CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206843Orig1s000

CHEMISTRY REVIEW(S)

THIS ACTION

Overall Quality Assessment

To: NDA 206843 / Resubmission

From: Chunchun Zhang, ONDP

Date: May-13-2015

Re: Recommend for approval

All the CMC related issues have been resolved in the original NDA cycle; refer to Dr. Chunchun Zhang's quality review on Nov 17, 2014. There is no change on the CMC related labels, the original labels have adequate CMC information as required, refer to Dr. Chunchun Zhang's review on Aug 28, 2014. An overall recommendation of Acceptable has been made by the Office of Process and Facilities on Mar 11, 2015 and the re-evaluation date will be Jun 5, 2016. Therefore, from a CMC perspective, NDA 206843 is recommended for approval.

Chunchun Zhang -S

Digitally signed by Chunchun Zhang -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Chunchun Zhang -S, 0.9.2342.19200300.100.1.1=2001178137
Date: 2015.05.13 14:27:24 -04'00'

Chunchun Zhang, Ph.D.
ATL for NDA 206843

Stephen Miller -S

Digitally signed by Stephen Miller -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Stephen Miller -S, 0.9.2342.19200300.100.1.1=1300087013
Date: 2015.05.15 11:02:34 -04'00'

Stephen Miller, Ph.D.
CMC Lead

Facility Re-evaluation Report: Overall recommendation.

Application Type	Application Number	Submission Type	Submission Number	Sponsor Name	Application Goal Date	Target Action Date	Application Status	Drug Name	OPF Overall Application Recommendation	OPF Overall Application Re Evaluation Date	Overall Manufacuring Inspection Recommendation Task Completion Date	OPF Overall Application Recommender
NDA	206843	Original	1	BRISTOL-MYERS SQUIBB CO				DAKLINZA	Approve	6/5/2016	3/12/2015	Denise Digiulio
NDA	206843	Original	1	BRISTOL MYERS SQUIBB CO				DAKLINZA			12/18/2014	Denise Digiulio

DUNS	Profile	OPF Facility Recommendation	OPF Facility Re-Evaluation Date	OPF Facility Recommendation Task Completion Date	Application Type	Application Number	Submission Type	Submission Number	Product Name	First Name	Last Name
557803743	CRU API NON-STERILE INTERMEDIATE NEC INORGANIC/MIN (b) (4) (b) (4)	Acceptable	7/11/2017	3/5/2015	NDA	206843	Original	1	DAKLINZA		
557803743	CRU API NON-STERILE INTERMEDIATE NEC INORGANIC/MIN (b) (4) (b) (4)		7/11/2017	3/5/2015	NDA	206843	Original	1	DAKLINZA		
557803743	CTL CONTROL TESTING LABORATORY			3/5/2015	NDA	206843	Original	1	DAKLINZA		
557803743	CRU API NON-STERILE INTERMEDIATE NEC INORGANIC/MIN (b) (4) (b) (4)	Acceptable	7/11/2017	11/24/2014	NDA	206843	Original	1	DAKLINZA	JUANDRIA	WILLIAMS
557803743	CRU API NON-STERILE INTERMEDIATE NEC INORGANIC/MIN (b) (4) (b) (4)		7/11/2017	11/24/2014	NDA	206843	Original	1	DAKLINZA	JUANDRIA	WILLIAMS
480143502	CRU API NON-STERILE INTERMEDIATE NEC INORGANIC/MIN (b) (4) (b) (4)	Acceptable	11/14/2016	3/5/2015	NDA	206843	Original	1	DAKLINZA		
480143502	CRU API NON-STERILE INTERMEDIATE NEC INORGANIC/MIN (b) (4) (b) (4)		11/14/2016	3/5/2015	NDA	206843	Original	1	DAKLINZA		
480143502	CTL CONTROL TESTING LABORATORY			3/5/2015	NDA	206843	Original	1	DAKLINZA		
480143502	CRU API NON-STERILE INTERMEDIATE NEC INORGANIC/MIN (b) (4) (b) (4)	Acceptable	11/14/2016	3/5/2015	NDA	206843	Original	1	DAKLINZA		
480143502	CRU API NON-STERILE INTERMEDIATE NEC INORGANIC/MIN (b) (4) (b) (4)		11/14/2016	3/5/2015	NDA	206843	Original	1	DAKLINZA		
480143502	CTL CONTROL TESTING LABORATORY			3/5/2015	NDA	206843	Original	1	DAKLINZA		
969674148	CSN NON-STERILE API BY CHEMICAL SYNTHESIS	Acceptable	9/20/2016	3/5/2015	NDA	206843	Original	1	DAKLINZA		
969674148	CSN NON-STERILE API BY CHEMICAL SYNTHESIS		9/20/2016	3/5/2015	NDA	206843	Original	1	DAKLINZA		
969674148	CTL CONTROL TESTING LABORATORY			3/5/2015	NDA	206843	Original	1	DAKLINZA		
969674148	CSN NON-STERILE API BY CHEMICAL SYNTHESIS	Acceptable	9/20/2016	10/7/2014	NDA	206843	Original	1	DAKLINZA	DARRTS	MIGRATION
969674148	CSN NON-STERILE API BY CHEMICAL SYNTHESIS		9/20/2016	10/7/2014	NDA	206843	Original	1	DAKLINZA	DARRTS	MIGRATION
069777290	CTL CONTROL TESTING LABORATORY	Acceptable	6/27/2016	3/5/2015	NDA	206843	Original	1	DAKLINZA		
069777290	CTL CONTROL TESTING LABORATORY		6/27/2016	3/5/2015	NDA	206843	Original	1	DAKLINZA		
069777290	CTL CONTROL TESTING LABORATORY	Acceptable	6/27/2016	10/7/2014	NDA	206843	Original	1	DAKLINZA	DARRTS	MIGRATION
069777290	CTL CONTROL TESTING LABORATORY		6/27/2016	10/7/2014	NDA	206843	Original	1	DAKLINZA	DARRTS	MIGRATION
938368834	TCM TABLETS, PROMPT RELEASE	Acceptable	6/5/2016	3/11/2015	NDA	206843	Original	1	DAKLINZA	DENISE	DIGIULIO
938368834	TCM TABLETS, PROMPT RELEASE		6/5/2016	3/11/2015	NDA	206843	Original	1	DAKLINZA	DENISE	DIGIULIO
938368834	CTL CONTROL TESTING LABORATORY			3/5/2015	NDA	206843	Original	1	DAKLINZA		
938368834	TCM TABLETS, PROMPT RELEASE	Acceptable	10/25/2015	10/27/2014	NDA	206843	Original	1	DAKLINZA	DARRTS	MIGRATION
938368834	TCM TABLETS, PROMPT RELEASE		10/25/2015	10/27/2014	NDA	206843	Original	1	DAKLINZA	DARRTS	MIGRATION

NDA 206-843

Daklinza™ (Daclatasvir) Tablets, 30 mg and 60 mg

Bristol-Myers Squibb Company

Addendum 1 to Review # 1

Chunchun Zhang, Ph.D.

ONDQA
Division of Pre-Marketing Assessment II
Branch V

Table of Contents

Chemistry Review Data Sheet

1. NDA 206-843

2. REVIEW #: Addendum 1 to Review #1

3. REVIEW DATE: 17-Nov, 2014

4. REVIEWER: Chunchun Zhang

5. PREVIOUS DOCUMENTS:

None

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	28-Feb-2014
Amendment	31-Mar-2014
Amendment	28-Apr-2014
Amendment	25-Jun-2014
Amendment	23-Jul-2014
Amendment	25-Aug-2014

7. NAME & ADDRESS OF APPLICANT:

Name:	Bristol-Myers Squibb Company
Address:	5 Research Parkway, Wallingford, CT 06492

Chemistry Review Data Sheet

Representative:	Charles D. Wolleben, Ph.D.
Telephone:	203-677-5480

8. DRUG PRODUCT NAME/CODE/TYPE:

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

- Chem. Type: 1
- Submission Priority: Breakthrough therapy

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

10. PHARMACOL. CATEGORY: Antiviral

11. DOSAGE FORM: Tablet

12. STRENGTH/POTENCY: 30 mg and 60 mg

13. ROUTE OF ADMINISTRATION: Oral

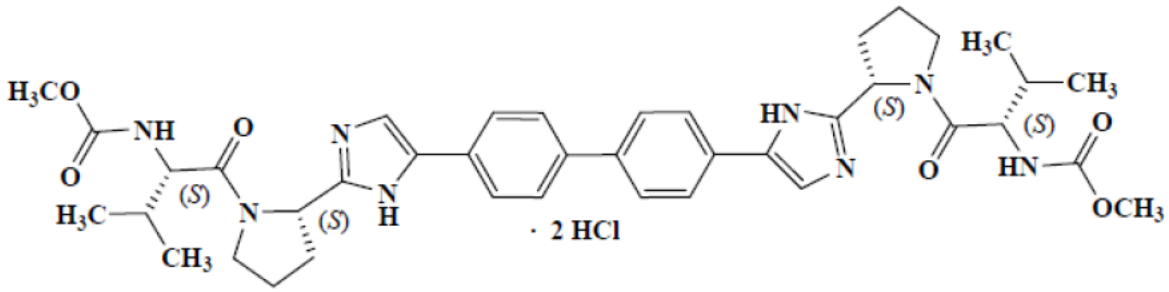
14. Rx/OTC DISPENSED: _X__Rx ___OTC

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:

USAN: Daclatasvir dihydrochloride
Chemical Name: Carbamic acid, *N*,*N*′-[[1,1'-biphenyl]-4,4'-diylbis[1*H*-imidazole-5,2-diyl-(2*S*)-2,1-pyrrolidinediyl[(1*S*)-1-(1-methylethyl)-2-oxo-2,1-ethanediyl]]]bis-, *C*,*C*′-dimethyl ester, hydrochloride (1:2)



Molecular Weight: 811.80 (738.88, free base)
Molecular Formula: $C_{40}H_{50}N_8O_6 \bullet 2HCl$
Chemical Abstract: 1009119-65-6

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	III		(b) (4)	4	Adequate		LoA: 10/4/2013
	III			4	Adequate		LoA: 5/20/2013
	III			4	Adequate		LoA: 5/30/2013
	IV			4	Adequate		LoA: 2/12/2013

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted

6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: N/A

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics			N/A
EES	Acceptable	17-Nov-2014	Krishnakali Ghosh
Pharm/Tox	Acceptable	28-Aug-2014	Mark Powley
Biopharm	Acceptable	28-Aug-2014	Sandra Suarez
LNC			NA
Methods Validation	Acceptable	29-Jul-2014	Michael Trehy
OPDRA			NA
EA	Categorical exclusion is requested, and granted (see review)	28-Aug-2014	Chunchun Zhang
Microbiology	Acceptable	29-May-2014	Bryan Riley

The Chemistry Review for NDA 206-843

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 products. All the chemistry, manufacturing and controls (CMC) information in this NDA was found adequate in CMC review #1 dated 28-Aug-2014. The labels have adequate CMC information as required. An overall recommendation of Acceptable has been made by the Office of Compliance on 17-Nov-2014. 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 Substance

Daclatasvir dihrochloride is a new molecular entity (NME) filed under NDA 206843 by BMS. The NDA was granted breakthrough and priority review status by the Division. The NDA contained relevant information regarding all aspects of the Daclatasvir drug substance.

Commercial drug substance is manufactured at (b) (4). Stability batches are manufactured at (b) (4) and tested at (b) (4).

Daclatavir is a (b) (4) white to yellow powder. It has poor aqueous solubility (b) (4) Daclatasvir has four chiral centers. It is manufactured as (b) (4) and particle size distribution is controlled with the acceptance criteria of D_{90} (b) (4) in the drug substance specification.

Specifications for Daclatasvir drug substance are adequate and include tests for appearance, color, identification, assay, impurity, residual solvents, HCl content and total inorganic impurities and particle size. The control strategy of three identified genotoxic impurities (b) (4) is found acceptable by Pharm/Tox reviewer Mark Powley. The stereochemical control of daclatasvir dihydrochloride drug substance is adequate.

Stability data including 12 months at long term storage condition (5°C, 25°C/60%RH, or

30°C/65%RH) and 6 months at accelerated condition (40°C/75%RH) supports a drug substance retest period of (b) (4) when stored at (b) (4)

Drug Product

Daclatasvir dihydrochloride (b) (4) tablet, 30 mg is a green, biconvex, pentagonal (b) (4) tablet with "BMS" debossed on one side and "213" debossed on the other side; Daclatasvir dihydrochloride (b) (4) tablet, 60 mg is a light green, biconvex, pentagonal (b) (4) tablet with "BMS" debossed on one side and "215" debossed on the other side. The maximum daily dose is 60 mg per day.

The (b) (4) tablets formulation contains (b) (4)% loading of daclatasvir dihydrochloride and the following compendial excipients: anhydrous lactose, microcrystalline cellulose, croscarmellose sodium, silicon dioxide and magnesium stearate, (b) (4) Opadry green (a green color for 30 mg strength; a light green color for 60 mg).

The commercial daclatasvir hydrochloride (b) (4) tablets manufacturing process has the following steps: (b) (4)

The manufacturing control strategy is based on th (b) (4)

The drug product quality is tested for the following final specifications: description, identification, assay, impurities, dissolution, content uniformity, microbial limits. The dissolution method was found adequate to ensure the desired drug product performance (See ONDQA biopharmaceutical review). Quality microbiology concluded that the microbiological purity test strategy is adequate. All methods have been adequately validated and the specification criteria acceptance justified appropriately.

Overall, the control manufacturing process and the drug product specification will ensure the drug product has the overall quality necessary for safe and effective treatment of patients.

Commercial drug product is manufactured at Mt. Vernon, Indiana. Stability batches are manufactured at (b) (4) and tested at (b) (4).

The stability of the drug product is under long term (5 °C, 25 °C/60% RH, 30 °C/75% RH) and accelerated conditions (40 °C/75% RH). 18 Month long term data on three stability batches at the minimum commercial scale (b) (4) show very little change in the drug product quality. No significant changes were observed under accelerated conditions. Overall, the stability data

supports a 30-month expiration dating period at 25 °C/ (b) (4)% RH when stored in 28-count (ct) HDPE bottles.

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

Daclatasvir dihydrochloride (b) (4) tablets, 30 mg and 60 mg are intended to be taken orally with or without food. The recommendation dosage is 60 mg, once daily for 12 (b) (4) weeks, administrated with (b) (4) Sofosbuvir.
Daclatasvir dihydrochloride (b) (4) tablets, 30 mg and 60 mg are available in a 95-mL high density polyethylene (HDPE) bottles, with (b) (4) closure and induction seal liner. Bottles will be filled with 28 counts. The bottles label instruction has been recommended to be "store at 25°C (77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) " with a 30-month shelf life.

C. Basis for Approvability or Not-Approval Recommendation

The applicant has provided sufficient information on raw material controls, manufacturing processes and process controls, and adequate specifications for assuring consistent product quality of the drug substance and drug product. The NDA has also provided sufficient stability information on the drug product to assure strength, quality, purity, potency, and bioavailability of the drug product throughout the expiration dating period 30 months. Biopharm and Quality Micro also recommended approval of this NDA. Labeling will be finalized during team labeling review. An overall recommendation of Acceptable has been made by the Office of Compliance on 17-Nov, 2014. Therefore, From the CMC perspective, this NDA is recommended for approval.

Executive Summary Section

From Initial Quality Assessment			Review Assessment		
Product attribute/ CQA	Factors that can impact the CQA	Risk Ranking	Risk Mitigation approach	Risk Evaluation	Lifecycle Considerations/ Comments
Impurities	drug substance assay	low	Genotoxic impurity levels are acceptable by Pharm/Tox reviewer Dr. Mark Powley. Most impurities are controlled in the drug substance; no additional impurities or degradants detected in the drug product.	Acceptable	NA
Content Uniformity	particle size	low	(b) (4)	Acceptable	NA
Microbial limits	(b) (4)	low	Refer to product Quality Micro Dr. Bryan Riley's review.	Acceptable	NA
Dissolution	particle size, (b) (4) form	high	See Dr. Sandra Suarez's Biopharmaceutics review.	Acceptable	NA
Stability of tablets	assay, impurity, (b) (4) content uniformity, dissolution, microbial limits	medium	No significant trend on stability. 30-month shelf life is acceptable based on the availlabe 18 month stability data from primary stability batches and 3 month stability data from commercial batches.	Acceptable	NA

III. Administrative

A. Reviewer's Signature

Chunchun Zhang
On file

B. Endorsement Block

Rapti Madurawe
On file

C. CC Block

On file

Chemistry Assessment

CMC Review #1 dated 28-Aug-2014 contains a complete assessment of the NDA. The overall recommendation from the Office of Compliance is PENDING at that time for the establishment evaluation. This addendum #1 to CMC Review #1 contains an overall recommendation of acceptable for the establishments.

S DRUG SUBSTANCE [Daclatasvir Dihydrochloride, BMS]

S.2 Manufacture [Daclatasvir Dihydrochloride, BMS]

S.2.1 Manufacturers

Reviewer's Evaluation: Acceptable. Facilities involved in the manufacture of daclatasvir dihydrochloride drug substance and their responsibilities are provided in the table below. The EES overall recommendations were acceptable on 17-Nov-2014.

Facility	Responsibilities
(b) (4)	Manufacture, testing, and release of intermediate BMS-(b) (4)
	Manufacture, testing, and release of intermediate BMS-(b) (4)
	Testing and release of intermediate BMS-(b) (4) Manufacture, testing, and release of final intermediate BMS-(b) (4) Manufacture, packaging, testing, and release of daclatasvir dihydrochloride

[a] Swords Laboratories is a Bristol-Myers Squibb facility.

P DRUG PRODUCT [Daclatasvir Dihydrochloride, (b) (4) Tablets]

P.3 Manufacture [Daclatasvir Dihydrochloride, (b) (4) Tablets]

P.3.1 Manufacturers

Reviewer Evaluation: Adequate. The drug product manufacturing facilities are shown in the table P.3.1-1. The EES recommendations were acceptable for Mt. Vernon 10-Jun-2014 and for (b) (4) on 28-Apr-2014.

Table 3.2.P.3.1-1: Facilities and Responsibilities

Facility	Responsibility
Bristol-Myers Squibb Company 4601 Highway 62 East Mount Vernon, Indiana 47620 USA	Drug product manufacture, testing packaging, labeling, and release of drug product
(b) (4)	Testing of drug product

EES Summary Report: Acceptable.

As this application cannot be processed in IMS Panorama at this time due to system issues, Krishnakali Ghosh emailed the manual processing of the OC Overall Recommendation for NDA 206843 in the attachment as shown below on 17-Nov-2014.

Facility Name	FEI	CFN	DUNS	Country	Profile	Responsibility: Stage	Responsibility: Process	OPF Facility Recommendation	Inspection Classification
BRISTOLMYERS SQUIBB COMPANY INC	1825662	1825662	938368834	UNITED STATES	TCM	FINISHED DOSAGE	MANUFACTURER	Acceptable	NAI
(b) (4)					CTL	FINISHED DOSAGE	OTHER TESTER	Acceptable	NAI
					(b) (4)	NTERMEDIATE	MANUFACTURER	Acceptable	NAI
						DRUG SUBSTANCE	MANUFACTURER	Acceptable	NAI
						DRUG SUBSTANCE NTERMEDIATE	MANUFACTURER/TESTER	Acceptable	NAI

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

/s/

CHUNCHUN N ZHANG
11/17/2014

RAPTI D MADURAWE
11/17/2014

NDA 206-843

Daklinza™ (Daclatasvir) Tablets, 30 mg and 60 mg

Bristol-Myers Squibb Company

Chunchun Zhang, Ph.D.

ONDQA
Division of Pre-Marketing Assessment II
Branch V

Table of Contents

Chemistry Review Data Sheet

1. NDA 206-843

2. REVIEW #: 1

3. REVIEW DATE: 28-Aug, 2014

4. REVIEWER: Chunchun Zhang

5. PREVIOUS DOCUMENTS:

None

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	28-Feb-2014
Amendment	31-Mar-2014
Amendment	28-Apr-2014
Amendment	25-Jun-2014
Amendment	23-Jul-2014
Amendment	25-Aug-2014

7. NAME & ADDRESS OF APPLICANT:

Name:	Bristol-Myers Squibb Company
Address:	5 Research Parkway, Wallingford, CT 06492

Chemistry Review Data Sheet

Representative:	Charles D. Wolleben, Ph.D.
Telephone:	203-677-5480

8. DRUG PRODUCT NAME/CODE/TYPE:

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

- Chem. Type: 1
- Submission Priority: Breakthrough therapy

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

10. PHARMACOL. CATEGORY: Antiviral

11. DOSAGE FORM: Tablet

12. STRENGTH/POTENCY: 30 mg and 60 mg

13. ROUTE OF ADMINISTRATION: Oral

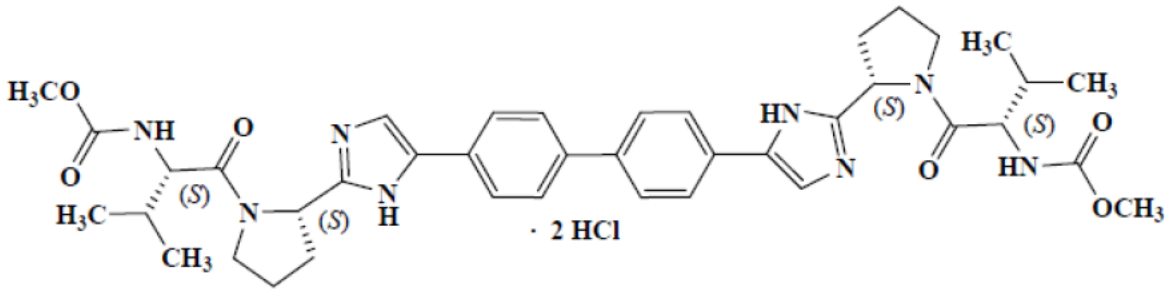
14. Rx/OTC DISPENSED: _X__Rx ___OTC

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:

USAN: Daclatasvir dihydrochloride
Chemical Name: Carbamic acid, *N*,*N*′-[[1,1'-biphenyl]-4,4'-diylbis[1*H*-imidazole-5,2-diyl-(2*S*)-2,1-pyrrolidinediyl[(1*S*)-1-(1-methylethyl)-2-oxo-2,1-ethanediyl]]]bis-, *C*,*C*′-dimethyl ester, hydrochloride (1:2)



Molecular Weight: 811.80 (738.88, free base)
Molecular Formula: $C_{40}H_{50}N_8O_6 \bullet 2HCl$
Chemical Abstract: 1009119-65-6

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	III		(b) (4)	4	Adequate		LoA: 10/4/2013
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[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
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6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: N/A

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics			N/A
EES	Pending		
Pharm/Tox	Acceptable	28-Aug-2014	Mark Powley
Biopharm	Acceptable	28-Aug-2014	Sandra Suarez
LNC			NA
Methods Validation	Acceptable	29-Jul-2014	Michael Trehy
OPDRA			NA
EA	Categorical exclusion is requested, and granted (see review)	28-Aug-2014	Chunchun Zhang
Microbiology	Acceptable	29-May-2014	Bryan Riley

The Chemistry Review for NDA 206-843

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 products. Labeling comments are marked up in this review and will be finalized during team labeling review. The overall recommendation from the Office of Compliance is PENDING as of 28-Aug-2014 for the establishment evaluation. Therefore, from the CMC perspective, this NDA is not recommended for approval until an overall recommendation of acceptable is made for the establishments.

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 Substance

Daclatasvir dihrochloride is a new molecular entity (NME) filed under NDA 206843 by BMS. The NDA was granted breakthrough and priority review status by the Division. The NDA contained relevant information regarding all aspects of the Daclatasvir drug substance.

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Stability data including 12 months at long term storage condition (5°C, 25°C/60%RH, or

30°C/65%RH) and 6 months at accelerated condition (40°C/75%RH) supports a drug substance retest period of [redacted] when stored at [redacted]

Drug Product

Daclatasvir dihydrochloride [redacted] tablet, 30 mg is a green, biconvex, pentagonal [redacted] tablet with "BMS" debossed on one side and "213" debossed on the other side; Daclatasvir dihydrochloride [redacted] tablet, 60 mg is a light green, biconvex, pentagonal [redacted] tablet with "BMS" debossed on one side and "215" debossed on the other side. The maximum daily dose is 60 mg per day.

The [redacted] tablets formulation contains [redacted]% loading of daclatasvir dihydrochloride and the following compendial excipients: anhydrous lactose, microcrystalline cellulose, croscarmellose sodium, silicon dioxide and magnesium stearate, and the [redacted] Opadry green (a green color for 30 mg strength; a light green color for 60 mg).

The commercial daclatasvir hydrochloride [redacted] tablets manufacturing process has the following steps: [redacted].

The manufacturing control strategy is based on the [redacted].

The drug product quality is tested for the following final specifications: description, identification, assay, impurities, dissolution, content uniformity, microbial limits. The dissolution method was found adequate to ensure the desired drug product performance (See ONDQA biopharmaceutical review). Quality microbiology concluded that the microbiological purity test strategy is adequate. All methods have been adequately validated and the specification criteria acceptance justified appropriately.

Overall, the control manufacturing process and the drug product specification will ensure the drug product has the overall quality necessary for safe and effective treatment of patients.

Commercial drug product is manufactured at [redacted]. Stability batches are manufactured at [redacted] and tested at [redacted].

The stability of the drug product is under long term (5 °C, 25 °C/60% RH, 30 °C/75% RH) and accelerated conditions (40 °C/75% RH). 18 Month long term data on three stability batches at the minimum commercial scale [redacted] show very little change in the drug product quality. No significant changes were observed under accelerated conditions. Overall, the stability data

supports a 30-month expiration dating period at 25 °C/ (b) (4) % RH when stored in 28-count (ct) HDPE bottles.

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

Daclatasvir dihydrochloride (b) (4) tablets, 30 mg and 60 mg are intended to be taken orally with or without food. The recommendation dosage is 60 mg, once daily for 12 (b) (4) weeks, administrated with (b) (4) Sofosbuvir.
Daclatasvir dihydrochloride (b) (4) tablets, 30 mg and 60 mg are available in a 95-mL high density polyethylene (HDPE) bottles, with (b) (4) closure and induction seal liner. Bottles will be filled with 28 counts. The bottles label instruction has been recommended to be "store at 25°C (77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) " with a 30-month shelf life.

C. Basis for Approvability or Not-Approval Recommendation

The applicant has provided sufficient information on raw material controls, manufacturing processes and process controls, and adequate specifications for assuring consistent product quality of the drug substance and drug product. The NDA has also provided sufficient stability information on the drug product to assure strength, quality, purity, potency, and bioavailability of the drug product throughout the expiration dating period 30 months. Biopharm and Quality Micro also recommended approval of this NDA. Labeling will be finalized during team labeling review. However, the overall recommendation from the Office of Compliance is PENDING as of 28-Aug-2014 for the establishment evaluation. Therefore, this NDA is not recommended for approval until an overall recommendation of acceptable is made for the establishments.

Executive Summary Section

From Initial Quality Assessment			Review Assessment		
Product attribute/ CQA	Factors that can impact the CQA	Risk Ranking	Risk Mitigation approach	Risk Evaluation	Lifecycle Considerations/ Comments
Impurities	drug substance assay	low	Genotoxic impurity levels are acceptable by Pharm/Tox reviewer Dr. Mark Powley. Most impurities are controlled in the drug substance; no additional impurities or degradants detected in the drug product.	Acceptable	NA
Content Uniformity	particle size	low	(b) (4)	Acceptable	NA
Microbial limits	(b) (4)	low	Refer to product Quality Micro Dr. Bryan Riley's review.	Acceptable	NA
Dissolution	particle size, (b) (4) form	high	See Dr. Sandra Suarez's Biopharmaceutics review.	Acceptable	NA
Stability of tablets	assay, impurity, (b) (4), content uniformity, dissolution, microbial limits	medium	No significant trend on stability. 30-month shelf life is acceptable based on the availlabe 18 month stability data from primary stability batches and 3 month stability data from commercial batches.	Acceptable	NA

III. Administrative

A. Reviewer's Signature

Chunchun Zhang
On file

B. Endorsement Block

Rapti Madurawe
On file

C. CC Block

On file

Chemistry Assessment

I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data

S DRUG SUBSTANCE [Daclatasvir Dihydrochloride, BMS]

Reviewer's evaluation: Adequate. Daclatasvir exhibits low solubility and it is (b) (4) Daclatasvir has four stereocenters and is chirally pure. It is noted that (b) (4) is observed through the manufacturing process development and on stability. The particle size distribution is a critical quality attribute and is controlled below (b) (4) in the drug substance specification.

S.1 General Information [Daclatasvir Dihydrochloride, BMS]- *ADEQUATE*

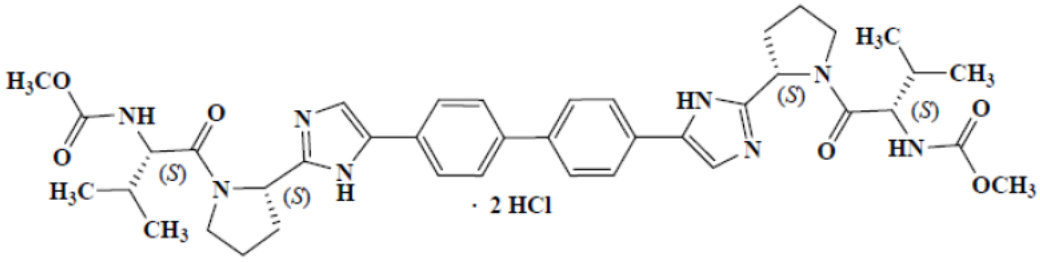
S.1.1 Nomenclature

- **Chemical Name:** Methyl((1*S*)-1-(((2*S*)-2-(5-(4'-(2-((2*S*)-1-((2*S*)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1*H*-imidazol-5-yl)-4-biphenylyl)-1*H*-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate dihydrochloride
- **USAN:** Daclatasvir dihydrochloride
- **CAS Registry Number:** 1009119-65-6
- **Janssen Code Number:** BMS-790052-05, BMS-790052

Evaluation: *Adequate.*

S.1.2 Structure

- **Formula:** $C_{40}H_{50}N_8O_6 \bullet 2HCl$
- **Molecular Weight:** 811.80 (738.88, free base)
- **Chemical Structure:**



S.1.3 General Properties

Daclatasvir dihydrochloride drug substance is a white to yellow powder. [(b) (4)] (refer to section 3.2.S.3.1 "physicochemical characterization" for detailed discussion). Daclatasvir has four stereocenters with specific rotation [(b) (4)] °C. The solubility is low by BCS criteria but it is very soluble [(b) (4)] refer to Table 3.2.S.1.3-1. [(b) (4)]

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(b) (4)

P DRUG PRODUCT [Daclatasvir Dihydrochloride, (b) (4) Tablets]

P.1 Description and Composition of the Drug Product [Daclatasvir Dihydrochloride, (b) (4) Tablets]

Daclatasvir dihydrochloride (b) (4) tablets, 30 mg and 60 mg are intermediate release tablets for oral administration. The content of the 30 mg strength tablet is proportionally to the content of the 60 mg strength tablet with different Opadry Green used in the tablet coating. The 30 mg tablet has a green color whereas the 60 mg tablet has a light green color.

Table 3.2.P.1-1: Descriptions of Daclatasvir Dihydrochloride (b) (4) Tablets

Strength (mg/tablet)	Description
30	A green, biconvex, pentagonal (b) (4) tablet with "BMS" debossed on one side and "213" debossed on the other side
60	A light green, biconvex, pentagonal (b) (4) tablet with "BMS" debossed on one side and "215" debossed on the other side

Tables below show the drug products composition for daclatasvir dihydrochloride tablets, 30 mg and 60 mg. Daclatasvir tablets are proposed to be packaged in 28-count 95 mL HDPE bottles.

Table 3.2.P.1-2: Composition of Daclatasvir Dihydrochloride Film-Coated Tablet, 30 mg

Component	Quality Standard	Function	Quantity per Tablet (%w/w)	Quantity per Tablet (mg)
(b) (4)				
Daclatasvir Dihydrochloride (BMS-790052-05)[a]	In-house[b]	Active	22.0	33.00
Anhydrous Lactose[c]	NF/Ph.Eur./JP			(b) (4)
Microcrystalline Cellulose	NF/Ph.Eur./JP			
Croscarmellose Sodium	NF/Ph.Eur./JP			
Silicon Dioxide	NF/Ph.Eur.[d]/JPE			
Magnesium Stearate	NF/Ph.Eur./JP			
(b) (4)				
Opadry® Green[e]	In-house[f]			
(b) (4)	USP/Ph.Eur.			
Total Tablet Weight				156.00

(b) (4)

Table 3.2.P.1-3: Composition of Opadry® Green (b) (4)

Component	Quality Standard	%w/w
(b) (4)		

Table 3.2.P.1-2: Composition of Daclatasvir Dihydrochloride (b) (4) Tablet, 60 mg

Component	Quality Standard	Function	Quantity per Tablet (%w/w)	Quantity per Tablet (mg)
(b) (4)				
Daclatasvir Dihydrochloride (BMS-790052-05)[a]	In-house[b]	Active	22.0	66.00
Anhydrous Lactose[c]	NF/Ph.Eur./JP			(b) (4)
Microcrystalline Cellulose	NF/Ph.Eur./JP			
Croscarmellose Sodium	NF/Ph.Eur./JP			
Silicon Dioxide	NF/Ph.Eur.[d]/JPE			
Magnesium Stearate	NF/Ph.Eur./JP			
(b) (4)				
Opadry® Green[e]	In-house[f]			
(b) (4)	USP/Ph.Eur.			
Total Tablet Weight				315.00

(b) (4)

Table 3.2.P.1-3: Composition of Opadry® Green (b) (4)

Component	Quality Standard	%w/w
(b) (4)		

Reviewer Evaluation: Adequate. The components and composition of daclatasvir (b) (4)

[redacted] tablets have been adequately identified. The development of this [redacted] formulation, and the function of each component, have been adequately characterized. And as documented elsewhere in this review, the components are of suitable quality for use in this formulation.

P.2 Pharmaceutical Development [Daclatasvir Dihydrochloride, [redacted] Tablets]

Daclatasvir dihydrochloride [redacted] tablets are manufactured from a [redacted]. Product requirements are outlined in the Quality Target Product Profile (Table P.2.-1).

Table 3.2.P.2-1: QualityTarget Product Profile

QTPP Element	Target
Route of administration	Oral
Dosage form	[redacted] tablet, immediate release
Dosage strengths	30-mg and 60-mg unit doses (strengths stated as free base)
Excipient selection	Common excipients widely used in oral solid dosage forms, meeting compendial status where appropriate.
Patient population targeted	Adult
Container closure system	[redacted] high-density polyethylene (HDPE) bottles, according to market requirements
Stability	[redacted] shelf-life at room temperature in all climate zones
Appearance (Description)	Color, shape, and markings to comply with product description
Assay	95.0% to 105.0% of label claim
Content uniformity	Should comply with harmonized compendial requirements
Impurities/Degradants	Should meet ICH Q3B(R2) guidelines
Dissolution	Rapid dissolution to facilitate rapid absorption from the gastrointestinal tract
Microbial quality	Should meet acceptance criteria for microbial limits as per the harmonized pharmacopoeial monograph

The drug product critical quality attributes (CQA) are defined for the product to ensure that the QTPP were satisfied as follows: description, assay, impurity/degradation products, content uniformity and dissolution. Therefore, the identified QTPP and CQAs provide the framework for the drug product; the CQAs are adequate for the development of a target formulation process.

Drug Product CQA	Justification
Appearance	Needed for patient acceptability
Assay	Needed for clinical effectiveness
Impurity/degradants	Needed to ensure safety
Content Uniformity	Needed for clinical effectiveness
Dissolution	Needed for clinical effectiveness

Reviewer Evaluation: Adequate. The identified QTPP and CQAs provide the framework for products and process development as discussed below.

P.2.1 Components of the Drug Product

P.2.1.1 Drug Substance

As documented is Section S.1.3., General Property, daclatasvir dihydrochloride is a (b) (4). Its permeability (b) (4).

Stability data in section S.7 demonstrates that daclatasvir is stable at long term and accelerated condition. (b) (4).

The critical attributes of the drug substance and their potential impact on drug products performance were evaluated and addressed by the Applicant. The impact of (b) (4) form, particle size and impurity level are adequately addressed.

(b) (4)

Particle size: Particle size distribution on drug substance is a critical for the performance for the drug product. It has potential effect on the drug products content uniformity and dissolution. Particle size is controlled in the drug substance specification with the acceptance criteria (b) (4).

Impurity Level: Impurities from the drug substance potentially affect the drug products assay and impurities/degradants. Impurities are controlled in the drug substance specification.

Reviewer Evaluation: Adequate.
The critical attributes of the drug substance and their potential impact on drug products performance were evaluated and addressed by the Applicant. The impact of (b) (4) form, particle size and impurity level are adequately addressed.

P.2.1.2 Excipients

There are no novel and critical excipients used in this formulation. Besides the coating agents Opadry Green as the non-compendial excipient, all the other excipients are compendial, anhydrous lactose, microcrystalline cellulose, croscarmellose sodium, silicon dioxide and magnesium stearate are (b) (4) respectively. Each excipient amount in the drug products is described in the section P.3.2 *Batch Formula*.

Reviewer Evaluation: Adequate.
The excipients used in the drug product and their function have been identified. Refer to P.4 for review of excipients specifications.

P.2.2 Drug Product

P.2.2.1 Formulation Development

Formulation development history and formulation change: The daclatasvir dihydrochloride formulation development from the the initial formulation Phase I to the final proposed commercial (b) (4) tablets is described in the table below.

(b) (4)

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Table 3.2.P.3.2-1: Proposed Commercial Batch Size Range

(b) (4)

Component[a]	Amount per Batch (kg)
(b) (4)	(b) (4)
Intra-granular	
Daclatasvir dihydrochloride (BMS-790052-05)[b]	
Anhydrous lactose[c]	
Microcrystalline cellulose	
Croscarmellose sodium	
Silicon dioxide	
Magnesium stearate	
(b) (4)	
Opadry® Green	(b) (4)
(b) (4)	
(b) (4)	

Table 3.2.P.3.2-2: Representative Batch Formula for Daclatasvir Dihydrochloride (b) (4) Tablet, 60 mg

Component[a]	Amount per Batch (kg)
(b) (4)	
Intra-granular	(b) (4)
Daclatasvir dihydrochloride (BMS-790052-05)[b]	
Anhydrous lactose[c]	
Microcrystalline cellulose	
Croscarmellose sodium	
Silicon dioxide	
Magnesium stearate	
(b) (4)	
Opadry® Green	(b) (4) 6.00
(b) (4)	
(b) (4)	

P.3.3 Description of Manufacturing Process and Process Controls

Reviewer Evaluation: Adequate.

The applicant provided a process flow diagram and a narrative description of drug products manufacturing and process parameters for each step. In addition, executed batch records on (b) (4), 30 mg and 60 mg (b) (4) tablets are submitted in the Amendment dated on 3/30/2014.

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(b) (4)

[redacted]

P.5 Control of Drug Product [Daclatasvir Dihydrochloride, (b) (4) Tablets]

P.5.1 Specification(s)

Reviewer Evaluation: Adequate. The proposed acceptable criteria for description, identification, assay, impurity, content uniformity, dissolution, and microbial limits are adequately justified and the test methods are defined and validated. As proposed, the specification for the drug products are acceptable.

Test	Acceptance Criteria		Test Method
	30 mg tablets	**60 mg tablets**	
Decription	A green, biconvex, pentagonal (b) (4) tablet with "BMS" debossed on one side and "213" debossed on the other side.	A light green, biconvex, pentagonal (b) (4) tablet with "BMS" debossed on one side and "215" debossed on the other side.	visual
Identification	IR-ATR: The IR-ATR spectrum obtained from daclatasvir dihydrochloride (b) (4) tablets exhibits maxima at the wavenumbers around 1726 cm-1 , 1643 cm-1 , 1523 cm-1, 1494 cm-1 and 1437 cm-1.		0100(G), 95019321(S) USP/EP/JP/ChP
	HPLC: The retention time of the major peak in the sample chromatogram must correspond to that in the standard chromatogram.		95012738(S) HPLC
Assay	90.0 - 110.0 % of Label		95012738(S) HPLC
Impurities	individual impurity (b) (4) % The following compounds are process impurities in the drug substance and are not considered in the individual impurities or degradants in this test: (b) (4)		95012738(S) HPLC
	Total impurities (b) (4) %		95012738(S) HPLC
Dissolution	(b) (4) in 30 minutes.		0311(G), 95014081(S) USP/EP/JP/ChP
Content Uniformity	Complies with the harmonized requirements (USP/EP/JP).		356X(G), 95013996(S) USP/EP/JP/ChP
Microbial Limits	Total Aerobic Microbial Count (b) (4) g		5450A(G), 250630(S)
	Total Yeasts and Molds Count (b) (4)		5450A(G), 250631(S)
	E. Coli: Absent in (b) (4) .		5450A(G), 250150(S)

P.5.2 Analytical Procedures

The compendial methods 0100, 356X, 0311 and 5450A methods are for IR, content uniformity, dissolution and microbial limits, respectively, in accordance with USP, Ph Eur and JP. The following non-compendial methods are reviewed in this section, as part of the specification proposed in section P.5.1.

Identity, Content Uniformity, Potency, and Impurities by HPLC method: 95012738. Adequate.

The reversed-phase VHPLC (Very High Performance Liquid Chromatography)/HPLC method used for determination of assay, content uniformity, potency and impurity of the daclatasvir hydrochloride salt is adequately described in the submission. A summary of the method is shown below.

Method	VHPLC	HPLC
Column	(b) (4)	
Mobile Phase A		
Mobile Phase B		
Diluent		
Column temperature		
Sample temperature		
Detector wavelength		
Injection volume		
Flow rate		
Run time		
Gradient		
System suitablity		
Calculations		
Impurities with relative retention time		

Identity, potency and content uniformity HPLC (alternative method): 95013996. Adequate.

An isocratic HPLC method 95013996 is an alternative method used for the identity,

potency and content uniformity of daclatasvir tablets. Table below summarizes this method.

Column	(b) (4)
Mobile Phase	
Diluent	
Column temperature	
Sample temperature	
Detector wavelength	
Injection volume	
Flow rate	
Run time	
System suitablity	
Calculations	
Chromatogram	

Dissolution by HPLC: 95014081. Adequate.

Refer to ONDQA biopharmaceutics review.

Reviewer Evaluation: Adequate. The analytical procedures used to ensure the identity, strength, quality, purity, potency and bioavailability of the drug products have been described in sufficient detail. The suitability of the analytical procedures is further demonstrated in the following section on the methods validation.

P.5.3 Validation of Analytical Procedures

Reviewer evaluation: Adequate. The method validation results for drug product proposed for specification in P.5.1 are reviewed in this section. The methods proposed to support the specification for the drug product have been adequately validated for their intended use. See discussion above for details on the methods description.

ID by IR-ATR: 9321. Adequate.

The IR method for identifying daclatasvir was successfully validated. Validation includes specificity, intermediate precision (reproducibility), and robustness.

Identity, content uniformity, potency and impurity by HPLC: 95012738. Adequate.

The reverse phase HPLC/VHPLC method was successfully validated against established criteria. The method is robust and validated for its intended use. Method validation includes specificity, linearity, accuracy, precision, reproducibility, sensitivity and robustness.

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(b) (4)

[redacted]

B. Environmental Assessment Or Claim Of Categorical Exclusion

A claim of categorical exclusion was made by BMS daclatasvir (b) (4) tablets referring to 21 CFR §25.31(b). No extraordinary circumstances exist in regards to these

actions. The categorical exclusion from the preparation of an environment assessment (EA) is acceptable based on the applicant's proposed concentration of an EIC of below 1 ppb (part per billion).

III. List Of Deficiencies To Be Communicated

IR #1, 6/12/2014

1. In Section 3.2.S.2.6, several open-ended parameter temperatures settings such as (b) (4) are used in the process descriptions. Revise these to include specific ranges for the operating parameters (i.e., with both lower and upper limits) or provide a scientific rationale as to why a (b) (4) parameter is acceptable.

2. Include residual solvents in the specification of the starting material (b) (4)

3. In your impurity control (b) (4) Please provide information on these impurities, including their structures, if known.

4. The "critical in-process controls" listed in Section 3.2.P.3.4-1 have the potential to impact critical quality attributes. Please identify the critical process parameters for the proposed manufacturing process based on preselection of operating ranges or magnitude of product quality response. Please note that changes from the preselected targets/ranges (i.e. changes outside of the Proven Acceptable Ranges) could have a minor, moderate or substantial potential to adversely affect product quality. The Agency's expectation is that the potential impact of changes to process parameters and in-process controls, including those designated as non-critical process parameters, as well as the parameters in Master Batch Record, be assessed under the firm's quality system at the time of the change. As appropriate, changes with a potential to adversely affect product quality should be notified to the Agency in accordance with 21 CFR 314.70.

5. Confirm the proposed 30-months shelf life for the 28-ct HDPE bottles is calculated from the date of manufacture (DOM).

IR #2 on 7/9/2014

1. Please indicate if any change has been observed in the HCl content of daclatasvir drug substance on storage or during stability studies. If information is not available at present, we recommend that you include the test for HCl content in the stability protocol for the drug substance until sufficient manufacturing/stability experience is gained (we suggest monitoring 10 stability batches) to support the elimination of this test.

IR #3 on 8/18/2014

Provide stability update for commercial image batches 3A9009X for Daclatasvir Tablets 30 mg, 3A9010X and 2K9011X for Daclatasvir Tablets 60 mg manufactured at Mt. Vernon site.

EES Summary Report:

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application:	NDA 206843/000	**Sponsor:**	BRISTOL MYERS SQUIBB
Org. Code:	530		5 RESEARCH PKY 2DW 223
Priority:	1		WALLINGFORD, CT 06492
Stamp Date:	31-MAR-2014	**Brand Name:**	DACLATASVIR
PDUFA Date:	30-NOV-2014	**Estab. Name:**	
Action Goal:		**Generic Name:**	DACLATASVIR
District Goal:	31-JUL-2014	**Product Number; Dosage Form; Ingredient; Strengths**	001; TABLET; DACLATASVIR DIHYDROCHLORIDE; 30MG 002; TABLET; DACLATASVIR DIHYDROCHLORIDE; 60MG

FDA Contacts:	K. GHOSH	Facility Reviewer		3017962644
	C. ZHANG	Prod Qual Reviewer		3017965168
	A. CUFF	Product Quality PM	(HF-01)	3017964061
	S. MOSADDEGH	Regulatory Project Mgr	(HFD-530)	3017964876
	S. MILLER	Team Leader		3017961418

Overall Recommendation:	PENDING	on 24-APR-2014	by EES_PROD
	PENDING	on 24-APR-2014	by EES_PROD
	PENDING	on 22-APR-2014	by EES_PROD

Establishment:	**CFN:** (b) (4)	**FEI:** (b) (4)	(b) (4)
DMF No:		**AADA:**	
Responsibilities:	INTERMEDIATE MANUFACTURER INTERMEDIATE OTHER TESTER INTERMEDIATE RELEASE TESTER		
Profile:	API NON-STERILE/ (b) (4) (b) (4)	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	24-APR-2014		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		

Chemistry Assessment Section

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Establishment: **CFN:** 1825662 **FEI:** 1825662
BRISTOL-MYERS SQUIBB COMPANY, INC.
MOUNT VERNON, , UNITED STATES 476209682
DMF No: **AADA:**
Responsibilities: FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE PACKAGER
FINISHED DOSAGE RELEASE TESTER
Profile: TABLETS, PROMPT RELEASE **OAI Status:** NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 10-JUN-2014
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Establishment: **CFN:** (b) (4) **FEI:** (b) (4)
(b) (4)
DMF No: **AADA:**
Responsibilities: FINISHED DOSAGE OTHER TESTER
Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 28-APR-2014
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Establishment: **CFN:** **FEI:** (b) (4)
(b) (4)
DMF No: **AADA:**
Responsibilities: INTERMEDIATE MANUFACTURER
INTERMEDIATE OTHER TESTER
INTERMEDIATE RELEASE TESTER
Profile: API NON-STERILE/ (b) (4) (b) (4) **OAI Status:** NONE
Last Milestone: INSPECTION SCHEDULED
Milestone Date: 12-MAY-2014

CHEMISTRY REVIEW TEMPLATE

Chemistry Assessment Section

Establishment:	**CFN:** (b) (4)	**FEI:** (b) (4)	
	(b) (4)		
DMF No:		**AADA:**	
Responsibilities:	DRUG SUBSTANCE MANUFACTURER		
	DRUG SUBSTANCE PACKAGER		
	DRUG SUBSTANCE RELEASE TESTER		
Profile:	(b) (4)	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	24-APR-2014		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		

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

/s/

CHUNCHUN N ZHANG
08/28/2014

RAPTI D MADURAWE
08/28/2014