CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205123Orig1s000

CHEMISTRY REVIEW(S)

NDA 205-123

Tradename™

(Simeprevir) 150 mg Capsules

Janssen Therapeutics Div Janssen Products LP

CMC Review Team	Section
Celia N. Cruz, Ph.D.*	Drug Product
Chunchun Zhang, Ph.D. *	Drug Substance
Kareen Riviere, Ph.D. **	Biopharmaceutics

*DPA II/Branch V
**Biopharmaceutics
Office of New Drug Quality Assessment

Table of Contents

Chemistry Review Data Sheet

1. NDA 205123

2. REVIEW #: 1.0 Ammendment 1.0

3. REVIEW DATE: 01-November-2013

4. REVIEWERS:

Primary:

Reviewer	NDA CTD Section
Chunchun Zhang, Ph.D.	Drug Master File Type II
Celia N. Cruz, Ph.D.	Drug Product DP Method Validation DP Master Batch Record Labeling Drug Master File Type IV

Secondary:

Reviewer	Section
Rapti Madurawe, Ph.D.	All Overall Recommendation

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
IND 75391: EoP2b Meeting Response	29-July-2011
IND 75391: Pre NDA Meeting Minutes Type B	30-Jan-2013
IND 75391: CMC Teleconference Minutes	06-Feb-2013

1. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
SDN 000 New/NDA	28-Mar-2013
SDN 015 Quality/Quality Information	24-June-2013
SDN 016 Quality/Response Quality Information	26-June-2013
SDN 017 Quality/Quality Information	03-July-2013
SDN 020 Quality/Response to Quality Information	24-July-2013

SDN 025 Quality/Quality Information	09-Aug-2013
SDN 038 Quality/Quality Information	13-Sep-2013
SDN 041 Quality/Stability Information	25-Sep-2013
SDN 042 Labeling/Conatiner-Carton Draft; Labeling/Package Insert	01-Oct-2013
SDN 048 Labeling/Conatiner-Carton Draft; Labeling/Package Insert	31-Oct-2013

2. NAME & ADDRESS OF APPLICANT:

Name:	Janssen Research and Development, LLC
Address:	1125 Trenton-Harbourton Road Titusville, NJ 08560 USA
Representative:	Michele Dias 920 Route 202 Raritan, NJ 08869
Telephone:	908-218-6014

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: to be determined
b) Non-Proprietary Name (USAN): Simeprevir capsule
c) Code Name/#: TMC435, R494617
d) Chem. Type/Submission Priority:

- Chem. Type: 1 new molecular entity
- Submission Priority: P

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

10. PHARMACOLOGICAL CATEGORY: Antiviral

11. DOSAGE FORM: Capsule

12. STRENGTH/POTENCY: 150 mg per capsule

13. ROUTE OF ADMINISTRATION: Oral

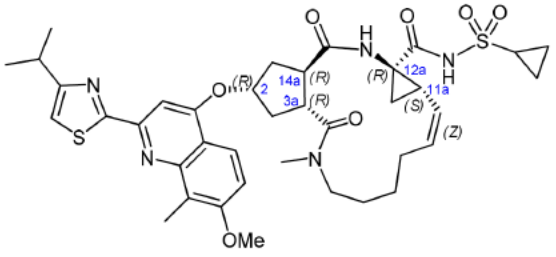
14. Rx/OTC DISPENSED: _X__Rx ___OTC

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

_____SPOTS product – Form Completed

__X__Not a SPOTS product

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

Name: simeprevir (2*R*,3a*R*,10*Z*,11a*S*,12a*R*,14a*R*)-*N*-(cyclopropylsulfonyl)-2-[[2-(4-isopropyl-1,3-thiazol-2-yl)-7-methoxy-8-methyl-4-quinolinyl]oxy]-5-methyl-4,14-dioxo-2,3,3a,4,5,6,7,8,9,11a,12,13,14,14a-tetradecahydrocyclopenta[*c*]cyclopropa[*g*][1,6]diazacyclotetradecine-12a(1*H*)-carboxamide	 $C_{38}H_{47}N_5O_7S_2$ MW = 749.94

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	REVIEW DATE	COMMENT
26864	II	Janssen Pharmceutica	Simeprevir (R494617)	1	Adequate	02-Aug-2013 C.Zhang	Adequate. LoA Confirmed 22-Mar-2013
(b) (4)	IV		(b) (4)	1	Adequate	08-Aug-2013 C. Cruz	Adequate. LoA Confirmed 07-Aug-2012
	III			4	N/A		LoA confirmed, 21-Nov-2011
	III			4	N/A		LoA confirmed. 21-Nov-2011
	III			4	N/A		LoA confirmed. 06-Dec-2011
	III			4	N/A		LoA confirmed. 06-Dec-2011
	III			4	N/A		LoA confirmed. 25-Aug-2011

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 Product Quality Reviews:

REVIEW	RECOMMENDATION	DATE	REVIEWER
Biopharmaceutics	**Acceptable** Method: Apparatus II, 75 rpm, 900 ml media volume, 37 ºC, 50 mM phosphate buffer pH 6.8 with 1.0% Polysorbate 20. Criterion: Q= (b) (4) at 30 minutes	26-Sep-2013	Kareen Riviere

C. Consults or Outside CMC Review Team input:

CONSULTS	RECOMMENDATION	DATE	REVIEWER
EES	**Overall Acceptable.** Janssen Cilag (drug product facility) was inspected in this review cycle.	20-Aug-2013 EES Report	Christina Capacci Daniel
Quality Micro	**Recommend Approval.** Microbiology testing added to drug product specifications, to be tested on stability only. Based on completion of all commitment stability studies and sufficient data, microbiological testing may be eliminated via future Supplement.	13-Aug-2013 Quality Micro Review	Steven Donald
Pharm/Tox	All specified impurities have been qualified. All acceptance criteria for drug substance and drug product impurities are significantly lower than specified level. There are no new drug product degradants. Also see, DMF 26864 Review 02-Aug-2013.	22-Aug-2013 Pharm/Tox Review	Janice Lansita
Methods Validation	**Acceptable:** UPLC method AD-TM-R494617-DS-LC-006634-V4: "Methods are acceptable for control and	26-Aug-2013	Michael Trehy

	regulatory purposes". Methods validation data were provided in the submission and are also adequate based on review.		
Environmental Analysis	N/A		

D. Other Applications or Submissions Referenced:

DOCUMENT Referenced	APPLICATION NUMBER	DESCRIPTION
All	IND 75391	TMC 435 (simeprevir)

The Chemistry Review for NDA 205123

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA has provided sufficient information to assure the identity, strength, purity, and quality of the drug product. The dissolution method and specification are acceptable based on the Biopharmaceutics review. The drug master file for the drug substance has been reviewed and found acceptable. An overall facilities recommendation of "Overall Acceptable" has been made by the Office of Compliance (20-Aug-2013). All methods have been adequately validated and found suitable for their intended purpose. CMC edits to the bottle and package insert were incorporated by the Sponsor and the final label is acceptable. 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.

II. Summary of Chemistry Assessments

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

Drug Product

Description

Simeprevir 150 mg capsules, oral dose, contain 154.4 mg of simeprevir sodium, equivalent to 150 mg simeprevir (b) (4). The capsule is a (b) (4) white body/white hard gelatin capsule printed with "TMC435 150" in black. The maximum daily dose is 150 mg per day.

The capsule formulation contains approximately (b) (4) of simeprevir sodium and the following compendial excipients: sodium lauryl sulfate, magnesium stearate, colloidal anhydrous silica, croscarmellose sodium, and lactose monohydrate. (b) (4)

Manufacturing and Control Strategy

The simeprevir 150 mg capsules manufacturing process has the following steps: (b) (4)

(b) (4)

The drug product quality is tested for the following final specifications: appearance, identification, assay, chromatographic purity (each specified, any unspecified, and total sum of degradation products), uniformity of dosage form by content uniformity, and dissolution. The drug product specifications were updated to include microbiological purity and an (b) (4) test, which are performed as part of the stability monitoring of the capsules. Quality Microbiology concluded that the microbiological purity testing strategy is adequate. All methods have been adequately validated and the specification criteria limits justified appropriately.

Biopharmaceutics

The proposed dissolution method and the dissolution specification of Q = (b) (4) at 30 min are acceptable for product quality control. At 12 months of strorage, there is a trend of decreasing % dissolved in the early time points, during the primary stability study. Reasons for the decrease are currently unknown. It is evident from (b) (4) testing, that this dissolution decrease is not due to changes (b) (4) (b) (4). Also, the decrease is observed at all T and RH conditions. Conclusion on the acceptability of the dissolution specification was completed after review of additional stability data at 18 months of storage at 25 ºC/60% RH and 30 ºC/ 75% RH. The acceptance criteria of Q = (b) (4) at 30 min was found to be acceptable to ensure drug product performance.

Stability

Stability data are presented at long term conditions of 25 ºC/60% RH and 30 ºC/ 75% RH, and accelerated condition of 40 ºC/75% RH. Overall, there are no significant changes in degradants and assay, and no changes are detected for (b) (4) appearance or microbiological purity for the drug product intermediate and the in-package drug product upon storage. Though capsules can achieve (b) (4) across the stability study, it has no

apparent correlation to degradation products, assay, appearance, (b) (4) or microbiological purity.

The greatest risk to drug product stability is light exposure, if unprotected. Significant potency losses could occur if the product is left out of package and exposed to natural light.

There is an early trend of decreasing % dissolved at 25 and 30 minutes, during the primary stability study. It is evident from (b) (4) testing, that this dissolution decrease is not due to changes (b) (4) (b) (4). Also, the decrease is observed at all T and RH conditions. However, at 18 months of stability, the capsules had acceptable dissolution at 25 ºC/60% RH and 30 ºC/ 75% RH and there were no changes on dissolution stability between 12 and 18 months.

Overall, the stability results for storage at 30 ºC/ 75% RH, 25 ºC/60% RH, and 40 ºC/75% RH (with the FDA proposed dissolution specification) currently support a 24-month shelf life for the drug product in the current (b) (4) HDPE bottle for all climatic zones. This shelf life recommendation may be updated based on additional stability data to support dissolution to be submitted in the late cycle. The date of manufacture of the drug product will start at (b) (4) (b) (4)

Based on the totality of the submitted stability and physicochemical characterization data for the drug product and drug product intermediate, (b) (4) (b) (4) is acceptable. This shelf life is not to be extended, without the submission of additional primary stability data.

Drug Substance

The drug substance, simeprevir, is a new molecular entity. Drug substance information was referenced to Janssen's DMF 26864. The DMF was reviewed and found adequate on 02-Aug-2013. The drug substance is manufactured at Janssen Pharmaceutical NV manufacturing site and the stability testing is performed at Johnson-Johnson Limited DBA site.

Simeprevir drug substance is a (b) (4) white to almost white powder. It is practically insoluble in aqueous solutions. (b) (4) (b) (4)

The specifications for Simeprevir: appearance, identification, water content, assay, impurity content, residual solvent (b) (4)
Manufacturing process and control strategy are provided in the DMF.

Stability data in the DMF supports a drug substance retest period (b) (4) for all climatic zones when protected from light.

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

Simeprevir 150 mg capsules are intended to be taken orally with food. The recommended dosage is 150 mg once daily for 12 weeks, administered with peg interferon alfa and ribavirin and followed by treatment with peg interferon alfa and ribavarin alone.

The Simeprevir 50 mg capsules are available in a (b) (4) high density polyethylene bottles (b) (4) Two bottle configurations are available: a 28 count bottle for a 4-week supply and a 7 count bottle for "Emergency supply only". The bottle label instructions have been recommended to be "Store TRADENAME below 30 ºC (86 ºF)". The label also contains bolded language to store in original container to protect from light. Final bottle label submission is pending.

C. Basis for Approvability or Not-Approval Recommendation

This NDA has provided sufficient information to assure the identity, strength, purity, and quality of the drug product and there are no pending CMC deficiencies. The drug substance and drug product specifications and the referenced DMFs have been found to be acceptable. CMC and DMEPA revisions to the bottle label and package insert were accepted by the Applicant and submitted to the NDA. Quality Microbiology has recommended approval of the NDA and the Office of Compliance recommendation for the facilities is "Overall Acceptable." There are no outstanding CMC deficiencies. Therefore, from the CMC perspective, this NDA is recommended for approval.

III. Administrative

A. Reviewer's Signature
Celia N. Cruz, Chunchun Zhang
On file

B. Endorsement Block
Rapti Madurawe
On file

C. CC Block
On file

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

/s/

CELIA CRUZ
11/01/2013

CHUNCHUN N ZHANG
11/01/2013

RAPTI D MADURAWE
11/04/2013

NDA 205-123

Tradename™

(Simeprevir) 150 mg Capsules

Janssen Therapeutics Div Janssen Products LP

CMC Review Team	Section
Celia N. Cruz, Ph.D.*	Drug Product
Chunchun Zhang, Ph.D. *	Drug Substance
Kareen Riviere, Ph.D. **	Biopharmaceutics

*DPA II/Branch V
**Biopharmaceutics
Office of New Drug Quality Assessment

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Chemistry Review Data Sheet

1. NDA 205123

2. REVIEW #: 1.0

3. REVIEW DATE: 28-Aug-2013

4. REVIEWERS:

Primary:

Reviewer	NDA CTD Section
Chunchun Zhang, Ph.D.	Drug Master File Type II
Celia N. Cruz, Ph.D.	Drug Product DP Method Validation DP Master Batch Record Labeling Drug Master File Type IV

Secondary:

Reviewer	Section
Rapti Madurawe, Ph.D.	All Overall Recommendation

5. PREVIOUS DOCUMENTS:

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IND 75391: CMC Teleconference Minutes	06-Feb-2013

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SDN 016 Quality/Response Quality Information	26-June-2013
SDN 017 Quality/Quality Information	03-July-2013
SDN 020 Quality/Response to Quality Information	24-July-2013

SDN 025 Quality/Quality Information	09-Aug-2013

7. NAME & ADDRESS OF APPLICANT:

Name:	Janssen Research and Development, LLC
Address:	1125 Trenton-Harbourton Road Titusville, NJ 08560 USA
Representative:	Michele Dias 920 Route 202 Raritan, NJ 08869
Telephone:	908-218-6014

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: to be determined
b) Non-Proprietary Name (USAN): Simeprevir capsule
c) Code Name/#: TMC435, R494617
d) Chem. Type/Submission Priority:

- Chem. Type: 1 new molecular entity
- Submission Priority: P

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

10. PHARMACOLOGICAL CATEGORY: Antiviral

11. DOSAGE FORM: Capsule

12. STRENGTH/POTENCY: 150 mg per capsule

13. ROUTE OF ADMINISTRATION: Oral

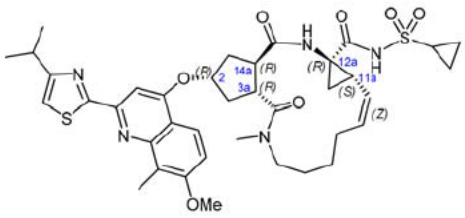
14. Rx/OTC DISPENSED: _X__Rx ___OTC

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

_____SPOTS product – Form Completed

__X__Not a SPOTS product

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

Name: simeprevir (2*R*,3a*R*,10*Z*,11a*S*,12a*R*,14a*R*)-*N*-(cyclopropylsulfonyl)-2-[[2-(4-isopropyl-1,3-thiazol-2-yl)-7-methoxy-8-methyl-4-quinolinyl]oxy]-5-methyl-4,14-dioxo-2,3,3a,4,5,6,7,8,9,11a,12,13,14,14a-tetradecahydrocyclopenta[*c*]cyclopropa[*g*][1,6]diazacyclotetradecine-12a(1*H*)-carboxamide	 $C_{38}H_{47}N_5O_7S_2$ MW = 749.94

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	REVIEW DATE	COMMENT
26864	II	Janssen Pharmceutica	Simeprevir (R494617)	1	Adequate	02-Aug-2013 C.Zhang	Adequate. LoA Confirmed 22-Mar-2013
(b) (4)	IV	(b) (4)		1	Adequate	08-Aug-2013 C. Cruz	Adequate. LoA Confirmed 07-Aug-2012
	III			4	N/A		LoA confirmed, 21-Nov-2011
	III			4	N/A		LoA confirmed. 21-Nov-2011
	III			4	N/A		LoA confirmed. 06-Dec-2011
	III			4	N/A		LoA confirmed. 06-Dec-2011
	III			4	N/A		LoA confirmed. 25-Aug-2011

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 Product Quality Reviews:

REVIEW	RECOMMENDATION	DATE	REVIEWER
Biopharmaceutics	Criterion: **Pending** response from Applicant regarding FDA proposed Q = (b) (4) at 25 minutes. Final data and response expected by Sept 2013. Method: Acceptable	27-Aug-2013	Kareen Riviere

C. Consults or Outside CMC Review Team input:

CONSULTS	RECOMMENDATION	DATE	REVIEWER
EES	**Overall Acceptable.** Janssen Cilag (drug product facility) was inspected in this review cycle.	20-Aug-2013 EES Report	Christina Capacci Daniel
Quality Micro	**Recommend Approval.** Microbiology testing added to drug product specifications, to be tested on stability only. Based on completion of all commitment stability studies and sufficient data, microbiological testing may be eliminated via future Supplement.	13-Aug-2013 Quality Micro Review	Steven Donald
Pharm/Tox	All specified impurities have been qualified. All acceptance criteria for drug substance and drug product	22-Aug-2013 Pharm/Tox Review	Janice Lansita

	impurities are significantly lower than specified level. There are no new drug product degradants. Also see, DMF 26864 Review 02-Aug-2013.		
Methods Validation	**Acceptable:** UPLC method AD-TM-R494617-DS-LC-006634-V4: "Methods are acceptable for control and regulatory purposes". Methods validation data were provided in the submission and are also adequate based on review.	26-Aug-2013	Michael Trehy
Environmental Analysis	N/A		

D. Other Applications or Submissions Referenced:

DOCUMENT Referenced	APPLICATION NUMBER	DESCRIPTION
All	IND 75391	TMC 435 (simeprevir)

The Chemistry Review for NDA 205123

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The response to FDA's Information Request dated 18-Jul-2013 regarding the drug product specification for dissolution is pending additional data from the Applicant. This NDA has otherwise provided sufficient information to assure the identity, strength, purity, and quality of the drug product. The drug master file for the drug substance has been reviewed and found acceptable. An overall facilities recommendation of "Overall Acceptable" has been made by the Office of Compliance (20-Aug-2013). All methods have been adequately validated and found suitable for their intended purpose. CMC edits and revisions to the bottle and package insert have been completed and will be communicated to the Applicant through OND communications. Therefore, from the CMC perspective, this NDA is not recommended for approval until the dissolution acceptance criterion in the drug product specification has been finalized and the final labeling is found satisfactory.

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)

Drug Product

Description
Simeprevir 150 mg capsules, oral dose, contain 154.4 mg of simeprevir sodium, equivalent to 150 mg simeprevir (b) (4). The capsule is a (b) (4) white body/white hard gelatin capsule printed with "TMC435 150" in black. The maximum daily dose is 150 mg per day.

The capsule formulation contains approximately (b) (4) of simeprevir sodium and the following compendial excipients: sodium lauryl sulfate, magnesium stearate, colloidal anhydrous silica, croscarmellose sodium, and lactose monohydrate. (b) (4)

(b) (4)

Manufacturing and Control Strategy

The simeprevir 150 mg capsules manufacturing process has the following steps: (b) (4)

(b) (4)

The drug product quality is tested for the following final specifications: appearance, identification, assay, chromatographic purity (each specified, any unspecified, and total sum of degradation products), uniformity of dosage form by content uniformity, and dissolution. The drug product specifications were updated to include microbiological purity and an (b) (4) test, which are performed as part of the stability monitoring of the capsules. Quality Microbiology concluded that the microbiological purity testing strategy is adequate. All methods have been adequately validated and the specification criteria limits justified appropriately.

Biopharmaceutics

The proposed dissolution method is acceptable for product quality control. FDA's recommendation for an acceptance criterion Q = (b) (4) at 80 minutes has been communicated to the Applicant, but is pending resolution. According to the Applicant, it may be a challenge to achieve their proposed 24-month shelf life with a dissolution specification of Q= (b) (4) as there is a trend of decreasing % dissolved in the early time points, during the primary stability study. Reasons for the decrease are currently unknown. It is evident from (b) (4) testing, that this dissolution decrease is not due to changes (b) (4) (b) (4). Also, the decrease is observed at all T and RH conditions. Finalization of the dissolution specification is pending a late cycle stability update to the NDA. Therefore, the Biopharm review states that "the submission of essential dissolution information needed for the final determination on the acceptability the dissolution acceptance criterion is pending".

Stability

Stability data are presented at long term conditions of 25 ºC/60% RH and 30 ºC/ 75% RH, and accelerated condition of 40 ºC/75% RH. Overall, there are no significant changes in degradants and assay, and no changes are detected for (b) (4) appearance or microbiological purity for the drug product intermediate and the in-package drug product upon storage. Though capsules can achieve (b) (4) across the stability study, it has no apparent correlation to degradation products, assay, appearance, (b) (4) or microbiological purity.

The greatest risk to drug product stability is light exposure, if unprotected. Significant potency losses could occur if the product is left out of package and exposed to natural light.

There is a trend of decreasing % dissolved at 25 and 30 minutes, during the primary stability study. It is evident from (b) (4) testing, that this dissolution decrease is not due to changes (b) (4) (b) (4). Also, the decrease is observed at all T and RH conditions. According to the Applicant, it may be challenge to achieve a 24-month shelf life for the FDA proposed dissolution specification of Q= (b) (4) at 25 min.

Overall, the stability results for storage at 30 ºC/ 75% RH, 25 ºC/60% RH, and 40 ºC/75% RH (with the FDA proposed dissolution specification) currently support a (b) (4) shelf life for the drug product in the current (b) (4) HDPE bottle for all climatic zones. This shelf life recommendation may be updated based on additional stability data to support dissolution to be submitted in the late cycle. The date of manufacture of the drug product will start at (b) (4) (b) (4)

Based on the totality of the submitted stability and physicochemical characterization data for the drug product and drug product intermediate, a (b) (4) (b) (4) is acceptable. This shelf life is not to be extended, without the submission of additional primary stability data.

Drug Substance

The drug substance, simeprevir, is a new molecular entity. Drug substance information was referenced to Janssen's DMF 26864. The DMF was reviewed and found adequate on 02-Aug-2013. The drug substance is manufactured at Janssen Pharmaceutical NV manufacturing site and the stability testing is performed at Johnson-Johnson Limited DBA site.

Simeprevir drug substance is a (b) (4) white to almost white powder. It is practically insoluble in aqueous solutions. (b) (4) (b) (4)

The specifications for Simeprevir: appearance, identification, water content, assay, impurity content, residual solvent (b) (4).
Manufacturing process and control strategy are provided in the DMF.

Stability

Stability data are presented at long term conditions of 25 ºC/60% RH and 30 ºC/ 75% RH, and accelerated condition of 40 ºC/75% RH. Overall, there are no significant changes in degradants and assay, and no changes are detected for (b) (4) appearance or microbiological purity for the drug product intermediate and the in-package drug product upon storage. Though capsules can achieve (b) (4) across the stability study, it has no apparent correlation to degradation products, assay, appearance, (b) (4) or microbiological purity.

The greatest risk to drug product stability is light exposure, if unprotected. Significant potency losses could occur if the product is left out of package and exposed to natural light.

There is a trend of decreasing % dissolved at 25 and 30 minutes, during the primary stability study. It is evident from (b) (4) testing, that this dissolution decrease is not due to changes (b) (4) (b) (4). Also, the decrease is observed at all T and RH conditions. According to the Applicant, it may be challenge to achieve a 24-month shelf life for the FDA proposed dissolution specification of Q= (b) (4) at 25 min.

Overall, the stability results for storage at 30 ºC/ 75% RH, 25 ºC/60% RH, and 40 ºC/75% RH (with the FDA proposed dissolution specification) currently support a (b) (4) shelf life for the drug product in the current (b) (4) HDPE bottle for all climatic zones. This shelf life recommendation may be updated based on additional stability data to support dissolution to be submitted in the late cycle. The date of manufacture of the drug product will start at (b) (4) (b) (4)

Based on the totality of the submitted stability and physicochemical characterization data for the drug product and drug product intermediate, a (b) (4) (b) (4) is acceptable. This shelf life is not to be extended, without the submission of additional primary stability data.

Drug Substance

The drug substance, simeprevir, is a new molecular entity. Drug substance information was referenced to Janssen's DMF 26864. The DMF was reviewed and found adequate on 02-Aug-2013. The drug substance is manufactured at Janssen Pharmaceutical NV manufacturing site and the stability testing is performed at Johnson-Johnson Limited DBA site.

Simeprevir drug substance is a (b) (4) white to almost white powder. It is practically insoluble in aqueous solutions. (b) (4) (b) (4)

The specifications for Simeprevir: appearance, identification, water content, assay, impurity content, residual solvent (b) (4).
Manufacturing process and control strategy are provided in the DMF.

Stability data in the DMF supports a drug substance retest period of (b) (4) for all climatic zones when protected from light.

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

Simeprevir 150 mg capsules are intended to be taken orally with food. The recommended dosage is 150 mg once daily for 12 weeks, administered with peg interferon alfa and ribavirin and followed by treatment with peg interferon alfa and ribavarin alone.

The Simeprevir 50 mg capsules are available in a (b) (4) high density polyethylene bottles, (b) (4) . Two bottle configurations are available: a 28 count bottle for a 4-week supply and a 7 count bottle for "Emergency supply only". The bottle label instructions have been recommended to be "Store TRADENAME below 30 ºC (86 ºF)". The label also contains bolded language to store in original container to protect from light. Final bottle label submission is pending.

C. Basis for Approvability or Not-Approval Recommendation

As of the date of this review, the dissolution specification review is waiting a response from the Applicant regarding a request for information. The recommended drug product shelf life of (b) (4) may be updated, based on the pending dissolution data. Labeling review by the review team is in progress. Minor CMC revisions to the bottle label and package insert have been communicated to the review team and will be finalized during OND labeling team review. This NDA has otherwise provided sufficient information to assure the identity, strength, purity, and quality of the drug product. Quality Microbiology has recommended approval of the NDA and the Office of Compliance recommendation for the facilities is "Overall Acceptable." Therefore, from the CMC perspective, this NDA is not recommended for approval until the dissolution specification is finalized, and the final labeling is found satisfactory.

III. Administrative

A. Reviewer's Signature
Celia N. Cruz, Chunchun Zhang
On file

B. Endorsement Block
Rapti Madurawe
On file

C. CC Block
On file

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/s/

CELIA CRUZ
08/28/2013

CHUNCHUN N ZHANG
08/28/2013

RAPTI D MADURAWE
08/28/2013

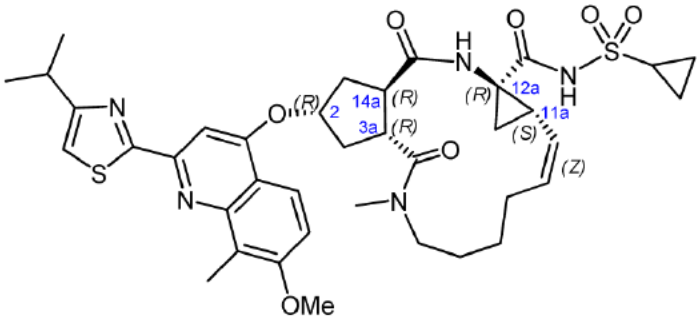
Initial Quality Assessment (IQA) and Filing Review for Pre-Marketing Applications

Review Cover Sheet

1. NEW DRUG APPLICATION NUMBER: **205-123**
   Submission Date: March 28, 2013
   ONDQA Kick-Off: Apr 18
   OND Filing Mtg: Apr 22
   Mid-Cycle OND Mtg: Jun 20
   CMC/BP GAM: July 30
   GRMP Goal Date: Aug 28
   6-month date: Sept 28 (inspectional goal)
   Late-Cycle Meeting Oct 8
   OND Action Goal: Nov 22, 2013
   PDUFA Goal Date: Nov 28 (Thanksgiving)

Review Team Assignments	
Drug Substance	Chunchun Zhang
Drug Product	Celia Cruz
Biopharmaceutics	Kareen Riviere
QbD	
Product Quality Microbiology	
ONDQA PM	Althea Cuff

2. PRODUCT PROPERTIES:

Structure:	 **Simeprevir, a.k.a. "TMC-435"**
Trade or Proprietary Name:	Sovriad (proposed)

Established or Non-Proprietary Name (USAN) and strength:	simeprevir
Dosage Form:	capsules

3. NAME OF APPLICANT:

Name:	Janssen Research & Development

4. SUBMISSION PROPERTIES:

Review Priority :	PRIORITY
Classification (Code):	Type 1 (New Molecular Entity)
Property (Legal Basis):	505 (b)(1)
Responsible Organization:	DAVP

Review Information

1. INDICATION: Treatment of chronic infection with Hepatitis C virus, in combination with PEF-Interferon and Ribavirin

2. ROUTE OF ADMINISTRATION: Oral

3. STRENGTH/POTENCY: 150 mg

4. Rx/OTC DISPENSED: ☒Rx ☐OTC

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

   Is this a SPOTS product? ☐Yes ☒No ☐ Not evaluated at time of IQA.

6. RELATED REVIEW DOCUMENTS:

a. Drug Master Files listed on 356h form:

DMF #	TYPE	HOLDER	ITEM REFERENCED	LOA DATE	COMMENTS
26864	II	Janssen Pharmaceutica NV	Simeprevir DS	Mar 22, 2013	
(b) (4)	V	(b) (4)		Feb 5, 2013	
				Aug 21, 2012	
	IV			Jan 11, 2013	
5 other LOAs are included for packaging components					

b. Consults Recommended by CMC and Biopharmaceutics

CONSULT	YES	NO	COMMENTS: (list date of request if already sent)
Biometrics		X	
Clin Pharm		X	
EES	X		
Pharm/Tox		X	Part of review team; coordinate on impurity control
Methods Validation	X		
EA		X	
New Drug Micro		X	To be evaluated further in second ONDQA review mtg
CDRH		X	
Other ( )		X	

c. Other Applications or Submissions to note (if any):

DOCUMENT NAME	DATE	APPLICATION NUMBER	DESCRIPTION

d. Previous Communications with the Applicant to note (if any):

DOCUMENT NAME	DATE	APPLICATION NUMBER	DESCRIPTION
IND 75,391	Feb 2013		BP and CMC PreNDA

			Meeting Minutes
IND 75,391	July 2011		Preliminary FDA responses to June 29, 2011 EOP-2 questions and meeting background package.

Overall Conclusions and Recommendations

Is the Product Quality Section of the application fileable from a CMC perspective?		
Yes	No	CMC Filing Issues
X		1.

Are there potential CMC review issues to be forward to the applicant with the 74 day letter?		
Yes	No	CMC Comments for 74 Day Letter
X		Listed below in "Summary or Highlights of the Application"

Is the Product Quality Section of the application fileable from a biopharmaceutics perspective?		
Yes	No	Biopharmaceutics Filing Issues
X		See Dr Riviere's separate filing review in DARRTS

CMC Summary:
Critical Issues and Complexities

CMC Critical Issues or Complexities			
Issues noted are listed in Summary below, but are not considered critical.			
Does the submission contain any of the following elements? No			
Nanotechnology	QbD Elements	PET	Other, please explain
☐	☐	☐	

Is a team review recommended?		
Yes	No	Suggested expertise for team
X		DS, DP, and BP
Review Team Assignments are listed on Page 1		

Summary or Highlights of the Application ***(not already mentioned in other sections)***

Changes between Clinical DP and Proposed Commercial DP

Clinical Tablets	Commercial Tablets
This was discussed extensively in the Feb 2013 PreNDA meeting	

Simeprevir is an inhibitor of the Hepatitis C protease enzyme. The proposed treatment chronic infection with Hepatitis C virus is 150 mg once per day in combination with PEG-interferon and ribavirin. The duration of use is 24 week, although some patients will require an additional 24 weeks of PEG-interferon and ribavirin (without simeprevir) to eliminate the infection.

After discussion at the ONDQA Kick-Off meeting, we conclude that while a PQMM will be composed, this NDA does not qualify to be tracked as a QbD application.

Drug Substance

With sulfonamide subgroup in the structure, it may be good to talk with the clinical reviewer whether it would be appropriate to discuss in labeling the use in patients with pre-existing allergies to sulfonamide drugs.

Some DS information should be included in the NDA. E.g.:

- DS specification
- Discussion of physical properties of DS that may impact quality of the (b) (4) capsule
- Manufacturing facilities ? (they are included in Module 1)
- Methods for DS specification ? (low risk, since DS manufacturer and applicant are parts of the same company)

Perhaps consult with Pharm/Tox reviewer to verify that (b) (4) is the appropriate safety target in the drug substance (didn't find it in the current draft of ICH (b) (4) guidance, Q3D). Should P/T reviewer also verify the accuracy of the qualification values for the routine (normal) impurities in S.3.2?

Steps (b) (4) of the synthesis are categorized as critical based on a criticality analysis summarized in Table 1, and the critical control points in each of those steps are described in Table 2 (see 3.2.S.2.4).

Draft 74-Day Letter Comments:
Consider sending a request to include appropriate information on drug substance in the NDA. See bullet points listed above.

Drug Product

(b) (4)

In the process description in P.3.3, "Multivariate PARs" and PARs are given for some process parameters, most of which are identified as CPPs.

Is the omission of (b) (4) content from the specification for the (b) (4) (b) (4) appropriately justified? This was discussed during CMC EOP-2 meeting.

The capsules are packaged in HDPE bottles (b) (4) in bottles of 28 and bottles of 7.

Clarification was received on Apr 26 regarding the intended use of the 7-capsule bottles. These could be used in the event that a patient's insurance is waiting for the viral response data after 4 weeks of treatment, in order to determine whether the patient should receive a second month of simeprevir.

Draft 74-Day Letter Comments:
None identified as part of IQA/Filing review.

Description of Facility-Related Risks or Complexities (i.e. number of foreign sites,

large number of sites involved, etc.)
See EES for complete list of facilities related to this application.

APPEARS THIS WAY ON ORIGINAL

FILING REVIEW CHECKLIST

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

A. GENERAL				
	Parameter	**Yes**	**No**	**Comment**
1.	Is the CMC section organized adequately?	X		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	X		
3.	Are all the pages in the CMC section legible?	X		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?			See question in "Summary or Highlights of the Application"

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.**			NA

7.	Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	X		In 356h and in DMF
8.	Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	X		
9.	Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	X		

10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	X		356h attachment

* 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		21 CFR 25.31[b]

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

E. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	**Yes**	**No**	**Comment**
13.	Does the section contain a description of the DS manufacturing process?	X		Information is provided in DMF 26864 Process descriptions include reasonable detail at (b) (4) scale. Commercial scale is approx (b) (4)
14.	Does the section contain identification and controls of critical steps and intermediates of the DS(in process parameters?	X		Information is provided in DMF 26864
15.	Does the section contain information on impurities?	X		Information is provided in DMF 26864
16.	Does the section contain information regarding the characterization of the DS?	X		Information is provided in DMF 26864
17.	Does the section contain controls for the DS?	X		No DS information is provided in the NDA. See notes under "Summary or Highlights of the Application" for possible early info request Information is provided in DMF 26864
18.	Has stability data and analysis been provided for the drug substance?	X		18 mo on three batches (b) (4) at 25/60 and 30/75 12 mo on one batch (b) (4) from commercial (Geel) site. 12 mo (b) (4) on all 4 batches Photo stab on Geel and one more.
19.	Does the application contain Quality by Design (QbD) information regarding the DS?		X	
20.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		X	
21.	Does the section contain container and closure information?	X		Information is provided in DMF 26864

F. DRUG PRODUCT (DP)				
	Parameter	**Yes**	**No**	**Comment**
22.	Does the section contain quality controls of excipients?			
23.	Does the section contain information on composition?			
24.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	X		Narrative description is included in P.3.3 Unexecuted batch record for commercial ?? kg batch (??? tablets) is included as required for b2 application? Executed batch records are provided each of the following processes: (b) (4) [redacted] Unexecuted batch records are provide in 3.2.R at the following scale: (b) (4) [redacted]
25.	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		
26.	Is there a batch production record and a proposed master batch record?	X		As noted in Point 24, above
27.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	X		
28.	Have any Comparability Protocols been requested		X	None in Regional Info in NDA or in DMF 26864
29.	Does the section contain description of to-be-marketed container/closure system and presentations?	X		

30.	Does the section contain controls of the final drug product?	X		Attached below
31.	Has stability data and analysis been provided to support the requested expiration date?	X		3 batches of (b) (4) made at develop site (Beerse) and one batch made completely at commercial site (Geel). All (b) (4) scale. 12 mo of data at 25/60 and 30/75 on three lots of caps ((b) (4) made with Beerse (b) (4) at Beerse. 3 mo of data for one lot (b) (4) made from Geel (b) (4) and (b) (4) at commercial Latina facility. All lots in both bottles of 28 and bottles of 7 (5 for three of the NDA lots)
32.	Does the application contain Quality by Design (QbD) information regarding the DP?			See discussion in "Summary or Highlights of the Application"
33.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		X	

G. METHODS VALIDATION (MV)				
	Parameter	**Yes**	**No**	**Comment**
34.	Is there a methods validation package?			

H. MICROBIOLOGY				
	Parameter	**Yes**	**No**	**Comment**
35.	If appropriate, is a separate microbiological section included discussing sterility of the drug product?			NA – not a sterile product

I. LABELING				
	Parameter	**Yes**	**No**	**Comment**
36.	Has the draft package insert been provided?	X		
37.	Have the immediate container and carton labels been provided?	X		Attached below
38.	Does section contain tradename and established name?	X		

ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications

FILING CONCLUSION				
	Parameter	**Yes**	**No**	**Comment**
39.	**ARE THE PRODUCT QUALITY SECTIONS OF THE APPLICATION FILEABLE?**	X		
40.	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.
41.	Are there any potential review issues identified?			Listed above in "Summary or Highlights of the Application"

REVIEW AND APPROVAL

See appended electronic signature page}
Stephen Miller, Ph.D.
CMC-Lead
Division of Pre-Marketing Assessment II, Branch V
Office of New Drug Quality Assessment

{See appended electronic signature page}
Rapti Madurawe, Ph.D.
Branch Chief
Division of Pre-Marketing Assessment II, Branch V
Office of New Drug Quality Assessment

Appendix 1. Composition of Drug Product

(b) (4)

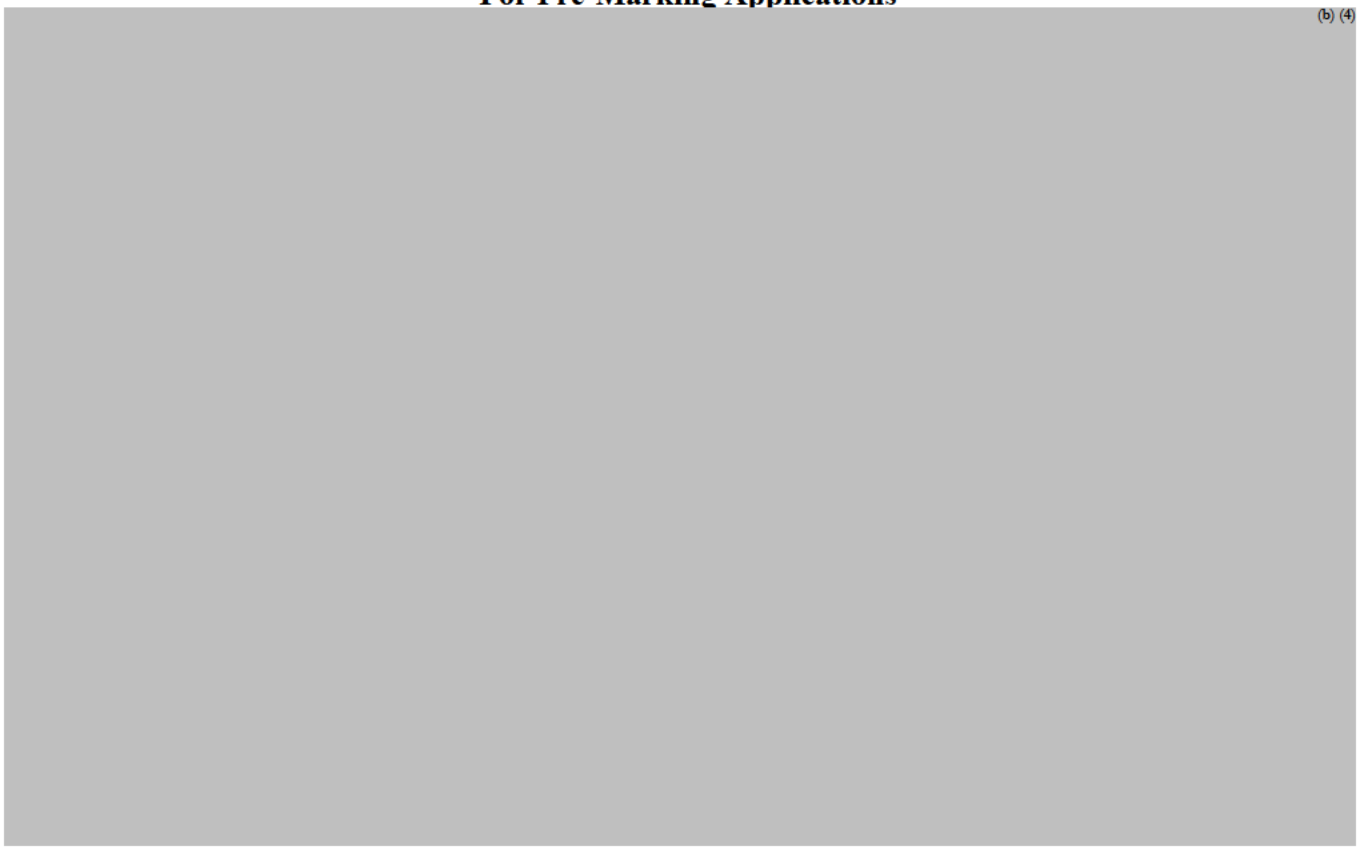
Table 2: Target Composition of the 150-mg Capsule (G028)

Component	Quality Reference[a]	Function	Quantity per Capsule (mg)
Simeprevir (b) (4)	Control of Critical Steps and Intermediates	Active	154.60
Sodium lauryl sulphate	Ph. Eur., NF	(b) (4)	
Magnesium stearate[b]	Ph. Eur., NF		
Colloidal anhydrous silica	Ph. Eur., NF		
Croscarmellose sodium	Ph. Eur., NF		
Lactose monohydrate	Ph. Eur., NF		
Nominal weight:			
Hard gelatin capsule (b) (4) white body/white cap with black "TMC435 150" print	Control of Excipients	Capsule	1 piece

[a] Where multiple compendia are listed, the compendium that is applied, is specific to the applicable region of the submission.

(b) (4)

(b) (4)



Appendix 3. DP Specification

Table 1: Drug Product Specification

Test Parameter	Acceptance Criteria	Test Methods
1. Appearance	Hard gelatin capsule ((b) (4) white body with black "TMC435 150" print/white cap filled with white to almost white powder	Visual examination
2. Identification[a] a. UV b. HPLC	(b) (4)	
3. Assay of Simeprevir		
4. Chromatographic Purity a. Each specified degradation product (b) (4) b. Any unspecified degradation product c. Total degradation products		
5. Uniformity of Dosage Units[a]		
6. Dissolution		

[a] Initial release test only

Appendix 4. Container Labels

Appendix 5. DS Specification

Table 1: Specifications for Drug Substance

Parameters	Regulatory Acceptance Criteria	Test Methods
1. Appearance	White to almost white powder	Visual examination
2. Identification[a]	(b) (4)	
a. IR		
3. Assay		
4. Chromatographic Purity		
a. Each specified impurity (b) (4)		
b. Any unspecified impurity		
c. Total impurities		
5. Water Content		
6. Residue on (b) (4)		
7. (b) (4)		

[a] Initial release test only

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/s/

STEPHEN MILLER
05/10/2013

RAPTI D MADURAWE
05/17/2013