aS)-2-[(2S)-2-({(2S)-2-cyclohexyl-2-[(pyrazin-2-ylcarbonyl)amino]acetyl} amino)-3,3-dimethylbutanoyl]-N-[(3S)-1-(cyclopropylamino)-1,2-dioxohexan-3-yl]-3,3a,4,5,6,6a-hexahydro-1H-cyclopenta[c]pyrrole-1-carboxamide



Molecular formula $C_{36}H_{53}N_7O_6$

Molecular weight 679.85

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS LOA dated
(b) (4)	II	(b) (4)	(b) (4)	1	Adequate	Apr 25, 2011 (G.Lunn)	07/07/2010
	II			1	Under Review	IR sent Apr 8, 2011 (B.Kurtyka)	07/06/2010
	IV			1	Adequate	4/19/11 (Reviewed by Lin Qi)	06/12/2009
	III			4			07/27/2009
	III			4			07/27/2009
	III			4			08/28/2009
	III			4			05/12/2010
	III			4			07/17/2009

Chemistry Review Data Sheet

(b) (4)	(b) (4)				
(b) (4)	(b) (4)	III	4		05/14/2010
(b) (4)	(b) (4)	III	4		07/21/2009
(b) (4)	(b) (4)	III	4		07/21/2009
(b) (4)	(b) (4)	III	4		07/21/2009
(b) (4)	(b) (4)	III	4		07/29/2009
(b) (4)	(b) (4)	III	4		07/21/2009

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:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	71,832	Full IND development process

18. STATUS:

Chemistry Review Data Sheet

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Feedback on mathematical models. Contains background for Information Requests already sent to applicant	4/12/11	Meiyu Shen
EES	Pending		
Pharm/Tox	NA		
Biopharm	Acceptable	4/20/11	Sandra Suarez
LNC	NA		
Methods Validation	Not required		
DMEPA	NA		
EA	Categorical exemption claimed, claim accepted	09/10/2010	G. Lunn
Microbiology	NA		

19. ORDER OF REVIEW (OGD Only)

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

The Chemistry Review for NDA 201-917

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 substance, [REDACTED] (b) (4), and drug product. The labels have adequate information as required. However, three manufacturing sites will be inspected between Apr 26 and May 13, so a recommendation from the Office of Compliance on the overall site acceptability has not been made as of the date of this review. Therefore, from the CMC perspective, this NDA is recommended for approval pending completion of satisfactory manufacturing inspections.

There is an additional minor CMC issue: an acceptable response is needed to the April 8th Information Request for DMF [REDACTED] (b) (4). We anticipate that this issue will be resolved by May 13, 2011. No other issues have been identified which would prevent approval from the CMC perspective.

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)

A Quality by Design approach has been used for the manufacture of telaprevir drug substance. Each step in the procedure has been evaluated and for each parameter a Normal Operating Range (NOR) and a Proven Acceptable Range (PAR) have been determined on the basis of experiments in which the parameter was varied. These experiments are described in detail and the NORs and PARs are acceptable. The critical/non-critical nature of each step was also assessed. The drug substance is manufactured following the process description together with the knowledge of the NOR and the PAR. Together this information is used to produce the manufacturing batch record. The NOR is given in the batch record and the PAR is available in the Process Support Document. As experience is gained the process can be adapted. Adequate specifications are provided for the starting materials, solvents, and reagents.

Executive Summary Section

(b) (4)

An acceptable drug substance specification that has tests for appearance, identity, assay, impurities, (b) (4), heavy metals, and residue on ignition is provided. (b) (4)

The specified impurities have been qualified based on toxicological studies. The analytical methods are described at an acceptable level of detail and have been validated.

Satisfactory stability data obtained at 25°C/60% RH, 30°C/65% RH, and 40°C/75% RH for up to 24 months are provided for 9 batches. There are no out of specification results and no trends.

(b) (4)

Two attributes critical to final product quality, particle size and bulk density, are tested for each batch according to the specification. Established specification limits assure proper safety, bioavailability and efficacy of the final drug product. (b) (4)

Telaprevir drug product is an immediate-release tablet for oral administration. Each tablet contains 375 mg of telaprevir drug substance, with a total target weight of 1 g. The tablet is capsule-shaped, film-coated purple and debossed with the characters “V 375” on one side. Each tablet contains as inactive ingredients colloidal silicon dioxide, croscarmellose sodium, dibasic calcium phosphate (anhydrous), hypromellose acetate succinate, microcrystalline cellulose, sodium lauryl sulfate, and sodium stearyl fumarate. In addition, (b) (4) contains FD&C Red No. 40, FD&C Blue No. 2, polyethylene glycol (b) (4), polyvinyl alcohol, talc, and titanium dioxide.

(b) (4)

A QbD approach was applied to the drug product manufacturing process to define the NOR and PAR for material attributes and operating parameters of each unit operating process. Excipients were selected to provide a chemically and physically stable formulation with optimized performance. The applicant described in detail how some ranges were determined and how the process parameters were classified as critical, key, or non-critical by DoEs, process capability ratio (C_{pk}), stability models, and tablet lot histories. Detailed manufacturing process description and controls were provided in the master batch record.

Executive Summary Section

A conventional specification, which includes tests for appearance, identity, assay, impurities, dosage uniformity by weight variation, physical form, dissolution, and (b) (4), is provided for the tablet. As part of the control strategy, in-process controls/checks are established (b) (4), including average tablet hardness (critical), average tablet weight, and average tablet thickness. The analytical methods are reasonably well described and have been validated.

The tablets are packaged in a 3 x 2-tablet (b) (4) blister packs or a 168-count 400 cc high-density polyethylene (HDPE) in induction sealed hospital unit dose bottle containing a desiccant. The blister packs are child resistant and are packaged in cartons containing a 1-week supply. Four weekly cartons are packed in a 28-day packer. The hospital bottle is not required to be child resistant and also contains a 28-day supply for a single patient. Up to 24 months of stability data obtained at 25°C/60% RH are provided and a shelf life of 24 months is proposed for the tablets.

Telaprevir drug substance, (b) (4), and drug product are manufactured in a number of facilities around the world. An Establishment Evaluation Request has been submitted but three inspections are scheduled for April 26-May 13, 2011, so an Overall Recommendation of Acceptable has not yet been made.

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

INCIVEK is a HCV NS3-4A protease inhibitor indicated, in combination with peginterferon alfa and ribavirin, for the treatment of genotype 1 chronic hepatitis C in adult patients with compensated liver disease, including cirrhosis, who are treatment naïve or who have been previously treated, including prior null responders, partial responders, and relapsers.

Telaprevir tablets must not be administered as monotherapy and must only be prescribed with both peginterferon alfa and ribavirin. The recommended dose of INCIVEK tablets is 750 mg (two 375-mg tablets) taken orally 3 times a day (7-9 hours apart) with food. The total daily dose is 6 tablets (2250 mg).

C. Basis for Approvability or Not-Approval Recommendation

The applicant has provided sufficient information on raw material controls, manufacturing processes and process controls, and adequate specifications for assuring consistent product quality of the drug substance, (b) (4), and drug product. The NDA also has provided sufficient stability information on the drug product to assure strength, purity, and quality of the drug product during the expiration dating period.

All labels have the required information. CMC recommendations for the package insert, bottle, blister and carton labels have been provided for review team discussion.

Approval is recommended from the CMC perspective, pending successful completion of inspections, and adequate responses to the minor CMC issues for DMF (b) (4).

Executive Summary Section

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

Christopher Hough, Ph.D. {Signed Electronically in DFS}

Bogdan Kurtyka, Ph.D. {Signed Electronically in DFS}

George Lunn, Ph.D. {Signed Electronically in DFS}

Lin Qi, Ph.D. {Signed Electronically in DFS}

B. Endorsement Block

CMC-Lead: Stephen P. Miller, Ph.D. {Signed Electronically in DFS}

C. CC Block

Project Managers: Don Henry; Myung-Joo P. Hong

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/s/

GEORGE LUNN
04/25/2011

BOGDAN KURTYKA
04/25/2011

LIN QI
04/25/2011

STEPHEN P MILLER
04/25/2011

I concur - the telaprevir NDA is recommended for approval from the CMC perspective pending successful completion of manufacturing inspections.

DATE: January 10, 2011

TO: Extended Telaprevir (NDA 201-917) Review Team

FROM: George Lunn, Ph.D. 301-796-1701, george.lunn@fda.hhs.gov (on behalf of the CMC review team)

THROUGH: Christine Moore, Ph.D.

SUBJECT: CMC (Chemistry, Manufacturing & Controls) Considerations for upcoming Pre Approval Inspection (PAI) at [REDACTED] (b)(4)

NDA 201-917 is submitted by Vertex Pharmaceuticals, Inc. for telaprevir immediate release tablet for oral administration containing 375 mg of drug substance telaprevir (VX-950). Telaprevir is a new molecular entity. The proposed indication is treatment of hepatitis C. The application has been granted "Priority" review status.

The sponsor proposes separate manufacturing sites for drug substance, [REDACTED] (b)(4), and the drug product. This memo contains background information on [REDACTED] (b)(4), which manufactures drug substance using the process described in the NDA under DMF [REDACTED] (b)(4). [REDACTED] (b)(4) is proposed as a contract manufacturer of the drug substance, and the proposed manufacturing process and its control involves QbD elements.

The objective of this memo is to provide: a brief overview of the drug substance manufacturing process, a summary of QbD approaches proposed in this application, and the reviewer's suggested considerations for inspections.

Manufacturers

The sponsor has provided a list of names, addresses and testing sites of drug substance manufacturer. See Appendix I.

Manufacturing Process

The telaprevir drug substance is a large peptidomimetic molecule with 6 chiral centers [REDACTED] (b)(4)

[REDACTED] (b)(4) A flow diagram of the manufacturing process is provided in Appendix II. The applicant has adopted a Quality by Design (QbD) based approach for drug substance development. Critical process parameters have been identified. Numerous experiments were

conducted to determine a Normal Operating Range (NOR) and a Proven Acceptable Range (PAR) for all the process parameters. Table in Appendix II lists the target and the NOR and PAR for all the process parameters. The in-process controls (IPC) in the fifth column are critical except when indicated as non-critical.

In addition, the sponsor proposes to implement continuous process verification as per the FDA draft guidance on process validation. Plans for implementing continuous process verification is documented in the firm's Quality System.

For a description of the manufacturing process look for DMF (b)(4) in the EDR. In the original submission, dated 6/24/10, it appeared that the process was controlled in a traditional fashion. However, in response to questions from FDA, the DMF holder presented clarifications in the Amendment of 11/3/10 and it is clear that the DMF holder has knowledge of the QbD strategy, the design space, and the NOR and PAR. Tables 1-3 (reproduced in Appendix II below) show the target, NOR, and PAR for all parameters.

Considerations for Inspection

To be noted that the (b)(4) manufacturing site referred to in this memo, is a Contract Manufacturing Organization, that is responsible for manufacturing many different products that follow the traditional development approach. As a part of our commitment to share QbD information across offices, the CMC review team submits the following risk items for drug substance synthesis for consideration while on inspection:

1. Close interaction between the CMO (b)(4) and the sponsor (i.e. Vertex) is warranted for successful implementation of proposed QbD concepts. For example, this could include sharing information for the following: risk management strategies, procedures for handling of movements within design space, methods for performance trending and strategies for continuous process verification. The Quality Systems associated with knowledge sharing between (b)(4) and Vertex should be suitable for these approaches.
2. This application includes a design space for drug substance manufacturing given in terms of PAR. Typically, plans for handling movement within the design space are documented within the firm's Quality System, which includes procedures for handling movements within design space

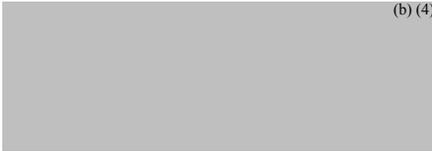
The CMC reviewer would like to participate in PAI and to share their knowledge with the investigator prior to and during the inspection. If you have any question, please contact George Lunn, Ph.D. (george.lunn@fda.hhs.gov or at 301-796-1701).

Appendix I

List of drug substance manufacturing and testing sites

The drug substance is manufactured from agreed starting materials, packaged, tested, and released at:

(b) (4)

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Release and stability testing of drug substance takes place at:

(b) (4)

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/s/

GEORGE LUNN

01/10/2011

Considerations for Inspection at (b)(4) drug substance manufacturing site

STEPHEN P MILLER

01/10/2011

DATE: January 10, 2011

TO: Extended Telaprevir (NDA 201-917) Review Team

FROM: George Lunn, Ph.D. 301-796-1701, george.lunn@fda.hhs.gov (on behalf of the CMC review team)

THROUGH: Christine Moore, Ph.D.

SUBJECT: CMC (Chemistry, Manufacturing & Controls) Considerations for upcoming Pre Approval Inspection (PAI) at (b) (4)

NDA 201-917 is submitted by Vertex Pharmaceuticals, Inc. for telaprevir immediate release tablet for oral administration containing 375 mg of drug substance telaprevir (VX-950). Telaprevir is a new molecular entity. The proposed indication is treatment of hepatitis C. The application has been granted "Priority" review status.

The sponsor proposes separate manufacturing sites for drug substance, (b) (4), and the drug product. This memo contains background information on (b) (4) which manufactures drug substance using the process described in the NDA. Drug substance is also manufactured by (b) (4). This memo pertains to the (b) (4) manufacturing site.

The objective of this memo is to provide: a brief overview of the drug substance manufacturing process, a summary of QbD approaches proposed in this application, and the reviewer's suggested considerations for inspections.

Manufacturers

The sponsor has provided a list of names, addresses and testing sites of drug substance manufacturer. See Appendix I. .

Manufacturing Process

The telaprevir drug substance is a large peptidomimetic molecule with 6 chiral centers (b) (4). (b) (4)

(b) (4) A flow diagram of the manufacturing process is provided in Appendix II. The applicant has adopted a Quality by Design (QbD) based approach for drug substance development. Parameters were delineated as key and critical process parameters. Numerous experiments were conducted to determine a Normal Operating Range (NOR) and a Proven Acceptable Range (PAR) for all the process parameters. Table in Appendix II lists the NOR and PAR for all the process parameters as well as the assessment of criticality of each parameter. (b) (4) The NOR is given in

the batch record and the PAR is available in the Process Support Document. In addition, the sponsor proposes to implement continuous process verification as per the FDA draft guidance on process validation. Plans for implementing continuous process verification is documented in the firm's Quality System.

For the current manufacturing batch record look for NDA 201-917 in the EDR. See:

Amendment 0009 dated 12/10/2010

Quality

3.2.R

3.2.R.1 Master Batch Record – Drug Substance

3.2.R.1 Master Batch Record Annex – Drug Substance

The batch records are presented in the NDA as a collection of PDF documents (see Appendix III for further details on batch records). Based on feedback from the agency an amendment was made to the batch records that was submitted as Amendment 009 to the submission. The amended batch record reflects various process changes, (b) (4). Refer to Appendix III for detailed description of a process change in the amended batch record.

Considerations for Inspection

To be noted that the (b) (4) manufacturing site referred to in this memo, is a Contract Manufacturing Organization, that is responsible for manufacturing many different products that follow the traditional development approach. As a part of our commitment to share QbD information across offices, the CMC review team submits the following risk items for drug substance synthesis for consideration while on inspection:

1. Close interaction between the CMO (b) (4) and the sponsor (i.e. Vertex) is warranted for successful implementation of proposed QbD concepts. For example, this could include sharing information for the following: risk management strategies, procedures for handling of movements within design space, methods for performance trending and strategies for continuous process verification. The Quality Systems associated with knowledge sharing between (b) (4) and Vertex should be suitable for these approaches.
2. This application includes a design space for drug substance manufacturing given in terms of PAR. The master batch record includes the NOR for each parameter and a Process Support document includes the PAR for each parameter. Typically, plans for handling movement within the design space are documented within the firm's Quality System, which includes procedures for handling movements within design space.
3. Understanding procedures in place for updating batch records and the associated training.

The CMC reviewer would like to participate in PAI and to share their knowledge with the investigator prior to and during the inspection. If you have any question, please contact George Lunn, Ph.D. (george.lunn@fda.hhs.gov or at 301-796-1701).

Appendix I

List of drug substance manufacturing and testing sites

The drug substance is manufactured from agreed starting materials at:

(b) (4)

Stability samples are stored by:

(b) (4)

Release and stability testing of drug substance manufactured by (b) (4) or (b) (4) may take place at:

(b) (4)

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/s/

GEORGE LUNN

01/10/2011

Considerations for Inspection at (b) (4) drug substance manufacturing site

STEPHEN P MILLER

01/10/2011

DATE: December 15, 2010

TO: Extended Telaprevir (NDA 201-917) Review Team

FROM: Bogdan Kurtyka, Ph.D. 301-796-1431, Bogdan.kurtyka@fda.hhs.gov (on behalf of the CMC review team)

THROUGH: Christine Moore, Ph.D

SUBJECT: CMC (Chemistry, Manufacturing & Controls) Considerations for upcoming Pre Approval Inspection (PAI)

NDA 201-917 is submitted by Vertex Pharmaceuticals, Inc. for telaprevir immediate release tablet for oral administration containing 375 mg of drug substance telaprevir (VX-950). Telaprevir is a new molecular entity. The proposed indication is treatment of hepatitis C. The application has been granted "Priority" review status.

Telaprevir drug substance has very low aqueous solubility and poor bioavailability.

(b) (4)

The sponsor proposes separate manufacturing sites for drug substance, (b) (4), and the drug product. This memo contains background information on (b) (4), one of two proposed manufacturers of (b) (4), and includes an overview of drug (b) (4) manufacturing and a CMC perspective on areas of consideration for the upcoming PAI. The manufacturing process and control of (b) (4) is proposed as the contract manufacturer (b) (4), and the proposed manufacturing process and its control does not involve any QbD elements (as opposed to the other proposed (b) (4) manufacturing site at (b) (4)).

(b) (4)

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/s/

BOGDAN KURTYKA
01/06/2011

STEPHEN P MILLER
01/10/2011

DATE: December 13, 2010

TO: Extended Telaprevir (NDA 201-917) Review Team

FROM: Lin Qi, Ph.D., 301-796-1438, lin.qi@fda.hhs.gov (on behalf of the CMC review team)

THROUGH: Christine Moore, Ph.D.

SUBJECT: CMC (Chemistry, Manufacturing & Controls) Considerations for upcoming Pre Approval Inspection (PAI)

NDA 201-917 is submitted by Vertex Pharmaceuticals, Inc. for telaprevir immediate release tablet for oral administration containing 375 mg of drug substance telaprevir (VX-950). At the time this memo is written no trade name has been proposed. Telaprevir is a new molecular entity. The proposed indication is treatment of hepatitis C. The application has been granted "Priority" review status.

Because of its low aqueous solubility (0.0047 mg/mL) at room temperature, telaprevir is

(b) (4)



QbD elements for tablet development and manufacturing include:

1. Based on the Quality Target Product Profile the sponsor identified Critical Quality Attributes (CQA) for telaprevir tablet as shown in the first column of the table below.
2. Detailed criticality analysis identified key or critical control points shown as shaded green cells in the table below.
3. Normal operating range (NOR) and proven acceptable range (PAR) were defined for almost each parameter of the (b) (4). The proposed operating ranges were determined by DoEs, process capability ratio (C_{pk}), stability models, or tablet lot histories. NORs and PARs are shown in the appendix.
4. A conventional specification, which includes tests for appearance, identity, assay, impurities, dosage uniformity by weight variation, morphic form, dissolution, and (b) (4), is provided for the tablet. As part of the control strategy, in-process controls are established (b) (4), including average tablet hardness, average tablet weight, and average tablet thickness.

Reviewer's assessment of risk:

To be noted that the (b) (4) manufacturing site referred to in this memo, is a Contract Manufacturing Organization, that is responsible for manufacturing many different products that follow the traditional development approach. (b) (4)

(b) (4) As a part of our commitment to share QbD information across offices, the CMC review team submits the following risk items of the manufacturing process for consideration while on pre-approval inspection:

1. Close interaction between the CMO (b) (4) and the sponsor (i.e. Vertex) is warranted for successful implementation of proposed QbD concepts. For example, this could include sharing information for the following: risk management strategies, procedures for handling of movements within design space, methods for performance trending and strategies for continuous improvement. The Quality Systems associated with knowledge sharing between (b) (4) and Vertex should be suitable for these approaches.
2. This application includes a design space for (b) (4). Typically, plans for handling movement within the design space are documented within the firm's Quality System, which includes procedures for handling movements within design space as well as methodologies for implementing continuous verification (e.g. trending approaches).
3. (b) (4)

(b) (4) These controls would be implemented via the CMO's operating procedures for manufacturing and storing.

4. Evaluation of hold time procedures. Hold time could potentially impact tablet CQA of organic impurities/degradation products and tablet (b) (4). It is stated in the submission (b) (4) as shown in the master batch record.
5. Understanding procedures in place to determine target operating for the (b) (4) during commercial production. In the master batch record, wide NOR and PAR are provided for (b) (4) with no target range. We note that specific target ranges were provided in earlier executed batch records (e.g., batch 3060434R). Furthermore, the applicant observed that (b) (4) is dependent on (b) (4) properties, (b) (4).

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/s/

LIN QI
01/06/2011

STEPHEN P MILLER
01/10/2011

Initial Quality Assessment
Branch V
Pre-Marketing Assessment Division II

OND Division: Division of Anti-Viral Products
NDA: 210-917
Applicant: Vertex Pharmaceuticals, Inc.
Stamp Date: 23-Nov-2010
PDUFA Date: 23-May-2011
Trademark: (b) (4)
Established Name: Telaprevir
Dosage Form: Tablets
Route of Administration: Oral
Indication: Treatment of infection with hepatitis C virus

PAL: Dorota Matecka

	YES	NO
ONDQA Fileability:	<input checked="" type="checkbox"/>	<input type="checkbox"/>
Comments for 74-Day Letter	<input type="checkbox"/>	<input checked="" type="checkbox"/>

Summary and Critical Issues:

A. Summary

The drug substance is a large peptidomimetic molecule with 6 chiral centers that is manufactured by (b) (4). The manufacturing process is only vaguely described but an executed batch record has been provided. A more detailed process description would help the reviewer to understand the process. A Quality by Design (QbD) approach has been adopted to define a Normal Operating Range (NOR) and a Proven Acceptable Range (PAR) for almost every parameter. In most cases these ranges are acceptable but the applicant describe in more detail how some ranges were determined. The specifications are conventional for a molecule of this nature and are acceptable. The analytical methods are reasonably well described and have been validated. Up to 24 months of stability data obtained at 25°C and 30°C are provided and the retest date of 36 months is acceptable.

(b) (4)
A QbD approach has been used to define a design space for the manufacture of the (b) (4). The control strategy includes design space equations for the critical quality attributes of particle size and bulk density.

It is noted that QbD approach is used only for the (b) (4) (b) (4) DMF (b) (4) that describes manufacturing and control of (b) (4) refers in some sections to the NDA under review. However, no Letter of Authorization to the NDA is included in the DMF and the application.

A detailed specification, which includes tests for appearance, identity, assay, impurities, residual solvents, morphic form, bulk density, and particle size, is provided for the (b) (4). The analytical methods are well described and have been validated. A justification of the specification is provided. Up to 24 months of stability data obtained at 25°C/60% RH are provided and a retest date of (b) (4) is proposed for the (b) (4). Comparability Protocols are provided for (b) (4) Rework and for the Design Space Model for the (b) (4).

(b) (4) A QbD approach has been adopted to define the NOR and PAR for almost each parameter of the (b) (4). The applicant described in detail how some ranges were determined and how the process parameters were classified as critical, key, or non-critical by DoEs, process capability ratio (C_{pk}), stability models, and tablet lot histories. A conventional specification, which includes tests for appearance, identity, assay, impurities, dosage uniformity by weight variation, morphic form, dissolution, and (b) (4), is provided for the tablet. As part of the control strategy, in-process controls are established (b) (4), including average tablet hardness, average tablet weight, and average tablet thickness. An Average Tablet Hardness Model was developed for the in-process control. The analytical methods are reasonably well described and have been validated. A justification of the specification is provided. The tablets are packaged in blister packs and 168-count in induction sealed HDPE bottles containing a desiccant. The blister packs are child resistant but the bottle cap does not appear to be child resistant. Up to 24 months of stability data obtained at 25°C/60% RH are provided and a retest date of 24 months is proposed for the tablets. In addition to the traditional stability studies, data from 2 QbD studies, including the End-to-End stability study and the Temperature and Relative Humidity Stability Studies, are also provided to support the stability.

All sites are ready for inspection and have been entered into EES in draft status awaiting the submission of the complete NDA.

B. Critical issues for review

The application does not include Letters of Authorization giving (b) (4) (b) (4), permission to reference the NDA. The DMFs cannot be reviewed without these LoAs. The LoAs have been requested.

Equation 3 in section 3.2.P.2.3 (tablet manufacturing process development section) is the basis for the establishment of a design space for the (b) (4). This equation prescribes the functional dependence between particle size and bulk density to achieve

dissolution [REDACTED] (b) (4). The equation was derived assuming a tablet hardness of [REDACTED] (b) (4). However, the proposed design space includes hardness [REDACTED] (b) (4). Figure 14 in this section clearly shows that dissolution [REDACTED] (b) (4). Resolution of this issue is critical.

C. Comments for 74-Day Letter

None identified to date.

D. Recommendation:

This NDA is fileable from a CMC perspective. It has several critical issues which need to be critically evaluated during the review. Comments have already been submitted to the applicant.

George Lunn

Filing Checklists

A. Administrative Checklists;

YES	NO		Comments
x		On its face, is the section organized adequately?	
x		Is the section indexed and paginated adequately?	
x		On its face, is the section legible?	
x		Are ALL of the facilities (including contract facilities and test laboratories) identified with full street addresses and CFNs?	
x		Has an environmental assessment report or categorical exclusion been provided?	

B. Technical Checklists;

1. Drug Substance

x		Does the section contain synthetic scheme with in-process parameters?	
x		Does the section contain structural elucidation data?	
x		Does the section contain specifications?	
x		Does the section contain information on impurities?	
x		Does the section contain validation data for analytical methods?	
x		Does the section contain container and closure information?	
x		Does the section contain stability data?	

2. Drug Product

X		Does the section contain manufacturing process with in-process controls?	
x		Does the section contain quality controls of excipients?	
X		Does the section contain information on composition?	
X		Does the section contain specifications?	
X		Does the section contain information on degradation products?	
X		Does the section contain validation data for analytical methods?	
X		Does the section contain information on container and closure systems?	
x		Does the section contain stability data with a proposed expiration date?	
x		Does the section contain information on labels of container and cartons?	
	x	Does the section contain tradename and established name?	

C. Review Issues

x		Has all information requested during the IND phases, and at the pre-NDA meetings been included?	
x		Is a team review recommended?	
x		Are DMFs adequately referenced?	

DMF No.	Holder	Description	LOA Included	Status
			(b) (4) Yes	Active
			Yes	Active
Yes	Active			

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/s/

GEORGE LUNN
12/03/2010
Initial Quality Assessment

STEPHEN P MILLER
12/09/2010

**PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)**

NDA Number: 201-917 **Supplement Number and Type:** Original **Established/Proper Name:** Telaprevir

Applicant: Vertex Pharmaceuticals **Letter Date:** November 22, 2010 **Stamp Date:** November 23, 2010

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? This question is not applicable for synthesized API.			N/A

**PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)**

7.	<p>Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list:</p> <ul style="list-style-type: none"> • 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.	<p>Are drug product manufacturing 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"> • 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		

**PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (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"> • 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		

* 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?	X		

**PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)**

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	

**PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)**

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		Executed batch record provided, but no master batch record.
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		

**PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)**

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?			NA

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
(b) (4)	II	[REDACTED]	(b) (4)	6/7/10	
	II		6/10/10		
	IV		6/12/09		
	III		7/12/09		
	III		7/21/09		
	III		7/21/09		
	III		7/17/09		
	III		5/14/10		
	III		8/28/09		
	III		7/21/09		

**PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)**

(b) (4)	III		(b) (4)	7/29/09	
	III		7/27/09		
	III		7/27/09		
	III		5/12/10		

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		

**PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)**

J. FILING CONCLUSION				
	Parameter	Yes	No	Comment
34.	IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?	X		
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.			Describe filing issues here or on additional sheets
36.	Are there any potential review issues to be forwarded to the Applicant for the 74-day letter?		X	Describe potential review issues here or on additional sheets

{See appended electronic signature page}

George Lunn
CMC Reviewer
Division of New Drug Quality Assessment 2
Office of New Drug Quality Assessment

December 01, 2010

{See appended electronic signature page}

Stephen P. Miller
Acting Branch Chief, Branch V
Division of New Drug Quality Assessment 2
Office of New Drug Quality Assessment

Date

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/s/

GEORGE LUNN
12/03/2010

STEPHEN P MILLER
12/03/2010

DATE: December 01, 2010

TO: Extended Telaprevir (NDA 201-917) Review Team

FROM: Bogdan Kurtyka, Ph.D. 301-796-1431, Bogdan.kurtyka@fda.hhs. (on behalf of the CMC review team)

THROUGH: Christine Moore, Ph.D

SUBJECT: CMC (Chemistry, Manufacturing & Controls) Considerations for upcoming Pre Approval Inspection (PAI)

NDA 201-917 is submitted by Vertex Pharmaceuticals, Inc. for telaprevir immediate release tablet for oral administration containing 375 mg of drug substance telaprevir (VX-950). At the time this memo is written no tradename has been proposed. Telaprevir is a new molecular entity. The proposed indication is treatment of hepatitis C. The application has been granted "Priority" review status.

Telaprevir drug substance has very low aqueous solubility and poor bioavailability.

(b) (4)



The sponsor proposes separate manufacturing sites for drug substance, (b) (4), and the drug product. This memo contains background information on (b) (4) site, one of two proposed manufacturers of (b) (4), and includes an overview of drug (b) (4) manufacturing, discussion of QbD elements incorporated in development and manufacturing, and a CMC perspective on areas of consideration for the upcoming PAI.

(b) (4)



(b) (4) The following table shows the Critical Quality Attributes (CQA) identified for the (b) (4), specification attributes and overall of control strategy for (b) (4):

QbD elements for DP development/manufacturing:

The sponsor followed a QbD based approach for drug product development. The approach can be broadly broken down into the following steps:

Reviewer's assessment of risk:

To be noted that the (b) (4) manufacturing site referred to in this memo, is a Contract Manufacturing Organization, that is responsible for manufacturing many different products that follow the traditional development approach. Based upon initial review of the application, the review team has identified the following areas in (b) (4) manufacturing as primary risks to product quality both at launch and over time: (1) (b) (4) (2) (b) (4) (3) suitability of PS and BD conversion models, and (4) maintenance of the models and design space throughout the life cycle of the product. As a part of our commitment to share QbD information across offices, the CMC review team submits the following risk items of the manufacturing process for consideration while on pre-approval inspection:

1. Close interaction between the CMO (b) (4) and the sponsor (i.e. Vertex) is warranted for successful implementation of proposed QbD concepts. For example, this could include sharing information for the following: risk management strategies, procedures for handling of movements within design space, methods for performance trending and strategies for continuous improvement. The Quality Systems associated with knowledge sharing between (b) (4) and Vertex should be suitable for these approaches.
2. The sponsor proposed to implement RTRT for (b) (4) particle size based on mathematical models. For successful RTRT implementation, the following manufacturing aspects could be critical:
 - a. Sampling strategy for (b) (4)
 - b. Strategy for maintenance of mathematical models over the life cycle of the product
3. This application includes a design space for manufacturing (b) (4). Typically, plans for handling movement within the design space are documented within the firm's Quality System, which includes procedures for handling movements within design space as well as methodologies for implementing continuous verification.
4. In general there is an elevated risk of operation when manufacturing at areas within the design space that are unverified at commercial scale, especially during early commercial stage. These risks could be mitigated, in part, by a more detailed evaluation of potential risks to product quality and by adopting an appropriate change control strategy.
5. (b) (4). Thus, evaluation of methodologies associated with monitoring (b) (4) is critical.
6. It was stated by the firm at the pre-NDA meeting, (b) (4). It is thus essential to gain an understanding of the following:

a. (b) (4)

(b) (4)

The CMC reviewer is willing to share his knowledge with the investigator prior to and during the inspection. Please either e-mail or call Bogdan Kurtyka, Ph.D., CMC reviewer.

Appendix – Proposed design space table:

Table 3 Design Space for Particle Size and Bulk Density

Model Number and Description Model

(b) (4)

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/s/

BOGDAN KURTYKA
01/06/2011

STEPHEN P MILLER
01/10/2011