

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

206843Orig1s001, s003

OTHER REVIEW(S)

Division of Antiviral products

REGULATORY PROJECT MANAGER LABELING REVIEW

Application: NDA 206843/S-001, S-002, and S-003

Name of Drug: DAKLINZA, Daclatasvir 30 & 60 mg oral tablet

Applicant: Bristol-Myers Squibb Company

Labeling Reviewed

Submission Date: August 05, 2015

Receipt Date: labeling reviewed was received 02/03/2016

Background and Summary Description:

DAKLINZA (daclatasvir) was approved July 24, 2015 in combination with sofosbuvir for the treatment of chronic hepatitis C virus, genotype 3 infection.

S-001: expands the patient population to include patients with chronic hepatitis C virus (HCV) recurrence after liver transplantation and to update the labeling with information from the ALLY-1 clinical trial.

S-002: expands the indication to include the treatment of subjects with genotype-1 chronic hepatitis C virus infection, including subjects who are co-infected with human immunodeficiency virus (HIV-1) based on the results from the ALLY-2 clinical trial and to update the labeling with drug-drug interaction information for buprenorphine/naloxone and several HIV antiviral agents

S-003: expands the patient population to include the treatment of chronic hepatitis C virus infection in subjects with compensated or decompensated cirrhosis

Review

1. Under Highlights of the Prescribing Information the following changes were made:

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/s/

SOHAIL MOSADDEGH
02/05/2016

KAREN D WINESTOCK
02/05/2016

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: January 21, 2016

To: Debra Birnkrant, MD
Director
Division of Antiviral Products (DAVP)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Barbara Fuller, RN, MSN, CWOCN
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Rowell Medina, PharmD
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Kemi Asante, PharmD, RAC
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Patient Package Insert (PPI),

Drug Name (established name): DAKLINZA (daclatasvir)

Dosage Form and Route: tablet, for oral use

Application Type/Number: NDA 206843

Supplement Number: S-01, S-02, S-03

Applicant: Bristol-Myers Squibb

1 INTRODUCTION

On August 5, 2015, Bristol-Myers Squibb submitted for the Agency's review efficacy supplements to their approved New Drug Application (NDA) 206843/S-01, S-02 for DAKLINZA (daclatasvir) tablets. The Applicant submitted these supplements to expand the indication to include patients with compensated or decompensated cirrhosis, and those with hepatitis C virus (HCV) recurrence after liver transplantation and co-infected with human immunodeficiency virus (HIV-1). After a teleconference with the Agency on August 24, 2015, Bristol-Myers Squibb submitted another efficacy supplement to their approved NDA 206843/S-03 for DAKLINZA (daclatasvir) tablets on September 1, 2015. The Applicant submitted this supplement to split S-01 and clarify new supplements numbers:

- S-01 expands the indication to include post liver transplant patients
- S-02 expands indication to include human immunodeficiency virus (HIV-1) co-infected patients.
- S-03 expands the indication to include decompensated cirrhotic patients.

DAKLINZA (daclatasvir) tablets was originally approved on July 24, 2015 and is currently indicated for use with sofosbuvir for the treatment of chronic HCV genotype 3 infection.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Antiviral Products (DAVP) on September 11, 2015, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for DAKLINZA (daclatasvir) tablets.

2 MATERIAL REVIEWED

- Draft DAKLINZA (daclatasvir) PPI received on August 5, 2015, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on January 8, 2016.
- Draft DAKLINZA (daclatasvir) Prescribing Information (PI) received on August 5, 2015, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on January 8, 2016.
- Approved DAKLINZA (daclatasvir) labeling dated July 24, 2015.
- Approved OLYSIO (simeprevir) comparator labeling dated October 5, 2015.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the PPI the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APFont to make medical information more accessible for patients with vision loss. We have reformatted the PPI document using the Arial font, size 10.

In our collaborative review of the PPI we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the PPI is consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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/s/

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01/21/2016

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01/21/2016

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: January 21, 2016

To: Sohail Mosaddegh
Regulatory Project Manager
Division of Antiviral Products (DAVP)

From: Kemi Asante, PharmD, RAC
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: NDA 206843 S-01, 02, 03
Daklinza (daclatasvir) tablets, for oral use

In response to DAVP's September 11, 2015 consult request, OPDP has reviewed the proposed package insert (PI) and patient package insert (PPI) for Daklinza (daclatasvir) tablets for oral use.

Comments on the PI are provided below and are based on the review of the substantially complete version of the PI accessed from the following link provided by DAVP via email on January 8, 2016: <http://sharepoint.fda.gov/orgs/CDER-OAP-DAVP/davpactiveprojecsts/Shared%20Documents/Mosaddegh,%20Sohail/206843-s01-s02-PI-PPI.docx>

Please note that comments on the PPI will be provided under separate cover as a collaborative review between OPDP and the Division of Medical Policy Programs (DMPP).

OPDP appreciates the opportunity to provide comments. If you have any questions, please contact me at 301-796-7425 or Kemi.Asante@fda.hhs.gov.

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/s/

OLUWASEUN A ASANTE
01/21/2016

M E M O R A N D U M

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

CLINICAL INSPECTION SUMMARY

DATE: December 7, 2015

TO: Sohail Mosaddegh, PharmD, Regulatory Health Project Manager
Wendy Carter, D.O., Medical Officer
Division of Antiviral Products

FROM: Antoine El-Hage, Ph.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

THROUGH: Susan Thompson, M.D.
Team Leader
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

Kassa Ayalew, M.D., MPH
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 206843/S1-3

APPLICANT: Bristol Myers Squibb Co.

DRUG: Daklinza™ plus sofosbuvir (daclatasvir/sofosbuvir)

NME: No

THERAPEUTIC CLASSIFICATION: Priority review

INDICATION: Treatment of chronic genotype 1 HCV-infection in adults, both treatment experienced and naïve subjects, Human Immunodeficiency Virus (HIV-1) and patients with chronic Hepatitis C with either compensated or decompensated cirrhosis

CONSULTATION REQUEST DATE: September 18, 2015

DIVISION ACTION GOAL DATE: February 5, 2016

PDUFA DATE: February 5, 2016

INSPECTION SUMMARY DUE DATE: January 5, 2016

I. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

Three clinical investigator sites were inspected in support of this application. The inspection of the three clinical investigators listed below revealed no regulatory violations. The pending classification for Drs. Schiff, Wyles, and Yozviak sites are No Action Indicated (NAI). For the pending classifications, a summary addendum will be generated if conclusions change upon receipt and review of the EIRs. Overall, the data submitted from these three sites are considered acceptable and may be used in support of the pending application.

II. BACKGROUND:

Both sofosbuvir and daclatasvir (DCV and SOF) are approved for treatment of HCV-infected naïve and relapsed/experienced subjects. The Applicant sponsored two studies.

Study Protocol A1444215. S-001: Expands the patient population to include patients with chronic hepatitis C virus (HCV) recurrence after liver transplant and to update labeling with information from the ALLY-1 clinical trial.

Study Protocol A1444216. S-002: Expands the indication to include the treatment of subjects with genotype -1 chronic hepatitis C virus infection, including subjects who are co-infected with human immunodeficiency virus (HIV-1) based on the results from the ALLY-2 clinical trial and to update the labeling with drug-drug interaction information for buprenorphine/naloxone and several HIV antiviral agents. S-003 Expands the patient population to include the treatment of chronic hepatitis C virus infection in subjects with compensated or decompensated cirrhosis. The review division elected to inspect the two protocols listed below. Brief outlines of the submitted protocols are given below:

Protocol A1444215/ALLY-I

Protocol A1444215 is entitled “A Phase 3 Evaluation of Daclatasvir , Sofosbuvir, and Ribavirin in Genotype 1-6 Chronic Hepatitis C Infection Subjects with Cirrhosis who May Require Future Liver Transplant and Subjects Post-Transplant” (ALLY-1).

The objectives of this study were: 1) to demonstrate the SVR12 rate in GT-1 infected subjects with advanced cirrhosis, defined as HCV RNA < lower level of quantitation (LLOQ) target detected (TD) or target not detected (TND) 12 weeks after the end of treatment is greater than the composite estimated historical threshold, and 2) to demonstrate the SVR 12 rate in post-liver transplant GT-1 infected subjects, defined as HCV RNA < LLOQ TD or TND 12 weeks after the end of treatment is greater than the composite estimated historical threshold, and 3) to demonstrate the SVR 12 rate in post-liver transplant GT-1 infected subjects, defined as HCV RNA < LLOQ TD or TND 12 weeks after the end of treatment, is greater than the historical threshold achieved by pegIFN alpha /RBV.

This protocol was a phase 3 open label study assessing the combination of HCV/SOV/EBV

administered for 12 weeks in cirrhotic subjects who may require future liver transplantation, and in subjects who are post-liver transplant. Approximately 110 treated subjects (60 cirrhotic and 50 post-liver transplant subjects) were enrolled at U.S. sites. The study was 26 weeks (12 weeks of treatment + 24 weeks of follow-up post-treatment).

Protocol A1444216/ALLY-2

Protocol A1444216 is entitled “A Phase 3 Evaluation of Daclatasvir Plus, Sofosbuvir, in Treatment Naïve and Treatment-Experienced Chronic Hepatitis C (Genotype 1, 2, 3, 4, 5 or 6) Subjects Co-infected with Human Immunodeficiency Virus (HIV) (ALLY-2)”.

The objective of this study was to demonstrate the SVR12 rate, defined as HCV RNA < LLOQ TD or TND) at follow-up week 12, in treatment-naïve HCV GT-1 subjects co-infected with HIV who are treated with DCV/SOF therapy for 12 weeks is greater than the historical threshold achieved by peg-interferon alfa plus RBV peg-INFalpha/RBV.

This protocol was a phase 3 open label, 2 cohort, 3 arm study in HCV treatment-naïve and treatment-experienced subjects with HCV and HIV. The treatment-naïve subjects were randomized 2:1 (100:50) to receive DCV/SOF for either 12 (100 subjects planned) or 8 (50 subjects planned) weeks. Randomization was stratified by cirrhosis status (cirrhotic vs non-cirrhotic) and HCV genotype. Subjects infected with HCV GT-1 were further stratified by subtype (i.e, GT-1a, GT-1b). The treatment-experienced HCV/HIV co-infected subjects who previously failed anti-HCV therapy received 12 weeks of DCV/SOV (50 subjects). Approximately 203 subjects were enrolled at 37 sites all in the US.

The Division of Antiviral Products (DAVP) requested inspections of the following clinical investigator sites due to high subject enrollment, significant efficacy results pertinent to decision-making, and patterns of repeat digits for vital signs at Dr. Yozviak’s site.

III. RESULTS (by protocol/site):

Name of CI, Location, and Site #	Protocol and # of Subjects Randomized	Inspection Dates	Final Classification
Eugene Schiff, M.D University of Miami Miami, FL 33136 Site #0004	Protocol A1444215/ALLY-1 Number of subjects: 22	11/23- 12/2/2015	Pending (preliminary classification NAI)
David Wyles, M.D. UCSD Antiviral Res. Ctr. 220 Dickinson St. San Diego, CA 92103 Site #0018	Protocol A1444216/ALLY-2 Number of subjects: 11	11/18- 24/2015	Pending (preliminary classification NAI)
Joseph Yozviak, D.O Leigh valley Health	Protocol A1444216/ALLY-2	10/19- 20/2015	

Name of CI, Location, and Site #	Protocol and # of Subjects Randomized	Inspection Dates	Final Classification
network 17th and Chew Street Allentown, PA 18102 Site #0019	Number of subjects: 8		NAI

Key to Classifications

NAI = No deviations

VAI = Deviation(s) from regulations

OAI = Significant deviations from regulations. Data unreliable.

Pending = Preliminary classification based on e-mail communication from the field; the Establishment Inspectional Report (EIR) has not been received from the field and complete review of EIR is pending. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIRs.

1. Eugene Schiff, M.D.
Miami, FL 33136

At this site, a total of 22 subjects were screened, 22 subjects were randomized into the study, and 21 subjects completed the study, and one subject was a fatality post treatment week 24 (not study related).

The medical records/source data for 11 subjects were reviewed and compared to data listings. The review included drug accountability records, inclusion/exclusion criteria, vital signs, IRB records, sponsor correspondence, and adverse events. Source documents for all subjects reviewed were compared to case report forms and data listings including primary efficacy endpoints and adverse events listings. No deficiencies were noted.

At the conclusion of the inspection, no Form FDA 483 was issued to Dr. Schiff. However, the field investigator noted that at least two subjects (042 and 0102) required Relapse-Treatments (RR); as a result their treatment/enrollment lasted an additional 24 weeks. Subject #042 was a RR failure, and Subject #102 was a RR success.

The medical records reviewed were found to be in order, organized, and the data verifiable. There were no deaths (exception noted above) and no evidence of under-reporting of adverse events. There were no known limitations to the inspection.

The data generated by this site are considered reliable and appear acceptable in support of the pending applications.

2. David Wyles, M.D.
San Diego, CA 92103

At this site, a total of 11 subjects were screened, 11 subjects were randomized into the study, and 11 subjects completed the study

The medical records/source data for 11 subjects were reviewed including drug accountability records, vital signs, IRB records, informed consent documents, prior and current medications, and inclusion/exclusion criteria. Source documents for all subjects were compared to data listings for primary efficacy endpoints and adverse events listings.

At the conclusion of the inspection, no Form FDA 483 was issued to Dr. Wyles. However, the ORA investigator found three subjects experienced relapse during the follow-up Weeks 4, 12, and 24 visits. One subject was in the experienced DCV/SOV 12 week regimen, and two subjects were in the naïve DCV/SOV 8 week regimen. The medical records reviewed were verifiable based on the information available at the site. There were no known limitations to the inspection. There were no deaths and no evidence of under-reporting of adverse events at this site.

Overall, the data submitted in support of the clinical efficacy and safety from this site is considered reliable and may be used in support of the pending applications.

3. Joseph Yozviak, D.O.
Allentown, PA 18102

At this site, a total of eight subjects were screened, and eight subjects were randomized into the study. Six subjects completed the study, and two subjects were withdrawn from the study due to incarceration.

The medical records/source data for eight subjects were reviewed and compared to data listings. The review included drug accountability records, informed consent documents, inclusion/exclusion criteria, vital signs, IRB records, sponsor correspondence, and adverse events. Source documents for all subjects were compared to case report forms and data listings including for primary efficacy endpoints and adverse events listings. No deficiencies were noted.

At the conclusion of the inspection, a one-item Form FDA 483 was issued to Dr. Yozviak. The ORA investigator noted in at least three subjects, incorrect batch numbers were assigned to the subjects. However, the subjects received the corrected medication. In addition, the ORA investigator discussed with the clinical investigator the incorrect dates for resolved adverse events for three subjects. No evidence of repeat digits in vital signs was found.

With the exceptions noted above, the medical records reviewed were found to be in order, organized, and the data verifiable. There were no deaths and no evidence of under-reporting of adverse events. There were no known limitations to the inspection.

Overall the data generated by this site are considered reliable and appear acceptable in support of the pending applications.

{See appended electronic signature page}

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12/10/2015

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12/10/2015

KASSA AYALEW
12/10/2015

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Pharmacovigilance Review

Date: November 24, 2015

Reviewer: Mihaela Jason, PharmD
Division of Pharmacovigilance II

Team Leader: Kelly Cao, PharmD
Division of Pharmacovigilance II

Deputy Division Director: S. Christopher Jones PharmD, MS, MPH
Division of Pharmacovigilance II

Product Name: Daklinza (daclatasvir hydrochloride)

Subject: All adverse events with daclatasvir use

Application Type/Number: NDA 206843

Applicant/Sponsor: Bristol-Myers Squibb

OSE RCM #: 2015-2354

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EXECUTIVE SUMMARY

This review evaluates the FDA Adverse Event Reporting System (FAERS) for post-marketing reports of adverse events with the use of Daklinza (daclatasvir). The Division of Antiviral Products (DAVP) consulted the Division of Pharmacovigilance II (DPV II) to assess all adverse events in light of several supplements submitted by the sponsor to expand indications to patients with hepatitis C virus (HCV) genotype 1 infection, including those with decompensated cirrhosis, liver transplant, and HIV co-infection.

A review of the most frequently reported PTs for all reports, serious reports, and DMEs identified PTs that were labeled (e.g., headache, nausea, dizziness, fatigue, diarrhea) or disease related (e.g., ascites, encephalopathy, abdominal pain, decreased appetite).

Three cases of acute renal impairment with a temporal association to SOF and DCV and positive dechallenge following the discontinuation of SOF and DCV were noted in this review. Cases reporting the unlabeled events of renal failure and impairment were confounded by concomitant medications and comorbidities that could lead to renal dysfunction. However, there is a temporal association between initiation of SOF and DCV treatment and onset of renal dysfunction. Additionally, there was a positive dechallenge in all three cases when the HCV therapy was discontinued and no other medication changes were made. The mechanism by which DCV could be contributing to renal toxicity is unknown. Because DCV is indicated for use only in combination with SOF (in the U.S.), all three acute renal impairment cases identified in this review are confounded by SOF. Therefore, we cannot determine from these data alone whether DCV, SOF, or the combination contributed to the adverse renal outcome, if any. DPV II recommends that DAVP request a sponsor analysis of relevant data for both SOF and DCV for evidence of renal failure association with either drug. We also recommend that preapproval animal and clinical data be reviewed for a potential renal toxicity signal, particularly when SOF and DCV are coadministered. After these data are received by FDA, and DAVP has reviewed the content, DPV II would like to discuss potential labeling changes with DAVP based on the totality of evidence. However, based on the data that we present in this review alone, at a minimum, DPV II recommends adding the risk of renal impairment under Section 6.2 “Postmarketing Experience” to both the SOF and DCV labeling, if further data do not suggest more significant regulatory action.

Two cases of severe anemia with a temporal association to DCV were identified. However, the cases were confounded by concomitant medications and comorbidities associated with anemia. Due to the small number of cases and the confounding factors, a definitive causal relationship between DCV and severe anemia cannot be made at this time. DPV II will continue to monitor for cases of severe anemia reported with DCV use.

DPV II will assess hepatic decompensation and failure associated with DCV use in a follow up review.

DPV II will continue to monitor for all adverse events associated with the use of DCV.

1 INTRODUCTION

1.1 BACKGROUND

This review evaluates the FDA Adverse Event Reporting System (FAERS) for post-marketing reports of adverse events with the use of Daklinza (daclatasvir). The Division of Antiviral Products (DAVP) consulted the Division of Pharmacovigilance II (DPV II) to assess all adverse events in light of several supplements submitted by the sponsor to expand indications to patients with hepatitis C virus (HCV) genotype 1 infection, including those with decompensated cirrhosis, liver transplant, and HIV co-infection.

1.2 REGULATORY HISTORY

Daclatasvir (DCV) is a new molecular entity approved on July 24, 2015 for the treatment of chronic HCV genotype 3 infection in combination with sofosbuvir (SOF).¹ DCV is an inhibitor of HCV NS5A, a nonstructural protein encoded by HCV. DCV binds to the N-terminus of NS5A and inhibits both viral RNA replication and virion assembly.

DCV's efficacy has been established in subjects with HCV genotype 3. The recommended dosage of DCV is 60 mg orally once daily in combination with SOF for 12 weeks. The optimal duration of DCV and SOF for patients with cirrhosis has not been established.

1.3 PRODUCT LABELING

The WARNINGS AND PRECAUTIONS section of the label warns of the risk of adverse reactions or loss of virologic response due to drug interactions. For a list of drugs contraindicated with DCV due to loss of efficacy and possible development of resistance as well as additional steps to prevent or manage other possible and known significant drug interactions, please see full prescribing information.¹ Additionally, the label warns of the risk of serious symptomatic bradycardia when SOF in combination with another HCV direct-acting antiviral (DAA), including DCV, is coadministered with amiodarone.

The most common adverse events ($\geq 5\%$) for DCV were headache, fatigue, nausea, and diarrhea. Laboratory abnormalities included transient, asymptomatic lipase elevations of greater than 3 times the upper limit of normal (ULN) in 2% of subjects in the clinical studies.¹

2 METHODS AND MATERIALS

2.1 FAERS SEARCH STRATEGY

The FAERS database was searched with the strategy described in Table 1.

Table 1. FAERS Search Strategy*	
Date of search	November 2, 2015
Time period of search	July 24, 2015 [^] - November 2, 2015
Product Terms	Daklinza, daclatasvir, daclatasvir hydrochloride
Type of Search	Quick Query

* See Appendix A for description of the FAERS database.

[^] FDA Approval Date

2.1 DATA MINING SEARCH STRATEGY

A data mining analysis of FAERS was performed for this review using Empirica Signal[®] software and the strategy described in Table 2. See Appendix A for a description of data mining of FAERS using Empirica Signal.

Table 2. Data Mining Strategy to Identify PTs with EB05 Scores >2	
Data Refresh Date	September 20, 2015
Drug Names	Daclatasvir
Run Name	Generic by PT with EB05>2
MedDRA Search Terms	All adverse events retrieved at the MedDRA PT level

3 RESULTS

The results section is organized in three parts: 1) an overview of total counts of FAERS reports 2) an overview of data mining findings, and 3) a hands-on review of adverse events that were unlabeled and reported in high frequency, or deemed concerning by the reviewer (i.e., renal failure, anemia, hepatic failure).

3.1 FAERS OVERVIEW

For the FAERS overview, please note that these are total counts of FAERS reports. Report counts may include duplicate reports for the same patient from multiple reporters (e.g., manufacturer, family member, physician, pharmacist, nurse, etc.), miscoded reports, or unrelated reports. Reported outcomes for this section are the coded outcomes submitted to FDA; causality and the role of the product in the coded outcome have not been determined for this evaluation.

3.1.1

FAERS Search Results

The FAERS search on April 2, 2015 yielded 494 reports. In the U.S., DCV is only approved for use with sofosbuvir (SOF). Reports were excluded if they reported concomitant asunaprevir use because asunaprevir is not approved in the U.S. Many of the excluded reports were from Japan because the use of DCV and asunaprevir is approved in that country. Following the exclusion of asunaprevir reports, the search yielded 283 reports.

Table 3. Descriptive characteristics of FAERS Reports for DCV received by FDA between July 24, 2015 – November 2, 2015 (N=283)*		
Sex	Male	176
	Female	86
	Unknown	21
Country of reporter	United States	31
	Foreign	252**
Report type	Expedited	265
	Direct	3
	Periodic	15
Serious Outcomes[^]	Death	39
	Life-threatening	16
	Hospitalized	154
	Disability	13
	Congenital anomaly	0
	Other serious	230

* May include duplicates

** France reported 108 cases

[^] Serious adverse drug experiences per regulatory definition (CFR 314.80) include outcomes of death, life threatening, hospitalization (initial or prolonged), disability, congenital anomaly, and other serious important medical events. A report may have one or more outcome.

Table 4. Breakdown of FAERS Reports by age for DCV, received by FDA between July 24, 2015 – November 2, 2015 (N=283)*	
Age Group	Number of Reports* (US)
0 yrs - 16 yrs	1
17 yrs – 20 yrs	0
21 yrs – 30 yrs	1
31 yrs – 40 yrs	8
41 yrs – 50 yrs	49
51 yrs – 60 yrs	104
61 yrs – 70 yrs	38
71 yrs +	27
Unknown	55

* May include duplicates

The most frequently reported MedDRA Preferred Terms (PTs) are shown in the tables below. However, all reported PTs were screened, particularly for adverse events that we deemed adverse events of special interest (i.e., renal failure, anemia, hepatic failure). DPVII considered these adverse events of special interest because each is serious, has the potential to be drug induced, and was frequently reported to FAERS.

Table 5. MedDRA PTs with N ≥ 7 from FAERS Reports for DCV, received by FDA between July 24, 2015 – November 2, 2015, sorted by decreasing number of FAERS reports per PT			
Total Number of Reports* = 268			
Row	MedDRA PT	Number of FAERS Reports	Labeled for DCV[^] (Yes/No), Location
1	Ascites	26	No, DR
2	Hepatic Encephalopathy	19	No, DR
3	Headache	18	Yes, AR
4	Anemia	17	No
5	Nausea	17	Yes, AR
6	Insomnia	16	No
7	Death	15	No
8	Acute Kidney Injury	13	No
9	Asthenia	12	No
10	Dyspnea	12	No
11	Vomiting	12	No
12	Hepatocellular Carcinoma	11	No, DR
13	Peripheral edema	11	No
14	Pyrexia	11	No
15	Dizziness	10	Yes, W/P ^{**}
16	Fatigue	10	Yes, AR
17	Hepatic Cirrhosis	10	No, DR
18	Hepatic Failure	10	No
19	Liver Transplant	9	No
20	Diarrhea	8	Yes, AR
21	Drug Ineffective	8	No, U
22	Hepatitis C	8	Yes, IR
23	Jaundice	8	No
24	Pneumonia	8	No
25	Renal Failure	8	No
26	Restlessness	8	No
27	Abdominal Pain	7	No, DR
28	Decreased Appetite	7	No, DR
29	Encephalopathy	7	No, DR
30	Renal Impairment	7	No

* A report may contain more than one preferred term

** Dizziness is part of the bradycardia warning when SOF and another DAA are used in combination with amiodarone

[^] Definitions: W/P = Warnings/Precautions, AR = Adverse Reactions, IR = Indication-related, DR = Disease-related

Table 6. MedDRA PTs with N ≥ 6 from FAERS Reports with Serious Outcomes for DCV, received by FDA between July 24, 2015 – November 2, 2015, sorted by decreasing number of FAERS reports per PT

Total Number of Reports* = 268			
Row	MedDRA PT	Number of FAERS Reports	Labeled[^] (Yes/No) Location
1	Ascites	26	No, DR
2	Hepatic Encephalopathy	19	No, DR
3	Anemia	17	No
4	Nausea	17	Yes, AR
5	Insomnia	16	No
6	Death	15	No
7	Acute Kidney Injury	13	No
8	Asthenia	12	No
9	Headache	12	Yes, AR
10	Vomiting	12	No
11	Hepatocellular Carcinoma	11	No, DR
12	Peripheral Edema	11	No
13	Pyrexia	11	No
14	Dyspnea	10	No
15	Fatigue	10	Yes, AR
16	Hepatic Cirrhosis	10	No, DR
17	Hepatic Failure	10	No
18	Dizziness	9	Yes, W/P**
19	Liver Transplant	9	No
20	Diarrhea	8	No
21	Drug Ineffective	8	No, U
22	Hepatitis C	8	Yes, IR
23	Jaundice	8	No
24	Pneumonia	8	No
25	Renal Failure	8	No
26	Restlessness	8	No
27	Abdominal Pain	7	No, DR
28	Decreased Appetite	7	No, DR
29	Encephalopathy	7	No, DR
30	Renal Impairment	7	No
31	Arthralgia	6	No
32	Pleural Effusion	6	No
33	Sepsis	6	No
34	Thrombocytopenia	6	No

* A report may contain more than one preferred term

** Dizziness is part of the bradycardia warning when SOF and another DAA are used in combination with amiodarone

[^] Definitions: W/P = Warnings/Precautions, AR = Adverse Reactions, IR = Indication-related

Designated Medical Events (DMEs) are events that are inherently medically important and often product-related. OSE created the DME list for working purposes; it has no regulatory significance. See Appendix B for a list of OSE’s Designated Medical Events.

Table 7. MedDRA DME-related PTs with N ≥ 3 from FAERS Reports for DCV, received by FDA between July 24, 2015 – November 2, 2015, sorted by decreasing number of FAERS reports per PT			
Total Number of Reports* = 62			
Row	MedDRA DME-related PT	Number of FAERS Reports	Labeled[^] (Yes/No) Location
1	Hepatic Encephalopathy	19	No, DR
2	Acute Kidney Injury	13	No
3	Ascites	13	No, DR
4	Hepatic Failure	10	No
5	Liver Transplant	9	No
6	Renal Failure	8	No
7	Renal Impairment	7	No
8	Hepatic Cirrhosis	6	No, DR
9	Renal Tubular Disorder	5	No
10	Anemia	4	No
11	Diarrhea	4	Yes, AR
12	Pleural Effusion	4	No
13	Asthenia	3	No
14	Gastrointestinal Hemorrhage	3	No
15	Hematemesis	3	No
16	Hepatocellular Carcinoma	3	No, DR
17	Pancytopenia	3	No
18	Pneumonia	3	No
19	Septic Shock	3	No
20	Thrombocytopenia	3	No
21	Urinary Tract Infection	3	No

* A report may contain more than one preferred term

[^] Definitions: AR = Adverse Reactions, DR = Disease-related

Table 8. MedDRA PTs with N ≥ 3 from FAERS Reports for Fatal Outcomes for DCV, received by FDA between July 24, 2015 – November 2, 2015, sorted by decreasing number of FAERS reports per PT

Total Number of Reports* = 39

Row	MedDRA DME-related PT	Number of FAERS Reports	Labeled [^] (Yes/No) Location
1	Death	14	No
2	Hepatic Cirrhosis	7	No, DR
3	Ascites	6	No, DR
4	Diarrhea	4	Yes, AR
5	Hepatocellular Carcinoma	4	No, DR
6	Pyrexia	4	No
7	Renal Failure	4	No
8	Sepsis	4	No
9	Amnesia	3	No
10	Hepatic Encephalopathy	3	No, DR
11	Hepatic Failure	3	No
12	Hepatorenal Syndrome	3	No, DR
13	Pneumonia	3	No
14	Septic Shock	3	No

3.2 DATA MINING

Table 9 lists the disproportionality measures, ranked by descending EB05, for MedDRA PTs associated with DCV. An EB05 score >2 is indicative of a potential signal between a drug and adverse event pair.

Table 9: Data Mining: Disproportionality Scores (EB05>2) for DCV

PT	N	EBGM	EB05	EB95	Labeled (Yes/No), and Other Category*
Hepatic encephalopathy	26	52.269	37.347	71.559	No, DR
Hepatocellular carcinoma	16	45.784	29.645	68.207	No, DR
Esophageal varices haemorrhage	7	46.101	22.654	85.363	No, DR
Ascites	31	26.966	19.842	35.974	No, DR
Hyperbilirubinaemia	11	25.864	13.934	42.954	No
Varices esophageal	6	32.692	6.433	71.686	No, DR
Bradycardia	19	10.657	6.117	18.222	Yes, W/P
Hepatic failure	16	11.926	6.11	21.243	No
Alanine aminotransferase increased	22	9.319	5.906	15.24	No, DR
Encephalopathy	12	10.838	4.972	22.844	No, DR
Liver transplant	6	25.2	4.696	61.363	No
Aspartate aminotransferase increased	16	6.73	4.272	10.892	No, DR
Liver disorder	13	6.101	3.715	10.122	No, U
Jaundice	12	6.319	3.713	11.374	No, DR

Acute kidney injury	27	4.719	3.411	6.4	No
Bile duct stenosis	4	37.544	3.4	120.686	No
Hepatic cirrhosis	9	6.752	3.397	16.937	No, DR
Blood bilirubin increased	11	5.533	3.255	9.289	No
Renal impairment	16	4.966	3.246	7.368	No
Drug interaction	23	4.496	3.162	6.246	Yes, DI
Anaemia	33	3.826	2.855	5.042	No
Hepatitis C	8	4.893	2.631	8.854	Yes, IR
Hepatic function abnormal	8	4.175	2.283	7.2	No, DR
Eosinophil count increased	5	6.241	2.214	29.548	No
Restlessness	8	4.022	2.203	6.912	No
Hyponatraemia	9	3.542	2.013	5.883	No, DR

N= number of reports coded with a preferred term in that HLT, EBGGM=Empirical Bayes Geometric Mean, EB05=lower 90% confidence limit for the EBGGM, EB95= upper 90% confidence limit for the EBGGM.

*Other Categories: WP = Warnings and Precautions, DR=Disease-related, IR=Indication-related, DI = Drug Interactions, U = Uninformative

3.3 HANDS-ON REVIEW OF ADVERSE EVENTS

Based on the FAERS and datamining search results and a thorough evaluation of the PTs retrieved, adverse events that were unlabeled and reported in high frequency or deemed concerning by the reviewer (i.e., renal failure, anemia, hepatic failure) are further discussed below. Duplicate reports were excluded which may have led to a discrepancy in case numbers between the tables above and the discussion of individual adverse events below.

Adverse Event of Interest: Renal Failure and Impairment

The risk of renal failure and impairment is not listed in the DCV label. This unlabeled DME was further explored in order to assess cases of renal failure and impairment reported after drug approval. There were no postmarketing requirements established prior to approval to assess potential renal toxicity of DCV. We also reviewed the cross-discipline team leader review and did not detect a safety signal for renal toxicity with DCV at approval.

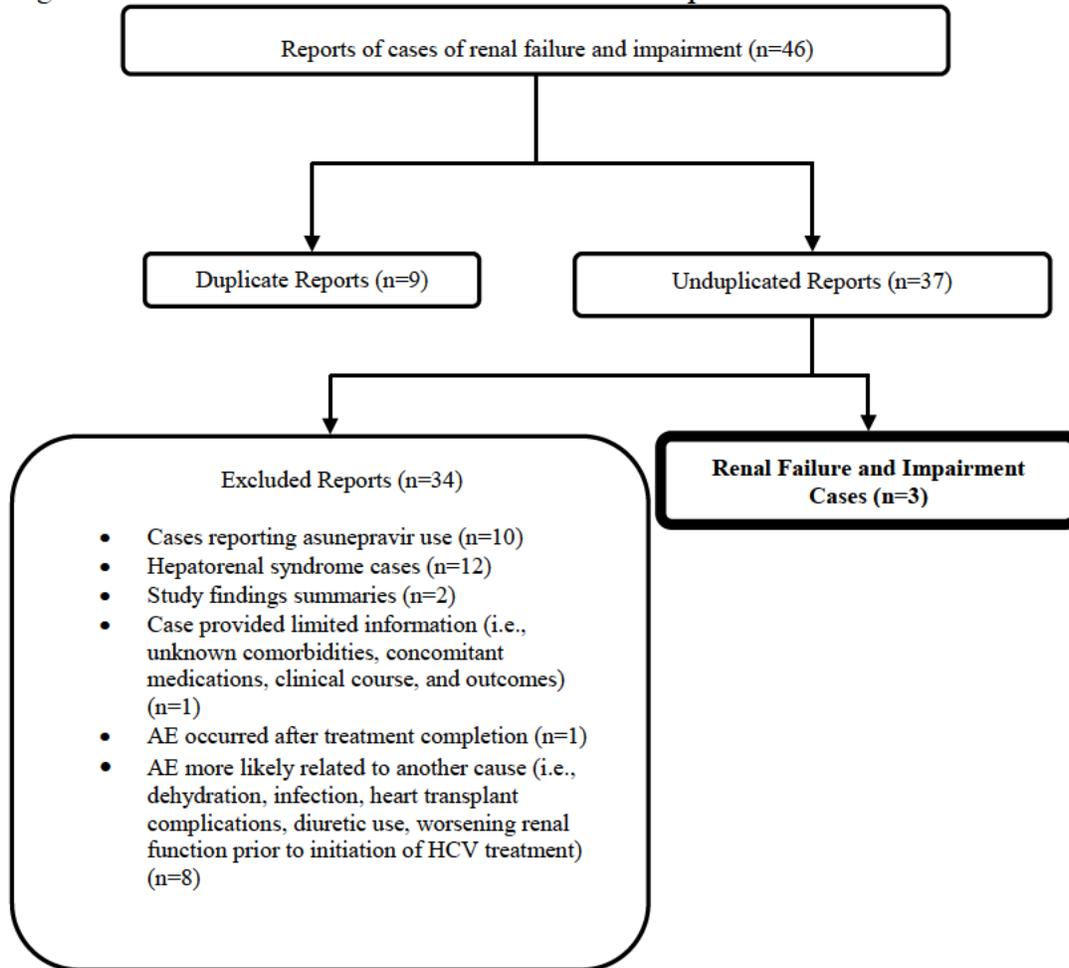
The FAERS database was searched with the strategy described in Table 10.

Table 10. FAERS Search Strategy*	
Date of search	November 6, 2015
Time period of search	July 24, 2015 [^] - November 6, 2015
Product Terms	Daklinza, Daclatasvir, Daclatasvir Hydrochloride
Type of Search	Quick Query
Search Parameters	HLT: Renal Failure and Impairment Outcome: Serious

* See Appendix A for description of the FAERS database.

[^] FDA Approval Date

Figure 1. Selection of Cases of Renal Failure and Impairment with DCV



FAERS Case# 11337223 describes a male HIV co-infected patient of unknown age who experienced renal dysfunction after 42 days of treatment with SOF and DCV. The patient’s medical history included cirrhosis, acute alcoholic pancreatitis, alcoholism in the past, ischemic heart disease, HIV-related candidiasis and lymphocytic meningitis. The patient was concomitantly receiving ritonavir, emtricitabine/tenofovir, darunavir, raltegravir, lysine, propranolol, and lorazepam. The patient’s baseline creatinine clearance (CrCL) was 78 ml/min. After 42 days of treatment, the CrCL decreased to 56 ml/min. Four days later, HCV treatment was discontinued when CrCL was 46 ml/min. Two days after HCV treatment discontinuation and while all other medications were continued, CrCL increased to 85 ml/min. Renal ultrasound was normal at the time of renal impairment. The patient was found to have hypophosphatemia and was diagnosed with renal tubular disease. *Reviewer’s Comments: This case is confounded by tenofovir, which is associated with acute renal failure and Fanconi syndrome (renal tubular injury with hypophosphatemia). Tenofovir is labeled for new onset or worsening renal impairment labeled in the “Warnings and Precautions” section of the label. Additionally, this patient has comorbidities that place him at a higher risk of renal dysfunction (i.e., cirrhosis,*

ischemic heart disease, HIV) and other concomitant medications labeled for the risk of renal dysfunction [i.e., ritonavir (renal insufficiency labeled in “Post-marketing” section), raltegravir (renal failure labeled in “Less Common Adverse Reactions” section)]. There is also a potential drug interaction occurring because concomitant administration of ritonavir with daclatasvir increases the concentration of daclatasvir. However, despite these potential confounders, we consider this case to be possibly related the DAAs as the time to onset supports a temporal association between DCV and SOF treatment and renal dysfunction and the positive dechallenge while all other medications were continued further strengthens this association.

FAERS Case# 11356488 describes a 74-year-old male with history of diabetes, congenital myopathy, chronic kidney disease, hypertension, cirrhosis, liver transplant, and anemia who experienced a decrease in renal function (CrCL 37 ml/min from baseline of 60 ml/min) requiring hospitalization after 35 days of treatment with SOF and DCV. The patient was concomitantly taking cyclosporine (nephrotoxicity labeled under the “Warnings and Precautions” section), perindopril, mycophenolate mofetil, and acetazolamide. At the time of the event, SOF was continued and DCV dose was reduced to 30 mg and renal function improved with CrCL 50 ml/min. There was no proteinuria or cyclosporine overdose (cyclosporine level 95 mg/ml). The outcome for acute renal failure was resolved. *Reviewer’s Comments: This case is confounded by comorbidities that place him at a higher risk of renal failure (i.e., diabetes, myopathy, pre-existing kidney disease, hypertension, cirrhosis) and concomitant medications labeled for the risk of renal dysfunction [i.e., cyclosporine (nephrotoxicity labeled under the “Warnings and Precautions” section) although no clinically relevant changes in exposure are expected for cyclosporine and DCV per the “Drug Interactions” section of the DCV label]. However, the time to onset supports a temporal association between SOF and DCV treatment and renal dysfunction and the improvement in renal function with DCV dose reduction while all other medications were continued further implicates the DCV component of the drug regimen.*

FAERS Case# 11696182 describes a 62-year-old cirrhotic HIV co-infected male patient who was hospitalized for acute renal insufficiency after 27 days of treatment with SOF and DCV. Prior to treatment initiation, his creatinine was 78 micromol/L and CrCL was 88.2 ml/min. After 25 days, his creatinine increased to 143 micromol/L. Three days later HCV therapy was discontinued after gradual creatinine increase and the patient’s renal function improved the day after discontinuation (please see table below for patient’s laboratory values). According to the physician reporter, the renal insufficiency was related to HCV treatment. The patient’s comorbidities included coronary heart disease, abdominal pain, and anxiety.

Table 11. Laboratory Values for FAERS Case# 11696182

	11/28/2014 (prior to HCV treatment)	12/31/2014 (week 2 of HCV treatment)	1/13/2015 (25 days of HCV treatment)	1/17/2015 (after HCV treatment discontinuation)
Creatinine (micromol/L, normal range 62-106)	78	114	143.4	90.3
CrCL (ml/min)	88.2	56.7	46	79
HCV RNA quantification (IU/ml)	1253929	354	unavailable	unavailable
ALT (IU/L)	69	23	unavailable	unavailable
AST (IU/L)	84	32	unavailable	unavailable

AlkPhos (IU/L)	87	79	unavailable	unavailable
Total bilirubin (micromol/L)	9.1	14.5	unavailable	unavailable
Platelets (/L)	83X10 ⁹	64	unavailable	unavailable
HIV RNA	unavailable	unavailable	unavailable	unavailable
CD4	unavailable	unavailable	unavailable	unavailable
INR	unavailable	1.1	unavailable	unavailable
MELD	unavailable	10	unavailable	unavailable

Reviewer's Comments: This case is confounded by comorbidities that place him at a higher risk of renal failure (i.e., coronary heart disease, HIV, cirrhosis). Additionally, our analysis is limited by the lack of information on concomitant medications. However, the time to onset supports a temporal association between SOF + DCV treatment and renal dysfunction, and the improvement in renal function with HCV treatment discontinuation further strengthens this association.

Adverse Event of Interest: Anemia

The risk of anemia is not listed in the DCV label. This unlabeled DME was further explored in order to assess cases of anemia reported after drug approval.

The FAERS database was searched with the strategy described in Table 12.

Table 12. FAERS Search Strategy*	
Date of search	November 2, 2015
Time period of search	July 24, 2015 [^] - November 2, 2015
Product Terms	Daklinza, Daclatasvir, Daclatasvir Hydrochloride
Type of Search	Quick Query
Search Parameters	PTs: All Anemia and Hemolytic Anemia PTs **

* See Appendix A for description of the FAERS database.

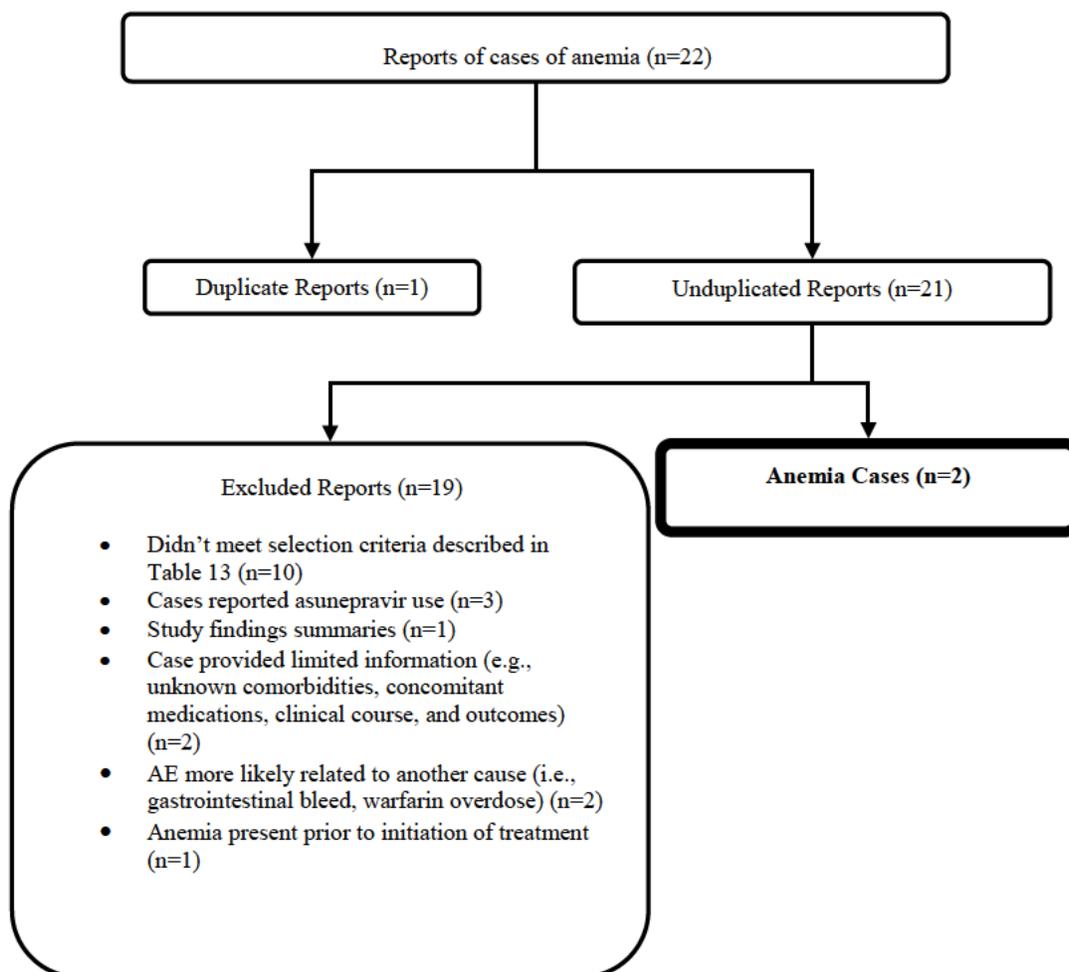
** Anemia and Hemolytic Anemia PTs include: ANAEMIA;ANAEMIA FOLATE DEFICIENCY;ANAEMIA HEINZ BODY;ANAEMIA MACROCYTIC;ANAEMIA MEGALOBLASTIC;APLASTIC ANAEMIA;AUTOIMMUNE APLASTIC ANAEMIA;AUTOIMMUNE HAEMOLYTIC ANAEMIA;BLOOD INCOMPATIBILITY HAEMOLYTIC ANAEMIA OF NEWBORN;CARDIAC HAEMOLYTIC ANAEMIA;COLD TYPE HAEMOLYTIC ANAEMIA;COOMBS NEGATIVE HAEMOLYTIC ANAEMIA;COOMBS POSITIVE HAEMOLYTIC ANAEMIA;DEFICIENCY ANAEMIA;HAEMOLYTIC ANAEMIA;HAEMOLYTIC ANAEMIA ENZYME SPECIFIC;HAEMOLYTIC ICTEROANAEMIA;HAEMORRHAGIC ANAEMIA;HEXOKINASE DEFICIENCY ANAEMIA;HYPERCHROMIC ANAEMIA;HYPOCHROMIC ANAEMIA;HYPOPLASTIC ANAEMIA;IRON DEFICIENCY ANAEMIA;LEUKOERYTHROBLASTIC ANAEMIA;MICROANGIOPATHIC HAEMOLYTIC ANAEMIA;MICROCYTIC ANAEMIA;NEPHROGENIC ANAEMIA;NORMOCHROMIC NORMOCYTIC ANAEMIA;PERNICIOUS ANAEMIA;PROTEIN DEFICIENCY ANAEMIA;PYRUVATE KINASE DEFICIENCY ANAEMIA;REFRACTORY ANAEMIA WITH AN EXCESS OF BLASTS;REFRACTORY ANAEMIA WITH RINGED SIDEROBLASTS;SICKLE CELL ANAEMIA;SICKLE CELL ANAEMIA WITH CRISIS;SIDEROBLASTIC ANAEMIA;SPHEROCYTIC ANAEMIA;SPUR CELL ANAEMIA;WARM TYPE HAEMOLYTIC ANAEMIA

[^] FDA Approval Date

From the FAERS reports retrieved (above), we identified reports of severe anemia by selecting reports with a serious outcome, blood transfusion, or cardiac events (Table 13).

Table 13. Selection of FAERS Anemia Cases
Serious outcome
(or) Blood transfusion: Excel Text Search for <i>transfusion, transfuse, unit (of blood)</i>
(or) Cardiac event: Excel Text Search for <i>arrest, heart, stroke, angina, coronary, congestive</i>

Figure 2. Selection of Cases of Anemia with DCV



FAERS Case# 11417208 describes a 57-year-old HIV co-infected male patient with a history of acute coronary syndrome who experienced anemia [hemoglobin (Hgb) 5.4 mg/dL] 21 days after DCV and SOF treatment initiation. The patient was also receiving emtricitabine/tenofovir, dolutegravir, clopidogrel, aspirin, and bisoprolol. The patient was treated with a blood transfusion. Endoscopy and colonoscopy were negative. It was noted that HCV treatment had been suspended and not re-introduced. Anemia was thought to be life-threatening and the outcome was resolving. *Reviewer's Comments: This case is confounded by clopidogrel (labeled*

for aplastic anemia/pancytopenia under “Postmarketing Experience” section). However, the time to onset supports a temporal association between SOF + DCV treatment and anemia.

FAERS Case# 11679072 describes a 49-year-old male patient who developed severe anemia after 54 days of treatment with SOF and DCV. Hgb was 7.1 mg/dL and the patient improved after receiving a blood transfusion. The patient’s comorbidities included severe ascites, cirrhosis, fibrosis, diabetic nephropathy, diabetes, and arterial hypertension. *Reviewer’s Comments: This case is confounded by concomitant medications [i.e., furosemide (labeled for anemia, aplastic anemia, and hemolytic anemia under “Adverse Reactions” section), repaglinide (labeled for hemolytic anemia under “Postmarketing Experience” section)] and comorbidities (i.e., nephropathy). However, the time to onset supports a temporal association between SOF + DCV treatment and anemia.*

Adverse Event of Interest: Hepatic decompensation and failure

The risk of hepatic decompensation and failure are not listed in the DCV label. There were several PTs related to hepatic dysfunction noted (e.g., hepatic failure, liver transplant, hepatic encephalopathy) and due to the complexity of assessing this AE in patients with HCV, this AE will be discussed in a separate DPV II review.

4 DISCUSSION

A review of the most frequently reported PTs for all reports, serious reports, and DMEs identified PTs that were labeled (e.g., headache, nausea, dizziness, fatigue, diarrhea) or disease related (e.g., ascites, encephalopathy, abdominal pain, decreased appetite).

Three cases of acute renal impairment with a temporal association to SOF and DCV and positive dechallenge following the discontinuation of SOF and DCV were noted in this review. Cases reporting the unlabeled events of renal failure and impairment were confounded by concomitant medications and comorbidities that could lead to renal dysfunction. However, there is a temporal association between initiation of SOF and DCV treatment and onset of renal dysfunction. The time to onset ranged from 27 to 42 days (median 35 days). Additionally, there was a positive dechallenge in all three cases when the HCV therapy was discontinued and no other medication changes were made. We view these cases with a high index of suspicion and believe this warrants further investigation of the potential renal toxicity of the SOF and DCV combination.

The mechanism by which DCV could be contributing to renal toxicity is unknown. No signal for renal toxicity was noted in the development program for DCV per the medical officer’s clinical review. We also searched the published literature but were unable to find any preclinical or clinical evidence that DCV is toxic to the kidney. The possibility of a relevant drug interaction appears remote because no clinically significant drug interactions were observed in drug interaction trials with DCV or SOF with cyclosporine or tenofovir, according to the DCV and SOF labels. However, given the complex medication profiles reported or expected in this patient population, an unrecognized drug interaction cannot be ruled out.

Because DCV is indicated for use only in combination with SOF (in the U.S.), all three acute renal impairment cases identified in this review are confounded by SOF. Therefore, we cannot determine from these data alone whether DCV, SOF, or the combination contributed to the adverse renal outcome, if any. Neither DCV nor SOF is labeled for renal toxicity. We are currently working on the SOF 915 review where acute kidney injury (AKI) was identified as a potential signal; therefore, SOF-AKI will be reviewed in detail in a follow up review. This follow up review may shed light on the contribution of SOF (without DCV) to AKI.

Two cases of severe anemia with a temporal association to DCV were identified. However, the cases were confounded by concomitant medications and comorbidities associated with anemia. Due to the small number of cases and the confounding factors, a definitive causal relationship between DCV and severe anemia cannot be made at this time. DPV II will continue to monitor for cases of severe anemia reported with DCV use.

Cases reporting the unlabeled event of hepatic decompensation and failure will be assessed in a separate DPV II review. Hepatic decompensation and failure in patients with HCV infection are not unexpected, however, given the concerns of hepatotoxicity with other direct acting antivirals, such as simeprevir and Viekira Pak, we plan to evaluate this signal further.

5 CONCLUSION

A new safety signal for renal impairment was identified with DCV use in this review of FAERS post-marketing reports.

6 RECOMMENDATIONS

- DPV II recommends that DAVP request a sponsor analysis of relevant data for both SOF and DCV for evidence of renal failure association with either drug.
- We also recommend that preapproval animal and clinical data be reviewed for a potential renal toxicity signal, particularly when SOF and DCV are coadministered.

After these data are received by FDA, and DAVP has reviewed the content, DPV II would like to discuss potential labeling changes with DAVP based on the totality of evidence. However, based on the data that we present in this review alone, at a minimum, DPV II recommends adding the risk of renal impairment under Section 6.2 “Postmarketing Experience” to both the SOF and DCV labeling, if further data do not suggest more significant regulatory action.

- DPV II will assess hepatic decompensation and failure associated with DCV use in a follow up review.
- DPV II will continue to monitor for all adverse events associated with the use of DCV.

7 REFERENCES

1. (Daklinza[®]) [package insert]. Princeton, NJ 08543: Bristol-Myers Squibb 2015.

8 APPENDICES

8.1 APPENDIX A. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FDA implemented FAERS on September 10, 2012, and migrated all the data from the previous reporting system (AERS) to FAERS. Differences may exist when comparing case counts in AERS and FAERS. FDA validated and recoded product information as the AERS reports were migrated to FAERS. In addition, FDA implemented new search functionality based on the date FDA initially received the case to more accurately portray the follow up cases that have multiple receive dates.

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

Data Mining of FAERS using Empirica Signal

Empirica Signal refers to the software that OSE uses to perform data mining analyses while using the Multi-item Gamma Poisson Shrinker (MGPS) data mining algorithm. "Data mining" refers to the use of computer algorithms to identify patterns of associations or unexpected occurrences (i.e., "potential signals") in large databases. These potential signals can then be evaluated for intervention as appropriate. In OSE, the FDA Adverse Event Reporting System (FAERS) database is utilized for data mining. MGPS analyzes the records in FAERS and then quantifies reported drug-event associations by producing a set of values or scores that indicate varying strengths of reporting relationships between drugs and events. These scores, denoted as Empirical Bayes Geometric Mean (EBGM) values, provide a stable estimate of the relative reporting of an event for a particular drug relative to all other drugs and events in FAERS. MGPS also calculates lower and upper 90% confidence limits for EBGM values, denoted EB05 and EB95, respectively. Because EBGM scores are based on FAERS data, limitations relating to FAERS data also apply to data mining-derived data. Further, drug and event causality cannot be inferred from EBGM scores

8.2 APPENDIX B. LIST OF OSE DESIGNATED MEDICAL EVENTS AND ASSOCIATED MEDDRA PREFERRED TERMS

Designated Medical Event	MedDRA Preferred Terms
Acute pancreatitis	Pancreatic necrosis, Pancreatitis acute, Pancreatitis haemorrhagic, Pancreatitis necrotising, Pancreatitis
Acute respiratory failure	Acute respiratory distress syndrome, Acute respiratory failure, Respiratory failure
Agranulocytosis	Agranulocytosis, Febrile neutropenia, Neutropenia
Amyotrophic lateral sclerosis	Amyotrophic lateral sclerosis
Anaphylaxis and anaphylactoid reactions	Anaphylactic reaction, Anaphylactic shock, Anaphylactoid reaction, Anaphylactoid shock
Aplastic anemia	Aplasia pure red cell, Aplastic anemia, Bone marrow failure
Blind	Blindness, Blindness transient, Blindness unilateral, Optic ischaemic neuropathy, Sudden visual loss
Colitis ischaemic	Colitis ischaemic, Intestinal infarction
Congenital anomalies	Congenital anomaly
Deaf	Deafness bilateral, Deafness neurosensory, Deafness permanent, Deafness transitory, Deafness unilateral, Deafness, Sudden hearing loss
Diss. intravascular coagulation	Disseminated intravascular coagulation
Endotoxic shock, confirmed or suspected	Endotoxic shock, Septic shock
Haemolysis	Haemoglobinaemia, Haemoglobinuria, Haemolysis, Haptoglobin decreased, Intravascular haemolysis
Hemolytic anemia	Coombs negative haemolytic anaemia, Coombs positive haemolytic anaemia, Haemolytic anaemia
Liver failure	Acute hepatic failure, Hepatic encephalopathy, Hepatic failure, Subacute hepatic failure
Liver necrosis	Hepatitis acute, Hepatitis fulminant, Hepatic necrosis
Liver transplant	Liver transplant
Neuroleptic malignant syndrome	Neuroleptic malignant syndrome
Pancytopenia	Pancytopenia
Progressive multifocal leukoencephalopathy	Progressive multifocal leukoencephalopathy
Product infectious disease transmission	Product contamination microbial Transfusion-transmitted infectious disease Transmission of an infectious agent via a medicinal product
Pulmonary fibrosis	Pulmonary fibrosis
Pulmonary hypertension	Cor pulmonale, Pulmonary hypertension
Renal failure	Renal failure, Renal failure acute, Renal impairment
Rhabdomyolysis	Rhabdomyolysis
Seizure	Convulsion, Epilepsy, Grand mal convulsion
Serotonin syndrome	Serotonin syndrome
Stevens-Johnson syndrome	Erythema multiforme, Stevens-Johnson syndrome
Sudden death	Sudden cardiac death, Sudden death
Suicide	Completed suicide
Torsade de Pointes	Torsade de pointes
Toxic epidermal necrolysis	Dermatitis exfoliative, Toxic epidermal necrolysis
TTP	Thrombotic thrombocytopenic purpura
Ventricular fibrillation	Ventricular fibrillation

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/s/

MIHAELA P JASON
11/24/2015

KELLY Y CAO
11/24/2015

STEVEN C JONES
11/24/2015

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review: November 18, 2015
Requesting Office or Division: Division of Antiviral Products (DAVP)
Application Type and Number: NDA 206843/S-01 through 03
Product Name and Strength: Daklinza
(daclatasvir) Tablets
30 mg and 60 mg
Product Type: Single Ingredient Product
Rx or OTC: Rx
Applicant/Sponsor Name: Bristol-Myers Squibb
Submission Date: August 5, 2015
OSE RCM #: 2015-2061
DMEPA Primary Reviewer: Mónica Calderón, PharmD, BCPS
DMEPA Team Leader: Vicky Borders-Hemphill, PharmD

1 REASON FOR REVIEW

Bristol-Myers Squibb (BMS) submitted three efficacy supplements (S-01 through S-03) in support of proposed changes to the approved full prescribing information (FPI) to expand the indication for the treatment of hepatitis C virus (HCV) with sofosbuvir to include post liver transplant patients (S-01), HIV-1 co-infected patients (S-02), and decompensated cirrhotic patients (S-03). Thus, the Division of Antiviral Products (DAVP) requested DMEPA evaluate the Sponsor's revised FPI.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C
ISMP Newsletters	D
FDA Adverse Event Reporting System (FAERS)*	E
Other	F (N/A)
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Bristol-Myers Squibb is proposing to expand the indications and use of Daklinza to include post liver transplant patients, HIV-1 co-infected patients, and decompensated cirrhotic patients. DMEPA performed a risk assessment of the proposed FPI to identify deficiencies that may lead to medication errors and areas of improvement.

FAERS cases

DMEPA conducted a FAERS search to inform our review of the proposed label and labeling (see Appendix E). We identified one wrong frequency medication error case. No root cause was identified and no adverse events were reported. We note the proposed FPI and current patient package insert (PPI) clearly states the frequency of administration. We have no risk mitigation strategies to recommend at this time for this error.

FPI- Dosage and Administration Section

We evaluated the revised Dosage and Administration section (see Appendix G) for the current efficacy supplements which includes recommendations for the treatment of post liver transplant patients, HIV-1 co-infected patients, and decompensated cirrhotic patients and we find the proposed changes acceptable.

4 CONCLUSION & RECOMMENDATIONS

DMEPA concludes the Sponsor's proposed Dosage and Administration section of the FPI is acceptable. We have no recommendations at this time.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Daklinza that Bristol-Myers Squibb submitted on August 5, 2015.

Table 2. Relevant Product Information for Daklinza	
Initial Approval Date	July 24, 2015
Active Ingredient	daclatasvir
Indication	Current: Use with sofosbuvir for the treatment of chronic hepatitis C virus genotype 3 infection Proposed: in combination with sofosbuvir in adults with chronic HCV infection including those coinfecting with HIV-1, those with compensated or decompensated cirrhosis, and those with HCV recurrence after liver transplantation.
Route of Administration	Oral
Dosage Form	Tablet
Strength	30 mg and 60 mg
Dose and Frequency	60 mg once daily
How Supplied	Bottle of 28 tablets
Storage	25°C (77°F), with excursions permitted between 15°C and 30°C (59°F and 86°F)

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On November 2, 2015, we searched the L:drive and AIMS using the terms, Daklinza to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified one previous review¹, and we confirmed that our previous recommendations were implemented.

¹ Calderon, M. Label and Labeling Review for Daklinza NDA 206843. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2014 06 29. RCM No.: 2014-672.

APPENDIX D. ISMP NEWSLETTERS

D.1 Methods

On November 2, 2015, we searched the Institute for Safe Medication Practices (ISMP) newsletters using the criteria below, and then individually reviewed each newsletter. We limited our analysis to newsletters that described medication errors or actions possibly associated with the label and labeling.

ISMP Newsletters Search Strategy	
ISMP Newsletter(s)	Acute Care Nursing Community
Search Strategy and Terms	Match Exact Word or Phrase: Daklinza

D.2 Results

No cases were identified.

APPENDIX E. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

E.1 Methods

We searched the FDA Adverse Event Reporting System (FAERS) on November 4, 2015 using the criteria in Table 3, and then individually reviewed each case. We limited our analysis to cases that described errors possibly associated with the label and labeling. We used the NCC MERP Taxonomy of Medication Errors to code the type and factors contributing to the errors when sufficient information was provided by the reporter.²

Table 3: FAERS Search Strategy	
Date Range	November 4, 2015
Product	Daklinza [product name]
Event (MedDRA Terms)	DMEPA Official FBIS Search Terms Event List: Contraindicated Drug Administered (PT) Drug Administered to Patient of Inappropriate Age (PT) Inadequate Aseptic Technique in Use of Product (PT) Medication Errors (HLGT) Overdose (PT) Prescribed Overdose (PT) Prescribed Underdose (PT) Product Adhesion Issue (PT) Product Compounding Quality Issue (PT) Product Formulation Issue (PT) Product Label Issues (HLT) Product Packaging Issues (HLT) Product Use Issue (PT) Underdose (PT)

E.2 Results

Our search identified 3 cases, of which 1 described an error relevant for this review.

- Wrong frequency (n=1)

We identified one wrong frequency medication error. The patient was taking Daklinza twice daily versus once daily as prescribed. No root cause was identified and no adverse events were reported. We note the current and proposed full prescribing information and patient package insert clearly state the frequency of administration of Daklinza.

² The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Taxonomy of Medication Errors. Website <http://www.nccmerp.org/pdf/taxo2001-07-31.pdf>.

We excluded 2 cases because they described:

- Dose omission (n=2)

E.3 List of FAERS Case Numbers

Below is a list of the FAERS case number and manufacturer control numbers for the cases relevant for this review.

Case number	Case version	Manufacturer Control Number
11558768	1	US-BRISTOL-MYERS SQUIBB COMPANY-BMS- 2015-064958

E.4 Description of FAERS

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's postmarket safety surveillance program for drug and therapeutic biologic products. The informatic structure of the FAERS database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. FDA's Office of Surveillance and Epidemiology codes adverse events and medication errors to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Product names are coded using the FAERS Product Dictionary. More information about FAERS can be found at: <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm>.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,³ along with postmarket medication error data, we reviewed the following Daklinza labels and labeling submitted by Bristol-Myers Squibb on August 5, 2015.

- FPI

G.2 Label and Labeling Images

Proposed FPI- Dosage and Administration Section

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The recommended dosage of DAKLINZA is 60 mg, taken orally, once daily, (b) (4) with or without food.

DAKLINZA should be used in combination with sofosbuvir or with sofosbuvir and ribavirin. The recommended regimen and treatment duration for DAKLINZA combination therapy by patient population is provided in Table 1. 1, 2, 3, 4 (b) (4)

For specific dosage recommendations for sofosbuvir or ribavirin, refer to Clinical Studies (14) and the respective prescribing information.

Table 1: Recommended Treatment Regimen and Duration in HCV Monoinfected and HCV/HIV-1 Coinfected Patients

<u>Patient Population</u>	<u>Treatment</u>	<u>Duration</u>
<u>Patients without cirrhosis</u>	<u>DAKLINZA + sofosbuvir</u>	<u>12 weeks</u>
<u>Patients with cirrhosis: Child-Pugh A, B, and C</u>	<u>DAKLINZA + sofosbuvir + ribavirin^a</u>	<u>12 weeks</u>
<u>Patients with posttransplant recurrence of HCV infection</u>	<u>DAKLINZA + sofosbuvir + ribavirin</u>	<u>12 weeks</u>

^a For patients with HCV genotype 1 infection who have compensated cirrhosis (Child-Pugh A), DAKLINZA + sofosbuvir without ribavirin may be considered.

³ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

MONICA M CALDERON
11/18/2015

BRENDA V BORDERS-HEMPHILL
11/19/2015

REGULATORY PROJECT MANAGER PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW OF THE PRESCRIBING INFORMATION

Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements

Application: NDA 206843/S-001, S-002, and S-003

Application Type: Efficacy Supplements

Name of Drug/Dosage Form: DAKLNIZA, Daclatasvir 30 & 60 mg oral tablet

Applicant: Bristol-Myers Squibb Company

Receipt Date: August 05, 2015 (labeling reviewed was received 09/22/2015)

Goal Date: February 05, 2016

1. Regulatory History and Applicant's Main Proposals

DAKLINZA (daclatasvir) was approved July 24, 2015 in combination with sofosbuvir for the treatment of chronic hepatitis C virus, genotype 3 infection.

S-001: expands the patient population to include patients with chronic hepatitis C virus (HCV) recurrence after liver transplantation and to update the labeling with information from the ALLY-1 clinical trial.

S-002: expands the indication to include the treatment of subjects with genotype-1 chronic hepatitis C virus infection, including subjects who are co-infected with human immunodeficiency virus (HIV-1) based on the results from the ALLY-2 clinical trial and to update the labeling with drug-drug interaction information for buprenorphine/naloxone and several HIV antiviral agents

S-003: expands the patient population to include the treatment of chronic hepatitis C virus infection in subjects with compensated or decompensated cirrhosis

2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

3. Conclusions/Recommendations

No SRPI format deficiencies were identified in the review of this PI.

Selected Requirements of Prescribing Information

Highlights

See Appendix A for a sample tool illustrating the format for the Highlights.

HIGHLIGHTS GENERAL FORMAT

- YES** 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment:

- YES** 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. Instructions to complete this item: If the length of the HL is one-half page or less, select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select “NO” unless a waiver has been granted.

Comment:

- YES** 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.

Comment:

- YES** 4. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.

Comment:

- YES** 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.

Comment:

- YES** 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment:

- YES** 7. Section headings must be presented in the following order in HL:

Section	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required
• Product Title	Required
• Initial U.S. Approval	Required
• Boxed Warning	Required if a BOXED WARNING is in the FPI
• Recent Major Changes	Required for only certain changes to PI*
• Indications and Usage	Required
• Dosage and Administration	Required
• Dosage Forms and Strengths	Required

Selected Requirements of Prescribing Information

• Contraindications	Required (if no contraindications must state “None.”)
• Warnings and Precautions	Not required by regulation, but should be present
• Adverse Reactions	Required
• Drug Interactions	Optional
• Use in Specific Populations	Optional
• Patient Counseling Information Statement	Required
• Revision Date	Required

* RMC only applies to the BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS sections.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

- YES** 8. At the beginning of HL, the following heading must be **bolded** and should appear in all UPPER CASE letters: “**HIGHLIGHTS OF PRESCRIBING INFORMATION**”.

Comment:

Highlights Limitation Statement

- YES** 9. The **bolded** HL Limitation Statement must include the following verbatim statement: “**These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).**” The name of drug product should appear in UPPER CASE letters.

Comment:

Product Title in Highlights

- YES** 10. Product title must be **bolded**.

Comment:

Initial U.S. Approval in Highlights

- YES** 11. Initial U.S. Approval in HL must be **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit year**.

Comment:

Boxed Warning (BW) in Highlights

- N/A** 12. All text in the BW must be **bolded**.

Comment:

- N/A** 13. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”). The BW heading should be centered.

Comment:

- N/A** 14. The BW must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” This statement should be centered immediately beneath the heading and appear in *italics*.

Selected Requirements of Prescribing Information

Comment:

- N/A** 15. The BW must be limited in length to 20 lines (this includes white space but does not include the BW heading and the statement “*See full prescribing information for complete boxed warning.*”).

Comment:

Recent Major Changes (RMC) in Highlights

- YES** 16. RMC pertains to only the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in FPI.

Comment:

- YES** 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Warnings and Precautions, Acute Liver Failure (5.1) --- 9/2013”.

Comment:

- YES** 18. The RMC must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage in Highlights

- YES** 19. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: “(Product) is a (name of established pharmacologic class) indicated for (indication)”.

Comment:

Dosage Forms and Strengths in Highlights

- YES** 20. For a product that has several dosage forms (e.g., capsules, tablets, and injection), bulleted subheadings or tabular presentations of information should be used under the Dosage Forms and Strengths heading.

Comment:

Contraindications in Highlights

- YES** 21. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.

Comment:

Selected Requirements of Prescribing Information

Adverse Reactions in Highlights

- YES** 22. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment:

Patient Counseling Information Statement in Highlights

- YES** 23. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product **has** FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide**”

Comment:

Revision Date in Highlights

- YES** 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., “**Revised: 9/2013**”).

Comment:

Selected Requirements of Prescribing Information

Contents: Table of Contents (TOC)

See Appendix A for a sample tool illustrating the format for the Table of Contents.

YES 25. The TOC should be in a two-column format.

Comment:

YES 26. The following heading must appear at the beginning of the TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”. This heading should be in all UPPER CASE letters and **bolded**.

Comment:

YES 27. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.

Comment:

YES 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.

Comment:

YES 29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].

Comment:

YES 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.

Comment:

YES 31. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “FULL PRESCRIBING INFORMATION: CONTENTS” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the full prescribing information are not listed.”

Comment:

Selected Requirements of Prescribing Information

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

- NO** 32. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below (section and subsection headings should be in UPPER CASE and title case, respectively). If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment: 8.2 is labeled lactation, under review by ADL.

- YES** 33. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, “[*see Warnings and Precautions (5.2)*]” or “[*see Warnings and Precautions (5.2)*]”.

Comment:

YES

Selected Requirements of Prescribing Information

34. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

- YES** 35. The following heading must be **bolded** and appear at the beginning of the FPI: “**FULL PRESCRIBING INFORMATION**”. This heading should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

- N/A** 36. In the BW, all text should be **bolded**.

Comment:

- N/A** 37. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”).

Comment:

CONTRAINDICATIONS Section in the FPI

- YES** 38. If no Contraindications are known, this section must state “None.”

Comment:

ADVERSE REACTIONS Section in the FPI

- YES** 39. When clinical trials adverse reactions data are included (typically in the “Clinical Trials Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.”

Comment:

- YES** 40. When postmarketing adverse reaction data are included (typically in the “Postmarketing Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Comment:

PATIENT COUNSELING INFORMATION Section in the FPI

- YES** 41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and

Selected Requirements of Prescribing Information

include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

Comment:

- YES** 42. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

Selected Requirements of Prescribing Information

Appendix A: Format of the Highlights and Table of Contents

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use [DRUG NAME] safely and effectively. See full prescribing information for [DRUG NAME].

[DRUG NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol]
Initial U.S. Approval: [year]

WARNING: [SUBJECT OF WARNING]

See full prescribing information for complete boxed warning.

- [text]
- [text]

RECENT MAJOR CHANGES

[section (X.X)] [m/year]
[section (X.X)] [m/year]

INDICATIONS AND USAGE

[DRUG NAME] is a [name of pharmacologic class] indicated for [text]

DOSAGE AND ADMINISTRATION

- [text]
- [text]

DOSAGE FORMS AND STRENGTHS

[text]

CONTRAINDICATIONS

- [text]
- [text]

WARNINGS AND PRECAUTIONS

- [text]
- [text]

ADVERSE REACTIONS

Most common adverse reactions (incidence > x%) are [text].

To report SUSPECTED ADVERSE REACTIONS, contact [name of manufacturer] at [phone #] or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- [text]
- [text]

USE IN SPECIFIC POPULATIONS

- [text]
- [text]

See 17 for PATIENT COUNSELING INFORMATION [and FDA-approved patient labeling OR and Medication Guide].

Revised: [m/year]

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: [SUBJECT OF WARNING]

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

2.1 [text]

2.2 [text]

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

5.1 [text]

5.2 [text]

6 ADVERSE REACTIONS

6.1 [text]

6.2 [text]

7 DRUG INTERACTIONS

7.1 [text]

7.2 [text]

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Labor and Delivery

8.3 Nursing Mothers

8.4 Pediatric Use

8.5 Geriatric Use

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

9.2 Abuse

9.3 Dependence

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.2 Pharmacodynamics

12.3 Pharmacokinetics

12.4 Microbiology

12.5 Pharmacogenomics

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES

14.1 [text]

14.2 [text]

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

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/s/

SOHAIL MOSADDEGH
09/28/2015

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
NDA # 206843 BLA#	NDA Supplement #:S- 001 S-002, & S-003 BLA Supplement #	Efficacy Supplement Type S-001, S003 =SE-5 S-002=SE-1
Proprietary Name: DAKLNIZA Established/Proper Name: Daclatasvir Dosage Form: oral tablet Strengths: 30 & 60 mg		
Applicant: Bristol-Myers Squibb Company Agent for Applicant (if applicable):		
Date of Application: 08/05/2015 Date of Receipt: 08/05/2015 Date clock started after UN:		
PDUFA Goal Date: 02/05/2016		Action Goal Date (if different):
Filing Date: 10/04/2015		Date of Filing Meeting: 09/22/2015
Chemical Classification: (1,2,3 etc.) (original NDAs only)		
Proposed indication(s)/Proposed change(s): S-001: expands the patient population to include patients with chronic hepatitis C virus (HCV) recurrence after liver transplantation and to update the labeling with information from the ALLY-1 clinical trial. S-002: expands the indication to include the treatment of subjects with genotype-1 chronic hepatitis C virus infection, including subjects who are co-infected with human immunodeficiency virus (HIV-1) based on the results from the ALLY-2 clinical trial and to update the labeling with drug-drug interaction information for buprenorphine/naloxone and several HIV antiviral agents S-003: expands the patient population to include the treatment of chronic hepatitis C virus infection in subjects with compensated or decompensated cirrhosis		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:</i> http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 .		
Type of BLA	<input type="checkbox"/> 351(a) <input type="checkbox"/> 351(k)	
<i>If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team</i>		
Review Classification: <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i> <i>If a tropical disease priority review voucher or pediatric rare disease priority review voucher was submitted, review classification is Priority.</i>	<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted <input type="checkbox"/> Pediatric Rare Disease Priority Review Voucher submitted	
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>	

Part 3 Combination Product? <input type="checkbox"/> <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)
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<input checked="" type="checkbox"/> Fast Track Designation <input checked="" type="checkbox"/> Breakthrough Therapy Designation <i>(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)</i> S-001 has BTDR S-002 does not S-003 has BTDR <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
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Collaborative Review Division (if OTC product):

List referenced IND Number(s): 79599, (b) (4)

Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at: http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm</i> <i>If no, ask the document room staff to make the appropriate entries.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Application Integrity Policy	YES	NO	NA	Comment

Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
If yes, explain in comment column.				
If affected by AIP, has OC/OMPQ been notified of the submission? If yes, date notified:	<input type="checkbox"/>	<input type="checkbox"/>		
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<u>User Fee Status</u> <i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i>	Payment for this application: <input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required			
<i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i>	Payment of other user fees: <input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears			
505(b)(2) (NDAs/NDA Efficacy Supplements only)	YES	NO	NA	Comment
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]? <i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Is there unexpired exclusivity on any drug product containing the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? <i>Check the Electronic Orange Book at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
If yes, please list below:				

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.

Exclusivity	YES	NO	NA	Comment
Does another product (same active moiety) have orphan exclusivity for the same indication? Check the Orphan Drug Designations and Approvals list at: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
If another product has orphan exclusivity , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]? <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>) If yes, # years requested: 3 <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)? If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? <i>If yes, contact the Orange Book Staff (CDER-Orange Book Staff).</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
For BLAs: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? <i>If yes, notify Marlene Schultz-DePalo, OBP Biosimilars RPM</i> <i>Note: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

Format and Content				
<p><i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i></p>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic)			
	<input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
<p>If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?</p>				
Overall Format/Content	YES	NO	NA	Comment
<p>If electronic submission, does it follow the eCTD guidance?¹ If not, explain (e.g., waiver granted).</p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<p>Index: Does the submission contain an accurate comprehensive index?</p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<p>Is the submission complete as required under 21 CFR 314.50 (NDAs/NDA efficacy supplements) or under 21 CFR 601.2 (BLAs/BLA efficacy supplements) including:</p> <p><input checked="" type="checkbox"/> legible <input type="checkbox"/> English (or translated into English) <input type="checkbox"/> pagination <input type="checkbox"/> navigable hyperlinks (electronic submissions only)</p> <p>If no, explain.</p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<p>BLAs only: Companion application received if a shared or divided manufacturing arrangement?</p> <p>If yes, BLA #</p>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Forms and Certifications				
<p><i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i></p>				
Application Form	YES	NO	NA	Comment
<p>Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?</p> <p><i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR</i></p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

¹

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

<i>314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? <i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i> <i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature? <i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i> <i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature? <i>Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i> <i>Note: Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge..."</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? <i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i> <i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<p><u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p><u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i></p>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Pediatrics	YES	NO	NA	Comment
<p><u>PREA</u></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC RPM (PeRC meeting is required)²</i></p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		S-002 triggers PREA
<p>If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?</p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<p>If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included?</p> <p><i>If no, request in 74-day letter</i></p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Agreed to PSP with original NDA
<p>If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)?</p> <p><i>If no, request in 74-day letter</i></p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<p><u>BPCA</u> (NDAs/NDA efficacy supplements only):</p> <p>Is this submission a complete response to a pediatric Written Request?</p> <p><i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i></p>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
Proprietary Name	YES	NO	NA	Comment
<p>Is a proposed proprietary name submitted?</p> <p><i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for</i></p>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	

² <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

³ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

<i>Review.</i> ”				
REMS	YES	NO	NA	Comment
Is a REMS submitted?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>				
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input checked="" type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input type="checkbox"/> Carton labels <input type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If no, request applicant to submit SPL before the filing date.</i>				
Is the PI submitted in PLR format? ⁴	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send <i>WORD</i> version if available)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			

4

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>		
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) <i>If yes, specify consult(s) and date(s) sent:</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? <i>If yes, distribute minutes before filing meeting</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? <i>If yes, distribute minutes before filing meeting</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Any Special Protocol Assessments (SPAs)? <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		

ATTACHMENT

MEMO OF FILING MEETING

DATE: 09/22/2015

BLA/NDA/Supp #: 206843/S-001, S-002, S-003

PROPRIETARY NAME: DAKLINZA

ESTABLISHED/PROPER NAME: daclatasvir

DOSAGE FORM/STRENGTH: oral tablet

APPLICANT: BRISTOL-MYERS SQUIBB CO

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): treatment of Hepatitis C virus

BACKGROUND:

S-001: expands the patient population to include patients with chronic hepatitis C virus (HCV) recurrence after liver transplantation and to update the labeling with information from the ALLY-1 clinical trial.

S-002: expands the indication to include the treatment of subjects with genotype-1 chronic hepatitis C virus infection, including subjects who are co-infected with human immunodeficiency virus (HIV-1) based on the results from the ALLY-2 clinical trial and to update the labeling with drug-drug interaction information for buprenorphine/naloxone and several HIV antiviral agents

S-003: expands the patient population to include the treatment of chronic hepatitis C virus infection in subjects with compensated or decompensated cirrhosis

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Sohail Mosaddegh	Y
	CPMS/TL:	Karen Winestock	Y
Cross-Discipline Team Leader (CDTL)	Kim Struble		Y
Clinical	Reviewer:	Wendy Carter	Y
	TL:	Kim Struble	Y
Social Scientist Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
OTC Labeling Review (<i>for OTC</i>)	Reviewer:		

<i>products)</i>			
	TL:		
Clinical Microbiology (<i>for antimicrobial products)</i>)	Reviewer:	Lalji Mishra/Patrick Harrington	Y
	TL:	Julian O’Rear	N
Clinical Pharmacology	Reviewer:	Stanley Au	Y
	TL:	Shirley Seo	Y
Biostatistics	Reviewer:	Wen Zeng	Y
	TL:	Fraser Smith	N
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Peyton Myers	N
	TL:	Hanan Ghantous	N
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) (<i>for BLAs/BLA efficacy supplements</i>)	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:		
	TL:		
Quality Microbiology (<i>for sterile products</i>)	Reviewer:		
	TL:		
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:		
	TL:		
OSE/DRISK (REMS)	Reviewer:		
	TL:		

OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		
Bioresearch Monitoring (OSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Patient labeling	Rowe Medina (Barbara Fuller TL)		Y
OPDP labeling reviewer (marketing)	Kemi Asante		N
Other attendees			

FILING MEETING DISCUSSION:

GENERAL	
<ul style="list-style-type: none"> • 505(b)(2) filing issues: <ul style="list-style-type: none"> ○ Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? ○ Did the applicant provide a scientific “bridge” demonstrating the relationship between the proposed product and the referenced product(s)/published literature? <p>Describe the scientific bridge (e.g., BA/BE studies):</p> 	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Per reviewers, are all parts in English or English translation? <p>If no, explain: <input type="text"/></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Electronic Submission comments <p>List comments:</p>	<input type="checkbox"/> Not Applicable
CLINICAL	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE

<p>Comments:</p>	<input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical study site(s) inspections(s) needed? <p>If no, explain: <input type="text"/></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an NME NDA or original BLA , include the reason. For example:</i></p> <ul style="list-style-type: none"> <i>this drug/biologic is not the first in its class</i> <i>the clinical study design was acceptable</i> <i>the application did not raise significant safety or efficacy issues</i> <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	<input type="checkbox"/> YES Date if known: <input type="text"/> <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason: <i>the application did not raise significant safety or efficacy issues</i>
<ul style="list-style-type: none"> Abuse Liability/Potential <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL PHARMACOLOGY</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical pharmacology study site(s) inspections(s) needed? 	<input type="checkbox"/> YES <input type="checkbox"/> NO

<p>BIOSTATISTICS</p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p>PRODUCT QUALITY (CMC)</p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><u>Environmental Assessment</u></p> <ul style="list-style-type: none"> • Categorical exclusion for environmental assessment (EA) requested? <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO If no, was a complete EA submitted? <input type="checkbox"/> YES <input type="checkbox"/> NO If EA submitted, consulted to EA officer (OPS)? <input type="checkbox"/> YES <input type="checkbox"/> NO <p>Comments:</p>	
<p><u>Quality Microbiology (for sterile products)</u></p> <ul style="list-style-type: none"> • Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) <input type="checkbox"/> YES <input type="checkbox"/> NO <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable</p>

<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><u>CMC Labeling Review</u></p> <p>Comments:</p>	<p><input type="checkbox"/> Review issues for 74-day letter</p>
<p>APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)</p> <ul style="list-style-type: none"> • Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days? 	<p><input checked="" type="checkbox"/> N/A</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<ul style="list-style-type: none"> • What late submission components, if any, arrived after 30 days? 	
<ul style="list-style-type: none"> • Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components? 	<p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>

<ul style="list-style-type: none"> • Is a comprehensive and readily located list of all clinical sites included or referenced in the application? 	<input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application? 	<input type="checkbox"/> YES <input type="checkbox"/> NO
REGULATORY PROJECT MANAGEMENT	
<p>Signatory Authority: Debra Birnkrant, Division Director</p> <p>Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V):</p> <p>21st Century Review Milestones (see attached) (listing review milestones in this document is optional):</p> <p>Comments:</p>	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> <input checked="" type="checkbox"/> No review issues have been identified for the 74-day letter. <input type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional): <u>Review Classification:</u> <input type="checkbox"/> Standard Review <input checked="" type="checkbox"/> Priority Review
ACTIONS ITEMS	
<input checked="" type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter

<input checked="" type="checkbox"/>	<p>If priority review:</p> <ul style="list-style-type: none"> • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
<input checked="" type="checkbox"/>	<p>Send review issues/no review issues by day 74</p>
<input checked="" type="checkbox"/>	<p>Conduct a PLR format labeling review and include labeling issues in the 74-day letter</p>
<input type="checkbox"/>	<p>Update the PDUFA V DARRTS page (for NME NDAs in the Program)</p>
<input type="checkbox"/>	<p>BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at: http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f]</p>
<input type="checkbox"/>	<p>Other</p>

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

/s/

SOHAIL MOSADDEGH
09/25/2015