

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

205786Orig1s000

CHEMISTRY REVIEW(S)

**ONDQA Quality Assessment
Division II**

**NDA 22-145 / S-031 (EDR-271; DS-865)
NDA 203-045 / S-009 (EDR-049; SD-60)
NDA 205-786 Original**

**Isentress
Merck**

**Submission Dates: June 26, 2013
PDUFA Date: Dec 26, 2013**

	<p>Inhibitor of HIV integrase enzyme</p>
<p>Isentress (Raltegravir) Tablets, 400 mg Isentress (Raltegravir) Chewable Tablets, 25 and 100 mg Isentress (Raltegravir) For Oral Suspension</p>	<p>Approved and Marketed Approved and Marketed Original under Review</p>

Summary:

Because all raltegravir products share common labeling, two efficacy supplements were submitted to reflect labeling changes caused by the planned approval of the new dosage form for pediatric use: Isentress (Raltegravir) For Oral Suspension.

For information about this new pediatric product, see reviews of NDA 205-786. Please note that Dr. Zhang's and Dr. Riviere's reviews were finalized before a nomenclature issue (described below) was recognized, and the dosage form name in those reviews follows the name as originally submitted.

When this new product was submitted, the proposed name was Isentress (raltegravir) (b)(4) Suspension. At the time of the labeling review from the SEALD team (Dec 12, 2013), the SEALD reviewer (Dr. Elizabeth Donohoe) expressed concern about the product name, indicating that (b)(4) Suspension is not a USP-recognized term. Subsequently, Dr. Yana Mille confirmed that (b)(4) should not be part of the nonproprietary name for this product, because the product is used to prepare a dosage form that is then administered. This is based on this recommendation from the USP nomenclature guidelines: (b)(4)

The conclusion was that the correct name for this new pediatric product should be:
Isentress (raltegravir) For Oral Suspension

The applicant was asked to revise the name of the new product throughout the labeling. There are some places in the labeling where it is more appropriate to refer to the oral suspension (in lower case letters) (b)(4). In other areas, where the product before reconstitution is the focus, it is more appropriate to use

**ONDQA Quality Assessment
Division II**

For Oral Suspension (with capitalization). Some recommended examples are shown below.



(b) (4)

ONDQA Quality Assessment Division II

(b) (4)

Section 17 Patient Counseling Information

Physicians should instruct parents and/or caregivers to read the Instructions for Use before preparing and administering **ISENTRESS For Oral Suspension** to pediatric patients. Physicians should instruct parents and/or caregivers that [REDACTED] (b) (4) [REDACTED] should be administered within 30 minutes of mixing.

Packet and Carton Labels

Given the short time remaining before approval, the revised container labels will be submitted to NDA 205-786 after action.

Note: Concerns expressed by Drs. Donohoe, Mille and Lostritto with the existing language in the labels [REDACTED] (b) (4) [REDACTED]

Conclusions:

These two efficacy supplements and the original NDA are recommended for approval from the CMC perspective, once these recommended changes are made to the Prescribing Information. The recommendations in this review are suggestions to balance accuracy and readability, and it is anticipated that some adjustments will be made based on recommendations from the applicant or other reviewers.

Stephen P. Miller, Ph.D.

CMC-Lead

See DARRTS

Date

Rapti Madurawe, Ph.D.

Branch Chief

See DARRTS

Date

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/s/

STEPHEN MILLER
12/18/2013

RAPTI D MADURAWA
12/19/2013

NDA 205-786

ISENTRESS[®] (raltegravir) (b) (4) Suspension, 100 mg

Merck Sharp & Dohme Corp.

Addendum 1 to Review # 1

Chunchun Zhang, Ph.D.

**ONDQA
Division of Pre-Marketing Assessment II
Branch V**

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Chemistry Review Data Sheet

1. NDA 205-786
2. REVIEW #: Addendum 1 to Review #1
3. REVIEW DATE: 10-December, 2013
4. REVIEWER: Chunchun Zhang
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Original submission	26-Jun-2013
IR	14-Aug-2013
BC	28-Aug-2013
IR	11-Oct-2013
BC	21-Oct-2013
IR	12-Nov-2013
BC	15-Nov-2013
BC	2-Dec-2013

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original submission	26-Jun-2013
BC	28-Aug-2013
BC	21-Oct-2013
BC	15-Nov-2013
BC	2-Dec-2013

7. NAME & ADDRESS OF APPLICANT:

Chemistry Review Data Sheet

Name:	Merck Sharp & Dohme Corp.
Address:	One Merck Drive, P.O. Box 100, Whitehouse Station, NJ 08889-0100
Representative:	Ursula Marek
Telephone:	908-740-3359

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: ISENTRESS (b) (4) Suspension
b) Non-Proprietary Name (USAN): Raltegravir
c) Code Name/# (ONDC only): N/A
d) Chem. Type/Submission Priority (ONDC only):
- Chem. Type: 3
 - Submission Priority: P

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

10. PHARMACOL. CATEGORY: Antiviral

11. DOSAGE FORM: Granules for Suspension

12. STRENGTH/POTENCY: 100 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: Rx OTC15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

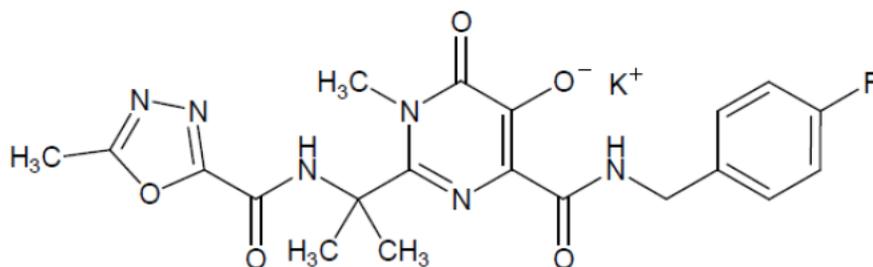
Not a SPOTS product

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

USAN: Raltegravir

Chemical Name: N-[(4-Fluorophenyl)methyl]-1,6-dihydro-5-hydroxy-1-methyl-2-[1-methyl-1-[[[(5-methyl-1,3,4-oxadiazol-2-yl)carbonyl]amino]ethyl]-6-oxo-4-pyrimidinecarboxamide monopotassium salt

Chemistry Review Data Sheet



Molecular Weight: 482.51

Molecular Formula: C₂₀H₂₀FN₆O₅

Chemical Abstract: [871038-72-1]

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	III	(b) (4)	(b) (4)	4	Adequate		
	III		4	Adequate			
	III		4	Adequate			
	III		4	Adequate			
	III		4	Adequate			
	IV		1	Adequate	9/15/11 A. Yu		
	IV		1	Adequate	9/15/11 A. Yu	Review #3	
	IV		3	Adequate	2-Feb-2000 By K. Swiss	Review #2 for (b) (4)	

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

Chemistry Review Data Sheet

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: N/A

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATI ON	DATE	REVIEWER
Biometrics			N/A
EES	Acceptable	10/3/2013	Tracie Sharp
Pharm/Tox			N/A
Biopharm	Acceptable	12/09/2013	Kareen Riviere
LNC			N/A
Methods Validation			N/A
OPDRA			N/A
EA	Acceptable	11/12/2013	Raanan Bloom
Microbiology	Acceptable	7/22/2013	Bryan Riley

Addendum 1 to Chemistry Review #1 for NDA 205-786

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 outstanding biopharmaceutics information request has been satisfactorily addressed and the biopharmaceutics review now recommends approval of the NDA. All the chemistry, manufacturing and controls (CMC) information in this NDA was found adequate in CMC review #1 dated Nov-18-2013. An overall recommendation of Acceptable has been made by the Office of Compliance. The labels have adequate CMC information as required. 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

N/A

II. Summary of Chemistry Assessments

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

Drug substance:

The drug substance raltegravir potassium salt is manufactured by Merck Pharmaceuticals Inc., and is referenced by NDA 22-145. There are no outstanding supplemental changes to NDA 22-145. The drug substance information is found adequate based on the approved status of NDA 22-145.

Drug product:

NDA 205-786 provides for raltegravir (b)(4) Suspension, 100 mg for HIV-infected infants (b)(4) (4 weeks (b)(4)) use. The applicant's raltegravir tablets, 400 mg for adults, and raltegravir chewable tablets, 25 mg and 100 mg for children, were approved on October 12, 2007 and December 21, 2011 under NDA 22-145 and NDA 203-045, respectively.

Executive Summary Section

The raltegravir (b) (4) Suspension formulation is similar to the chewable tablet formulation, both contain adequate sweeteners and flavors for taste masking and other commonly used excipients. The 3 DMFs for flavors and taste masking were reviewed for chewable tablets and found adequate.



The drug product specification, as amended, is generally acceptable. Tests for granule solubility, (b) (4) and fineness of dispersion were added upon FDA request. The biopharmaceutics review dated 12/9/2013 found the new drug release ("solubility") specification acceptable. The drug product specification will be updated with the test for fineness of dispersion on or before 03/31/2014 (after NDA action).

The drug product is granted a shelf life of 24 months at controlled room temperature based on three formal stability batches of long term stability data at 30°C/75%RH for 12 months and accelerated stability data at 40°C/75% for 6 months. The three formal stability batches are manufactured at greater than (b) (4) commercial scale by the proposed commercial process, but differ from the commercial batches in manufacturing site, equipment and scale. The composite stability data provided are adequate. The lack of microbial testing on stability is found acceptable by the product quality microbiology reviewer Dr. Bryan S. Riley on 7/22/2013.

A dosing syringe is included in the commercial package for weight-based dosing. The NDA includes a dose accuracy study. The dose variations observed, particularly at the lowest 1 ml dose, were found acceptable by the clinical reviewer, Dr. Yodit Belew, on 11/08/2013.

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

Raltegravir (b) (4) Suspension are supplied as a kit holding 60 unit dose sachets, (b) (4) mixing cup (with lid) and 2 oral dosing syringes. The ancillary components are necessary to prepare doses. Each sachet is for single use and contains 108.6 mg of raltegravir (as potassium salt), equivalent to 100 mg of raltegravir free phenol, in (b) (4) of powder. The mixing cups and oral dosing syringes are designed for multiple uses and washings between doses.

Executive Summary Section

Prior to dosing, granules in one entire sachet are suspended in 5 mL of water in the mixing cup and mixed by inverting the lidded cup. The syringe is used to withdraw the appropriate dosing volume based on patient weight (chart included in the labeling) for delivery in the patient's mouth.

The (b) (4) Suspension are recommended to be stored at 20-25°C (68-77°F); excursions permitted to 15-30 °C (59-86 °F) (See USP Controlled Room Temperature). The expiration dating period granted is 24 months when stored under recommended conditions.

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. An overall recommendation of Acceptable has been made by the Office of Compliance on Oct 3, 2013. The labels have adequate CMC information as required and labels will be finalized during team review of labeling. From the CMC perspective, this NDA is recommended for approval.

III. Administrative

A. Reviewer's Signature

Chunchun Zhang, CMC Reviewer, Branch V, ONDQA

B. Endorsement Block

Rapti Madurawe, Branch Chief, Branch V, ONDQA

C. CC Block

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/s/

CHUNCHUN N ZHANG
12/11/2013

RAPTI D MADURawe
12/11/2013

NDA 205-786

ISENTRESS[®] (raltegravir) [REDACTED]^{(b) (4)} Suspension, 100 mg

Merck Sharp & Dohme Corp.

Chunchun Zhang, Ph.D.

**ONDQA
Division of Pre-Marketing Assessment II
Branch V**

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Chemistry Review Data Sheet

1. NDA 205-786
2. REVIEW #: 1
3. REVIEW DATE: 18-November, 2013
4. REVIEWER: Chunchun Zhang
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Original submission	26-Jun-2013
IR	14-Aug-2013
BC	28-Aug-2013
IR	11-Oct-2013
BC	21-Oct-2013
IR	12-Nov-2013
BC	15-Nov-2013

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Original submission	26-Jun-2013
BC	28-Aug-2013
BC	21-Oct-2013
BC	15-Nov-2013

7. NAME & ADDRESS OF APPLICANT:

Name:	Merck Sharp & Dohme Corp.
-------	---------------------------

Chemistry Review Data Sheet

Address:	One Merck Drive, P.O. Box 100, Whitehouse Station, NJ 08889-0100
Representative:	Ursula Marek
Telephone:	908-740-3359

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: ISENTRESS (b) (4) Suspension
b) Non-Proprietary Name (USAN): Raltegravir
c) Code Name/# (ONDC only): N/A
d) Chem. Type/Submission Priority (ONDC only):
- Chem. Type: 3
 - Submission Priority: P

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

10. PHARMACOL. CATEGORY: Antiviral

11. DOSAGE FORM: Granules for Suspension

12. STRENGTH/POTENCY: 100 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: Rx OTC15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

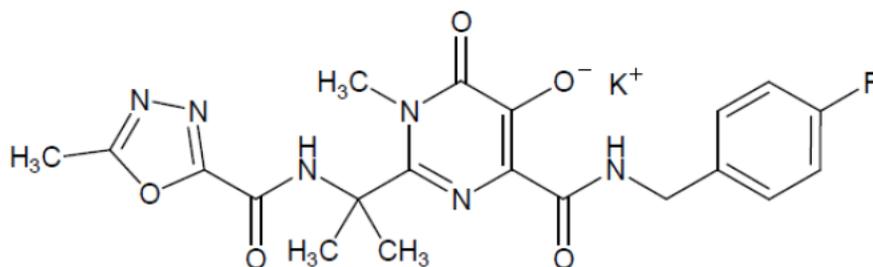
Not a SPOTS product

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

USAN: Raltegravir

Chemical Name: N-[(4-Fluorophenyl)methyl]-1,6-dihydro-5-hydroxy-1-methyl-2-[1-methyl-1-[[[(5-methyl-1,3,4-oxadiazol-2-yl)carbonyl]amino]ethyl]-6-oxo-4-pyrimidinecarboxamide monopotassium salt

Chemistry Review Data Sheet



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Molecular Formula: C₂₀H₂₀FN₆O₅

Chemical Abstract: [871038-72-1]

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	III		4	Adequate			
	III		4	Adequate			
	III		4	Adequate			
	IV		1	Adequate	9/15/11 A. Yu		
	IV		1	Adequate	9/15/11 A. Yu	Review #3	
	IV		3	Adequate	2-Feb-2000 By K. Swiss	Review #2 for (b) (4)	

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7 – Other (explain under "Comments")

Chemistry Review Data Sheet

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: N/A

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATI ON	DATE	REVIEWER
Biometrics			N/A
EES	Acceptable	10/3/2013	Tracie Sharp
Pharm/Tox			N/A
Biopharm	Pending; final data and response expected by 11/29/2013.	11/18/2013	Kareen Riviere
LNC			N/A
Methods Validation			N/A
OPDRA			N/A
EA	Acceptable	11/12/2013	Raanan Bloom
Microbiology	Acceptable	7/22/2013	Bryan Riley

The Chemistry Review for NDA 205-786

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The biopharmaceutics review recommendation is pending as of the date of this review due to an outstanding information request. Therefore, this NDA is not recommended for approval from a quality perspective at this time. All other chemistry, manufacturing and controls (CMC) information in this NDA was found adequate. An overall recommendation of Acceptable has been made by the Office of Compliance. The labels have adequate CMC information as required. Approval of this NDA is contingent upon receipt of a satisfactory response to the outstanding biopharmaceutics information request and a recommendation of approval from the biopharmaceutics reviewer.

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

N/A

II. Summary of Chemistry Assessments

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

Drug substance:

The drug substance raltegravir potassium salt is manufactured by Merck Pharmaceuticals Inc., and is referenced by NDA 22-145. There are no outstanding supplemental changes to NDA 22-145. The drug substance information is found adequate based on the approved status of NDA 22-145.

Drug product:

NDA 205-786 provides for raltegravir (b)(4) Suspension, 100 mg for HIV-infected infants (b)(4) (4 weeks (b)(4)) use. The applicant's raltegravir tablets, 400 mg for adults, and raltegravir chewable tablets, 25 mg and 100 mg for children, were approved on October 12, 2007 and December 21, 2011 under NDA 22-145 and NDA 203-045, respectively.

The raltegravir (b)(4) Suspension formulation is similar to the chewable tablet formulation, both contain adequate sweeteners and flavors for taste masking and other

Executive Summary Section

commonly used excipients. The 3 DMFs for flavors and taste masking were reviewed for chewable tablets and found adequate.



Although the drug product specification is generally acceptable, the biopharmaceutics reviewer has requested the addition of a test for granule solubility as the applicant does not propose to conduct dissolution testing. This information request is currently outstanding and the biopharmaceutics review recommendation as of this review date is "Pending." The applicant has agreed to include (b) (4) and fineness of dispersion in the drug product specification in the Amendment dated on 11/15/2013; the revised specification will be submitted in the subsequent amendment.

The drug product is granted a shelf life of 24 months at controlled room temperature based on three formal stability batches of long term stability data at 30°C/75%RH for 12 months and accelerated stability data at 40°C/75% for 6 months. The three formal stability batches are manufactured at greater than (b) (4) commercial scale by the proposed commercial process, but differ from the commercial batches in manufacturing site, equipment and scale. The composite stability data provided are adequate. The lack of microbial testing on stability is found acceptable by the product quality microbiology reviewer Dr. Bryan S. Riley on 7/22/2013.

A dosing syringe is included in the commercial package for weight-based dosing. The NDA includes a dose accuracy study. The dose variations observed, particularly at the lowest 1 ml dose, were found acceptable by the clinical reviewer, Dr. Yodit Belew, on 11/08/2013.

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

Raltegravir (b) (4) Suspension are supplied as a kit holding 60 unit dose sachets, (b) (4) mixing cup (with lid) and 2 oral dosing syringes. The ancillary components are necessary to prepare doses. Each sachet is for single use and contains 108.6 mg of raltegravir (as potassium salt), equivalent to 100 mg of raltegravir free phenol, in (b) (4) of powder. The mixing cups and oral dosing syringes are designed for multiple uses and washings between doses.

Executive Summary Section

Prior to dosing, granules in one entire sachet are suspended in 5 mL of water in the mixing cup and mixed by inverting the lidded cup. The syringe is used to withdraw the appropriate dosing volume based on patient weight (chart included in the labeling) for delivery in the patient's mouth.

The (b) (4) Suspension are recommended to be stored at 20-25°C (68-77°F); excursions permitted to 15-30 °C (59-86 °F) (See USP Controlled Room Temperature). The expiration dating period granted is 24 months when stored under recommended conditions.

C. Basis for Approvability or Not-Approval Recommendation

The biopharmaceutics review recommendation is pending as the applicant has not yet responded to a request for adding a solubility test to the drug product specification for product quality control. Apart from this outstanding issue, all other information in this NDA is sufficient to assure the identity, strength, purity and quality of the drug product. An overall recommendation of Acceptable has been made by the Office of Compliance on Oct 3, 2013. The labels have adequate CMC information as required and labels will be finalized during team review of labeling. From the CMC perspective, this NDA is not recommended for approval until the solubility specification is finalized.

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

Chunchun Zhang, CMC Reviewer, Branch V, ONDQA

B. Endorsement Block

Rapti Madurawe, Branch Chief, Branch V, ONDQA

C. CC Block

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/s/

CHUNCHUN N ZHANG
11/18/2013

RAPTI D MADURawe
11/18/2013

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

IQA and Filing Review Cover Sheet

1. NEW DRUG APPLICATION NUMBER: **205-786**

2. DATES AND GOALS:

Letter Date: June 25, 2013	Submission Received Date : June 26, 2013
PDUFA Goal Date: Dec 26, 2013	Action Goal Date: Dec 13, 2013

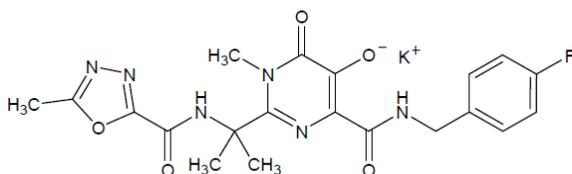
3. PRODUCT PROPERTIES:

Trade or Proprietary Name:	Isentress
Established or Non-Proprietary Name (USAN):	Raltegravir
Dosage Form:	Granules for Suspension
Route of Administration	Oral
Strength/Potency	100 mg raltegravir per pouch (as the potassium salt)
Rx/OTC Dispensed:	Rx

4. INDICATION:

In combination with other antiretroviral agents for the treatment of HIV-1 infection (raltegravir is an integrase strand transfer inhibitor).

5. DRUG SUBSTANCE STRUCTURAL FORMULA:



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

Merck Sharp & Dohme Corp.

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

7. SUBMISSION PROPERTIES:

Review Priority:	Priority
Submission Classification (Chemical Classification Code):	Type 3 (new dosage form – not previously approved in the US)
Application Type:	505(b)(1)
Breakthrough Therapy	No
Responsible Organization (Clinical Division):	DAVP

8. CONSULTS:

CONSULT	YES	NO	COMMENTS: (list date of request if already sent)
Biometrics		X	
Clinical Pharmacology		X	
Establishment Evaluation Request (EER)	X		
Pharmacology/Toxicology		X	
Methods Validation		X	
Environmental Assessment		X	
CDRH		X	
Other			NA

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

Overall Filing Conclusions and Recommendations

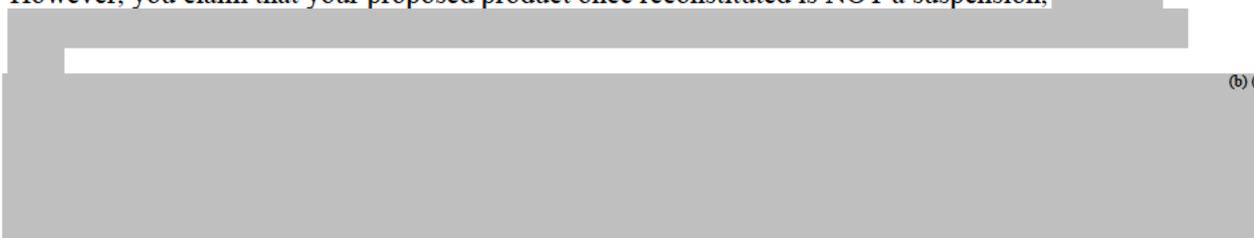
CMC:

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

Are there potential CMC review issues to be forwarded to the Applicant with the 74-Day letter?	
Yes	No
CMC Comments for 74-Day Letter:	
1. Dr. Chunchun Zhang identified 4 CMC information requests which were conveyed to the applicant on Aug 14, 2013 (see DARRTS)	

Biopharmaceutics:

Is the Product Quality Section of the application fileable from a Biopharmaceutics perspective?	
Yes	No
Biopharmaceutics Filing Issues:	
1. See Dr. Karen Riviere's BioPharm filing review in DARRTS	

Are there potential Biopharmaceutics review issues to be forwarded to the Applicant with the 74-Day letter?	
Yes	No
Biopharmaceutics Comments for 74-Day Letter (conveyed Aug 14, 2013):	
1. The dosage form of your proposed product, granules for suspension, requires dissolution testing. However, you claim that your proposed product once reconstituted is NOT a suspension, (b) (4)	
 (b) (4)	

Microbiology:

Is the Product Quality Section of the application fileable from a Microbiology perspective?	
Yes	No
Microbiology Filing Issues:	
See Dr. Bryan Riley's Microbiology Filing Review which recommends approval of the NDA.	

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

Summary of Initial Quality Assessment

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

Is a team review recommended?	Yes	No
Suggested expertise for team: Assigned Reviewers: Chunchun Zhang DS & DP Kareen Riviere BioPharm Althea Cuff ONDQA PM		

Summary of Critical Issues and Complexities

[Redacted content] (b) (4)

A

Biopharmaceutics question was included in the Aug 14 filing letter requesting data to address this issue.

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

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?			NA There were no CMC recommendations that apply to the pediatric powder in the June 2011 meeting that focused primarily on the chewable tablets.

B. FACILITIES*				
* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a <i>potential</i> filing issue or a <i>potential</i> review issue.				
	Parameter	Yes	No	Comment
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?			
6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? This question is not applicable for synthesized API.			NA

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

	Parameter	Yes	No	Comment
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 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		

**ONDQA Initial Quality Assessment (IQA) and Filing Review
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	Parameter	Yes	No	Comment
9.	Are additional manufacturing, packaging and control/testing laboratory sites identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: <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		356h PAI statement attachment

C. ENVIRONMENTAL ASSESMENT

	Parameter	Yes	No	Comment
11.	Has an environmental assessment or claim of categorical exclusion been provided?	X		21 CFR §25.31(b) (EIC below 1 ppb)

**ONDQA Initial Quality Assessment (IQA) and Filing Review
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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	References NDA 22-145
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?		X	References NDA 22-145
14.	Does the section contain information regarding the characterization of the DS?	X		
15.	Does the section contain controls for the DS?	X		Attached below
16.	Has stability data and analysis been provided for the drug substance?		X	References NDA 22-145
17.	Does the application contain Quality by Design (QbD) information regarding the DS?		X	Not in this application
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		X	Not in this application

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

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		Narrative description at (b) (4) scale is included
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		No unexecuted batch record for commercial production is included; this is acceptable for a 505b1 application Executed batch records for a (b) (4) sachet batch, and the 3 input (b) (4) batches ((b) (4) each) are included.
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		100 mg (b) (4) sachet
25.	Does the section contain controls of the final drug product?	X		Attached below
26.	Has stability data and analysis been provided to support the requested expiration date?	X		(b) (4) accelerated, etc
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	

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

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			A filing review was completed by Dr. Bryan Riley, which concludes that the NDA is recommended for approval from the product quality microbiology perspective.

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		No DMF exists for (b) (4) (monoammonium glycyrrhizinate), but adequate information is provided in 3.2.P.4.1 (CoA, and clarification that exposure is below level listed in FDA's IIG).

DMF #	TYPE	HOLDER	ITEM REFERENCED	LOA DATE	COMMENTS
			(b) (4)	2/15/11	
				2/7/11	
				2/17/11	
				4/1/13	

4 additional DMFs are referenced for packaging components

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		Attached below

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

This document will be sequentially signed in DARRTS by all of the following who authored or reviewed this assessment:

[See appended electronic signature page](#)

Stephen P. 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

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

Appendix 1. Composition of Drug Product

Batch Formula for Raltegravir (b)(4) Suspension.

Components	Theoretical Quantity per Sachet (mg)	Theoretical Quantity per Batch (kg)
Raltegravir †	108.6	(b)(4)
Hydroxypropyl Cellulose (b)(4)	(b)(4)	
(Ethylcellulose) (b)(4)		
Sucralose (b)(4)		
Natural banana flavor (b)(4)		
Crospovidone, (b)(4)		
Mannitol		
Microcrystalline Cellulose and Carboxymethyl cellulose Sodium ¹		
Magnesium Stearate		
Total Sachet (Net Fill) or Batch Weight Number of Sachets		(b)(4)

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

Appendix 2. DP Specification

Specification Established for Raltegravir Oral Granules For Suspension

Tests	Acceptance Criteria	Test Methods
Appearance (release and shelf-life)	White to off-white (b)(4) granular powder in which yellow to beige to tan particles may be observed	Test by visual observation.
Assay (release and shelf-life)	(b)(4) of Label Claim Label claim = 100 mg/sachet	Assay, Degradates, and Identity by HPLC (Sec. 3.2.P.5.2.1)
Degradation Products (release and shelf-life)	Open Ring: NMT (b)(4)% Acid: NMT (b)(4)% Any Unspecified: NMT (b)(4)% Total Degradation Products: NMT (b)(4)%	Assay, Degradates, and Identity by HPLC (Sec. 3.2.P.5.2.1)
Identity by FTIR (release)	The presence of raltegravir is confirmed if the sample spectrum displays minima at wavenumbers corresponding to the specified main peaks	Identity by FTIR (Sec. 3.2.P.5.2.3)
Identity by HPLC (release)	The retention times of the raltegravir peak in the sample and standard chromatograms are essentially the same (within (b)(4)%).	Assay, Degradates, and Identity by HPLC (Sec. 3.2.P.5.2.1)
Uniformity of Dosage Units (release)	Complies with the requirements of the USP <905> and Ph. Eur. 2.9.40	HPLC (Sec. 3.2.P.5.2.2)
Microbial Limits (release)	Total Aerobic Microbial Count: NMT (b)(4) Total Combined Yeasts and Molds Count: NMT (b)(4) Absence of <i>Escherichia coli</i> in (b)(4)	As per Ph. Eur. 2.6.12 and 2.6.13 and USP <61> and <62>

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

Appendix 3. Container Labels

Pouch Label Front Panel



Pouch Label Reverse Panel



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

Carton Label



(b) (4)

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

Appendix 4. DS Specification

Analytical Procedure	Acceptance Criteria	Test Method
Assay by HPLC (Release and Stability)	(b) (4)	HPLC – Sec. 3.2.S.4.2.1-0518
Characteristics (Release and Stability)	White to off-white powder	Test by visual observation
Identity by IR (Release)	The sample IR spectrum exhibits maxima in absorbance only at the same wavelengths as those of an authentic sample	IR – Sec. 3.2.S.4.2.5-0518
Identity by Flame Test (Release)	The sample imparts a violet color to the flame indicating the presence of potassium	Flame Test – Sec. 3.2.S.4.2.4-0518
Impurities by HPLC (Release and Stability)	(b) (4)	HPLC – Sec. 3.2.S.4.2.1-0518
	Maximum (b) (4) % Area	
	Maximum (b) (4) % Area	
	Maximum (b) (4) % Area	
	Maximum (b) (4) % Area	
	Maximum (b) (4) % Area	
	Maximum (b) (4) % Area	
	Maximum (b) (4) % Area	
	Maximum (b) (4) % Area	
Total impurities	Maximum (b) (4) % Area	
(b) (4)		
Particle size (Tablet, 400 mg) (Release)	(b) (4) microns Mean: (b) (4) microns	PSD- Sec. 3.2.S.4.2.6-0518
Particle size (Chewable Tablets, 25 and 100 mg and Granules for Suspension) (Release)	(b) (4) microns Mean: (b) (4) microns	PSD- Sec. 3.2.S.4.2.6-0518

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/s/

STEPHEN MILLER
09/18/2013

RAPTI D MADURawe
09/19/2013

PRODUCT QUALITY - BIOPHARMACEUTICS FILING REVIEW

NDA Number	205-786
Submission Date	June 27, 2013
Product name, generic name of the active	ISENTRESS® (raltegravir (b) (4))
Dosage form and strength	Granules for Suspension/ 100 mg
Applicant	Merck
Clinical Division	DAVP
Indication	in combination with other anti-retroviral agents for the treatment of HIV-1 infection
Type of Submission	505(b)(1) New Drug Application
Biopharmaceutics Reviewer	Kareen Riviere, Ph.D.
Biopharmaceutics Team Leader	Angelica Dorantes, Ph.D.
Biopharmaceutics Supervisor (acting)	Richard Lostritto, Ph.D.

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

ONDQA-BIOPHARMACEUTICS				
<u>A. INITIAL</u> OVERVIEW OF THE NDA APPLICATION FOR FILING				
	Parameter	Yes	No	Comment
1.	Does the application contain dissolution data?		x	Refer to the Initial Assessment.
2.	Is the dissolution test part of the DP specifications?		x	Refer to the Initial Assessment.
3.	Does the application contain the dissolution method development report?		x	Refer to the Initial Assessment.
4.	Is there a validation package for the analytical method and dissolution methodology?		x	Refer to the Initial Assessment.
5.	Does the application include a biowaiver request?		x	A biowaiver is not needed.
6.	Is there information provided to support the biowaiver request?		x	
7.	Does the application include a IVIVC model?		x	
8.	Is information such as BCS classification mentioned, and supportive data provided?	x		The Applicant reports that raltegravir is a BCS Class 2 compound.
9.	Is information on mixing the product with foods or liquids included?	x		The Applicant provided in-use stability data for the product dissolved in water.
10.	Is there any <i>in vivo</i> BA or BE information in the submission?	x		Data from BE Study P068 will be reviewed by the Clinical Pharmacology reviewer.

**PRODUCT QUALITY - BIOPHARMACEUTICS
FILING REVIEW**

B. FILING CONCLUSION				
	Parameter	Yes	No	Comment
11.	IS THE BIOPHARMACEUTICS SECTIONS OF THE APPLICATION FILEABLE?	x		
12.	If the NDA is not fileable from the biopharmaceutics perspective, state the reasons and provide filing comments to be sent to the Applicant.	-	-	
13.	Are there any potential review issues to be forwarded to the Applicant for the 60-day letter?	x		IR comments will be sent to the Applicant in the 60 day letter. The comments are outlined in the Initial Assessment.

{See appended electronic signature page}

Karen Riviere, Ph.D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

8/2/13
Date

{See appended electronic signature page}

Angelica Dorantes, Ph.D.
Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

8/2/13
Date

PRODUCT QUALITY - BIOPHARMACEUTICS FILING REVIEW

INITIAL BIOPHARMACEUTICS ASSESSMENT

The current submission is intended to support the use of raltegravir in infants (b) (4) aged ≥ 4 weeks (b) (4) (b) (4) dosed as a (b) (4) suspension formulation with a weight-based dose of 6 mg/kg twice daily. To prepare the suspension for dosing, the granules are mixed with 5 mL of water to prepare a 20 mg/ml suspension in a mixing cup. A dosing syringe is utilized to measure and administer the appropriate, weight based dose to the child.

The to-be marketed formulation was evaluated in the pediatric pharmacokinetic, safety, and efficacy study in HIV-infected pediatric patients (IMPAACT Protocol 1066). Additionally, the to-be marketed formulation was investigated in BE Study P068.

This submission does not include a dissolution method development report or a proposed dissolution acceptance criterion. Instead the Applicant provides limited justification for why a dissolution method and acceptance criterion is not needed for their proposed product.

The Biopharmaceutics review will focus on the acceptability of not having a dissolution method and acceptance criterion for the proposed product.

RECOMMENDATION:

The ONDQA Biopharmaceutics team has reviewed NDA 205786 for filing purposes. We found this NDA **fileable** from a Biopharmaceutics perspective. The Applicant has submitted a reviewable submission.

To aid the review of this NDA submission, the following comment will be conveyed to the Applicant:

1. The dosage form of your proposed product, granules for suspension, requires dissolution testing. However, you claim that your proposed product once reconstituted is NOT a suspension, (b) (4)

(b) (4)

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

/s/

KAREEN RIVIERE
08/02/2013

ANGELICA DORANTES
08/02/2013