

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**205395Orig1s000**

**CHEMISTRY REVIEW(S)**

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

**Application:** NDA 205395/000  
**Code:** 530  
**Priority:** 4Y  
**Stamp Date:** 31 MAR-2014  
**PDUFA Date:** 31 JAN 2015  
**Action Goal:**  
**District Goal:** 02-DEC 2014

**Sponsor:** JANSSEN PRODS  
 1125 TRENTON HARBOURTON RD  
 TITUSVILLE, NJ 08560  
**Brand Name:** DARUNAVIR/COBICISTAT  
**Estab. Name:**  
**Generic Name:**  
**Product Number; Dosage Form; Ingredient; Strengths**

001; TABLET (IMMED/COMP. RELEASE), FILM COATED;  
 DARUNAVIR; (b) (4) MG  
 001; TABLET (IMMED/COMP. RELEASE), FILM COATED;  
 COBICISTAT; 150MG

<b>FDA Contacts:</b>	R. XU	Facility Reviewer		3017966187
	F. LIU	Prod Qual Reviewer		3017961469
	E. PFEILER	Micro Reviewer	(HF-22)	3017960642
	A. CUFF	Product Quality PM	(HF 01)	3017964061
	N. MANI	Regulatory Project Mgr	(HFD-530)	2404020333
	S. MILLER	Team Leader		3017961418

<b>Overall Recommendation:</b>	ACCEPTABLE	on 04-SEP 2014	by R. MOORE	( )	2404029988
	PENDING	on 03-SEP 2014	by EES PROD		
	ACCEPTABLE	on 20-AUG 2014	by EES PROD		
	PENDING	on 23-APR 2014	by EES PROD		
	PENDING	on 09-APR 2014	by EES PROD		

**Establishment:** **CFN:** (b) (4) **FEI:** (b) (4)  
 (b) (4)

**DMF No:** **AADA:**

**Responsibilities:** DRUG SUBSTANCE MANUFACTURER  
 DRUG SUBSTANCE OTHER TESTER  
 DRUG SUBSTANCE RELEASE TESTER  
 INTERMEDIATE MANUFACTURER

**Profile:** NON-STERILE API BY CHEMICAL SYNTHESIS **OAI Status:** NONE

**Last Milestone:** OC RECOMMENDATION

**Milestone Date:** 24-APR-2014

**Decision:** ACCEPTABLE

**Reason:** DISTRICT RECOMMENDATION

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

**Establishment:** CFN: 9615378 FEI: 3001027806  
GILEAD ALBERTA ULC  
1021 HAYTER RD NW  
EDMONTON, ALBERTA, CANADA

**DMF No:** AADA:

**Responsibilities:** DRUG SUBSTANCE MANUFACTURER  
DRUG SUBSTANCE PACKAGER  
DRUG SUBSTANCE RELEASE TESTER

**Profile:** NON-STERILE API BY CHEMICAL SYNTHESIS OAI Status: NONE

**Last Milestone:** OC RECOMMENDATION

**Milestone Date:** 11 APR 2014

**Decision:** ACCEPTABLE

**Reason:** BASED ON PROFILE

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**Establishment:** CFN: 2952384 FEI: 1000523075  
GILEAD SCIENCES, INC.  
FOSTER CITY, , UNITED STATES 944041147

**DMF No:** AADA:

**Responsibilities:** DRUG SUBSTANCE RELEASE TESTER  
DRUG SUBSTANCE STABILITY TESTER

**Profile:** CONTROL TESTING LABORATORY OAI Status: NONE

**Last Milestone:** OC RECOMMENDATION

**Milestone Date:** 04 SEP 2014

**Decision:** ACCEPTABLE

**Reason:** DISTRICT RECOMMENDATION

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**Establishment:** CFN: 2650104 FEI: 3002942061  
JANSSEN ORTHO L.L.C.  
GURABO, , UNITED STATES 00778

**DMF No:** AADA:

**Responsibilities:** FINISHED DOSAGE LABELER  
FINISHED DOSAGE MANUFACTURER  
FINISHED DOSAGE PACKAGER  
FINISHED DOSAGE RELEASE TESTER

**Profile:** TABLETS, PROMPT RELEASE OAI Status: NONE

**Last Milestone:** OC RECOMMENDATION

**Milestone Date:** 22-APR 2014

**Decision:** ACCEPTABLE

**Reason:** DISTRICT RECOMMENDATION

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

**Establishment:** CFN: 9610034 FEI: 3002807337  
JANSSEN PHARMACEUTICA N.V.  
JANSSEN PHARMACETICALAAN 3  
GEEL, , BELGIUM

**DMF No:** AADA:

**Responsibilities:** INTERMEDIATE MANUFACTURER  
INTERMEDIATE RELEASE TESTER

**Profile:** NON-STERILE API BY CHEMICAL SYNTHESIS **OAI Status:** NONE

**Last Milestone:** OC RECOMMENDATION

**Milestone Date:** 11 APR 2014

**Decision:** ACCEPTABLE

**Reason:** BASED ON PROFILE

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**Establishment:** CFN: 9611011 FEI: 3002807361  
JANSSEN PHARMACEUTICAL, LTD.  
LITTLE ISLAND  
CORK, , IRELAND

**DMF No:** AADA:

**Responsibilities:** DRUG SUBSTANCE MANUFACTURER  
DRUG SUBSTANCE OTHER TESTER  
DRUG SUBSTANCE RELEASE TESTER

**Profile:** NON-STERILE API BY CHEMICAL SYNTHESIS **OAI Status:** NONE

**Last Milestone:** OC RECOMMENDATION

**Milestone Date:** 10 JUN-2014

**Decision:** ACCEPTABLE

**Reason:** DISTRICT RECOMMENDATION

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**Establishment:** CFN: 2242843 FEI: 2242843  
JANSSEN PHARMACEUTICALS, INC.  
,, UNITED STATES

**DMF No:** AADA:

**Responsibilities:** FINISHED DOSAGE STABILITY TESTER

**Profile:** CONTROL TESTING LABORATORY **OAI Status:** NONE

**Last Milestone:** OC RECOMMENDATION

**Milestone Date:** 11-APR-2014

**Decision:** ACCEPTABLE

**Reason:** BASED ON PROFILE





## Overall Manufacturing Inspection Recommendation

| [Next task >](#)

NDA 205395-Orig1-New/NDA(1)

Facility Inspection Overall Application Recommendation

Facility Inspection Overall Application Recommendation

**Approve**

Facility Inspection Overall Application Re evaluation Date

**2/22/15**

# **NDA 205395**

**Darunavir/Cobicistat Tablet, 800 mg/150 mg**

**Janssen Products, LP.**

**Fuqiang Liu, Ph.D.  
Branch V, ONDQA  
For the Division of Anti-Viral Products**

# Table of Contents

<b>Table of Contents .....</b>	<b>2</b>
<b>Chemistry Review Data Sheet.....</b>	<b>3</b>
<b>The Executive Summary .....</b>	<b>8</b>
I. Recommendations.....	8
A. Recommendation and Conclusion on Approvability.....	8
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.....	8
II. Summary of Chemistry Assessments.....	8
A. Description of the Drug Product(s) and Drug Substance(s) .....	8
B. Description of How the Drug Product is Intended to be Used.....	9
C. Basis for Approvability or Not-Approval Recommendation.....	9
III. Administrative.....	12
A. Reviewer's Signature.....	12
B. Endorsement Block.....	12
C. CC Block .....	12
<b>Chemistry Assessment .....</b>	<b>13</b>
I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data.....	13
S DRUG SUBSTANCE [Name, Manufacturer].....	13
P DRUG PRODUCT [Name, Dosage form].....	20
A APPENDICES .....	50
R REGIONAL INFORMATION .....	51
II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1 .....	51
A. Labeling & Package Insert .....	51
B. Environmental Assessment Or Claim Of Categorical Exclusion .....	53
III. List Of Deficiencies To Be Communicated.....	53

# Chemistry Review Data Sheet

1. NDA 205395

2. REVIEW #: 01

3. REVIEW DATE: 16-Dec-2014

4. REVIEWER: Fuqiang Liu, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents

Document Date

None

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Document Date

Original NDA

31-Mar-2014

SDN# 010 Multiple Categories/Subcategories

14-Jul-2014

SDN# 015 Quality/Quality Information

12-Sept-2014

SDN# 018 Quality/Response to Information Request

17-Oct-2014

7. NAME & ADDRESS OF APPLICANT:

Name: Janssen Products, LP

Address: 1125 Trenton-Harbourton Road,  
Titusville, NJ 08560

Representative: Karen Gerry, BSc, Global RA Manager

Telephone: 416-382-4819

8. DRUG PRODUCT NAME/CODE/TYPE:

## Chemistry Review Data Sheet

- a) Proprietary Name: Prezcofix  
b) Non-Proprietary Name (USAN): darunavir/cobicistat  
c) Code Name/# (ONDC only): DRV/COBI  
d) Chem. Type/Submission Priority (ONDC only):
- Chem. Type: 4
  - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOL. CATEGORY: Anti-Viral (Treatment of HIV infection)

11. DOSAGE FORM: Tablet

12. STRENGTH/POTENCY: 800 mg/150 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED:  Rx  OTC

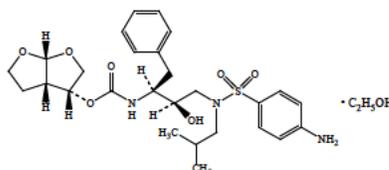
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

Not a SPOTS product

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

1) Darunavir



## Chemistry Review Data Sheet

**IUPAC name:** [(1*S*,2*R*)-3-[[[4-aminophenyl)sulfonyl](2-methylpropyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]-carbamic acid (3*R*,3*aS*,6*aR*)-hexahydrofuro[2,3-*b*]furan-3-yl ester monoethanolate.

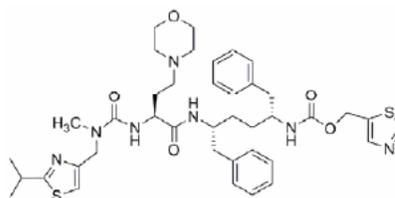
**USAN:** Darunavir

**Formula:** C<sub>27</sub>H<sub>37</sub>N<sub>3</sub>O<sub>7</sub>S • C<sub>2</sub>H<sub>5</sub>OH

**Molecular weight:** 593.73.

The defined drug substance is darunavir ethanolate.

## 2) Cobicistat



**IUPAC name:** 1,3-thiazol-5-ylmethyl [(2*R*,5*R*)-5-[[[(2*S*)2-[(methyl{2-(propan-2-yl)-1,3-thiazol-4-yl]methyl} carbamoyl)amino]-4-(morpholin-4-yl)butanoyl]amino]-1,6-diphenylhexan-2-yl]carbamate.

**USAN:** Cobicistat

**Formula:** C<sub>40</sub>H<sub>53</sub>N<sub>7</sub>O<sub>5</sub>S<sub>2</sub>

**Molecular weight:** 776.0

The defined drug substance is cobicistat

(b) (4)

## 17. RELATED/SUPPORTING DOCUMENTS:

## A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
25188	II	Gilead	Cobicistat	3	Adequate	July 2014	Reviewed by G. Lunn
18825	II	Janssen	Darunavir	3	Adequate	May 2014	Reviewed by A. Banerjee
(b) (4)	IV	(b) (4)	(b) (4)	4	Adequate		

Chemistry Review Data Sheet

(b) (4)	III	(b) (4)	4	Adequate		
	III		3, 4	Adequate	Mar. 2012	Reviewed by G. Holbert
	III		4	Adequate		
	III		3, 4	Adequate	Oct. 2013	Reviewed by Y. Chen
	III		4	Adequate		

<sup>1</sup> 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")

<sup>2</sup> 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	113198	darunavir/cobicistat IND
IND	62477	darunavir tablets IND
NDA	21976	darunavir tablets NDA
NDA	202895	darunavir oral suspension NDA
NDA	203100	Stribild tablets NDA (FDC, including Cobicistat) by Gilead
NDA	203094	Tybost (Cobicistat) tablets NDA by Gilead

18. STATUS:

**ONDQA:**

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics			
EES	Acceptable	04-Sept-2014	Rose Xu, Ph.D.
Pharm/Tox	N/A		Laine (Peyton) Myers, Ph.D.
Biopharm	Recommends AP	05-Dec-2014	Minerva Hughes, Ph.D.
LNC	N/A		
Methods Validation	N/A		



# CHEMISTRY REVIEW



## Chemistry Review Data Sheet

OPDRA	N/A		
EA	Consult sent by A. Cuff	16 Dec 2014	James Laurenson
Microbiology	Approval	16-Jul-2014	Erika A Pfeiler, Ph.D.

# The Chemistry Review for NDA 205395

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

NDA 205395 has provided adequate CMC information to assure the identity, strength, purity, and quality of the drug product. The Drug Master Files (DMF 25188 and DMF 18825) for the cobicistat on silicon dioxide and darunavir ethanolate drug substances supporting this NDA are adequate. The labels and labeling are adequate from a CMC perspective, but are pending OND team review for finalization. The overall recommendation from the Office of Compliance is ACCEPTABLE as of Sept. 4, 2014 for the establishment evaluation. The Product Quality Microbiology review from Dr. Pfeiler and the Biopharmaceutics review from Dr. Hughes both recommend approval. The Environmental Assessment data supplied for Darunavir was found to be acceptable by James Laurenson (EA Staff), and a Finding of No Significant Impact (FONSI) was issued. From the Quality 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 Substances

All cobicistat drug substance information is referenced to Gilead's Drug Master File (DMF) 25188. The drug substance, as defined in DMF 25188, is cobicistat on silicon dioxide. Cobicistat is (b) (4) (b) (4) adsorption onto silicon dioxide (b) (4) (b) (4)

DMF 25188 was found adequate on July 22, 2014 by Dr. George Lunn. No new information has been submitted since then, thus DMF 25188 remains adequate. NDA 205395 sources cobicistat on silicon dioxide drug substance manufactured at the Yuhan, Korea and Gilead Alberta sites.

All darunavir drug substance information is referenced to Janssen's DMF 18825. The drug substance, as defined in DMF 18825, is darunavir ethanolate (b) (4) DMF 18825 was found adequate on May 8, 2014 by Dr. Anamitro Banerjee. No new information has been submitted since then, thus DMF 18825 remains adequate. NDA 205395 sources darunavir drug substance manufactured at the Cilag AG, Switzerland and Janssen Cork, Ireland sites.

##### Drug Product

## Executive Summary Section

The drug product is an immediate release, film-coated tablet consisting of a fixed dose combination (FDC) of 800 mg equivalent of darunavir (b) (4) and 150 mg equivalent of cobicistat (b) (4). The tablets are oval shaped, debossed, and film-coated with pink color.

The darunavir/cobicistat tablets contain excipients commonly used in tablet dosage forms: colloidal silicon dioxide, crospovidone, hypromellose, silicified microcrystalline cellulose and magnesium stearate. The film-coats contain iron oxide black, iron oxide red, polyethylene glycol, polyvinyl alcohol (partially hydrolyzed), talc and titanium dioxide. The drug product is packaged in a white HDPE, 120 mL bottle with (b) (4).

The tablets are manufactured by Janssen Ortho, Gurabo, Puerto Rico using (b) (4). The drug product specifications are reasonable and include appearance, identification, assay, degradation products, content uniformity, dissolution, etc. There are no specified darunavir related degradation products. The three specified cobicistat related degradation products are all reported in NDA 203100 and NDA 203094. The proposed specification is adequately justified for the drug product both at release and at the proposed shelf life.

Stability data were provided for the three primary stability batches, indicating that the drug product is stable for 18 months when stored in the proposed commercial container closure system at (b) (4). No degradation of darunavir above the level of (b) (4) % is observed throughout the stability studies. The three specified cobicistat degradation products remained at below (b) (4) %, far below the specification criteria. Dissolution over shelf life was found acceptable by the biopharmaceutics reviewer. Please refer to the biopharmaceutics review for details.

A shelf life of 24 months is granted for all climatic zones for drug product packaged in the proposed commercial container closure system.

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

The darunavir/cobicistat 800 mg/150 mg tablet is a two drug fixed dose combination (FDC) of darunavir, a HIV-1 protease inhibitor and cobicistat, a CYP3A inhibitor for the treatment of HIV-1 infection in adult patients. The recommended dose is one tablet taken orally, once daily, with food.

The darunavir/cobicistat 800 mg/150 mg tablets are packaged in 120 mL, white, high density polyethylene (HDPE) bottles. Each bottle contains 30 tablets and is capped (b) (4). A shelf life of 24 months is granted for all climatic zones for drug product packaged in the proposed commercial container closure system.

**C. Basis for Approvability or Not-Approval Recommendation**

Information provided for NDA 205395 regarding drug product manufacturing, raw materials controls and specifications, analytical methods, and drug product stability is adequate to support the quality of

Executive Summary Section

the drug product through its shelf-life of 24 months. The DMFs for the darunavir and cobicistat drug substances are adequate. The labels and package insert are adequate from a CMC-perspective although the labels and labeling are pending final OND team review.

The overall recommendation from the Office of Compliance is “ACCEPTABLE” as of September 4, 2014 for the establishment evaluation. Therefore, from the CMC perspective, this NDA is recommended for approval.

**D. Lifecycle Knowledge Management**

**a) Drug Product – Initial Risk Identification:**

Product attribute/CQA	Factors that can impact the CQA	Probability of Occurrence (O)	Severity of Effect (S)	Detectability (D)	FMECA RPN Number	Comment, if any
Assay, stability	Formulation Container closure Raw materials Process parameters Scale/equipments Site	3	2	3/1	18/6	Although darunavir is highly stable, cobicistat is considered moderately stable thus O=3. RPN=18 is assigned for stability (D=3) and RPN=6 is for release (D=1) (both low risk).
Physical stability (solid state)	Formulation Raw materials Process parameters Scale/equipments Site	4	3	4	48	Although darunavir is crystalline, cobicistat is amorphous thus O=4
Content uniformity	See Physical stability	2	2	4	16	(b) (4)
Microbial limits	See Physical stability	1	2	3	6	
Dissolution	See Physical stability	4	2	4	32	

RPN Values: Low Risk (1-25); Moderate Risk (26-60); High Risk (61-125)

**b) Drug Product – Final Risk Assessment**

From Initial Quality Assessment			Reviewer Assessment		
Product attribute/CQA	Factors that can impact the CQA	Risk Ranking	Risk Mitigation Approach	Risk Evaluation	Lifecycle Considerations/ Comments
Assay, stability	Formulation Container closure Raw materials Process parameters Scale/equipments Site	L		Acceptable	
Physical stability (solid state)	Formulation Raw materials Process parameters	M		Acceptable	Both drug substances are used in other approved drugs and covered by

Executive Summary Section

	Scale/equipments Site				adequate DMFs, where solid state is well controlled.
Content uniformity	See Physical stability	L		Acceptable	
Microbial limits	See Physical stability	L		Acceptable See Dr. Pfeiler's Review	
Dissolution	See Physical stability	M		Acceptable See Dr. Hughes' Review	Keep monitoring

Risk ranking applies to product attribute/CQA

**III. Administrative****A. Reviewer's Signature****Fuqiang Liu -S**

Digitally signed by Fuqiang Liu -S  
DN: c=US, o=U.S. Government, ou=HHS,  
ou=FDA, ou=People, cn=Fuqiang Liu -S,  
0.9.2342.19200300.100.1.1=2000778114  
Date: 2014.12.16 16:19:02 -05'00'

**Fuqiang Liu, Ph.D.**  
**CMC Reviewer**

**B. Endorsement Block****Stephen Miller -A**

Digitally signed by Stephen Miller -A  
DN: c=US, o=U.S. Government, ou=HHS,  
ou=FDA, ou=People, cn=Stephen Miller -A,  
0.9.2342.19200300.100.1.1=1300087013  
Date: 2014.12.16 16:37:18 -05'00'

“I concur, this NDA is recommended for approval from the CMC perspective.”  
**Stephen Miller, Ph.D.**  
**CMC-Lead**

**Rapti D.  
Madurawe -A**

Digitally signed by Rapti D. Madurawe -A  
DN: c=US, o=U.S. Government, ou=HHS,  
ou=FDA, ou=People,  
0.9.2342.19200300.100.1.1=1300220251,  
cn=Rapti D. Madurawe -A  
Date: 2014.12.16 17:16:13 -05'00'

**Rapti Madurawe, Ph.D.**  
**Branch Chief**

**C. CC Block**

54 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

# Initial Manufacturing (CGMP/Facilities) Assessment (IMA) and Filing Review for Pre- Marketing Applications (Original)

- I. Review Cover Sheet
- II. Application Detail
- III. Filing Checklist
- IV. Manufacturing Summary
- V. Overall Conclusions and Recommendations

## I. Review Cover Sheet

- 1. OMPQ Reviewer: **Rose Xu**
  
- 2. NDA/BLA Number: **NDA 205395**  
Submission Date: **3/31/2014**  
21<sup>st</sup> C. Review Goal Date:  
PDUFA Goal Date: **1/31/2015**

### 3. PRODUCT PROPERTIES:

Trade or Proprietary Name:	None
Established or Non-Proprietary Name (USAN) and strength:	Darunavir/Cobicistat 800 mg/150 mg
Dosage Form:	Tablet

### 4. SUBMISSION PROPERTIES:

Review Priority :	Standard Review
Applicant Name:	Janssen Products, LP
Responsible Organization (OND Division):	DAVP

OMPQ Initial Manufacturing (CGMP/Facilities) Assessment and Filing Review  
For Pre-Marking Applications

## II. Application Detail

1. INDICATION: Treatment of HIV-1 infection
2. ROUTE OF ADMINISTRATION: Oral
3. STRENGTH/POTENCY: 800 mg/ 150 mg
4. Rx/OTC DISPENSED:   Rx       OTC
5. ELECTRONIC SUBMISSION (yes/no)? Yes
6. PRIORITY CONSIDERATIONS: N/A

	Parameter	Yes	No	Unk	Comment
1.	NME / PDUFA V		X		
2.	Breakthrough Therapy Designation		X		
3.	Orphan Drug Designation		X		
4.	Unapproved New Drug		X		
5.	Medically Necessary Determination		X		
6.	Potential Shortage Issues [either alleviating or non-approval may cause a shortage]		X		
7.	Rolling Submission		X		
8.	Drug/device combination product with consult		X		
9.	Complex manufacturing		X		
10.	Other (e.g., expedited for an unlisted reason)		X		

OMPQ Initial Manufacturing (CGMP/Facilities) Assessment and Filing Review  
For Pre-Marking Applications

### III. FILING CHECKLIST

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

<b>A. COMPLETENESS OF FACILITY INFORMATION</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
11.	Is a single comprehensive list of all involved facilities available in one location in the application?	X		
12.	Is all site information complete (e.g., contact information, responsibilities, address)?	X		
13.	For testing labs, is complete information provided regarding which specific test is performed at each facility and what stage of manufacturing?	X		
14.	Do all sites indicate they are ready to be inspected (on 356h)?	X		
15.	Additional notes (non-filing issue) 1. Are all sites registered or have FEI #? 2. Do comments in EES indicate a request to participate on inspection(s)? 3. Is this first application by the applicant?	X	X  X	

\*If any information regarding the facilities is missing/omitted, communicate to OPS/ONDQA regarding missing information and copy EESQ. Notify OMPQ management if problems are not resolved within 3 days and it can be a *potential* filing issue.

OMPQ Initial Manufacturing (CGMP/Facilities) Assessment and Filing Review  
For Pre-Marking Applications

<b>B. DRUG SUBSTANCE (DS) / DRUG PRODUCT (DP)</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
16.	Have any Comparability Protocols been requested?		X	

<b>IMA CONCLUSION</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
17.	Does this application fit one of the EES Product Specific Categories?		X	
18.	Have EERs been cross referenced against the 356h and product specific profile for accuracy and completion? Have all EERs been updated with final PAI recommendation?	X X		
19.	<b>From a CGMP/facilities perspective, is the application fileable?</b>  If the NDA is not fileable from a product quality perspective, state the reasons and provide filing comments to be sent to the Applicant.	X		

## IV. Manufacturing Summary: Critical Issues and Complexities

Does the submission contain any of the following elements?			
Nanotechnology <input type="checkbox"/>	RTRT Proposal <input type="checkbox"/>	PAT <input type="checkbox"/>	Drug/Device Combo <input type="checkbox"/>
PET <input type="checkbox"/>	Design Space <input type="checkbox"/>	Continuous Mfg <input type="checkbox"/>	Naturally derived API <input type="checkbox"/>
Other (explain):			

Manufacturing Highlights				
<b>1. Drug Substance</b>				
	Parameter	Yes	No	Comment
	Is manufacturing process considered complex (e.g., unusual unit operations, innovative manufacturing technology, unusual control strategy)?		X	

OMPQ Initial Manufacturing (CGMP/Facilities) Assessment and Filing Review  
For Pre-Marking Applications

**2. Drug Product**

	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
	Is manufacturing process considered complex (e.g., unusual unit operations, innovative manufacturing technology, unusual control strategy)?	X		(b) (4)

**3. Facility-Related Risks or Complexities (e.g., number of foreign sites, large number of sites involved, etc.)**

None

**Additional information on Manufacturing issues or Complexities**

(b) (4)

OMPQ Initial Manufacturing (CGMP/Facilities) Assessment and Filing Review  
For Pre-Marking Applications

(b) (4)



OMPQ Initial Manufacturing (CGMP/Facilities) Assessment and Filing Review  
For Pre-Marking Applications

**darunavir/cobicistat  
Film-Coated Tablet**

**3.2.P.3.3 Description of Manufacturing Process and Process Controls  
Flowchart**

(b) (4)



OMPQ Initial Manufacturing (CGMP/Facilities) Assessment and Filing Review  
For Pre-Marking Applications

**Manufacturing Facilities Chart** (generated from 602A DARRTS report and OMPQ macro):

Note: See Coki Chart

For each EER, indicate PAI recommendation on the Manufacturing Facilities Chart above (e.g., PS, GMP, 10 Day, AC based on file review).

Establishment Name	CFN/FEI	Responsibilities	Firm Profiles – Current Status	Most Recent Inspection	Inspection History Date: Covered processes - Classification	Comments	OC Recommendation
Gilead Alberta ULC 1021 Hayter Rd NW Edmonton, Canada	3001027806	DS manufacture packaging release testing	CSN- Acceptable until Oct 2015	Date: Oct 2012 Coverage: - CGMP (AC) - PAI (AC)	10/25/2012 – NAI 8/5/2011 – NVAI	Acceptable based on NAI classification	Acceptable
Cilag AG Hochstrasse 201 Schffhausen, Switzerland	3002806695	(b) (4) 2. manufacture (b) (4) f (b) (4) drug substance	CSN- Acceptable until Feb 2017	Date: Feb 2014 Coverage: - CGMP (VAI) - PAI (AC)	(b) (4)	Acceptable based on firm's responses	Acceptable
Janssen Pharmaceutica N.V. Janssen Pharmaceuticaaan 3 Geel, Belgium	3002807337	manufacture, testing (b) (4) 1 (b) (4)	CSN- Acceptable until Sept 2016	Date: Sept 2013 Coverage: - CGMP (NAI) - PAI (AC)	9/12/2013 – NAI 10/18/2012 – VAI	Acceptable based on NAI classification	Acceptable
Janssen Pharmaceutical, Ltd. Little Island Cork, Ireland	3002807361	1. manufacture (b) (4) testing (b) (4) 2. manufacture, testing, release and (b) (4)	CSN- Acceptable as of April 2013	Date: April 2009 Coverage: - CGMP	(b) (4)	assigned inspection to (b) (4) (4)	PENDING

OMPQ Initial Manufacturing (CGMP/Facilities) Assessment and Filing Review  
For Pre-Marking Applications

		packaging of final drug substance		(VAI) - TCM (AC)	(b) (4)		
(b) (4)						Acceptable based on firm's responses	Acceptable
						Acceptable based on NAI classification	Acceptable
Janssen Pharmaceuticals, Inc. 1125 Trenton Harbourton Rd. Titusville, New Jersey, 08560-1503, United States	2242843	FDC stability testing	CTL- Acceptable until June 2015	Date: Dec 2013 Coverage: - PAI (AC)	12/12/2013 – NAI 11/16/2012 - NAI	Acceptable based on NAI classification	Acceptable
Janssen Ortho L.L.C. Carr # 933 Km 0.1, Mamey Ward Gurabo, Puerto Rico, 00778, United States	3002942061	Drug Product manufacture packaging labeling release testing stability testing (micro only)	TCM – Acceptable until Feb 2015	Date: Feb 2013 Coverage: - PAI (AC) - CGMP (VAI)	2/22/2013 –VAI- 483 was issued on firm's adverse drug events reporting system, FAR, and root cause investigation  6/13/2011 -VAI	Acceptable based on firm's responses* May need a PAI.	Acceptable* (may need a PAI)

OMPQ Initial Manufacturing (CGMP/Facilities) Assessment and Filing Review  
For Pre-Marking Applications

Gilead Sciences, Inc. 333 Lakeside Drive Foster City, California, 94404- 1147, United States	1000523075	release testing stability testing	CTL-need follow up on final result	Date: Jan 2014 Coverage: - CGMP (VAI)	(b) (4)	assigned inspection to (b) (4)	PENDING
Johnson & Johnson Limited, Consumer Global R&D Operations Opp Fire Brigade, L.B.S.,Marg, Muland (West) Mumbai, India	3007543295	DS stability testing	CTL- Acceptable as of Oct 2013	Date: Oct 2010 Coverage: - CGMP (NAI) - PAI (AC)	10/15/2010 -NAI	assigned inspection to (b) (4)	PENDING

## V. Overall Conclusions and Recommendations

<b>Is the application fileable? (yes/no)</b>
<b>Yes</b>
<b>At this time, is a KTM warranted for any PAI? A potential KTM (Need input from CMC reviewer)</b>
<b>Are there comments/issues to be included in the 74 day letter, including appropriate identification of facilities? No</b>
Comments for 74 Day Letter
1. N/A
2.
3.

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For Pre-Marking Applications

**REVIEW AND APPROVAL**  
(DARRTS)

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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RUO H XU  
05/08/2014

MAHESH R RAMANADHAM  
05/08/2014