CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214787Orig1s000

PRODUCT QUALITY REVIEW(S)

U.S. FOOD & DRUG ADMINISTRATION

RECOMMENDATION

☒ Approval
☐ Approval with Post-Marketing Commitment
☐ Complete Response

NDA 214787
Assessment # 2

Drug Product Name	Veklury (remdesvir) for injection Veklury (remdesivir) Injection
Dosage Form	Lyophilized powder Solution
Strength	100 mg (remdesivir for injection) 100 mg/20 mL (5 mg/mL) (remdesivir injection)
Route of Administration	Intravenous infusion
Rx/OTC Dispensed	Rx
Applicant	Gilead Sciences, Inc.
US agent, if applicable	

Submission(s) Assessed	Document Date	Discipline(s) Affected
eCTD 0046	9/18/2020	Quality and labeling
eCTD 0047	9/22/2020	Quality
eCTD 0049	9/23/2020	Quality and labeling
eCTD 0050	9/24/2020	Quality
eCTD 0051	9/25/2020	Quality and labeling
eCTD 0052	9/28/2020	Quality
eCTD 0053	9/29/2020	Multiple
eCTD 0055	10/1/2020	Quality
eCTD 0056	10/5/2020	Quality
eCTD 0057	10/6/2020	Quality
eCTD 0058	10/7/2020	Quality and labeling
eCTD 0059	10/8/2020	Quality
eCTD 0060	10/9/2020	Quality
eCTD 0061	10/13/2020	Multiple
eCTD 0062	10/15/2020	Quality
eCTD 0063	10/10/2020	Quality
eCTD 0064	10/19/2020	Quality

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessment	Secondary Assessment
Application Technical Lead	Erika Englund	
Drug Substance	Katherine Windsor	Ali Al Hakim
Drug Product	Shalini Anand	Thomas Oliver
Manufacturing	Ying Zhang	Derek Smith
Microbiology	Erika Pfeiler	John Arigo
Biopharmaceutics	Elsbeth Chikhale	Angelica Dorantes
Regulatory Business Process Manager	Anh-Thy Ly	
Laboratory (OTR)	NA	
Environmental	Refer to DP Review	

QUALITY ASSESSMENT DATA SHEET

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
(b) (4)	V		(b) (4)	Active	9/16/2020	Maritere Carattini found adequate
	V			Active	9/16/2020	Maritere Carattini found adequate
	V			Active	9/16/2020	Maritere Carattini found adequate
	III			Active	8/29/2019 (microbiology review) 3/13/2019 (CMC Review)	Yan Zheng found adequate Jane Chang found adequate

(b) (4)		(b) (4)			
	III		Active	Refer to DP section of review	
	III		Active	Refer to DP section of review	
	III		Active	4/11/2014	Milagros Salazar found adequate
	III		Active	Refer to DP section of review	
	V		Active	9/16/2020	Bethanie Lee found adequate

B. OTHER DOCUMENTS: *IND, RLD, RS, Approved NDA*
Refer to CMC Review #1

2. CONSULTS

Discipline	Status	Recommendation	Date	Assessor
Biostatistics	**Complete**	Based on the statistical analysis and ICH Q1E Guidance, the CMC statistical team recommended a shelf life of 12 months for remdesivir injection and 30 months for remdesivir for injection	10/14/ 2020	Yu-Ting Weng (primary) Meiyu Shen (secondary)
Pharmacology /Toxicology	NA	Refer to CMC Review #1 regarding the qualification of the impurities		
CDRH-ODE	NA			
CDRH-OC	NA			
Clinical	NA			
Other	NA			

EXECUTIVE SUMMARY

IQA NDA Assessment Guide Reference

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

The applicant has provided adequate CMC information to recommend approval of the amended NDA at this time. All information requests and review issues have been addressed and there are no pending approvability issues. The Overall Manufacturing Inspection Recommendation was entered into Panorama as "Approve" on October 15, 2020. Therefore, this NDA is recommended for approval by the Office of Pharmaceutical Quality (OPQ). A complete list of the **Quality PMCs** can be found on pp 9-13 of this review. Gilead agreed to the Quality PMCs in the 10/19/2020 submission to the NDA.

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

Remdesivir is an NME and SARS-CoV-2 nucleotide analog RNA polymerase inhibitor indicated for treatment of coronavirus disease 2019 (COVID-19). This NDA describes two formulations: remdesivir injection in a single strength of 100 mg/20 mL (5 mg/mL) and remdesivir for injection in a single strength of 100 mg/vial. Following the reconstitution of remdesivir for injection with sterile water, both formulations (remdesivir for injection and remdesivir injection) contain the same concentration of remdesivir in the same volume of solution. Both reconstituted remdesivir for injection and remdesivir injection are then further diluted with 0.9% NaCl in an infusion bag prior to IV administration. ***Refer to CMC Review #1 for a complete description of the two formulations***.

In CMC Review #1, there were multiple pending issues including: pending receipt of batch data from (b) (4), pending receipt of batch data from Line (b) (4), agreement on the drug product shelf lives, and agreement with the post-marketing commitments. The resolution of the pending review issues from CMC Review #1 will be discussed in this executive summary. For additional details of the CMC review of this NDA, refer to CMC Review #1.

Proposed Indication(s) including Intended Patient Population	Treatment of coronavirus disease (COVID-19)

Duration of Treatment	The recommended treatment duration is 5 days. If a patient does not demonstrate clinical improvement, treatment may be extended for up to an additional 5 days, for a total treatment duration of 10 days.
Maximum Daily Dose	200 mg
Alternative Methods of Administration	N/A

B. Quality Assessment Overview

Drug Substance: Adequate

There are three drug substance manufacturers listed in 3.2.S.2.1: Gilead Alberta, (b) (4) (b) (4) Batch release data were received for Alberta and (b) (4) however, no registration batch data had been received from (b) (4) at the time of CMC Review #1.

Following CMC Review #1, updates were received about the quality of the drug substance intermediate manufactured at (b) (4) and the batch analysis of the final API manufactured at (b) (4) was submitted on 10/15/2020.

Remdesivir drug substance is manufactured using the same process and control strategy at all three proposed manufacturers. The batches manufactured at (b) (4) and Gilead Alberta were considered to be of comparable quality. Remdesivir drug substance produced at (b) (4) appears comparable to that produced at (b) (4) and Gilead Alberta. Batch size at Gilead Alberta and (b) (4) ranged from (b) (4) kg. The batch size for the first registration batch at (b) (4) was (b) (4) kg. There were no notable scale dependent impacts on product quality.

Comparability Protocol:
Refer to CMC Review #1. The comparability protocol was found adequate.

Postmarketing Commitments (PMCs):
Confirmatory quality data – including release data for additional (b) (4) drug substance registration batches, stability data for (b) (4) and (b) (4) drug substance, and batch data for drug product manufactured using (b) (4) drug substance – will be obtained post-approval through agreed upon PMCs. Gilead agreed to the drug substance PMCs on 10/19/2020.

This NDA is recommended for approval from a drug substance perspective. For additional details, refer to the drug substance review by Katherine Windsor, Ph.D.

Drug Product: Adequate

The NDA includes two different formulations of the drug product: remdesivir for injection (lyophilized powder) and remdesivir injection (solution). Refer to CMC Review #1 for a complete description of the product. In CMC Review #1, one of the deficiencies concerned the pending batch data from (b) (4) Since this site was removed from the NDA, this data is no longer required during this review cycle. In addition, batch data had not been received from all of the drug product manufacturing sites and lines (b) (4) (b) (4) at the time of completion of CMC Review #1. The batch data for these lines has now been received and found adequate for the inclusion of these lines in the NDA from a drug product perspective.

The pH for remdesivir injection is a critical quality attribute. (b) (4) (b) (4) (b) (4) The acceptance criteria for pH in the remdesivir injection drug product batches is pH (b) (4) but most of the batches in the stability program had a pH of (b) (4) To further support the stability of the drug product at the lower limit of the pH range, Gilead agreed to a PMC to evaluate the stability of the remdesivir injection solution at pH (b) (4) through 6 months at the 5 °C storage conditions.

There are multiple stoppers proposed in the NDA, and limited leachables data were provided during the NDA review cycle. Gilead agreed to a PMC to submit additional leachables data for remdesivir for injection and remdesivir injection.

Gilead's proposed long-term storage conditions are 2 ºC-8 ºC for the solution, and to store below 30 °C for the lyophilized powder. Gilead had originally proposed a (b) (4) month shelf life for remdesivir injection, and a (b) (4) month shelf life for remdesivir for injection. The proposed shelf life was discussed with Yu-Ting Weng, Ph.D. and Meiyu Shen, Ph.D. from the biostatistics group. Refer to the statistical review in DARRTS submitted on 10/14/2020 for further details. The granted shelf life communicated to Gilead was 12 months for remdesivir injection and 30 months for remdesivir for injection. Gilead accepted these shelf lives. In the 10/15/2020 amendment, Gilead had proposed updating section 3.2.P.8.1 with the new shelf life the week of October 19th. Due to the expedited review, a request was sent on 10/19/2020 for no additional changes to be

made to the NDA regarding shelf life at this time, which Gilead agreed to on the same day. Limited stability data was provided for some of the manufacturing sites and lines. Gilead also agreed to PMCs to submit additional stability data in CBE-0 supplements.

Environmental Assessment:
Refer to CMC Review #1

Comparability Protocol:
The comparability protocol was discussed with Ramesh Gopalaswamy, Ph.D. in OLDP. Gilead's proposal for the addition of new manufacturing sites and lines post-approval, and the supporting CMC data to be submitted in the CBE-0 supplement was found acceptable. Refer to the drug product review for additional details.

Postmarketing Commitments (PMC):
Gilead agreed to PMCs for the submission of additional leachables data, a pH stability study, and for stability updates of drug product batches in the ongoing stability studies on 10/19/2020.

This NDA is recommended for approval from a drug product perspective. For additional details, refer to the drug product review #1 and addendum by Shalini Anand, Ph.D.

Labeling: Adequate

The labeling recommendations were communicated to the OND PM. In CMC Review #1, all of the recommendations were accepted by the applicant with the exception of the storage conditions for remdesivir for injection, which was proposed to be "store below 30 °C". This storage statement is commonly used in PEPFAR applications, but the preference is for the USP controlled temperature conditions to be used for products intended for room temperature storage in the US. Gilead provided additional justification for these storage statement conditions, including that unused products from the US could be used in other parts of the world, and the precedence in other products. The storage conditions of store below 30 °C were found acceptable for this NDA due to the global public health emergency.

Updated carton and container labeling was also submitted and found adequate.

For additional details, refer to the labeling review by Shalini Anand, Ph.D.

Manufacturing: Adequate

In CMC review #1, incomplete information had been submitted for the facilities and lines listed in the NDA. One of the deficiencies from CMC Review #1 was the pending batch data and facility evaluation for (b) (4) (b) (4) was removed as a drug product manufacturing site from the NDA on 10/01/2020, therefore no data is needed for (b) (4) during this review cycle. At the time of CMC Review #1, no batch release data had been received from line (b) (4)
The supporting information for both of these lines was received and found adequate.

CMC Review #1 described one potential postmarketing commitment (PMC) for the analytical method transfer at the Gilead Ireland facility. Per the amendment on 10/08/2020, this facility's responsibilities were updated, and it is no longer responsible for the release testing, primary labeling, secondary labeling, and packaging for remdesivir injection. Therefore, no PMC will be requested for this site.

The Overall Manufacturing Inspection Recommendation was entered as "Approve" on 10/15/2020.

This NDA is recommended for approval from an OPMA perspective. For additional details, refer to the manufacturing review #1 and addendum by Ying Zhang, Ph.D.

Biopharmaceutics: Adequate

A review addendum was not needed from a Biopharmaceutics perspective for the additional CMC information submitted since Review #1.

This NDA is recommended for approval from a Biopharmaceutics perspective. For additional details, refer to CMC Review #1 for the Biopharmaceutics review by Elsbeth Chikhale, Ph.D.

Microbiology (if applicable): Adequate

This NDA was recommended for approval in CMC Review #1. Two additional changes were made to the NDA following that review related to microbiology.

1. Microbiology Review #1 covered the sterility assurance at (b) (4) and found it acceptable. After the microbiology review was

completed, (b) (4) was removed as a drug product manufacturing site for remdesivir for injection on 10/01/2020.

2. An IR was sent on 9/21/2020 regarding the Product Lifecycle Management Plan (PLCM). The IR included the comment that studies related to sterility assurance should be performed prior to submission of a supplement. The PLCM was updated per the requests on 09/22/2020.

This NDA is recommended for approval from a microbiology perspective. For additional details, refer to the microbiology review in CMC Review #1 and the review addendum by Erika Pfeiler, Ph.D.

C. Postmarketing Commitments (PMCs)

Drug Substance PMCs:

a) (b) (4)

i) Release data for three batches of remdesivir drug substance manufactured at (b) (4) were submitted to the NDA. Conduct stability studies on these three registration batches and submit three months of long-term and accelerated stability data for each batch in a CBE-0 supplement.

Final report submission: February 15, 2021

ii) Submit in a CBE-0 supplement release data for one batch of remdesivir for injection manufactured at an approved manufacturing site to at least 1/10 production scale using drug substance from (b) (4)

Final report submission: November 16, 2020

b) (b) (4)

i) Release data for one registration batch of remdesivir drug substance manufactured at (b) (4) were submitted to the NDA. Two additional registration batches of remdesivir drug

substance are to be manufactured at (b) (4) and the release data for each submitted under this PMC. The interim report should include release data for the second registration batch (displayed in a manner to facilitate comparison to previously submitted batch data). The final submission report should include release data for the third registration batch. Both reports should be submitted as CBE-0 supplements.

Interim report submission: November 16, 2020
Final report submission: November 30, 2020

ii) Release data for one registration batch of remdesivir drug substance manufactured at (b) (4) were submitted to the NDA. Two additional registration batches of remdesivir drug substance are to be manufactured at (b) (4) and the release data for both submitted under a separate PMC. Conduct stability studies on these three registration batches and submit three months of long-term and accelerated stability data for each batch in a CBE-0 supplement.

Final report submission: March 31, 2021

iii) Submit in a CBE-0 supplement release data for one batch of remdesivir for injection drug product manufactured at an approved manufacturing site to at least 1/10 production scale using drug substance from (b) (4).

Final report submission: January 7, 2021

Drug Product PMCs:

(b) (4) ***Site***

1. Submit in a CBE-0 supplement three months of long-term and accelerated stability data for three batches (#EW2019A1, # EW2020A1, # EW2021A1) of remdesivir for injection, 100 mg, manufactured on the (b) (4) line at the (b) (4) site.

Final report submission- February 15, 2021

2. Submit in a CBE-0 supplement, three months of long term and accelerated stability data for two batches (# D20PV141 and D20PV142) of remdesivir for injection, manufactured on the (b) (4) line at the (b) (4) site.

Final report submission- February 15, 2021

(b) (4)

3. Submit in a CBE-0 supplement three months of long term and accelerated stability data for two batches (# AN7049B, # AN7050C) of remdesivir for injection, 100 mg, manufactured using the line (b) (4) at the (b) (4) site.

Final report submission- February 15, 2021

4. Submit in a CBE-0 supplement six months of long term and accelerated stability data for three batches (EW2014A1, # EW2016A1, # EW2018A1) of remdesivir for injection, 100 mg, manufactured on the line (b) (4) l (b) (4) at the (b) (4) site, to support the stoppers from (b))

Final report submission- February 15, 2021

5. Submit in a CBE-0 supplement three months of long-term and accelerated stability data for one batch of remdesivir for injection, 100 mg, manufactured on line (b) (4) at the (b) (4) site.

Final report submission: April 15, 2021

(b) (4)

6. The release data of two batches manufactured on lines (b) (4) (# 2041087.1, # 2041088.1), (b) (4) (# 2009106.1, # 2009107.1), and (b) (4) (2010131.1, 2010132.1) at (b) (4) was provided. Submit in a CBE-0 supplement three months of long-term and accelerated stability data of these batches of remdesivir for injection.

Final report submission- February 15, 2021

(b) (4)

7. Submit in a CBE-0 supplement three months of long-term and accelerated stability data for three batches (# 200553F, # 200613F and # 200653F) of remdesivir for injection manufactured at (b) (4)

   Final report submission- February 15, 2021

(b) (4)

8. Submit in a CBE-0 supplement three months of long term and accelerated stability data for three process validation batches (# 00001, # 00003 and 00004) of remdesivir for injection manufactured on the (b) (4) line at the (b) (4) site.

   Final report submission- February 15, 2021

9. Submit in a CBE-0 supplement three months of long-term and accelerated stability data for one batch of remdesivir for injection, 100 mg, manufactured on the (b) (4) Line at the (b) (4) site.

   Final report submission- April 15, 2021

Remdesivir Injection

10. The stability batches of remdesivir injection, 150 mg were packaged with (b) (4) stopper. This rubber stopper is different than the rubber stopper proposed for commercial remdesivir injection, 100 mg (i.e. (b) (4) (b) (4)). Submit as a CBE-0 supplement the six months of long-term and three months of accelerated stability data for three batches (#020953, #020954, #020955) to support the change in the stopper.

    Final report submission- February 15, 2021

11. Submit in a CBE-0 supplement the 6-month time point data for the pH stability studies of remdesivir injection, 5 mg/ml, at the 5°C condition to support the stability of remdesivir injection at the lower end (pH (b) (4)) of the proposed pH specification range.

Final report submission- Feb 28, 2021

Leachables

12. The 1-month leachable study data for three lots of each proposed commercial packaging configuration of remdesivir injection and remdesivir for injection was provided. The drug product representative batches should be tested for leachables through expiry. The data from these studies along with the final report should be submitted as a CBE-0 supplement. The interim reports should include the leachables study data for the 6-month, 12-month, and 24-month stability time points.

    Interim report submission- March 30, 2021; Sep 30, 2021.

    Final report submission- Sep 30, 2022

13. Per the quality submission dated 09-22-2020, the leachable data for lot # EW1805A1 (at 23-month time point) of remdesivir for injection, can be available by end of December 2020. Submit as a CBE-0 supplement the leachables data.

    Final report submission February 15, 2021

D. Risk Assessment

From Initial Risk Identification			Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments**
Sterility*	Formulation, container closure, Process parameters, scale/equipment, site	High	The sterility assurance and supporting microbiology data were found adequate in the microbiology review	Acceptable	

Endotoxin*		Medium	The supporting microbiology data was found adequate in the microbiology review	Acceptable	
Assay*	Formulation, container closure, Process parameters, scale/equipment, site	Low		Acceptable	(b) (4)
pH*	Formulation, Container closure, Raw materials, Process parameters, Scale/equipment, Site	Low	The pH range in the specification for remdesivir injection was tightened (b) (4) (b) (4)	Acceptable	The pH of the product needs to be controlled to ensure acceptable API solubility and stability
Leachables*	Formulation, container closure	Medium		**Acceptable with PMC**	The applicant is proposing multiple stoppers, and the (b) (4) applicant will be submitting additional leachables data as a PMC
Particulate matter*	Formulation, Container closure, Raw materials, Process parameters, Scale/equipment, Site	Medium		Acceptable	
Osmolality*	Formulation, raw materials, process parameters, scale/equipment, site	low		Acceptable	Refer to DP and labeling review concerning osmolality of diluted product.

Uniformity of dosage units	Formulation, Container Closure, Process Parameters, Scale/equipment, site	low		Acceptable	
Moisture Content (CQA for lyophilized powder only)	Formulation, Container Closure, Process Parameters, Scale/equipment, site	low		Acceptable	
Reconstitution time (CQA for lyophilized powder only)	Formulation, process parameters, scale/equipment, site	medium		Acceptable	The API exhibits low solubility; however, reconstitution time is included in the DP release and stability specifications (NMT (b)(4) min)
Physical stability (CQA for lyophilized powder only)	Formulation, Container closure, Raw materials, Process parameters, Scale/equipment, Site	medium		Acceptable	

* CQA that applies to both remdesivir for injection and remdesivir injection

E. List of Deficiencies for Complete Response

1. Overall Quality Deficiencies (Deficiencies that affect multiple sub-disciplines)

None

2. Drug Substance Deficiencies

3. Drug Product Deficiencies

4. Labeling Deficiencies

5. Manufacturing Deficiencies

6. Biopharmaceutics Deficiencies

None

7. Microbiology Deficiencies

None

8. Other Deficiencies (Specify discipline, such as Environmental)

Application Technical Lead Name and Date:
Erika E. Englund

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Drug Product Labelling Review - Addendum

NDA #: 214787

Product Name: Remdesivir Injection 100 mg/20 mL (5 mg/ml) and Remdesivir for Injection 100 mg

Submission: SD# 0051; Date: 09/25/2020

Final review recommendation: Adequate

Only the pending review issues from the labelling review #1 are discussed in this review document. For additional details, please refer to NDA 214787 Labeling Review #1.

Pending Issue #1:

The in-use storage conditions of remdesivir for injection, after reconstitution, on the container and carton labels were not in line with the Prescribing Information (PI). In the IR response dated 09-25-2020, Gilead submitted the updated carton and container labels and revised the in-use storage conditions after reconstitution, to be in alignment with the Prescribing Information (PI).

Assessment:
The updated carton and container labels are acceptable from the CMC perspective.

Pending Issue #2:

Gilead was asked to revise the storage conditions for remdesivir for injection formulation to the USP controlled room temperature conditions (20ºC to 25ºC [68ºF to 77ºF]) from below 30°C (below 86°F) (IR issued on 09-03-2020 and 09-15-2020). In the IR response dated 09-18-2020, Gilead referenced several Gilead commercial products in the US market where the “Store below 30 °C” storage statement is currently applied. These products include Sovaldi®, Harvoni®, Epclusa®, Vosevi®, Vemlidy®, Odefsey®, Genvoya®, and Biktarvy®. The supporting long-term stability data of remdesivir for injection (up to 18-48 months) at 30 °C/75% RH is provided in section 3.2.P.8.

Assessment:
During the teleconference discussion dated 09-17-2020, Gilead also justified that the unused US product may be used in other parts of the world, and the storage condition of ‘below 30°C’ allows the storage of this drug product in the countries of different climate zones (I-IV). It is worth noting that the “Store below 30ºC” statement is used for PEPFAR applications; so, there is preference for using this labeling statement at least for the PEPFAR program. This issue was further discussed internally, and the preference is for the standard USP statement to be used (so products are consistently labeled in this country, however, Gilead’s justification was found to be acceptable for this NDA due to the global public health emergency.

Drug Product Reviewer: Shalini Anand, Ph.D.

Shalini Anand

Digitally signed by Shalini Anand
Date: 10/09/2020 12:41:50PM
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Thomas Oliver

Digitally signed by Thomas Oliver
Date: 10/09/2020 02:50:07PM
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M E M O R A N D U M

DATE: 14 October 2020

TO: Erika Englund, Ph.D.
Chemist
CDER/OPQ/ONDP/DNDPI/NDPB2

FROM: Erika Pfeiler, Ph.D.
Supervisory Microbiologist
CDER/OPQ/OPMA/DMAII/MAB6

THROUGH: John Arigo, Ph.D.
Supervisory Interdisciplinary Scientist
CDER/OPQ/OPMA/DMAI

SUBJECT: NDA 214787

This memo serves as an update of activities in NDA 214787 since the microbiology IQA chapter was submitted to Panorama.

On September 21, 2020, an information request was communicated to the applicant regarding
the product lifecycle management plan, and included the following language:

Please note that with supplements introducing additional manufacturing lines in a previously approved manufacturing site, release data for a minimum of one drug product batch manufactured at commercial scale is expected. Stability data for a minimum of one commercial scale drug product batch should be collected for the additional line. The stability data may be submitted in annual report. Studies related to sterility assurance (as previously outlined in the PLCM plan) should be performed prior to submission and information should be included in the supplement. Note that the conditions to be met prior to implementation, as outlined in the PAMCP for additional sites, apply for the addition of new lines in an approved site. Please update the PLCM plan submitted in the NDA accordingly, for our review.

On September 22, the applicant acknowledged the request and submitted an updated PLCM.

In the submission dated October 1, 2020 (sequence 0055) the applicant stated that

M E M O R A N D U M

[redacted] (FEI [redacted]) is withdrawn from the NDA.

END

Erika Pfeiler

Digitally signed by Erika Pfeiler
Date: 10/15/2020 07:59:22AM
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John Arigo

Digitally signed by John Arigo
Date: 10/15/2020 08:05:01AM
GUID: 508da70b00028eb5ce7d95d2ab482661

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ERIKA E ENGLUND
10/20/2020 11:10:20 AM

FDA U.S. FOOD & DRUG ADMINISTRATION

RECOMMENDATION

☐ Approval
☐ Approval with Post-Marketing Commitment
☒ Complete Response

NDA 214787
Assessment # 1

Drug Product Name	Veklury (remdesvir) for injection Veklury (remdesivir) Injection
Dosage Form	Lyophilized powder Solution
Strength	100 mg (remdesivir for injection) 100 mg/20 mL (5 mg/mL) (remdesivir injection)
Route of Administration	Intravenous infusion
Rx/OTC Dispensed	Rx
Applicant	Gilead Sciences, Inc.
US agent, if applicable	

Submission(s) Assessed	Document Date	Discipline(s) Affected
eCTD 0001	4/8/2020	Quality
eCTD 0002	4/15/2020	Quality and nonclinical
eCTD 0004	5/4/2020	Quality
eCTD 0005	5/12/2020	Quality
eCTD 0006	5/29/2020	Quality
eCTD 0007	6/3/2020	Labeling
eCTD 0008	6/11/2020	Labeling
eCTD 0010	6/24/2020	Quality
eCTD 0013	7/10/2020	Quality
eCTD 0016	7/24/2020	Quality
eCTD 0017	7/27/2020	Quality
eCTD 0019	7/31/2020	Quality
eCTD 0020	8/7/2020	All (NDA submitted)
eCTD 0021	8/7/2020	Quality
eCTD 0023	8/12/2020	Quality
eCTD 0024	8/13/2020	Quality
eCTD 0027	8/19/2020	Quality and Clinical
eCTD 0029	8/21/2020	Quality
eCTD 0030	8/24/2020	Quality
eCTD 0034	8/31/2020	Quality

eCTD 0035	9/1/2020	Labeling
eCTD 0037	9/3/2020	Multiple
eCTD 0038	9/4/2020	Quality
eCTD 0040	9/9/2020	Labeling
eCTD 0042	9/11/2020	Quality
eCTD 0046	9/18/2020	Quality
eCTD 0049	9/23/2020	Quality and Labeling
eCTD 0050	9/24/2020	Quality
eCTD 0051	9/25/2020	Multiple

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessment	Secondary Assessment
Drug Substance	Katherine Windsor	Ali Al Hakim
Drug Product	Shalini Anand	Thomas Oliver
Manufacturing	Ying Zhang	Derek Smith
Microbiology	Erika Pfeiler	John Arigo
Biopharmaceutics	Elsbeth Chikhale	Angelica Dorantes
Regulatory Business Process Manager	Anh-Thy Ly	
Application Technical Lead	Erika Englund	
Laboratory (OTR)	NA	
Environmental	Refer to DP Review	

QUALITY ASSESSMENT DATA SHEET

IQA NDA Assessment Guide Reference

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
(b) (4)	V		(b) (4)	Active	9/16/2020	Maritere Carattini found adequate
	V			Active	9/16/2020	Maritere Carattini found adequate

(b) (4)		(b) (4)			
	V		Active	9/16/2020	Maritere Carattini found adequate
	III		Active	8/29/2019 (microbiology review) 3/13/2019 (CMC Review)	Yan Zheng found adequate Jane Chang found adequate
	III		Active	Refer to DP section of review	
	III		Active	Refer to DP section of review	
	III		Active	4/11/2014	Milagros Salazar found adequate
	III		Active	Refer to DP section of review	
	V		Active	9/16/2020	Bethanie Lee found adequate

B. OTHER DOCUMENTS: *IND, RLD, RS, Approved NDA*

Document	Application Number	Description
IND	147753	Remdesivir for the treatment of COVID-19
IND	125566	Remdesivir for the treatment of Ebola Virus Disease

2. CONSULTS

Discipline	Status	Recommendation	Date	Assessor
Biostatistics	**Pending**	The shelf life of the drug product will be covered in Review #2.		Yu-Ting Weng (primary) Meiyu Shen (secondary)
Pharmacology/ Toxicology				
CDRH-ODE	NA			
CDRH-OC	NA			
Clinical	NA			
Other	NA			

EXECUTIVE SUMMARY

IQA NDA Assessment Guide Reference

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

The applicant has not provided adequate CMC information to recommend approval of the amended NDA at this time. Batch analysis has not been received for one of the drug substance manufacturing sites, one of the drug product manufacturing sites, and two of the drug product manufacturing lines. In addition, additional stability data and leachables data were requested. The proposed shelf lives of the drug product, and the Post-Marketing Commitments (PMC) are still under negotiation.

A second CMC review (CMC Review #2) will be written during this current review cycle to cover the data from the pending issues described above.

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

Remdesivir is an NME and SARS-CoV-2 nucleotide analog RNA polymerase inhibitor indicated for treatment of coronavirus disease 2019 (COVID-19). Remdesivir was investigated under IND 147753 for the treatment of COVID-19 and received Fast Track designation. The NDA

was also granted Rolling Review with the first CMC submission received on 04/08/2020, and the NDA was considered complete on 08/07/2020.

This NDA describes two formulations: remdesivir injection in a single strength of 100 mg/20 mL (5 mg/mL) and remdesivir for injection in a single strength of 100 mg/vial. Both formulations are supplied in (b) (4) clear glass vials, with an elastomeric closure, aluminum overseal and a flip-off cap. Both formulations contain the following excipients: betadex sulfobutyl ether sodium (b) (4) and HCl or NaOH for pH adjustment. Other than water for injection in remdesivir injection, the primary difference between the two formulations is that there is a greater quantity of betadex sulfobutyl ether sodium in remdesivir injection in comparison to remdesivir for injection (6. (b) (4) g vs. 3. (b) (4) g).

Following the reconstitution of remdesivir for injection with sterile water, both formulations (remdesivir for injection and remdesivir injection) contain the same concentration of remdesivir in the same volume of solution. Both reconstituted remdesivir for injection and remdesivir injection are then further diluted with 0.9% NaCl in an infusion bag prior to IV administration. The (b) (4) (b) (4) remdesivir injection is only recommended to be diluted in a 250 mL infusion bag of 0.9% NaCl; whereas reconstituted remdesivir for injection can be diluted in either a 100 mL or 250 mL infusion bag of 0.9% NaCl.

Proposed Indication(s) including Intended Patient Population	Treatment of coronavirus disease (COVID-19)
Duration of Treatment	The recommended treatment duration is 5 days. If a patient does not demonstrate clinical improvement, treatment may be extended for up to an additional 5 days, for a total treatment duration of 10 days.
Maximum Daily Dose	200 mg
Alternative Methods of Administration	N/A

B. Quality Assessment Overview

Drug Substance: Inadequate

Remdesivir is a nucleotide prodrug that is metabolized to an analog of adenosine triphosphate (GS-441524). Remdesivir contains six stereocenters, and the absolute stereochemistry was confirmed through

single crystal X-ray analysis. The (b) (4) are controlled in the drug substance.

The drug substance is manufactured (b) (4) (b) (4) (b) (4) The control strategy, including the specifications of the starting materials and final drug substance, were found sufficient to limit impurities to acceptable levels in the final drug substance.

Gilead Alberta was the only drug substance manufacturing site included in the original Module 3 submission on April 8, 2020. Two additional drug substance manufacturing sites were added to the NDA on May 12, 2020: (b) (4) (b) (4) Batch data were provided for 15 batches from Gilead Alberta and three batches from (b) (4) **To date, registration batch data has not been received from** (b) (4) **(see pending information below).** The batches manufactured at (b) (4) and Gilead Alberta were considered to be of comparable quality.

The applicant submitted stability data for two batches through 48 months, one batch through 36 months and for the three process validation batches through 12 months. The retest period of remdesivir drug substance is (b) (4) months when stored (b) (4) °C.

Comparability Protocol:
The applicant provided a Post-Approval Change Management Protocol (PACMP) for the post-approval addition of alternative drug substance manufacturing and testing sites. The applicant proposed that the alternative manufacturing site would be submitted as a CBE-30 supplement to the NDA, provided that an acceptable cGMP status can be demonstrated. The PACMP details the conditions to be met prior to implementation, including the manufacture of three consecutive batches of the drug substance. As part of the "ongoing verification of the effectiveness of the change", stability studies will be initiated on these three batches and one drug product batch manufactured with the drug substance from the alternative manufacturing site. The stability data will be submitted in the annual report. The Office of Lifecycle Drug Products (OLDP) was consulted during the evaluation of the PACMP, and Ramesh

Gopalaswamy, Ph.D. found the plan acceptable from the Lifecycle Perspective.

Pending Information:

Gilead has proposed three drug substance manufacturing sites; however, registration batch data has not been received to date for the (b) (4) site. The evaluation of the (b) (4) drug substance data, and potential drug substance PMCs, will be covered in Review #2.

This NDA is not recommended for approval at this time from a drug substance perspective because (b) (4) is listed as a drug substance manufacturing site, but the registration batch data has not been received yet. Per the September 24, 2020 submission, the first batch of data from (b) (4) estimated to be available October 19th. An addendum to this review (CMC Review #2) will be written following an update to the drug substance information.

For additional details, refer to the drug substance review by Katherine Windsor, Ph.D.

Drug Product: Inadequate

The NDA includes two different formulations of the drug product: remdesivir for injection (lyophilized powder) and remdesivir injection (solution). Both formulations contain betadex sulfobutyl ether sodium and NaOH or HCl for pH adjustment. All excipients are USP/NF grade, and the levels of betadex sulfobutylether sodium were found acceptable per input from the pharmacology/toxicology team. The proposed overfill volume (b) (4) recommended by USP <1151>; however, the applicant provided extractable volume studies to justify the overfill and this was found acceptable.

The drug product specifications for both formulations are acceptable, and the limits for the specified and unspecified impurities were found acceptable per input from the pharmacology/ toxicology team. The elemental impurity analysis was provided, and the levels were below the permitted daily exposure listed in ICH Q3D. Therefore, the control of these elemental impurities in the drug product specification are not required. The pH for remdesivir injection is a critical quality attribute. The (b) (4) (b) (4) Following information requests for additional supporting solubility and stability data, the applicant tightened the pH range (b) (4) (b) (4) in the remdesivir injection specification. Due to the shorter time

that the reconstituted lyophilized powder is stored in solution, the pH range (b) (4) was found acceptable for remdesivir for injection.

The batch analysis from both formulations received to date were within acceptable limits. However; batch data has not been received from the (b) (4) site, (b) (4) The supporting data for these sites will be covered in CMC review #2.

In-use stability data were provided for reconstituted remdesivir for injection, and the diluted product in the IV infusion bag. The diluted solutions in 0.9% NaCl were found to be stable for 24 hours at room temperature or 48 hours refrigerated. Gilead's proposed long-term storage conditions are 2 ºC-8 ºC for the solution, and to store below 30 °C for the lyophilized powder. The proposed shelf life was discussed with the CMC statistical team, and the granted shelf life will be discussed in CMC review #2.

Environmental Assessment:
The applicant submitted a claim for a categorical exclusion from an environmental assessment (EA) in accordance with 21 CFR 25.31(b). Given the potential for pandemic use of remdesivir, FDA asked for a screening-level analysis to support the claim for this categorical exclusion. The applicant subsequently submitted EA data to support the exclusion claim, including an alternative Expected Introduction Concentration (EIC) based on pandemic use and toxicity estimates to environmental organisms based on similar substances. The FDA EA Team reviewed the data and determined that the margin of exposure between the EIC and toxicity estimates is acceptable, and thus approval of this application would not result in significant environmental impact. Therefore, the claim for an exclusion from an EA is acceptable.

For further details, refer to the Environmental section of the drug product review by Shalini Anand, Ph.D.

Comparability Protocol: *Will be discussed in CMC review #2.*

Pending Information:

This NDA is not recommended for approval at this time from a drug product perspective because batch data has not been received from all of the drug product manufacturing sites and lines (b) (4) (b) (4) An addendum to this review (CMC Review #2) will be written to cover any updated batch data, updated stability data, extractable/leachables reports, granted shelf life, and potential PMCs.

For additional details, refer to the drug product review by Shalini Anand, Ph.D.

Labeling: Inadequate

The labeling recommendations were communicated to the OND PM. All the recommendations were accepted by the applicant with the exception of the storage conditions for remdesivir for injection. The labeled storage conditions of remdesivir for injection will be discussed in CMC review #2.

For additional details, refer to the labeling review by Shalini Anand, Ph.D.

Manufacturing: Inadequate

Remdesivir for Injection is manufactured with the following operations: (b) (4) The applicant proposed to manufacture this product at multiple different filling lines located in six different facilities. Remdesivir Injection is manufactured with the following operations: (b) (4) The applicant proposed to manufacture this product at one site (Gilead Sciences).

There is no overage but there is a (b) (4)% overfill for the lyophilization formulation, and a (b) (4)% overfill for the solution formulation to ensure adequate withdrawal volume. OPMA evaluated the executed batch records, and found them to be consistent with the description of the manufacturing process for both formulations.

For the process and facilities review, there is one potential post-marketing commitment (PMC) for the analytical method transfer at the Gilead Ireland facility. The details of the PMC will be covered in CMC Review #2. Post-approval inspections are recommended (b) (4) A comparability protocol was also submitted for the additional of alternative drug substance and drug product manufacturing sites. The proposal in the comparability protocol to submit the new sites as a CBE-30 was found adequate.

Pending Information:

No registration batch release data have been received to date from (b) (4) line (b) (4) These site and lines will be addressed in review #2. Due to the pending data, the NDA is not recommended for approval at this time.

For additional details, refer to the manufacturing review by Ying Zhang, Ph.D.

Biopharmaceutics: Adequate

To support this NDA, the applicant conducted four Phase-1 pharmacokinetics (PK) studies in healthy subjects, and several Phase-3 clinical studies in patients with COVID-19. The drug product used in the Phase 3 clinical studies was remdesivir for injection (100 mg and 150 mg). Both remdesivir for injection and remdesivir injection were used in the Phase 1 studies.

The Biopharmaceutics review evaluated the bridging between remdesivir powder for injection (100 mg) and remdesivir injection (100 mg/20 mL). To support the bridge between the powder and solution formulations, the composition, physical properties, and pharmacokinetics of the diluted infusion solutions were compared. As described above, after dilution, the primary difference between the products is in the concentration of betadex sulfobutyl ether sodium.

Based on the totality of the provided in vitro and in vivo information, the difference in betadex sulfobutyl ether sodium concentrations is not expected to alter the PK, efficacy, and safety of remdesivir and its metabolites; therefore, the infusions prepared from the solution formulation and the lyophilized powder formulation are expected to be comparable.

This NDA is recommended for approval from a Biopharmaceutics perspective. For additional details, refer to the Biopharmaceutics review by Elsbeth Chikhale, Ph.D.

Microbiology (if applicable): Adequate

The microbiology review covered both sterile drug product formulations: remdesivir for injection and remdesivir injection. Both formulations are manufactured (b) (4)

(b) (4)

At the time of this review, remdesivir injection is proposed to be manufactured at the Gilead La Verne site, and remdesivir for injection is manufactured at six sites, many of which contain multiple lines. The site-specific supporting microbiology data was included in both the NDA and in

the referenced DMFs (DMF (b) (4), DMF (b) (4), DMF (b) (4), DMF (b) (4), and DMF (b) (4)). Refer to the DMF table above for the details of the individual DMF reviews. The lines to manufacture remdesivir injection at (b) (4) were found adequate from a microbiology perspective, but these lines were removed from the NDA before the review was finalized. The sterility assurance validation assessments were retained in the review. Sterility and endotoxins test methods were compendial, and appropriate method suitability studies were provided.

The package insert proposes hold times for diluted (remdesivir injection) and reconstituted (remdesivir for injection) of 24 hours at room temperature and 48 hours under refrigeration. The applicant provided microbiological data to support these times.

The applicant also included a comparability protocol for the post-approval addition of alternative drug product manufacturing sites. The applicant provided a general list of tests and acceptance criteria to demonstrate the sterility assurance program acceptability at the proposed site. The comparability protocol was accepted as-is from a microbiology perspective.

This NDA is recommended for approval from a microbiology perspective. For additional details, refer to the microbiology review by Erika Pfeiler, Ph.D.

C. Risk Assessment

From Initial Risk Identification			Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments**
Sterility*	Formulation, container closure, Process parameters, scale/equipment, site	High	The sterility assurance and supporting microbiology data were found adequate in the microbiology review	Acceptable	
Endotoxin*		Medium	The supporting microbiology data was found adequate in the microbiology review	Acceptable	

Assay*	Formulation, container closure, Process parameters, scale/equipment, site	Low		Acceptable	(b) (4)
pH*	Formulation, Container closure, Raw materials, Process parameters, Scale/equipment, Site	Low	The pH range in the specification for remdesivir injection was tightened to (b) (4) (b) (4)	Acceptable	The pH of the product needs to be controlled to ensure acceptable API solubility and stability
Leachables*	Formulation, container closure	Medium		**Will be covered in Review #2**	The applicant is proposing multiple stoppers, (b) (4) (b) (4)
Particulate matter*	Formulation, Container closure, Raw materials, Process parameters, Scale/equipment, Site	Medium		Acceptable	
Osmolality*	Formulation, raw materials, process parameters, scale/equipment, site	low		Acceptable	Refer to DP and labeling review concerning osmolality of diluted product.
Uniformity of dosage units	Formulation, Container Closure, Process Parameters, Scale/equipment, site	low		Acceptable	
Moisture Content (CQA for lyophilized powder only)	Formulation, Container Closure, Process Parameters, Scale/equipment, site	low		Acceptable	

Reconstitution time (CQA for lyophilized powder only)	Formulation, process parameters, scale/equipment, site	medium		Acceptable	The API exhibits low solubility; however, reconstitution time is included in the DP release and stability specifications (NMT (b)(4)min)
Physical stability (CQA for lyophilized powder only)	Formulation, Container closure, Raw materials, Process parameters, Scale/equipment, Site	medium		Acceptable	

* CQA that applies to both remdesivir for injection and remdesivir injection

D. List of Deficiencies for Complete Response

1. Overall Quality Deficiencies (Deficiencies that affect multiple sub-disciplines)

Additional data is expected during this review cycle, and CMC Review #2 will capture the evaluation of the received new information.

2. Drug Substance Deficiencies

3. Drug Product Deficiencies

4. Labeling Deficiencies

5. Manufacturing Deficiencies

6. Biopharmaceutics Deficiencies

None

7. Microbiology Deficiencies

None

8. Other Deficiencies (Specify discipline, such as Environmental)

Application Technical Lead Name and Date:

Erika E. Englund, 10/1/2020

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CHAPTER IV: LABELING

IQA NDA Assessment Guide Reference

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information:

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	VEKLURY is available in two dosage forms: a. VEKLURY (remdesivir) for injection, for intravenous use b. VEKLURY (remdesivir) injection, for intravenous use	Adequate.
Established name(s)	Two dosage forms: a. Remdesivir for injection, for intravenous use b. Remdesivir injection, for intravenous use	Adequate.
Route(s) of administration	Intravenous	Adequate.
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	Remdesivir is available in two dosage forms: a. Remdesivir for injection (lyophilized powder): 100 mg b. Remdesivir injection (solution): 100 mg/20 mL (5mg/mL)	Adequate.
Controlled drug substance symbol (if applicable)	N/A	
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	Single-dose vial	Adequate

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

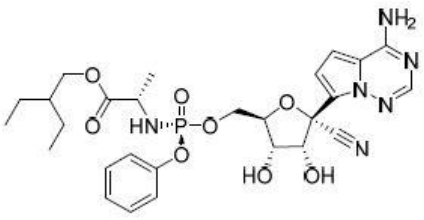
Item	Information Provided in the NDA	Assessor's Comments
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	**VEKLURY for injection** • VEKLURY for injection needs to be reconstituted with 19 mL of Sterile Water for Injection, followed by dilution in 100 mL or 250 mL 0.9% sodium chloride infusion bag. • Only use Sterile Water for Injection to reconstitute VEKLURY lyophilized powder. • After reconstitution, use vials immediately to prepare diluted solution. The diluted VEKLURY solution in the infusion bags can be stored up to 24 hours at room temperature (20°C to 25°C [68°F to 77°F]) prior to administration or 48 hours at refrigerated temperature (2°C to 8°C [36°F to 46°F]). **VEKLURY injection** • VEKLURY injection [supplied as 100 mg/20 mL (5 mg/mL)] must be diluted in 250 mL 0.9% sodium chloride infusion bag. • The prepared infusion solution is stable for 24 hours at room temperature (20°C to 25°C [68°F to 77°F]) or 48 hours at refrigerated temperature (2°C to 8°C ([36°F to 46°F]).	-The supporting in-use stability data for remdesivir injection and remdesivir for injection is provided in section 3.2.P.8. (refer reviewer's assessment of package insert section for additional details) - In the quality submission dated 08-21-2020, Gilead recommended to reconstitute remdesivir for injection with sterile water for injection (WFI) only (refer the reviewer's assessment section for the detailed assessment). -VEKLURY injection must be diluted only in 250 mL 0.9% saline IV bag, (b) (4) (b) (4) (refer drug product review document for additional details). - CMC team recommended to add the following dosage form description through-out the PI to ease the discrimination of two dosage forms and to minimize the dosing errors – • 'Supplied as 100 mg, Lyophilized Powder in Vial' for remdesivir for injection formulation • 'Supplied as 100 mg/20 mL (5 mg/mL) Solution in Vial' for remdesivir injection formulation Gilead accepted this recommendation (labelling response dated 09/09/2020).

1.2.2. Section 3 (DOSAGE FORMS AND STRENGTHS)

Item	Information Provided in the NDA	Assessor's Comments
Available dosage form(s)	**VEKLURY for injection** Sterile, preservative-free, white to off-white to yellow lyophilized powder in single-dose vial for reconstitution **VEKLURY injection** Clear, colorless to yellow, solution free of visible particles in single-dose vial.	Adequate.
Strength(s) in metric system	**VEKLURY for injection:** 100 mg **VEKLURY injection:** 100mg/20mL (5 mg/mL)	Adequate
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	N/A	Adequate.
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	**VEKLURY for injection** White to off-white to yellow powder (before reconstitution). Clear, colorless to yellow solution, free of visible particles (after reconstitution and dilution) **VEKLURY injection** Clear, colorless to yellow, solution free of visible particles (before and after dilution)	Adequate.
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for parental administration, use appropriate labeling term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	Single-dose vial	Adequate

1.2.3 Section 11 Description

Item	Information Provided in the NDA	Assessor's Comments
Proprietary and established name(s)	VEKLURY is available in two dosage forms: a. VEKLURY (remdesivir) for injection, for intravenous use b. VEKLURY (remdesivir) injection, for intravenous use	Adequate
Dosage form(s) and route(s) of administration	**VEKLURY for injection** Lyophilized powder, for intravenous use (after reconstitution and dilution) **VEKLURY injection** Solution, for intravenous use (after dilution in IV bag)	Adequate
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	N/A	Adequate.
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	betadex sulfobutyl ether sodium, Water for Injection, and may include hydrochloric acid and/or sodium hydroxide for pH adjustment.	Gilead originally proposed the excipient name as (b) (4) (b) (4) in the various labelling sections. Gilead was recommended to update the name to betadex sulfobutyl ether sodium to be consistent with the NF throughout labeling. Gilead accepted the recommendation and submitted revised PI (labelling response dated 09/09/2020)

For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	**VEKLURY for injection** 3 g betadex sulfobutyl ether sodium, Water for Injection, USP, and may include hydrochloric acid and/or sodium hydroxide for pH adjustment. **VEKLURY injection** 6 g betadex sulfobutyl ether sodium, Water for Injection, USP, and may include hydrochloric acid and/or sodium hydroxide for pH adjustment.	Adequate
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Statement of being sterile (if applicable)	**VEKLURY for injection** Sterile lyophilized powder in a single-dose clear glass vial. **VEKLURY injection** Sterile, preservative-free solution in a single-dose clear glass vial.	Adequate
Pharmacological/ therapeutic class	Antiviral (SARS-CoV-2 nucleotide analog RNA polymerase inhibitor)	Adequate.
Chemical name, structural formula, molecular weight	The chemical name for remdesivir is 2-ethylbutyl N-{(S)-[2-C-(4-aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)-2,5-anhydro-d-altrononitril-6-Oyl] phenoxyphosphoryl}-L-alaninate. Molecular formula - C27H35N6O8P Molecular weight - 602.6 g/mol. Structural formula: 	Adequate.
If radioactive, statement of important nuclear characteristics.	N/A	

Other important chemical or physical properties (such as pKa or pH)	pH (b) (4)	Adequate

1.2.4 Section 16 HOW SUPPLIED/STORAGE AND HANDLING section

Item	Information Provided in the NDA	Assessor's Comments
Available dosage form(s)	VEKLURY is available in two dosage forms: a. VEKLURY for injection- lyophilized powder b. VEKLURY injection- solution formulation	Adequate.
Strength(s) in metric system	a. VEKLURY for injection- 100 mg b. VEKLURY injection - 100 mg/20 mL (5 mg/mL)	Adequate
Available units (e.g., bottles of 100 tablets)	VEKLURY for injection-100 mg, in single dose vial VEKLURY injection - 100 mg/20 mL (5 mg/mL), in single dose vial	Adequate
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	See above	Adequate.
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	Single-dose vials	Adequate

Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to “Dispense in original container,” provide reason why (e.g. to protect from light or moisture, to maintain stability, etc.)	Do not reuse or save reconstituted or diluted VEKLURY for future use. These products contain no preservatives; therefore, partially used vials should be discarded	Both dosage forms are sterile formulations and do not contain any preservatives.
If the product contains a desiccant, ensure the size and shape differ from the dosage form and desiccant has a warning such as “Do not eat.”	N/A	
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	**VEKLURY for injection** Store below 30ºC **VEKLURY injection** Store VEKLURY injection vials at refrigerated temperature (2°C to 8°C [36°F to 46°F]) until required for use.	Gilead was asked to revise the proposed storage conditions for lyophilized formulation to USP controlled room temperature conditions (20ºC to 25ºC [68ºF to 77ºF]) below 30°C (below 86°F). In the labelling response dated 09-09-2020 and 09-17-2020, Gilead proposed to retain the original proposed storage conditions [Store below 30ºC) (see the detailed assessment in the section below)
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: “Not made with natural rubber latex. Avoid statements such as “latex-free.”	N/A	
Include information about child-resistant packaging	N/A	Drug product will be administered in the hospital settings, so child resistant packaging is not required.

1.2.1 Other Sections of Labeling

1.2.2 Manufacturing Information After Section 17 (for drug products)

Item	Information Provided in the NDA	Assessor's Comments
Manufacturing Information After Section 17		
Name and location of business (street address, city, state and zip code) of the manufacturer, distributor, and/or packer	Manufactured and distributed by: Gilead Sciences, Inc. Foster City, CA 94404	Adequate.

Reviewer's Assessment of Package Insert: Ina*dequate*

Section 2- Dosage and administration-

a. Remdesivir for injection-

The supporting in-use stability data for remdesivir for injection (after reconstitution and dilution) is provided in section 3.2.P.8.1.

- Originally, Gilead proposed the storage time (b) (4) (b) (4)

  Therefore, microbiology review team recommended to use the reconstituted vials immediately for dilution in the IV bag. Gilead accepted this recommendation, per the labelling response dated 09/09/2020. However, in this response document, Gilead proposed to extend the storage time after dilution in the IV bag to 24 hours at room temperature (20°C to 25°C [68°F to 77°F]) or 48 hours at refrigerated temperature (2°C to 8°C [36°F to 46°F]). The supporting chemical stability data for the diluted solution is provided in section 3.2.P.8.3 (in-use stability studies of remdesivir for injection). Gilead submitted supporting microbial data in the labelling IR response dated 09/09/2020. Per the OPQ microbiological review team, the proposed hold time duration after dilution in the IV bags, is acceptable (email dated 09/14/2020, from Erika Pfeiler, Ph.D.).

- Gilead proposed to use only sterile water for injection (WFI) for the reconstitution of remdesivir for injection. An IR was issued to question whether 0.9% saline can also be used for the reconstitution, along with sterile water for injection. In the quality submission dated 08-21-2020, Gilead provided data to demonstrate that the resultant osmolality after reconstitution with saline is relatively high (i.e. 763 ± 5 mOsm/kg), as compared to 498 ± 8 mOsm/kg after reconstitution with WFI. The osmolality after dilution in 100 ml of 0.9% saline IV bag is also high, i.e. 459 mOsm/kg (vs. 319- 351 mOsm/kg after dilution, when reconstituted with WFI). The osmolality of 459 mOsm/kg is higher than the recommended osmolality limit of 450 mOsm/kg to minimize the risk of phlebitis and is close to the Infusion Nursing Society's recommended upper limit of 500 mOsm/kg for cephalic and basilic veins in the upper arms {Stranz 2002}. The justification is in line with the available literature information (https://www.sciencedirect.com/science/article/pii/S0378517315004986?via%3Dihub). So, it is acceptable to reconstitute remdesivir for injection formulation, only with WFI (refer DP review document for additional details).

- All the drug product batches submitted in the NDA exhibited the reconstitution time of 1-3 mins. No significant change in the reconstitution time was observed over the period of 24-month to 48-month after storage at 30ºC/75%RH or 6-month storage under accelerated conditions (40ºC/75% RH). The proposed limit for the reconstitution time is NMT (b)(4)mins (section 3.2.P.5). Therefore, Gilead was asked to include the following statement in the reconstitution instructions for lyophilized formulation – '*The contents of the vial should completely dissolve within* (b)(4)*minutes*'. In the labelling response dated 09/09/2020, Gilead proposed to delete this statement. Gilead justified that it is too specific and does not provide any instructions in the event of the contents not dissolving within (b)(4) minutes. However, since all the DP batches submitted in the NDA exhibit reconstitution time of 1-3 mins and it is not clear what would be the quality of lyophilized powder (i.e. impact on other CQAs, water content, chemical stability, particulate matter etc.) if it doesn't get reconstituted in (b)(4)mins. After discussion with the clinical and DMEPA team, Gilead was asked to add a statement i.e. '*Discard the vial if the contents are not completely dissolved*', instead of specifying the maximum reconstitution time in the PI. Gilead accepted this statement, per the labelling response dated 09-17-2020.

- In the quality submission dated 08-21-2020, Gilead clarified that the reconstitution instructions for lyophilized formulation on DP label are in line with the sample preparation directions used for the testing of reconstitution time at the release and stability.

b. Remdesivir Injection

- Remdesivir injection formulation can only be diluted in 250 mL of 0.9% sodium chloride infusion bag, (b) (4) (refer the drug product review document for additional details).
- The dilution instructions for remdesivir injection formulation includes following statement- '*the last 5 mL of solution requires more force to withdraw*'. Since this statement was not included in the dilution instruction of remdesivir for injection (after reconstitution), so Gilead was asked to comment on this discrepancy. Gilead clarified in the IR response dated 08-21-2020 that little extra force is needed to pull the last 5 mL of remdesivir injection, due to the building of a partial vacuum in the injection vials. This is not the case for the reconstituted lyophilized formulation vials, as those vials are being reconstituted with water for injection, just before dilution. There is no significant difference in the viscosity of two formulations before dilution in IV bags. The viscosity of the injection formulation is 1.123g/ mL (room temperature); and for remdesivir for injection, the viscosity after reconstitution with sterile water for injection is 1.103 g/mL (room temperature). The syringe needle size has no impact on the withdrawal procedure and no complaints have been reported to date for the withdrawability issues of remdesivir injection formulation. The provided information is acceptable.

Section 3 – Dosage Form and Strengths

Remdesivir Injection

Because of the marginal solubility of remdesivir drug substance (b) (4) in the formulation vehicle ((b) (4) % aqueous solution of betadex sulfobutyl ether sodium) at the proposed drug product pH range (pH (b) (4)), Gilead was recommended to include the wording 'free of visible particles' in the dosage form section of remdesivir injection. Gilead accepted this recommendation, as per the labelling response dated 09/09/2020.

Section 11- Description

Gilead originally proposed the excipient's (b) (4) name (b) (4) (b) (4) in the various labelling sections. Gilead was recommended to update the name to betadex sulfobutyl ether sodium to be consistent with the NF throughout labeling. Gilead accepted the recommendation and submitted revised PI (labelling response dated 09/09/2020)

Section 16- How supplied/Storage and Handling-

Remdesivir for injection-

Gilead was recommended to update the storage conditions for remdesivir for injection to USP controlled room temperature conditions (20ºC to 25ºC [68ºF to 77ºF]) from 'store below 30°C (below 86°F)'. In the labelling response dated 09/09/2020, Gilead proposed to retain the originally proposed storage conditions as the supporting drug product stability data is provided for 30°C/75% RH conditions. As per the Agency's practice, the storage condition of 'store below 30°C" is preferably allowed only for the PEPFAR products. The goal is to have a few storage statements and not to create unique storage statements in each NDA. For other drug products, it is recommended to use the USP controlled room temperature storage conditions, rather than storage at a single temperature. So, Gilead was asked again to revise the storage conditions for remdesivir for injection. In the IR response dated 09-18-2020, Gilead provided the reference of several Gilead commercial products in the US market where the "Store below 30 °C" storage statement is currently applied. These products include Sovaldi®, Harvoni®, Epclusa®, Vosevi®, Vemlidy®, Odefsey®, Genvoya®, and Biktarvy®.

This issue needs to be further discussed with the OPQ labelling expert team, PQL and will be addressed in the labelling review #2.

2 PATIENT LABELING

Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guide, Patient Information, Instructions for Use):

Patient Information:

As per the recommendation, Gilead updated betadex sulfobutyl ether sodium name to be consistent with the NF in the Patient Information document.

3 CARTON AND CONTAINER LABELING

IMAGES OF LABEL AND LABELING (updated on Sep 18, 2020)

3.1 Container Label

Remdesivir for injection:

(b) (4)

Remdesivir Injection

(b) (4)

3.2 Carton Labeling

Remdesivir for injection:

3 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

Assessment for Remdesivir for injection Carton and Container label-

Item	Information provided on the container label(s)	Information provided on the carton label(s)
Proprietary name, established name, and dosage form (font size and prominence	VEKLURY (remdesivir) for injection, for intravenous use	VEKLURY (remdesivir) for injection, for intravenous use
Dosage strength	100 mg/vial	100 mg/vial
Route of administration	Intravenous	Intravenous
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	N/A	N/A
Net contents (e.g. tablet count)	100 mg/vial (single-dose vial)	100 mg/vial (single-dose vial)
"Rx only" displayed on the principal display	Yes	Yes
NDC number	NDC 61958-2901-2	NDC 61958-2901-2
Lot number and expiration date	Yes	Yes
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	- Store below 30ºC * Gilead was asked to revise the storage conditions for remdesivir for injection formulation to USP controlled room temperature conditions (20ºC to 25ºC [68ºF to 77ºF]) from below 30°C. Refer the reviewer's assessment section for the detailed assessment.	- Store below 30ºC * Gilead was asked to revise the storage conditions for remdesivir for injection formulation to USP controlled room temperature conditions (20ºC to 25ºC [68ºF to 77ºF]) from below 30°C. Refer the reviewer's assessment section for the detailed assessment.
	(b) (4)	
	* DMEPA issued an IR and asked Gilead to align the storage recommendations on the container and carton labels with the storage recommendations described in the Prescribing Information. Gilead submitted the revised container label on	DMEPA issued an IR and asked Gilead to align the storage recommendations on the container and carton labels with the storage recommendations described in the Prescribing Information. Gilead submitted the revised container label

	09-18-2020. The storage recommendations for lyophilized formulation after reconstitution are still not in line with PI. DMEPA was notified of this discrepancy via email dated 09-19-2020. A follow up IR was issued on 09-22-2020.	on 09-18-2020. The storage recommendation for lyophilized formulation after reconstitution are still not in line with PI. DMEPA was notified of this discrepancy via email dated 09-19-2020. A follow up IR was issued on 09-22-2020
Bar code	Yes	Yes
Name of manufacturer/distributor	The manufacturer name is included: **Gilead Sciences, Inc., Foster City, CA 94404**	The manufacturer name is included: **Gilead Sciences, Inc., Foster City, CA 94404.**
Medication Guide (if applicable)	N/A	N/A
No text on Ferrule and Cap overseal	Yes	Yes
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.	N/A	N/A
And others, if space is available	- Must be reconstituted and further diluted prior to use. - Discard Unused Portion - Keep out of the reach of children	- Must be reconstituted and further diluted prior to use. - Discard Unused Portion - Keep out of the reach of children

Assessment for Remdesivir injection Carton and Container label-

Item	Information provided on the container label(s)	Information provided on the carton label(s)
Proprietary name, established name, and dosage form (font size and prominence	VEKLURY (remdesivir) injection, for intravenous use	VEKLURY (remdesivir) injection, for intravenous use
Dosage strength	100 mg/20 mL (5mg/mL)	100 mg/20 mL (5mg/mL)
Route of administration	Intravenous	Intravenous
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	N/A	N/A
Net contents (e.g. tablet count)	100 mg/20 mL (per vial)	100 mg/20 mL (per vial)
"Rx only" displayed on the principal display	Yes	Yes
NDC number	NDC 61958-2902-2	NDC 61958-2902-2
Lot number and expiration date	Yes	Yes
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	Store refrigerated between 2 °C and 8 °C (36 °F and 46 °F) until required for use.	Store refrigerated between 2 °C and 8 °C (36 °F and 46 °F) until required for use.
Bar code	Yes	Yes
Name of manufacturer/distributor	The manufacturer name is included: **Gilead Sciences, Inc., Foster City, CA 94404**	The manufacturer name is included: **Gilead Sciences, Inc., Foster City, CA 94404**
Medication Guide (if applicable)	N/A	N/A
No text on Ferrule and Cap overseal	Yes	Yes
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.	N/A	N/A
And others, if space is available	- Must be diluted prior to use. - Discard Unused Portion - Keep out of the reach of children	- Must be diluted prior to use. - Discard Unused Portion - Keep out of the reach of children

Assessment of Carton and Container Labeling:

Remdesivir for injection:

- Gilead was asked to revise the storage conditions for remdesivir for injection formulation to USP controlled room temperature conditions (20ºC to 25ºC [68ºF to 77ºF]) from below 30°C (below 86°F) for carton and container labels (IR issued on 09-15-2020). In the IR response dated 09-18-2020, Gilead provided the reference of several Gilead commercial products in the US market where the "Store below 30 °C" storage statement is currently applied. These products include Sovaldi®, Harvoni®, Epclusa®, Vosevi®, Vemlidy®, Odefsey®, Genvoya®, and Biktarvy®. The supporting long-term stability data (up to 18-48 months) at 30 °C/75% RH is provided in section 3.2.P.8.
  This issue needs to be further discussed between the OPQ labelling expert team, PQL team and will be addressed in the labelling review #2.

- In the IR dated 09-15-2020. DMEPA recommended Gilead to align the storage recommendations on the container and carton labels with the storage recommendations described in the Prescribing Information. In the revised container-carton label, submitted on 09-18-2020, the storage recommendations for the lyophilized formulation, (after reconstitution) are not in line with the PI.
  For the Prescribing Information (PI), Gilead accepted that 'After reconstitution, use vials immediately to prepare diluted solution.' However, in the revised container and carton label, the storage recommendations for reconstituted vials are as follows- (b) (4) (b) (4)

  DMEPA was notified of this discrepancy in the email dated 09-19-2020. **A follow up IR was issued on 09-22-2020. This issue will be addressed in the labelling review #2.**

Remdesivir Injection:

The CMC information on carton/container labels of remdesivir injection is acceptable.

ITEMS FOR ADDITIONAL ASSESSMENT

N/A

Overall Assessment and Recommendation:

Refer to discussion above and recommendations in OND labeling.

Primary Labeling Reviewer Name and Date:

Shalini Anand, Ph.D. 09/11/2020; 09/19/2020

Secondary Reviewer Name and Date (and Secondary Summary, as needed):

Thomas F. Oliver, Ph.D. 09/22/2020

Shalini Anand

Digitally signed by Shalini Anand
Date: 9/24/2020 02:16:24PM
GUID: 52795e43000905f07ea0803d93709d84

Thomas Oliver

Digitally signed by Thomas Oliver
Date: 9/24/2020 01:43:29PM
GUID: 508da71f00029ed4697700cee3d31ca0

CHAPTER VI - BIOPHARMACEUTICS

NME-NDA:	**214787-ORIG-1** [505(b)(1)]
Drug Product Name / Strength:	VEKLURY® (remdesivir) for Injection, 100 mg VEKLURY® (remdesivir) Injection, 5 mg/mL
Route of Administration:	Intravenous Infusion
Applicant Name:	Gilead Sciences, Inc.
Indication:	Treatment of coronavirus disease 2019 (COVID-19)
RECOMMENDATION:	ADEQUATE

Submission:
On August 7, 2020, the Applicant submitted NME-NDA 214787 seeking approval of Veklury® (remdesivir) for Injection, 100 mg and Veklury® (remdesivir) Injection, 5 mg/mL for the treatment of COVID-19 as a 505(b)(1) application. To support NDA's approval, the Applicant conducted four Phase-1 PK studies in healthy subjects and several Phase-3 clinical studies in patients with COVID-19. The drug product used in the Phase-3 clinical studies is remdesivir powder for injection, 100 mg and 150 mg.

Background:
Remdesivir (GS-5734) is a novel antiviral drug that has been evaluated for the treatment of COVID-19. Remdesivir is a nucleotide prodrug that is intracellularly metabolized into an analog of adenosine triphosphate (GS-443902) that inhibits viral ribonucleic acid (RNA) polymerases and has broad-spectrum activity against members of the novel coronavirus (CoVs), filoviruses and paramyxoviruses (see Figure 1).

Review:
This Biopharmaceutics Review is evaluating the information supporting the bridging between remdesivir powder for injection, 100 mg and remdesivir solution, 5 mg/mL.

Recommendation:
Adequate and recommended for **APPROVAL** from a Biopharmaceutics perspective.

BIOPHARMACEUTICS ASSESSMENT

Drug Product:

The Applicant proposes to market two dosage forms of the proposed remdesivir product: lyophilized powder for injection and solution (injection). The remdesivir concentration in the proposed solution is 5 mg/mL. The remdesivir powder for injection, 100 mg is designed to be reconstituted in 19 mL sterile water, also resulting in a solution with a remdesivir concentration of 5 mg/mL. As shown in Tables 1 and 2 below, the instructions for further dilution of the concentrated 5 mg/mL solution into a 250 mL infusion solution are the same for both dosage forms. The lyophilized powder dosage form has an additional option for dilution in a 100 mL infusion solution, which is not an option for the solution dosage form per the proposed label. (b) (4) (b) (4) (b) (4) as discussed below and shown in Table 6 below), only 250 mL volume 0.9% NaCl (not 100 mL) can be used for dilution of the remdesivir injection formulation.

Table 1: Recommended Dilution Instructions—VEKLURY® Injection Concentrated Solution in Adults and Pediatric Patients 12 Years of Age and Older and Weighing at Least 40 kg

VEKLURY dose	0.9% sodium chloride infusion bag volume to be used	Volume to be withdrawn and discarded from 0.9% sodium chloride infusion bag	Required volume of VEKLURY injection concentrated solution
200 mg (2 vials)	250 mL	40 mL	40 mL (2 × 20 mL)
100 mg (1 vial)		20 mL	20 mL

Table 2: Recommended Dilution Instructions—Reconstituted VEKLURY® for Injection Lyophilized Powder in Adults and Pediatric Patients 12 Years of Age and Older and Weighing at Least 40 kg

VEKLURY dose	0.9% sodium chloride infusion bag volume to be used	Volume to be withdrawn and discarded from 0.9% sodium chloride infusion bag	Required volume of reconstituted VEKLURY for injection
200 mg (2 vials)	250 mL	40 mL	40 mL (2 × 20 mL)
	100 mL	40 mL	40 mL (2 × 20 mL)
100 mg (1 vial)	250 mL	20 mL	20 mL
	100 mL	20 mL	20 mL

The difference between the solution and the powder for injection is (b) (4) (b) (4)

(b) (4)

(b) (4) The quantitative composition of the remdesivir powder for injection formulation and the remdesivir solution formulation is show below in Tables 3 and 4, respectively.

Table 3. Quantitative Composition of Remdesivir Injection, 5 mg/mL

Components	% w/v	% w/w[a]	Quantity per 20 mL solution[b] (g)	Quality Standard	Function
Remdesivir[c]			(b) (4)	In-House	Active ingredient
Betadex Sulfobutyl Ether Sodium				NF	(b) (4)
Hydrochloric Acid[d]				NF/Ph. Eur.	pH adjustment
Sodium Hydroxide[d]				NF/Ph. Eur.	pH adjustment
Water for Injection[e]				USP/Ph. Eur.	(b) (4)
Total	100.0	100.0	(b) (4)	—	—

(b) (4)

Per the drug product review, the acceptance criterion for the pH of the Remdesivir Injection, 5 mg/mL, was tightened from pH (b) (4) to pH (b) (4)

Table 4. Quantitative Composition of Remdesivir for Injection, 100 mg

Components	Quantity per Vial (g)	% w/w	Quality Standard	Function
Remdesivir[b]	(b) (4)	(b) (4)	In-House	Active ingredient
Betadex Sulfobutyl Ether Sodium			NF	(b) (4)
Hydrochloric Acid[c]			NF/Ph. Eur.	pH adjustment
Sodium Hydroxide[c]			NF/Ph. Eur.	pH adjustment
Water for Injection[d]			USP/Ph. Eur.	(b) (4)
Total		100.0	—	—

(b) (4)

Bridging Throughout the Drug Product's Development:

Phase 1 Studies: Both dosage forms (lyophilized powder and solution) were used in the Phase 1 studies evaluating the pharmacokinetics, safety, and tolerability of the proposed remdesivir products (Table 5).

Table 5. Phase 1 clinical studies to determine the pharmacokinetics (PK), safety and tolerability of the proposed drug products in healthy volunteers.

Product	Formulation	Study
RDV for Injection	Solution (150 mg)	GS-US-399-1812 Phase 1, FIH
		GS-US-399-1954 Phase 1, MAD
	Lyophilized Powder (150 mg)	GS-US-399-1812 Phase 1, FIH
		GS-US-399-5505 Phase 1, MAD
		GS-US-399-4231 Phase 1, ADME

ADME = absorption, distribution, metabolism, and excretion; FIH = first in human; MAD = multiple-ascending dose; RDV = remdesivir (GS-5734™)

Phase 3 Studies: The pivotal clinical Phase 3 studies used remdesivir lyophilized powder, 100 mg and 150 mg, at a dose of 200 mg on day 1, followed by 100 mg once daily for up to 9 days.

Because the Phase 3 pivotal clinical safety and efficacy studies only used the lyophilized powder dosage form of the proposed drug product and these studies did not use the solution for Injection dosage form, the bridging between the two dosage forms should be established, in order to leverage the safety and efficacy information for the proposed solution dosage form and support its approval.

Information Supporting the Bridging:

- ***Comparative Compositions of Lyophilized powder and Solution Dosage Forms***:

Table 6 below shows the difference in the composition of the formulations of the concentrated solutions from both dosage forms, used for further dilution in the infusion solution.

Table 6. Comparative quantitative compositions of the concentrated solution (injection) and the concentrated solution after reconstitution of the lyophilized powder (for injection)

	Concentrated solution Remdesivir Injection, 5 mg/mL	Concentrated solution (100 mg/20 mL) after reconstitution of Remdesivir for Injection (lyophilized powder), 100 mg
	Quantity (g) per 20 mL concentrated solution	**Quantity (g) per 20 mL concentrated solution**
Remdesivin[a]	(b) (4)	
Betadex Sulfobutyl Ether Sodium		
Hydrochloric Acid[b]		
Sodium Hydroxide[b]		
Water for Injection		

a. (b) (4)% overfill/overage
b. Hydrochloric Acid and Sodium Hydroxide are used to adjust the pH (b) (4)

After reconstitution, remdesivir for injection, 100 mg, contains (b) (4)% w/v betadex sulfobutyl ether sodium and 5 mg/mL remdesivir. In comparison, the remdesivir injection, 5 mg/mL, solution formulation contains (b) (4)% w/v betadex sulfobutyl ether sodium. A lower amount of SBECD in the lyophilized powered formulation is proposed (b) (4) (b) (4)

The 5 mg/mL concentrated solutions (from either dosage form) should be further diluted in 0.9% NaCl before intravenous (i.v.) infusion, per labeling instructions shown in Tables 1 and 2 above. The concentration of betadexsulfobutyl ether sodium (SBECD) in the infusion prepared from the remdesivir solution dosage form is approximately twice the concentration of SBECD of the infusion prepared from the lyophilized powder, when both are diluted in 250 mL in 0.9% NaCl.

- ***Comparison of Physicochemical Parameters of the Diluted Infusion Solutions:***

  - ✓ **Osmolality of the Infusion Solutions:**

The (b) (4) (b) (4) Applicant was asked to provide osmolality data for the infusion solutions prepared from the solution and lyophilized powder formulations (IR dated 06/10/2020). The Applicant provided the following osmolality information in the amendment dated 06/24/2020:

Table 7. Osmolality of Remdesivir Injection 5 mg/mL (concentrated) and diluted with 0.9% Sodium Chloride to a final volume of 250 mL[a].

Dose (mg)	Volume of Remdesivir Injection (mL)	Diluted Remdesivir Concentration (mg/mL)	Remdesivir Injection Osmolality (mOsm/kg)	Diluted Remdesivir Osmolality[b] (mOsm/kg)
200	40	0.8	1116 ± 37	371 ± 1
			1272 ± 18	378 ± 3
			1357 ± 26	383 ± 2
100	20	0.4	1116 ± 37	332 ± 2
			1272 ± 18	330 ± 2
			1357 ± 26	333 ± 0

a Final volumes less than 250 mL are not recommended for remdesivir injection due to osmolality more than 400 mOsm/kg.
b Average ± standard deviation of osmolality from 3 measurements on same diluted solution.

For the remdesivir injection formulation, final volumes less than 250 mL are not proposed in the label because the resulting infusion solutions have osmolality values above 400 mOsm/kg.

The osmolality of the reconstituted remdesivir powder for injection (5 mg/mL after reconstitution with sterile water) was measured to be 498 mOsm/kg. After dilution, the osmolality values of this dosage form are shown in Table 8.

Table 8. Osmolality of Remdesivir for Injection Diluted with 0.9% Sodium Chloride to a Final Volume of 100 mL and 250 mL

Osmolality of Reconstituted Remdesivir for Injection, 100 mg	Dose (mg)	Final Diluted Volume[a] (mL)	Diluted Remdesivir Concentration (mg/mL)	Diluted Remdesivir Osmolality[b] (mOsm/kg)
498 ± 8	200	100	2.0	351 ± 3
		250	0.8	314 ± 1
	100	100	1.0	319 ± 2
		250	0.4	301 ± 2

a The final diluted volume is per the recommended preparation instructions for adults.
b Average ± standard deviation of osmolality from 3 measurements on same diluted solution.

✓ **pH of the Infusion Solutions:**

The pH for the infusion solution (0.6 mg/mL) prepared by diluting the remdesivir solution formulation is pH (b) (4) (Report REP-12974).

The pH for the infusion solution (2.0 mg/mL) prepared by diluting the remdesivir lyophilized powder formulation is pH (b) (4) (Report REP-22251).

The pH for the infusion solution (0.3 mg/mL) prepared by diluting the remdesivir lyophilized powder formulation is pH (b) (4) (Report REP-22251).

- ***Comparison of the Pharmacokinetics of the Diluted Infusion Solutions:***

The pharmacokinetics (PK) of remdesivir (RDV) and its two metabolites, GS-441524 and GS-704277 upon infusion of the solution prepared from the lyophilized formulation and the concentrated solution formulation of RDV were evaluated in healthy volunteers in Study GS-US-399-1812, at doses of 75 mg and 150 mg, infused over a 2 hour-time period.

The proposed intracellular metabolic pathway of RDV is described in Figure 1. The PK results from Study GS-US-399-1812, are shown in Tables 9 and 10.

Figure 1: Proposed intracellular metabolic pathway of RDV (GS-5734)

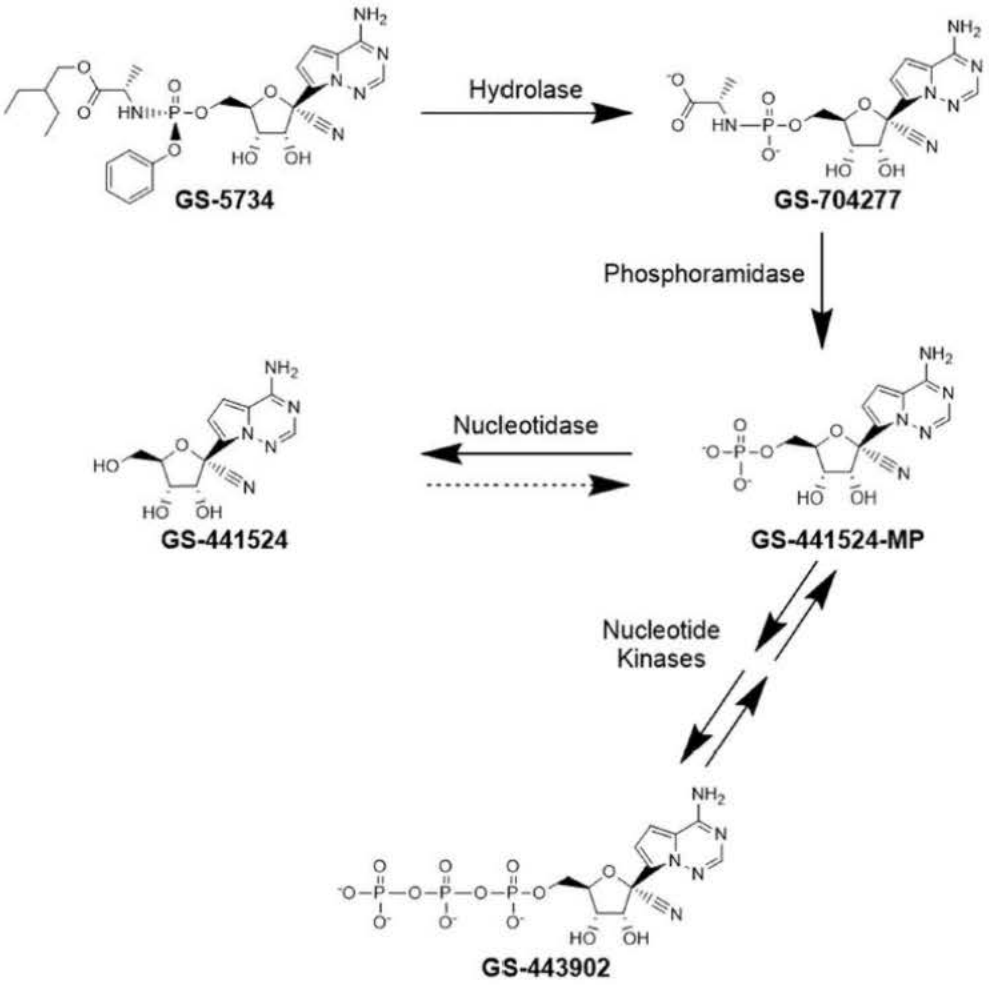


Table 9. Comparison of RDV and metabolites (GS-441524, and GS-704277) Plasma Pharmacokinetic Parameters Between Lyophilized and Solution Formulations at 75 mg Dose Infused Over 2 hours

Mean (%CV)[a]	Lyophilized Formulation (Test) 75 mg N = 10	Solution Formulation (Reference) 75 mg N = 8
RDV		
AUC_{inf} (h*ng/mL)	1839.9 (17.1)	1999.6 (27.1)
AUC_{last} (h*ng/mL)	1832.5 (17.1)	1989.9 (27.3)
C_{max} (ng/mL)	1722.0 (28.4)	1626.0 (38.6)
GS-441524		
AUC_{inf} (h*ng/mL)	2200.1 (18.4)	2471.8 (22.7)
AUC_{last} (h*ng/mL)	2091.1 (19.0)	2374.0 (23.2)
C_{max} (ng/mL)	77.5 (21.0)	85.8 (23.9)
GS-704277		
AUC_{inf} (h*ng/mL)	294.5 (27.9)	270.0 (49.0)
AUC_{last} (h*ng/mL)	286.8 (28.3)	262.5 (49.9)
C_{max} (ng/mL)	113.5 (25.7)	100.8 (57.9)

Table 10. Comparison of RDV and metabolites (GS-441524, and GS-704277) Plasma Pharmacokinetic Parameters Between Lyophilized and Solution Formulations at 150 mg Dose Infused Over 2 hours.

Mean (%CV)[a]	Lyophilized Formulation (Test) 150-mg N = 10	Solution Formulation (Reference) 150 mg N = 8
RDV		
AUC_{inf} (h*ng/mL)	3261.1 (22.2)[b]	2976.1 (19.0)
AUC_{last} (h*ng/mL)	3265.4 (21.3)	2965.4 (19.1)
C_{max} (ng/mL)	2722.0 (35.0)	2280.0 (30.1)
GS-441524		
AUC_{inf} (h*ng/mL)	4330.6 (22.2)[b]	4642.5 (16.2)
AUC_{last} (h*ng/mL)	4194.6 (22.2)	4517.4 (16.4)
C_{max} (ng/mL)	148.1 (26.5)	152.0 (23.6)
GS-704277		
AUC_{inf} (h*ng/mL)	618.7 (24.6)	459.8 (19.7)
AUC_{last} (h*ng/mL)	610.6 (24.9)	453.2 (20.0)
C_{max} (ng/mL)	233.6 (28.8)	171.3 (22.3)

The level of the active metabolite, GS-443902 (see Figure 1 above), which is formed intracellularly, is very low in plasma and not presented in Tables 9 and 10.

Reviewer's Assessment of Information Supporting the Bridging:

- The osmolality of the infusion solutions prepared from both dosage forms (solution and lyophilized powder formulations) are comparable and within an acceptable range of 300-385 mOsm/kg (refer to Tables 7 and 8). The provided data indicate that (b) (4) (b) (4) of the infusion solutions prepared from the solution formulation and lyophilized powder formulation.
- The pH of the infusion solutions prepared from both dosage forms (solution and lyophilized powder formulations) are comparable (pH (b) (4)).
- According to published literature (*Toxicol Pathol. 2008 Jan; 36(1): 30-42, Cyclodextrins, VJ Stella and Q He*), the PK properties of a drug should be unaffected by the use of cyclodextrins, provided that the binding constant of the drug for the cyclodextrin is below 1×10^5 M^{-1}, and even this strong a binding has been shown to have only a limited effect. The Applicant did not provide the binding constant of RDV to SBECD. However, the Applicant has shown that the PK parameters (C_{max} and AUC) of RDV and its metabolites for the infusion solutions prepared from both dosage forms (solution and lyophilized powder formulations) are comparable (refer to Tables 9 and 10).
- Pharmacokinetic Study GS-US-399-1812, conducted in healthy volunteers evaluated the BA/BE of remdesivir and its two metabolites, upon infusion of the solution prepared from the lyophilized and the concentrated solution formulations of RDV, at doses of 75 mg and 150 mg, infused over a 2 hour-time period. The study results showed that the PK parameters, C_{max} and AUC are comparable for both dosage forms (refer to Tables 9 and Table 10). It is noted that the number of subjects in this study was too low (8-10) and the study was not adequately powered to demonstrate bioequivalence. The overall results of this PK study indicate that the concentration of SBECD in the infusion solution have a minimum impact in the PK of RDV and its metabolites.
- The Clinical Pharmacology Reviewer, Dr. Mario Sampson, did not review the pilot PK Study GS-US-399-1812. However, he stated the following "*While only the lyophilized powder was evaluated in Phase 3 studies, there is no expectation that the other IV formulation (solution) would differ in bioavailability.*"
- The Pharmacology/Toxicology Reviewer, Dr. John Dubinion, found the proposed SBECD concentrations in the infusion solutions acceptable from a Pharmacology/ Toxicology perspective.

In conclusion, based on the totality of the provided in vitro and in vivo information, the difference in SBECD concentrations it is not expected to alter the PK, efficacy, and safety of remdesivir and its metabolites; therefore, the infusions prepared from the solution formulation and the lyophilized powder formulation are expected to be comparable.

In accordance with 21 CFR 320.24(b)(1-i and 6), the bridge between the solution formulation 5 mg/mL and lyophilized powder formulation of remdesivir, 100 mg is established.

RECOMMENDATION:

From a Biopharmaceutics perspective, the overall in vitro and in vivo information that was provided to support the bridging between the solution and the lyophilized powder formulations is deemed ADEQUATE and acceptable. NME-NDA 214787 for VEKLURY® (remdesivir) for Injection (Supplied as 100 mg Lyophilized Powder in Vial) and VEKLURY® (remdesivir) Injection (Supplied as 100 mg/20 mL [5 mg/mL] Solution in Vial), is recommended for **APPROVAL**.

Biopharmaceutics Team Lead Name and Date: Elsbeth Chikhale, Ph.D., 9/17/2020

Biopharmaceutics Branch Chief Name and Date: Angelica Dorantes, Ph.D., 9/17/2020

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CHAPTER VII: MICROBIOLOGY

IQA NDA Assessment Guide Reference

Product Information	
NDA Number	214787
Assessment Cycle Number	1
Drug Product Name/ Strength	Remdesivir for Injection and Remdesivir Injection
Route of Administration	Intravenous Injection
Applicant Name	Gilead Sciences, Inc.
Therapeutic Classification/ OND Division	Antiviral
Manufacturing Site	Remdesivir for Injection (b) (4) Remdesivir Injection (b) (4)
Method of Sterilization	

Assessment Recommendation: **Adequate**

Assessment Summary:

List Submissions being assessed (table):

Document(s) Assessed	Date Received
Original	**4/8/2020**
Amendment	**5/4/2020**
Amendment	**5/12/2020**
Amendment	**5/29/2020**
Amendment	**6/24/2020**
Amendment	**7/10/2020**
Amendment	**7/24/2020**
Amendment	**7/27/2020**
Amendment	**7/31/2020**
Amendment	**8/7/2020**
Amendment	**8/12/2020**
Amendment	**8/31/2020**

Amendment	**9/3/2020**
Amendment	**9/4/2020**

Highlight Key Issues from Last Cycle and Their Resolution: N/A

Remarks: This is an original application for a sterile drug product which proposes to treat Covid-19. This application is for two products – Remdesivir for Injection and Remdesivir Injection. Due to the prioritization of this project and the number of proposed drug product manufacturing sites, a team approach was taken for assessment of drug product manufacturing sites. The following assessors, and their contributions, are listed below:

Gilead Sciences, Inc.	Christine Craig
	(b) (4)

Erika Pfeiler was the primary assessor for the remainder of the application. John Arigo was the secondary assessor for the application.

Since this assessment covers seven manufacturing sites, many containing multiple manufacturing lines, each site is given its own section in which site-specific information is assessed.

Concise Description of Outstanding Issues: N/A

Supporting Documents:

DMF (b) (4)

(b) (4)

LOA 3/23/2020

- **D** (b) (4) **M05R01.docx**
- **D** (b) (4) **M06R01.docx**

DMF (b) (4)

(b) (4)

LOA 7/21/2020

- **D** (b) (4) **M04R01.docx**

DMF (b) (4)

(b) (4)

LOA 4/22/2020

- **D** (b) (4) **M045R01.docx**

DMF (b) (4)

(b) (4)

LOA 3/25/2020

- D (b) (4) M05R01.docx
- D (b) (4) M06R01.docx

(b) (4)

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LOA 4/23/2020

- D (b) (4) M14R01.docx
- D (b) (4) M15R01.docx

S DRUG SUBSTANCE

The drug substance is (b) (4)

(b) (4)

P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT

Remdesivir for Injection

- **Description of drug product –**
- Drug product is a sterile powder for injection, intended for single dose. Product is supplied as 100 mg of Remdesivir and intended for reconstitution in 19 mL of sterile WFI.

- **Drug product composition –**

Ingredient	Quantity per vial (g)	Function
Remdesivir	(b) (4)	Active ingredient
Betadex Sulfobutyl Ether Sodium		(b) (4)
Hydrochloric Acid		pH adjustment
Sodium Hydroxide		pH adjustment
Water for Injection		(b) (4)
Total		

Remdesivir Injection

- **Description of drug product –**
  Drug product is a sterile solution (preservative-free) for single-dose injection. Product is 5 mg/mL, 20 mL per vial.

- **Drug product composition –**

Ingredient	Quantity per 20 mL (g)	Function
Remdesivir	(b) (4)	Active ingredient
Betadex Sulfobutyl Ether Sodium		(b) (4)
Hydrochloric Acid		pH adjustment

Sodium Hydroxide	(b) (4)	pH adjustment
Water for Injection		(b) (4)
Total		

Container Closure Systems –

An information request was sent to the applicant on August 7 for more information on the container closure systems proposed for the seven drug product manufacturing sites. A response was received on August 12. For ease of interpreting the responses, the IRs are listed below in **bold** and the responses are listed below in *italics*.

1. **Please provide a table that outlines the container closure system (vial and stopper, CCS) that is proposed for each line at each drug product manufacturing site. Note whether information to support the vial/stopper has been submitted or when their submission will be expected. Note that newly introduced CCS components may have implications on the sterility assurance program (depyrogenation and/or sterilization). These implications should be addressed with appropriate sterilization/depyrogenation validation data at the time of submission.**

The applicant provided the following table, in addition to asserting that the vials from (b) (4) *are dimensionally equivalent and interchangeable.*

Table 5. Container Closure Systems for Remdesivir Drug Product

Container Closure System	Component	Description	Specification	Supplier
Remdesivir Injection, 5 mg/mL	Vial	(b) (4)		
	Elastomeric Closure			
	Seal			
CCS#1: Remdesivir for Injection, 100 mg	Vial			
	Elastomeric Closure			
	Seal			

Container Closure System	Component	Description	Specification	Supplier
CCS#2: Remdesivir for Injection, 100 mg	Vial	(b) (4)		
	Elastomeric Closure			
	Seal			
CCS#3: Remdesivir for Injection, 100 mg	Vial			
	Elastomeric Closure			
	Seal			
CCS#4: Remdesivir for Injection, 100 mg	Vial			
	Elastomeric Closure			
	Seal			(b) (4)

Assessment: ***{Adequate}***

Further information regarding the container closure system used at each manufacturing site can be found in its respective section.

The applicant has provided the information necessary to permit further assessment.

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John Arigo

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Erika Pfeiler

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