CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215596Orig1s000

PRODUCT QUALITY REVIEW(S)

RECOMMENDATION

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

NDA # 215596
Assessment # 1

Drug Product Name	**LIVTENCITY (maribavir) tablets**
Dosage Form	Tablet
Strength	200 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Takeda
US agent, if applicable	NA

Submission(s) Assessed	Document Date	Discipline(s) Affected
Original SD 0001(1)	March 23, 2021	All Quality
Amendment SD 0010(10)	May 21, 2021	Drug Product
Amendment SD 0013(13)	June 07, 2021	Drug Substance, Drug Product, Facility
Amendment SD 0016(16)	June 22, 2021	Labeling
Amendment SD 0019(19)	July 15, 2021	Drug Substance, Manufacturing, Biopharmaceutics
Amendment SD 0022(22)	August 03, 2021	Drug Product, Manufacturing, Labeling, Biopharmaceutics
Amendment SD 0024(24)	August 11, 2021	Drug Product, Labeling
Amendment SD 0028(28)	August 26, 2021	Labeling
Amendment SD 0029(29)	August 31, 2021	Drug Product
Amendment SD 0037(37)	September 22, 2021	Drug Product/labeling

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessor	Secondary Assessor
Drug Substance	Karina Zuck	Paresma Patel
Drug Product	Molly Lee	Thomas Oliver
Manufacturing	Nathan Davis	Bo Jiang
Microbiology	NA	NA

Biopharmaceutics	Qi Zhang	Elsbeth Chikhale
Regulatory Business Process Manager	Shamika Brooks	
Application Technical Lead	Anamitro Banerjee	
Laboratory (OTR)	NA	
Environmental		

QUALITY ASSESSMENT DATA SHEET

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
(b) (4)	III		(b) (4)	Adequate		DMFs for components of container closure system for solid oral dosage forms are not assessed for this NDA per current ONPD policy. All the DMFs are referenced by several approved NDAs and ANDAs.
	III			Adequate		
	III			Adequate		
	III			Adequate		
	III			Adequate		
	III			Adequate		
	III			Adequate		

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

Document	Application Number	Description
IND	51001	Clinical studies supporting the development of this product.

2. CONSULTS

Discipline	Status	Recommendation	Date	Assessor
Biostatistics	NA			
Pharmacology/Toxicology	NA			
CDRH	NA			

Clinical	NA			
Other				

EXECUTIVE SUMMARY

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

OPQ recommends APPROVAL for the NDA 215596 for LIVTENCITY (maribavir) tablets for oral use, 200 mg. As a part of this action, a 30-month expiration dating period may be granted for the drug product when stored in proposed container closure at 20ºC to 25ºC (68ºF to 77ºF), with brief exposure to 15ºC to 30ºC (59ºF to 89ºF) permitted.
No outstanding issues, deficiencies, or post-approval quality agreements are identified that need to be conveyed to the Applicant.

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

The proposed indication for maribavir in this NDA is for the treatment of adults with post-transplant cytomegalovirus (CMV) infection and/or disease, including infections resistant and/or refractory to ganciclovir, valganciclovir, cidofovir or foscarnet. The product was granted a breakthrough therapy designation and an orphan designation. The NDA was submitted with a request for a priority review.

The drug product will be provided as an immediate-release tablet, in a single strength of 200 mg. The tablet is blue, oval-shaped, convex, de-bossed with "SHP" on one side and 620 on the other side. It is (b) (4) not scored. The recommended dose is 400 mg twice daily (800 mg daily maximum daily dose).

Proposed Indication(s) including Intended Patient Population	treatment of adults with post-transplant cytomegalovirus (CMV) infection and/or disease, including infections resistant and/or refractory to ganciclovir, valganciclovir, cidofovir or foscarnet.
Duration of Treatment	NA
Maximum Daily Dose	800 mg
Alternative Methods of Administration	The product can be taken whole (b) (4)

B. Quality Assessment Overview

Drug Substance: Adequate

Maribavir drug substance, a new molecular entity (NME), is a white to off-white, non-hygroscopic crystalline powder with four chiral centers within the L-ribofuranosyl ring. The drug product is manufactured as a single isomer. The drug substance is a weak base that is soluble in low pH, but has low solubility in aqueous medium at pH above 4.7.

The drug substance is manufactured (b) (4). The manufacturing process produces the (b) (4) polymorphic (b) (4) (the desired polymorphic form) that does not change during (b) (4). The drug substance review team found (b) (4) (b) (4) as acceptable starting materials, consistent with ICH Q11 guidelines and both starting materials are adequately controlled. The manufacturing process is adequately described in the NDA. Three isolated intermediates are adequately controlled. In response to IR, the Applicant provided adequate stability data to support the proposed hold times of (b) (4) months for the three intermediates.

The drug substance and related impurities are adequately characterized using spectroscopic and spectrometric methods.

The drug substance specifications include: description, two identity methods: IR (specific) and HPLC (nonspecific), polymorphic form, assay, related substances, (b) (4), residual solvents, (b) (4), particle size, and microbial limits. The specifications are consistent with the relevant ICH guidances and USP monographs. The in-house analytical methods are adequately validated as per ICH Q2. The drug substance specifications adequately establish identity and purity of the drug substance. The batch data provided in the submission for 3 consecutive PPQ batches of the drug substance manufactured using the commercial process (b) (4) is consistent with the proposed specifications. The Applicant also included certificates on Analyses for the reference standard batches of the drug substance as well as the impurities (b) (4) (b) (4).

The Applicant provided 24 months stability data for three drug substance batches stored in the proposed commercial packaging (b) (4) (b) (4) under long term storage conditions (25ºC/60%RH) and 6 months data under accelerated storage conditions (40ºC/75%RH). The data does not show trends or any OOS results. The Applicant also provided adequate data from stress studies and a photostability study as per ICH Q1B. The Applicant committed to place three production batches and one annual batch per year (assuming adequate production) on stability through the proposed retest period as per a post-approval stability protocol submitted in the application.

Based on the evaluation of this data, the Applicant requested, and the review team agrees to grant a (b) (4) month retest date when stored in the

proposed container closure at (b) (4) (b) (4)
There are no pending issues from the drug substance perspective.

Drug Product: Adequate

The Applicant developed a total of five different immediate release solid oral formulations: one capsule, and four tablets (Formulations I, II, III, and IV). The Tablet formulation IV was the one chosen for commercialization. The proposed 200 mg, immediate release, (b) (4) oval shaped, blue convex tablet is debossed with "SHP" on one side and "620" on the other side. The drug product is packaged in a 28 or 56 count 60 mL HDPE bottles with an induction seal and a child resistant closure. In response to Agency's IR comment, the Applicant provided adequate details on the container closure (compliance to 16 CFR 1700, certificate of compliance for plastic closures, and technical drawings and photographs of the bottle and caps).
The drug product is composed of compendial ingredients: (b) (4) (b) (4)
Amounts of all the ingredients in the formulation are within the Inactive Ingredients Database limits. No novel excipients, or excipients derived from human, or animal sources are used in the formulation.
The drug product specifications include: description, two identity methods: HPLC and UV (both nonspecific), assay, related substances, uniformity of dosage units by weight variation, dissolution, and microbiological evaluations. The Applicant adequately justified not including tests for (b) (4) based on historical data trends, and elemental impurities based on risk assessment consistent with ICH Q3D. The specifications are consistent with the relevant ICH guidances and USP monographs.
The in-house analytical methods are adequately validated as per ICH Q2.
The drug product specifications adequately establish identity and purity of the drug product. The batch data for 3 drug product batches provided in the submission are consistent with the proposed specifications.
The Applicant provided 18 months of long term stability data (25ºC/60%RH) for three drug product primary batches (manufactured with (b) (4)) and 9 months data for one supportive batch (manufactured with (b) (4)) stored in proposed commercial packaging and 6 months data under accelerated storage conditions (40ºC/75%RH). The data does not show any trends (except for a minor (b) (4)) or any OOS results. The applicant also provided adequate data from photostability study as per ICH Q1B. The Applicant committed to place three production batches and one annual batch per year (assuming adequate production) on stability through the proposed expiration dating period as per a post-

approval stability protocol submitted in the application. The Applicant committed to report any extension of expiration dating period via Annual Reports based on real time stability data.
Based on the evaluation of this data, the Applicant requested, and the review team agrees to grant a 30-month expiry for the drug product when stored in the proposed container closure at 25ºC/60%RH consistent with ICH Q1E guidelines.

(b) (4)

The Applicant claims categorical exclusion from environmental assessment per 21 CFR 25.31(b), which may be granted.

Labeling: Adequate

The Sections 2 (DOSAGE AND ADMINISTRATION), 3 (DOSAGE FORM AND STRENGTHS), 11 (DESCRIPTION), and 16 (HOW SUPPLIED/STORAGE AND HANDING) of the USPI were evaluated and found to be acceptable from the CMC perspective. The Applicant deleted the section on (b) (4) as noted above. (b) (4)

(b) (4)

The carton and container labels are acceptable.

Manufacturing: Adequate

The drug product is manufactured by (b) (4)

(b) (4)

(b) (4)

The Applicant provided 9 months of supportive stability data under long term conditions for one batch manufactured using the proposed commercial method to demonstrate acceptability of the process.
Other manufacturing issues identified during the review were adequately addressed by the Applicant.
All the manufacturing and testing facilities listed by the Applicant are adequate to perform the functions. The review team did not identify any outstanding deficiencies during the review cycle.

Biopharmaceutics: Adequate

The Biopharmaceutics assessment focused on: i) bridging of the drug product through development, ii) the dissolution method and acceptance criterion, and iii) risk assessment.
The Applicant established PK bridging for a total of 5 oral IR formulations (refer to the drug product section above for the formulations). The proposed commercial formulation is Tablet IV that was also used in the pivotal phase 3 trial, with addition of debossing and changes in the product manufacturing site and process. The Applicant provided comparative dissolution data at pH 1.2, 4.5, and 6.8 for the Tablet IV (without debossing), primary registration/stability batches (with debossing, (b) (4)), and supportive batch representing commercial process (with debossing, (b) (4)). Overall, the results of the comparative dissolution testing show that the proposed changes in drug product manufacturing site and process did not significantly alter the dissolution rates for the proposed commercial drug product, thereby implying similar in-vivo performance of the proposed drug product to those tested in the pivotal phase 3 study.
The Applicant's proposed QC dissolution method was previously agreed upon by the Agency under IND 051001. The Applicant has revised the acceptance criterion to Q= (b) (4)% at 30 minutes as per the FDA's recommendation. Overall, the following dissolution method and acceptance criterion are acceptable for batch release and stability testing:

Dissolution Method and Acceptance Criterion for

LIVTENCITY™ (maribavir) Tablet 200 mg				
Apparatus	Speed	Medium	Volume/Temp	Acceptance Criterion
USP Apparatus 2 (Paddle)	*50 rpm*	*0.1 N HCl*	*900 mL/37℃*	*Q=(b) (4)% in 30 minutes*

The risk assessment performed by the Biopharmaceutics review team found the overall Biopharmaceutics risk low, based on the totality of the information and data provided in the submission.

Microbiology (if applicable): N/A

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**
Assay		Low		Acceptable	
Physical State		medium		Acceptable	
Content Uniformity		low		Acceptable	
Microbial Limits		Low		Acceptable	
Dissolution		Medium		Acceptable	

D. List of Deficiencies for Complete Response

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

NA

2. Drug Substance Deficiencies

NA

3. Drug Product Deficiencies

4. Labeling Deficiencies

NA

5. Manufacturing Deficiencies

NA

6. Biopharmaceutics Deficiencies

NA

7. Microbiology Deficiencies

NA

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

NA

E. Other Life Cycle Considerations

The Applicant indicated that they will (b) (4)

(b) (4)

The review team suggested that (b) (4)

(b) (4)

Application Technical Lead Name and Date: Anamitro Banerjee, PhD, October 15, 2021

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Nathan Davis

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Bo Jiang

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CHAPTER IV: LABELING
NDA 215596

For more details about the items in this template, please see Chapter IV (Labeling) of the NDA IQA Guide

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information: Recommended changes to Highlights and Sections 11 and 16 are listed below. An IR sent on July 26, 2021 regarding Section 2 is pending.

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Name: LIVTENCITY (Maribavir) tablets, for oral use
DOSAGE FORMS AND STRENGTHS
Tablets: 200 mg

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Product Title in Highlights		
Established name(s)[1]	Adequate	
Route(s) of administration	Adequate	
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system	Inadequate	To provide clarity and consistency with other recent labels, revise to: Tablets: 200 mg of maribavir
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	N/A	

[1] Established name = [Drug] [Route of Administration] [Dosage Form]

package and imaging bulk package.		
If the drug product contains an active ingredient that is a salt, clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (e.g., Tablets: 10 mg of drug-x hydrochloride).	N/A	

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

Information provided in original label submission:

(b) (4)

This information is inadequate and therefore the following IR was sent on July 26, 2021:

(b) (4)

The applicant committed to sending a revised dosage and administration section statement by September 1, 2021. In vitro studies to support the labeling were also requested, but, will not be submitted until November 1, 2021. This issue is pending at the time of this review.

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DOSAGE AND ADMINISTRATION section		
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)	Inadequate	IR pending
Important administration instructions supported by product quality information (e.g., do not crush or chew extended-release tablets, instructions for mixing with food)	Inadequate	IR pending
For parenteral products: include statement: *"Parenteral drug products must be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit"*	N/A	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled. Note the labeling requirement may be applicable to another section of the PI (e.g., Section 11).	N/A	

For radioactive products, include radiation dosimetry for the patient and healthcare practitioner(s) who administer the drug	N/A	
For hazardous products, include the statement *"DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures.*[x]*"* with x numerical citation to "OSHA Hazardous Drugs".	N/A	

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

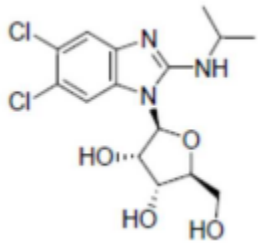
Tablet: 200 mg, blue, oval shaped convex tablet debossed with "SHP" on one side and "620" on the other side.

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Adequate	
Strength(s) in metric system	Adequate	
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance. Clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (Tablets: 10 mg of drug-x hydrochloride).	N/A	
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable	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 type terms include pharmacy bulk package and imaging bulk package.	N/A	

Section 11 (DESCRIPTION)

Information provided in original label submission:

(b) (4)



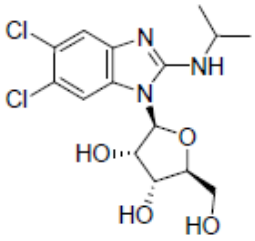
The molecular formula for LIVTENCITY is $C_{15}H_{19}Cl_2N_3O_4$ and its molecular weight is 376.(b) (4) Each 200 mg tablet for oral administration contains 200 mg maribavir and the following inactive ingredients: (b) (4)

(b) (4)

Section 11 with proposed OPQ edits:

(b) (4)

LIVTENCITY tablets contain maribavir, a benzimidazole riboside CMV pUL97 protein kinase inhibitor. The chemical name of maribavir is 5,6-Dichloro-*N*-(1-methylethyl)-1-β-L-ribofuranosyl-1*H*-benzimidazol-2-amine and the structural formula is:



The molecular formula for maribavir is $C_{15}H_{19}Cl_2N_3O_4$ and its molecular weight is 376.23.

Each 200 mg tablet for oral administration contains 200 mg maribavir and the following inactive ingredients: FD&C Blue #1, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polyvinyl alcohol, sodium starch glycolate, titanium dioxide, and talc.

QUALITY ASSESSMENT

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DESCRIPTION section		
Proprietary and established name(s)	Inadequate	Revise to include established name: LIVTENCITY tablets contain maribavir
Dosage form(s) and route(s) of administration	Adequate	
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per Salt Guidance and MAPP. For example: "TRADENAME contains 100 mg of drug-x (equivalent to 123.7 mg of drug-x hydrochloride)"	N/A	
List names of all inactive ingredients. Use USP/NF names in alphabetical order. Avoid brand names.	Inadequate	Comment to the applicant that inactive ingredients should be listed in alphabetical order
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.	N/A	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Sterility statement (if applicable)	N/A	
Pharmacological/Therapeutic class	Inadequate	Per Dr. Takashi Komatsu, Virology reviewer, the therapeutic class description should be revised to: LIVTENCITY tablets contain maribavir, a benzimidazole riboside CMV pUL97 protein kinase inhibitor

Chemical name, structural formula, molecular weight	Inadequate	After evaluating the USP dictionary file for maribavir, the following changes are recommended: • Revised chemical name to match USAN # (1): 5,6-Dichloro-*N*-(1-methylethyl)-1-β-L- ribofuranosyl-1*H*-benzimidazol-2-amine • Molecule weight = 376.23 "LIVENTICITY" is changed to the chemical name maribavir in this section when discussing the chemical properties. e.g. The molecular formula for ~~LIVTENCITY~~ maribavir is $C_{15}H_{19}Cl_2N_3O_4$
If radioactive, statement of important nuclear characteristics.	N/A	
Other important chemical or physical properties (such as pKa or pH)	N/A	

Section 11 (DESCRIPTION) Continued

Item	**Items in Proposed Labeling** (choose "Adequate", "Inadequate", or "N/A")	**Assessor's Comments** (If an item is Inadequate, provide more details on the issues, as appropriate)
For oral prescription drug products, include gluten statement (if applicable)	N/A	
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity")	Inadequate	Remove (b) (4) from the description (b) (4)
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling	N/A	

requirement is fulfilled. Note the labeling requirement may be applicable to another section of the PI (e.g., Section 2).		

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

Information provided in original label submission:

Tablet: 200 mg, blue, oval shaped convex tablet debossed with “SHP” on one side and “620” on the other side.

They are supplied as follows:

(b) (4)

Storage and Handling

Store at 20 to 25°C (68 to 77°F), (b) (4) 15 to 30°C (59 to 86°F) [see USP Controlled Room Temperature]

Section 16 with proposed OPQ edits:

Tablet: 200 mg, blue, oval shaped convex tablet debossed with “SHP” on one side and “620” on the other side. They are supplied as follows:

Bottles of 28 tablets with child-resistant caps (NDC 64764-800-28)

Bottles of 56 tablets with child-resistant caps (NDC 64764-800-56)

Storage and Handling

Store at 20 to 25°C (68 to 77°F), brief exposure to 15 to 30°C (59 to 86°F) permitted *[see USP Controlled Room Temperature].*

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	Adequate	
Strength(s) in metric system	Adequate	
Available units (e.g., bottles of 100 tablets)	Adequate	
Identification of dosage forms (e.g., shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable); Include NDC(s)	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.	N/A	
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.). For hazardous drugs, state "DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures.[x]" with x numerical citation to "OSHA Hazardous Drugs."	N/A	

Section 16 (HOW SUPPLIED/STORAGE AND HANDLING) (Continued)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Inadequate	Language revised slightly to match OPPQ's recommended storage statements: Store at 20°C to 25°C (68°F to 77°F); brief exposure to 15°C to 30°C (59°F to 86°F) permitted *[see USP Controlled Room Temperature]*
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	Inadequate	Revise to: Bottles of 28 tablets with child-resistant caps (NDC 64764-800-28) Bottles of 56 tablets with child-resistant caps (NDC 64764-800-56) Child-Resistant Packaging Statements in Drug Product Labeling (fda.gov)

1.2.5 Other Sections of Labeling

There may be other sections of labeling that contain product-quality related information. For example, there are specific required/recommended warnings for certain inactive ingredients [e.g., aspartame, aluminum in large and small volume parenterals, sulfites, FD&C Yellow Number 5 (tartrazine), and benzyl alcohol].

Please notify the prescription drug review division if the product contains any of these inactive ingredients.

Please include your comments about other sections of labeling if they contain product quality information.

1.2.6 Manufacturing Information After Section 17 (for drug products)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Manufacturing Information After Section 17		
Name and location of business (street address, city, state, and zip code) of the manufacturer, distributor, and/or packer	Adequate	

2.0 PATIENT LABELING

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

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Carton Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Established name[2]	Adequate	
Special preparation instructions (if applicable)	Inadequate	Pending IR (revised Section 2)
Storage and handling information (if applicable)	Adequate	
If the product contains a desiccant, ensure the desiccant has a warning (e.g., "Do not eat.") and the size and shape of the desiccant differs from the dosage form.	N/A	
Active ingredient(s) (if applicable)	Adequate	
Alphabetical listing of inactive ingredients (if applicable)	Inadequate	In Patient Information, inactive ingredient list should match Section 11 DESCRIPTION labeling.
Name and location of business (street address, city, state, and zip code) of manufacturer, distributor, and/or packer	Adequate	

Any deficiencies should be listed at the end in the "ITEMS FOR ADDITIONAL ASSESSMENT."

3.0 CONTAINER AND CARTON LABELING

3.1 Container Labels

(Copy/paste or refer to a representative example of a proposed container)

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

[2] Established name = [Drug] [Route of Administration] [Dosage Form]

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Carton Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Established name[3], (font size and prominence)	Adequate	
Strength(s) in metric system	Adequate	
Route(s) of administration	Adequate	
If the active ingredient is a salt, include the equivalency statement per Salt Guidance and MAPP.	N/A	
Net contents (e.g., tablet count, volume of liquid)	Adequate	
"Rx only" displayed on the principal display	Adequate	
NDC	Adequate	NDC number in carton and container labels match those listed in the Prescribing Information in Section 16.
Lot number and expiration date	Adequate	
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new beyond-use-date (BUD).	Adequate	
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, and these products require a "Not for direct infusion" statement.	N/A	

[3] Established name = [Drug] [Route of Administration] [Dosage Form]

For parenteral injectable dosage forms, include the name and quantities of all active and inactive ingredients in alphabetical order. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	N/A	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Linear Bar code	Adequate	

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Carton Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Name of manufacturer/distributor /packer	Adequate	
If there is a Medication Guide, must include a statement about dispensing a Medication Guide to each patient.	N/A	
No text on Ferrule and Cap overseal, unless a cautionary statement is required.	Adequate	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled.	N/A	
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	
And others, if space is available.	N/A	

Assessment of Carton and Container Labeling: ***Adequate***

Any deficiencies should be listed at the end in the "ITEMS FOR ADDITIONAL ASSESSMENT."

ITEMS FOR ADDITIONAL ASSESSMENT

Assess consistency of product-quality information in prescription drug labeling (PI, c/c labeling, and FDA-approved patient labeling). See

***Carton/Container Labeling Specific Resources* for a presentation about inappropriate inconsistencies of product quality information between labeling. If there are inappropriate inconsistencies between the labeling (e.g., established name, strength(s), package type term, discard statement, identifying characteristics, storage, reconstitution/dilution instructions), please list these as deficiencies in this section.**

Overall Assessment and Recommendation:

Changes have been communicated to OND for labeling negotiations with the applicant. An IR sent on July 26, 2021 regarding Section 2 is pending, and applicant has committed to submit the revised Section 2 by September 1.

Primary Labeling Assessor Name and Date: Molly Lee, Ph.D., Branch 2, ONDP Division of New Drug Products I, 8/19/2021

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

Thomas Oliver, Ph.D., ONDP Division of New Drug Products I, 8/19/2021

Molly Lee

Digitally signed by Molly Lee
Date: 8/19/2021 09:58:41PM
GUID: 5e2b04c70029e7c7580982b0a5cb16be

Thomas Oliver

Digitally signed by Thomas Oliver
Date: 8/20/2021 09:13:44AM
GUID: 508da71f00029ed4697700cee3d31ca0

CHAPTER VI: BIOPHARMACEUTICS

NDA Number/Type	215596; 505(b)(1); Priority Review; NME; Breakthrough Therapy Designation (12/15/17); Orphan Designation (6/7/2011)
Assessment Cycle	1
Drug Product	LIVTENCITY™ (maribavir) Tablet 200 mg
Dosage Form	Immediate Release Oral Tablet
Route of Administration	Oral (two 200 mg tablets twice daily with or without food)
Applicant	Takeda Pharmaceuticals USA, Inc.
OND Division	OND/OID/DAV
Associated INDs	IND 05001
Proposed Indication	Treatment of adults with post-transplant cytomegalovirus (CMV) infection and/or disease, including infections resistant and/or refractory to ganciclovir, valganciclovir, cidofovir or foscarnet.
Primary Reviewer	Qi Zhang, PhD
Secondary Reviewer	Elsbeth Chikhale, PhD
Assessment Recommendation	***Adequate***

Assessment Summary:

The Applicant, Takeda Pharmaceuticals, is seeking approval of NDA 215596 LIVTENCITY ™ (maribavir) Tablet for the treatment of adults with CMV infection. Maribavir (TAK-620) is a new molecular entity (NME) developed under IND 51001. On Jun 7, 2011, FDA granted Orphan Designation and on December 15, 2017, FDA granted Breakthrough Therapy designation for maribavir for the treatment of CMV infection. The mechanism of action of maribavir against human CMV may involve the inhibition of the UL97 protein kinase.

The maribavir drug substance is a weak base, BCS Class 2 like drug. The proposed to-be-marketed drug product is an immediate release tablet dosage form in a single strength of 200 mg for oral administration. The recommended dose is 400 mg twice daily. The labeling states that the product can be taken as a whole tablet, (b) (4) (refer to the Drug Product Review and OCP Review for further information). The clinical program in support of this NDA includes a pivotal phase 3 trial (Study SHP620-303) and two supportive phase 2 trials (Studies SHP620-202 and SHP620-203).

The Biopharmaceutics review is focused on (i) bridging throughout product development, (ii) evaluation of the adequacy of the proposed dissolution method and acceptance criterion, and (iii) risk assessment.

- *Bridging Throughout Product Development*

A total of five solid oral IR formulations of maribavir (capsule, and (b) (4) tablets I, II, III, and IV) were developed during product development. The tablet formulations were used in most clinical studies. PK bridging between the capsule and Tablet I, and among Tablet II, Tablet III, and Tablet IV has been established based on across-study BA/BE comparisons. Refer to the OCP and OND Reviews for the supporting PK, efficacy, and safety data.

The proposed commercial maribavir tablets 200 mg are identical in size, shape, and formulation composition to the pivotal phase 3 tablets 200 mg (Tablet IV) however, unlike the pivotal phase 3 tablets, the proposed commercial tablets contain debossing. In addition, the proposed commercial tablets have a different, product manufacturing site and (b) (4) compared to the pivotal phase 3 tablets. All the clinical batches were manufactured at (b) (4). However, the (b) (4) facility was used for manufacturing of the registration stability batches and is the proposed manufacturing site of the commercial drug product. The clinical and the primary stability registration batches were manufactured by (b) (4), whereas the proposed commercial drug product will be manufactured by (b) (4) (b) (4). In the pre-NDA meeting, the change from (b) (4) for the commercial batches was considered likely low risk. Bridging between the clinical and commercial drug products is deemed adequate based on the dissolution profiles comparisons in the proposed QC dissolution medium (0.1 N HCl pH 1.2) and two other media (i.e., pH 4.5 and pH 6.8 buffers), between the pivotal phase 3 and three primary stability batches, and one supportive stability batch using the new 3-step process.

- *Dissolution Method and Acceptance Criterion*

The Applicant's proposed QC dissolution method was previously agreed upon by the Agency under IND 051001. The Applicant's proposed dissolution acceptance criterion in the original NDA was found to be permissive. The Applicant has revised the acceptance criterion to Q= (b) (4)% at 30 minutes as per the FDA's recommendation. Overall, the following dissolution method and acceptance criterion are found acceptable for batch release and stability testing, based on the totality of the information and data provided:

Dissolution Method and Acceptance Criterion for LIVTENCITY™ (maribavir) Tablet 200 mg

Apparatus	Speed	Medium	Volume/Temp	Acceptance Criterion
USP Apparatus 2 (Paddle)	*50 rpm*	*0.1 N HCl*	*900 mL/37°C*	*Q= (b) (4)% in 30 minutes*

- *Biopharmaceutics Risk Assessment*

CQAs	Initial Risk Ranking	Comments	Updated Risk Ranking After Assessment Cycle #	Comments
Dissolution	Medium	BCS Class 2 like drug; exhibit pH dependent and low solubility at higher pH > 4; (b) (4) Tmax (1 to 3 h) is not critical. No clinically significant effects of food or antacid on maribavir.	Low	The risk is mitigated with the implementation of the dissolution method and acceptance criterion of Q=(b) (4)% at 30 minutes. In addition, (b) (4) drug substance and drug product controls [e.g., PSD and (b) (4) manufacturing control (tablet hardness)] are important and relevant for the proposed drug product.

List Submissions Being Assessed:

Document(s) Assessed	Date Received
Original Submission	03/23/2021
Response to Information Request	07/15/2021
Response to Information Request	08/03/2021

Concise Description of Outstanding Issues (List bullet points with key information and update as needed):

None.

Recommendation:

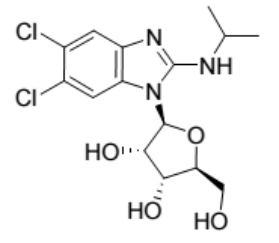
From a Biopharmaceutics perspective, NDA 215596 for LIVTENCITY™ (maribavir) Tablet 200 mg is recommended for APPROVAL.

B.1 BCS DESIGNATION

Assessment: *A BCS designation is not requested nor required*

The maribavir drug substance (**Figure 1**) is crystalline ((b) (4)) and non-hygroscopic. It is an ionizable weak base with a logP being 2.86 at pH 7.4 and pKa being 5.2. The Applicant claimed that the maribavir drug substance is a BCS Class 2 drug because maribavir exhibits low and pH dependent solubility, and high permeability based on a Caco-2 cell permeability study and a human mass balance study.

Figure 1. Chemical Structure of Maribavir Drug Substance



Molecular Formula: C15H19Cl2N3O4
Molecular Weight: 376.24 g/mol

- *Solubility*

The solubility of maribavir in USP buffer 50 mM phosphate buffer at pH 1.2, 2, and 3, and in 1 mM citrate buffer for pH range of 2.9 to 7.4, as well as in FaSSIF and FeSSIF, is shown in **Table 1**.

Table 1. Aqueous Solubility of Maribavir at 37°C

Medium	Sample pH	Solubility (mg/mL)
50 mM phosphate buffer	1.2	>160
50 mM phosphate buffer	2.0	>160
50 mM phosphate buffer	3.0	47.7

Medium	Temperature	Sample pH	Solubility (mg/mL)
1 M citrate buffer, I=0.25 M	Ambient	2.9	35.7
1 M citrate buffer, I=0.25 M	Ambient	3.9	2.14
1 M citrate buffer, I=0.25 M	Ambient	4.9	0.57
1 M citrate buffer, I=0.25 M	Ambient	7.4	0.78
Water	Ambient	N/A	0.82
Fasted state simulated intestinal fluid	37°C	6.6	0.80
Fed-state simulated intestinal fluid	37°C	5.1	1.49

Source: Module 2, Section 2.7.1 and Module 3, Section 3.2.P.2.2.4

The solubility data are consistent with the indicated BCS class (II) of the drug substance as the solubility dramatically increases below pH 3 and the solubility ranging from 0.57-1.49 mg/mL at pH >3.9 is lower than the minimal required

solubility for being classified as a highly soluble drug substance per BCS criteria, i.e., 1.6 mg/mL for the single dose of 400 mg in 250 mL aqueous media.
However, the solubility is sufficient to provide sink conditions for the proposed 200 mg strength tablet in the proposed dissolution medium (0.1 N HCl) as the solubility is high at lower pH.

- *Permeability*

The data provided indicate that maribavir has medium to high permeability. Using an in vitro permeability experiment with Caco-2 cells (Study V9053M-SHP620), the apical to basolateral (A-B) apparent permeability coefficient (Papp) was measured as 5.6×10^{-6} cm/sec at maribavir concentration of 10 µM.

In a human mass balance study (Study 1263-106), in which 400 mg [^{14}C]-maribavir was dosed orally as a solution (administered via nasogastric tube), total recovery of radioactivity was approximately 75%, with 61% of dose recovered in urine and 14% in feces. Unchanged maribavir only constituted 1.8% and 5.6% of the dose in urine and feces, respectively. The median Tmax of maribavir following an oral solution in this study was 1.5 h, consistent with Tmax observed from other clinical studies where a single dose of maribavir 400 mg was administered as a capsule, Tablet I, Tablet II, Tablet III, or Tablet IV formulations (1 to 3 h). An absolute bioavailability study was not conducted due to the unavailability of a formulation for intravenous administration.

B.2 PRODUCT BRIDGING

Assessment: *Adequate*

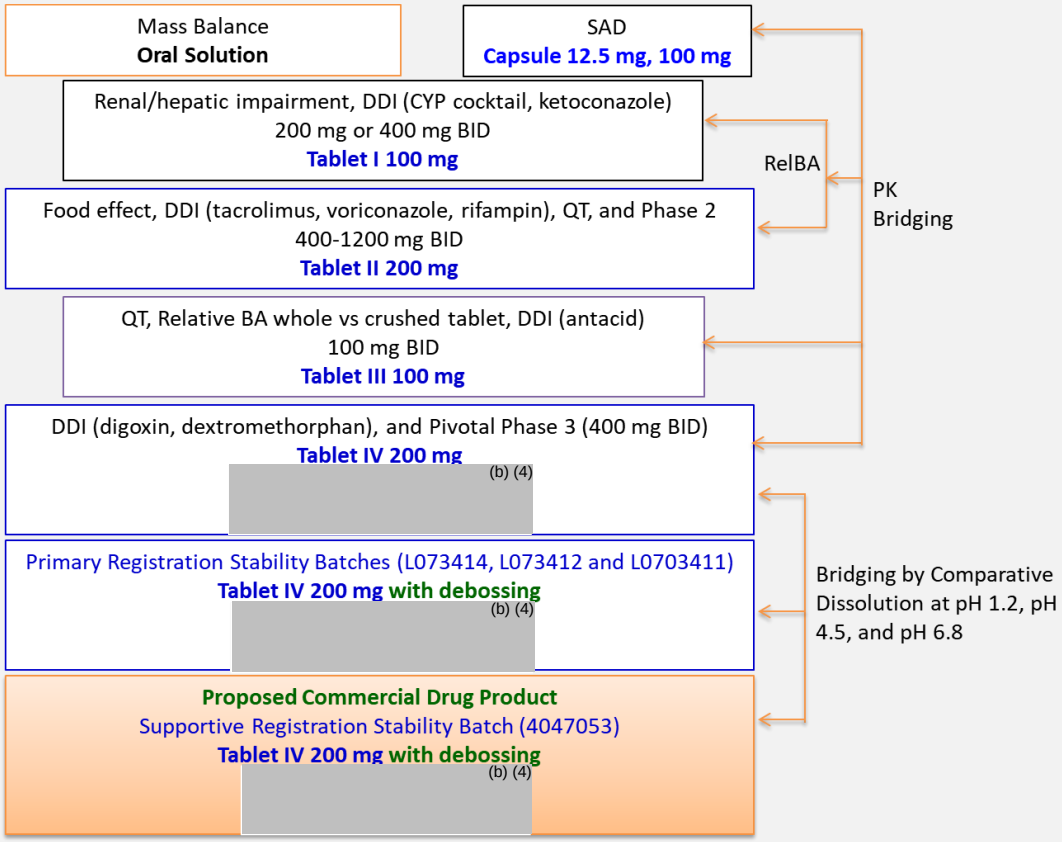
The proposed maribavir 200 mg tablet is a debossed, unscored, blue (b) (4) tablet containing 200 mg maribavir and the following inactive ingredients: microcrystalline cellulose (b) (4), sodium starch glycolate (b) (4), magnesium stearate (b) (4), (b) (4). The manufacturing process for the proposed commercial maribavir tablet will utilize a (b) (4) .

- Bridging Throughout Drug Product Development

The product bridging among the formulations used during drug product development is illustrated in **Figure 2**. A total of five solid oral IR formulations of maribavir (capsule, and tablets I, II, III, and IV) were developed during product development.

The initial capsule formulation was manufactured with (b) (4) (b) (4) whereas all the tablet formulations contain (b) (4) (b) (4). The proposed Tablet IV formulation differs from Tablet I, II and III formulations in the (b) (4) (b) (4) (b) (4) and composition. The proposed Tablet IV formulation also differs from Tablet I and III in the tablet strength (**Table 2**).

Figure 2. Schematic Diagram of Oral Formulations Used in Clinical Development and Formulation Bridging



Source: Plotted by Reviewer based on Applicant submitted clinical development information in Module 2. Section 2.7.1.

Table 2. Composition of Maribavir Tablet Formulations

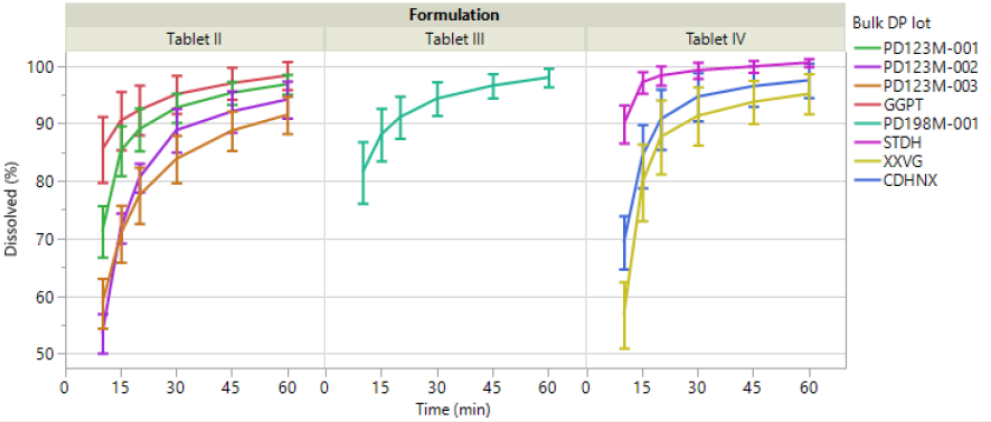
		Formulation and Dosage Strength			
		Tablet I	Tablet II	Tablet III	Tablet IV
Component	Function	100 mg	200 mg	100 mg	200 mg
Maribavir (b) (4)	Active ingredient (mg)	(b) (4)			

Source: Module 3, Section 3.2.P.2.2.1

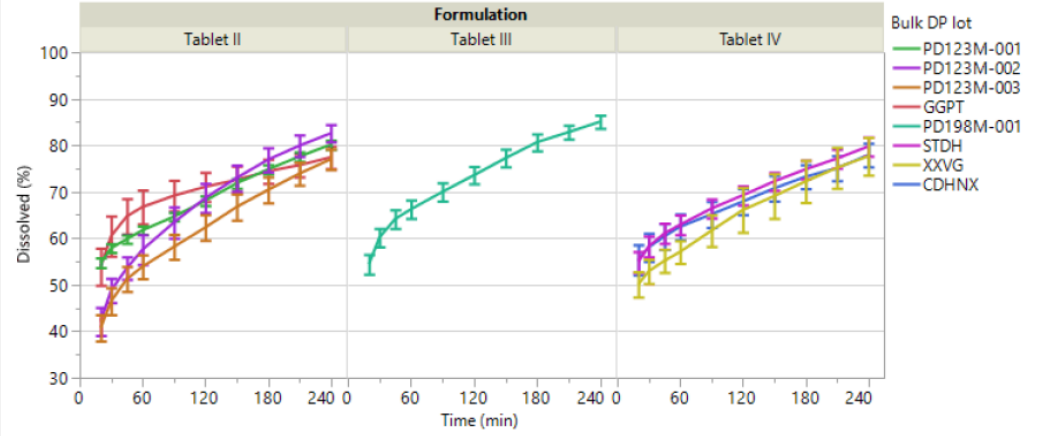
A dedicated BA study was conducted between Tablet I and Tablet II. Tablet II (200 mg) were used in the phase 2 studies (SHP620-202 and SHP620-203), and Tablet IV (200 mg) was used in the pivotal phase 3 study (400 mg BID; SHP620-303). PK bridging between the capsule and Tablet I, and among Tablet II, Tablet III, and Tablet IV has been established based on across-study BA/BE comparisons. Refer to the OCP and OND Reviews for the supporting PK, efficacy, and safety data. It is acknowledged that the Applicant provided comparative in vitro dissolution profile data to support bridging among Tablet II, Tablet III, and Tablet IV (**Figure 3**). Tablets II, III, and IV exhibited rapid and similar dissolution in 0.1 N hydrochloric acid (using the QC dissolution method), however, cases of not similar dissolution were observed between Tablets II and IV in pH 6.8 medium and between Tablets III and IV in pH 4.5 and 6.8 media based on the multivariate statistical distance test (**Table 3**). However, the differences observed in dissolution at pH 4.5 and 6.8 did not translate into clinically meaningful differences in drug exposure, as the provided PK data support comparability among the tablet formulations (**Table 4**).

Figure 3. Dissolution Comparison of Tablet II, III, and IV using the proposed dissolution parameters in different pH Dissolution Media

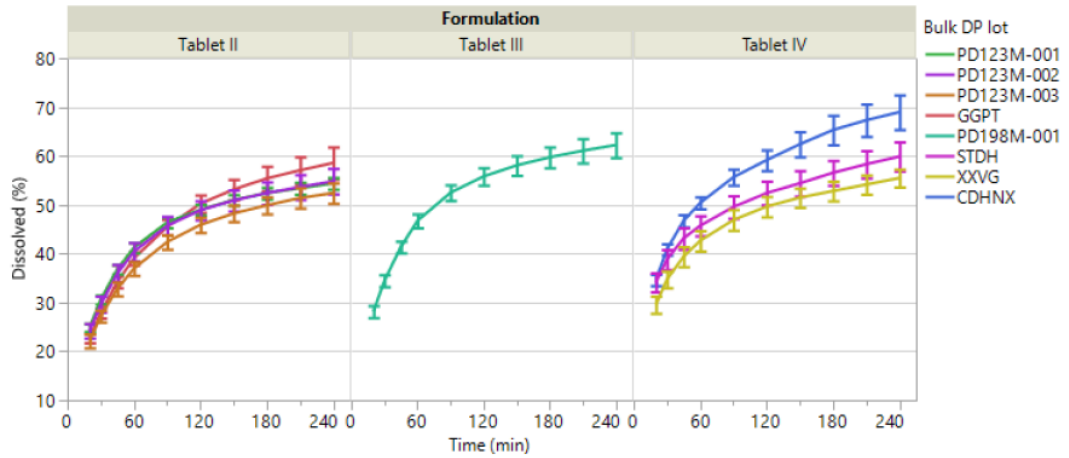
a. 0.1 N HCL



b. 50 mM Acetate Buffer pH 4.5



c. 50 mM Phosphate Buffer pH 6.8



USP Apparatus 2 with 50 RPM paddle speed in 900 mL of media at 37℃
Source: Module 3, Section 3.2.P.2.2.3

Table 3. Multivariate Statistical Distance Test for Dissolution of Tablet II-IV

Reference	Test	Medium	Mahalanobis Distance	Similarity Limit	p-value	Result
Tablet II	Tablet III	0.1 N HCl	1.6	6.4	9.1×10^{-6}	Equivalent
		pH 4.5	8.9	22	9.1×10^{-7}	Equivalent
		pH 6.8	9.9	32	4.3×10^{-11}	Equivalent
	Tablet IV	0.1 N HCl	1.3	7.2	4.6×10^{-12}	Equivalent
		pH 4.5	4.6	12	5.8×10^{-8}	Equivalent
		pH 6.8	26	18	0.87	Not equivalent
Tablet III	Tablet IV	0.1 N HCl	2.0	17	7.3×10^{-16}	Equivalent
		pH 4.5	23	11	0.90	Not equivalent
		pH 6.8	29	14	0.92	Not equivalent

Source: Module 3, Section 3.2.P.2.2.3

Source: Module 3, Section 3.2.P.2.2.3

Table 4. Descriptive Statistics for Pharmacokinetic Parameters of Maribavir Following Single Oral Doses of Maribavir Tablet II, Tablet III, or Tablet IV

Formulation Strength	Dose (mg)	N	T_{max}[a] (h)	C_{max}[b] (µg/mL)	DN[c] C_{max}[b] (µg/mL)	$AUC_{0-\infty}$[b] (µg*h/mL)	DN[c] $AUC_{0-\infty}$[b] (µg*h/mL)	$T_{1/2}$[b] (h)	CL/F[b] (L/h)	Vz/F[b] (L)
Tablet II 200 mg[d]	400	29	1.5 (1.0, 4.0)	16.7 (32.2)	16.7 (32.2)	106.1 (39.6)	106.1 (39.6)	5.04 (28.1)	4.30 (34.1)	29.3 (25.7)
Tablet III 100 mg[e]	100	15	1.0 (0.5, 2.0)	5.83 (33.1)	23.3 (33.0)	26.0 (41.0)	104.0 (41.0)	3.86 (35.0)	4.36 (34.6)	22.6 (29.0)
Tablet IV 200 mg[f]	200	18	1.0 (0.5, 2.0)	11.2 (31.4)	22.4 (31.4)	58.6 (52.1)	117.1 (52.1)	4.27 (44.2)	4.21 (47.3)	NC

$AUC_{0-\infty}$=area under the plasma concentration-versus-time curve from time 0 to infinity; CL/F=oral clearance; C_{max}=maximum measured plasma concentration; DN=dose normalized; NC=not calculated; $T_{1/2}$=terminal half-life; T_{max}=time to C_{max}; Vz/F=oral terminal-phase distribution volume
[a] Median (minimum, maximum).
[b] Arithmetic mean (%CV).
[c] Dose normalized to maribavir 400 mg.
[d] Study 1263-104, Treatment B, drug product lot PD123M-001.
[e] Study 1263-109, Treatment B, drug product lot PD198M-001.
[f] Study TAK-620-1019, Treatment A, drug product lot XXVG.
Source: Study 1263-104 CSR, Table 10.2.3.2; Study 1263-109 CSR, Table 10.2.5.2; Study TAK-620-1019 CSR, Table 14.2.5.2.1; and Appendix Table A13

The proposed to be marketed formulation of maribavir is Tablet IV (200 mg), with the addition of debossing and changes in [redacted](b) (4) and a change in the drug product manufacturing site. All clinical batches were manufactured at [redacted](b) (4) The [redacted](b) (4) facility was used for

manufacturing the registration stability batches and is the proposed manufacturing site of the commercial drug product. The clinical and primary stability batches were manufactured by (b) (4), whereas the proposed commercial drug product will be manufactured by (b) (4).

Comparison of clinical and commercial batches was discussed in a recent CMC dedicated pre-NDA meeting held on February 4, 2021. The Applicant described that the NDA would include three primary stability batches (L073414, L073412 and L0703411) manufactured with the (b) (4) and one additional stability batch (4047053) manufactured with the (b) (4). The Applicant also described that the (b) (4) was revised to a (b) (4) to improve process robustness (b) (4) and to reduce intra-batch variation. Per the meeting discussion, the change from (b) (4) for the commercial batches was considered likely to be low risk and the Agency agreed that the bridge between the clinical and commercial maribavir tablets can be established based on the dissolution profiles comparisons in the three different pH dissolution media, as summarized below. The Agency also requested that a detailed comparison of all equipment, and in-process parameters and test results (e.g. (b) (4), particle size distribution, etc.) for all drug product batches manufactured at both sites (b) (4) be included in the NDA. Refer to CMC reviews for further information.

Bridging Between Clinical and Commercial Tablets Via Dissolution Comparison

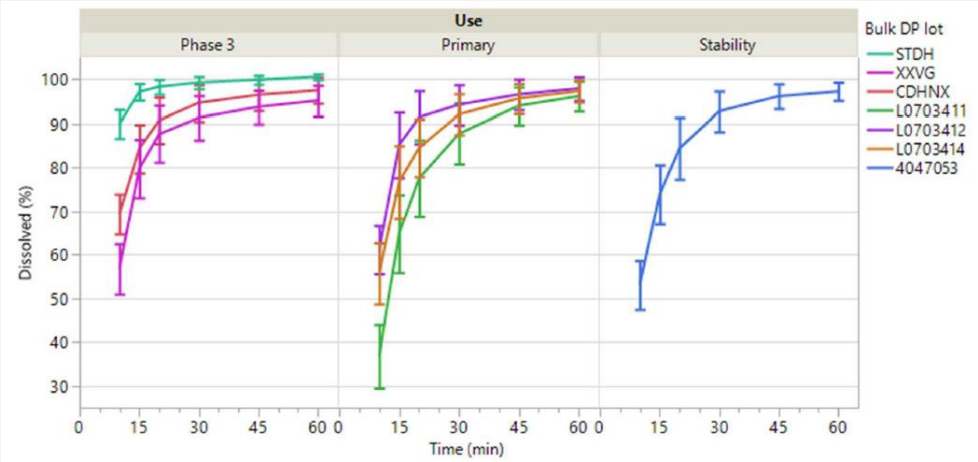
The comparative dissolution profiles among the pivotal phase 3 batches, the three primary stability batches, and the additional supportive registration stability batch in the proposed QC dissolution media of 0.1 N HCl (pH 1.2), and two other media (pH 4.5 acetate buffer and pH 6.8 phosphate buffer) are presented in **Figure 4**. Due to the observed high variability, the dissolution profile comparisons were based on two similarity analyses: 1) multivariate confidence region procedure; 2) similarity factor f2 analyses using bootstrap method.

- Multivariate statistical distance analyses were performed using a reference made up of composite dissolution data from the three Phase 3 clinical batches, lots STDH, XXVG, and CDHNX (**Table 5**). The pooled data set was used to account for the inter-batch variability observed in the Phase 3 batches.

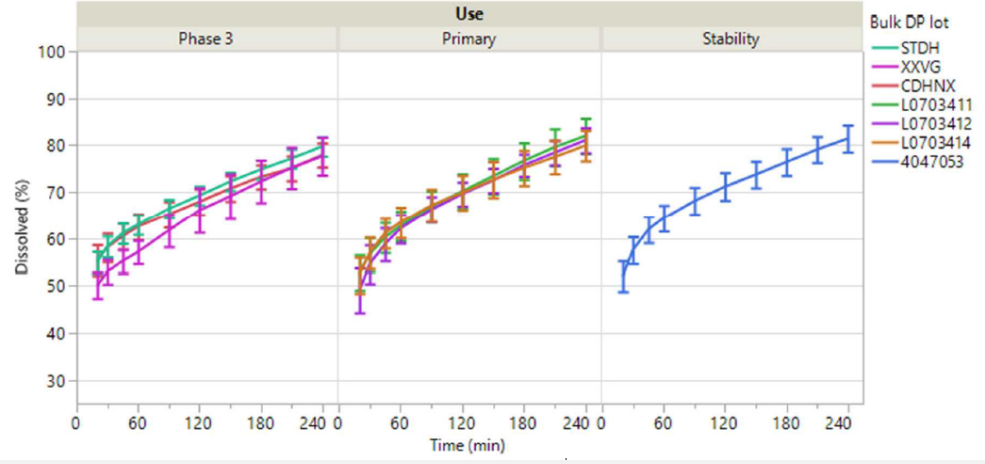
- Similarity factor (f2) analyses with bootstrap method were used to perform pairwise comparisons of clinical and stability batches (**Table 6**). Phase 3 clinical batch XXVG was used as the reference batch for comparative analysis, based on the availability of corresponding pharmacokinetic data, as indicated by the Applicant. In addition, it is noted that clinical batch XXVG represents a worst-case scenario for dissolution similarity testing due to the slowest dissolution among the clinical batches for this IR dosage form. Results showed that one primary batch L0703411 was not similar to XXVG at pH 1.2 (0.1 N HCl) but average dissolution was >85% at 30 minutes for L0703411, therefore, it's acceptable.

Figure 4. Dissolution Comparison of Pivotal Phase 3, Primary Stability, and Supportive Stability Batches in Different pH Dissolution Media

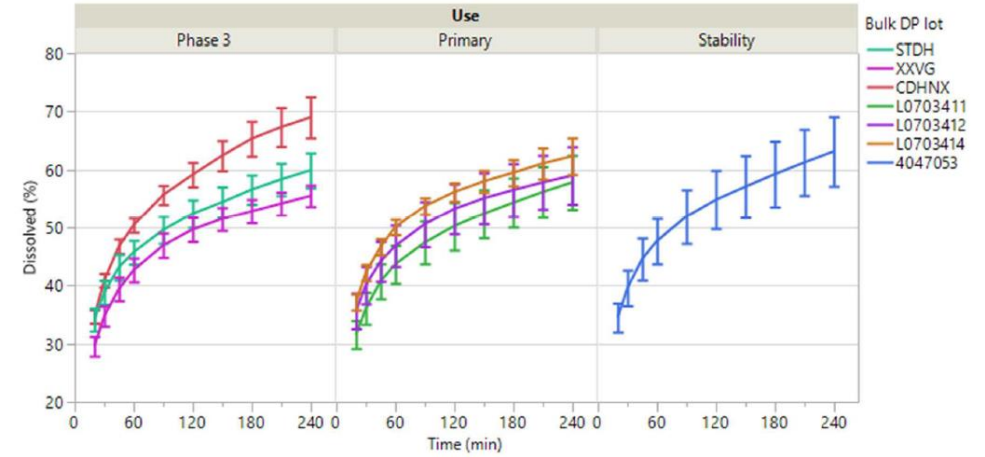
a. 0.1 N HCl



b. 50 mM Acetate Buffer pH 4.5



c. 50 mM Phosphate Buffer pH 6.8



USP Apparatus 2 with 50 RPM paddle speed in 900 mL of media at 37℃
Source: Module 3, Section 3.2.P.2.3.4

Table 5. Multivariate Statistical Distance Similarity Test* of Pivotal Clinical, Primary Stability, and Supportive Stability Batches

Reference	Test	Medium	Mahalanobis Distance	Similarity Limit	p-Value	Result
Composite of: STDH XXVG CDHNX	Composite of: L0703411 L0703412 L0703414	0.1 N HCl	3.4	14	1.3×10^{-12}	Equivalent
		pH 4.5	3.1	7.3	1.6×10^{-5}	Equivalent
		pH 6.8	2.6	7.9	9.0×10^{-8}	Equivalent
	L0703411	0.1 N HCl	11	12	0.17	Not equivalent
		pH 4.5	3.4	7.2	5.0×10^{-4}	Equivalent
		pH 6.8	2.2	11	7.4×10^{-10}	Equivalent
	L0703412	0.1 N HCl	2.3	18	5.2×10^{-15}	Equivalent
		pH 4.5	7.4	9.3	3.6×10^{-2}	Equivalent
		pH 6.8	5.6	11	5.1×10^{-4}	Equivalent
	L0703414	0.1 N HCl	5.8	19	1.3×10^{-7}	Equivalent
		pH 4.5	4.7	9.5	5.3×10^{-4}	Equivalent
		pH 6.8	6.3	13	1.5×10^{-4}	Equivalent
	4047053	0.1 N HCl	1.4	24	1.2×10^{-28}	Equivalent
		pH 4.5	1.3	8.5	8.0×10^{-10}	Equivalent
		pH 6.8	1.5	9.3	3.7×10^{-10}	Equivalent
Composite of: L0703411 L0703412 L0703414	4047053	0.1 N HCl	3.0	15	8.6×10^{-10}	Equivalent
		pH 4.5	5.4	9.4	2.3×10^{-3}	Equivalent
		pH 6.8	0.8	12	1.4×10^{-16}	Equivalent

*A p-value of less than 0.05 indicated that the comparison groups are equivalent. The analyses were performed using the software package R (version 3.8; T2EQ: Function for applying the T^2-test for equivalence). Source: Module 3, Section 3.2.P.2.3.4

Table 6. Similarity Factor Analysis* of Pivotal Clinical, Primary Stability, and Supportive Stability Batches

Reference	Test	Medium	5th Percentile of Bootstrapped f_2	Result
XXVG	L0703411	0.1 N HCl	42	Not similar
		pH 4.5	61	Similar
		pH 6.8	74	Similar
	L0703412	0.1 N HCl	57	Similar
		pH 4.5	65	Similar
		pH 6.8	62	Similar
	L0703414	0.1 N HCl	61	Similar
		pH 4.5	62	Similar
		pH 6.8	55	Similar
	4047053	0.1 N HCl	58	Similar
		pH 4.5	60	Similar
		pH 6.8	56	Similar

*Values of greater than 50 for the 5th percentile of the bootstrapped f2 indicated that the comparison groups have similar dissolution profiles. Source: Module 3, Section 3.2.P.2.3.4

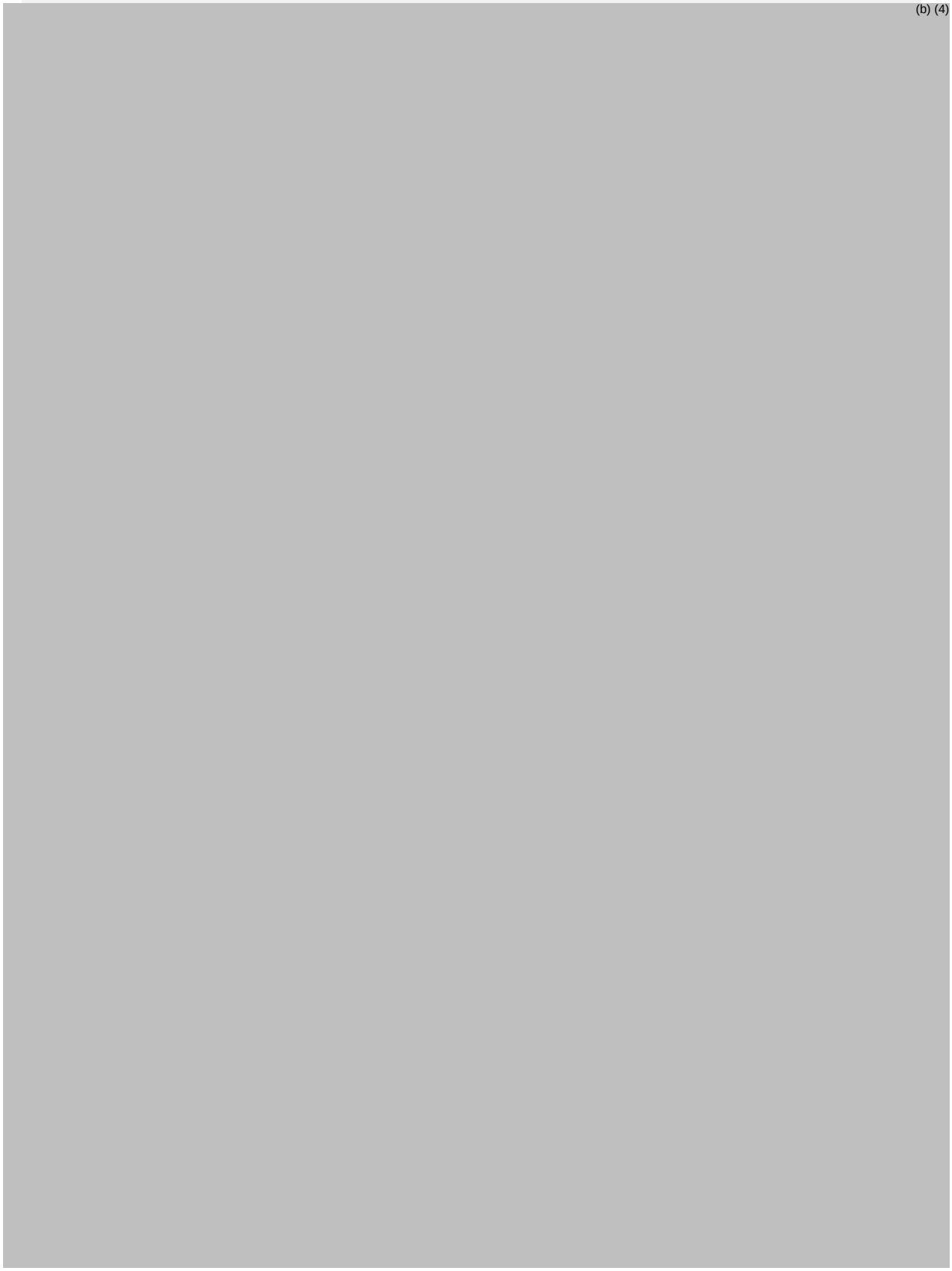
Overall, the results of the comparative dissolution testing show that the proposed changes in drug product manufacturing site and process did not significantly alter the dissolution rates for the proposed commercial drug product, thereby ensuring similar in-vivo performance of the proposed drug product. From a Biopharmaceutics perspective, bridging between the the clinical and commercial products is established, based on the dissolution profiles comparisons for the pivotal phase 3 batches manufactured at (b) (4), 3 primary stability and 1 supportive stability batches manufactured at (b) (4), in the three different pH dissolution media.

B.3 DISSOLUTION METHOD AND ACCEPTANCE CRITERION

Assessment: Adequate

- Dissolution Method Development

(b) (4)



Discriminating Ability of Dissolution Method with Respect to Tablet Hardness

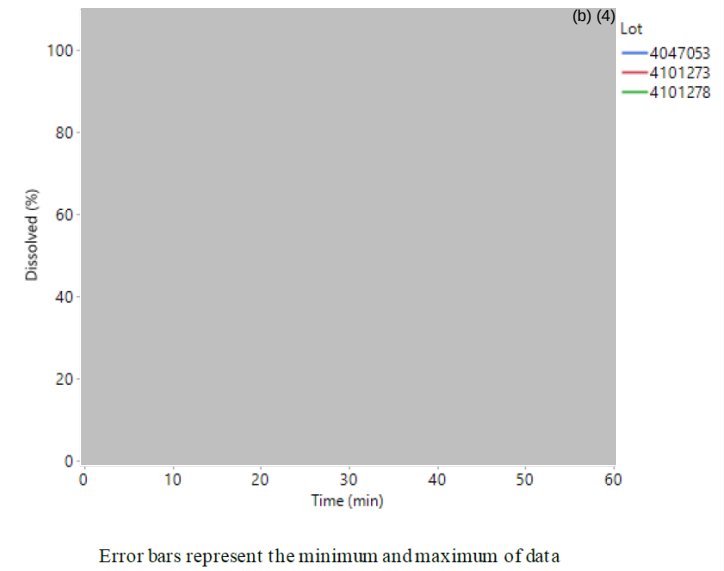
The dissolution method was shown to discriminate dissolution rates due to changes in tablet hardness. Tablet hardness exceeding (b) (4) kP (target range is (b) (4) kP) results in significant decrease in dissolution (refer to the Process Review for further information).

The Applicant presented two rejected registration stability lots 4101273 and 4101278 due to a deviation associated with the tablet hardness tester (b) (4) The incident was initially detected by dissolution testing results as part of the batch release testing. The results showed that lots 4101273 and 4101278 exhibited significantly slower dissolution profiles with mean values of 75% and 76%, respectively at 30 minutes. In contrast, the accepted lot 4047053 manufactured with target hardness exhibited a mean dissolution of 98% at 30 minutes (Figure 5).

Impact of Drug Substance Particle Size on Dissolution

The proposed QC dissolution method using 1 N HCl pH 1.2 0 has not been shown to be capable of detecting changes in drug substance particle size between (b) (4) drug substances (Table 8, also refer to Figure 3a and Table 3; Tablet II vs IV). However, the drug product with a lower d10 particle size (d10 (b) (4) µm, (b) (4) drug substance) resulted in a significantly reduced dissolution at 30 minutes. Therefore, the proposed dissolution method has some discriminating ability towards drug substance PSD. The proposed drug substance PSD: d(0.1): NLT (b) (4) µm; d(0.5): (b) (4) µm; d(0.9): NMT (b) (4) µm. Defer to the CMC for the adequacy of the control of drug substance particle size.

Figure 5. Dissolution Comparison of 200 mg Maribavir Tablet Manufactured at Target Hardness versus Higher Hardness



Supportive Registration Stability Batch 4047053 with tablet hardness (b) (4) kP (target)
Rejected Batches 4101273, and 4101278 with tablet hardness exceeding (b) (4) kP
USP Apparatus 2 with 50 RPM paddle speed in 900 mL of 0.1 N HCl at 37°C
Source: Module 3, Section 3.2.P.2.3.4

Table 8. Effect of Maribavir Particle Size on (b) (4) Tablet Breaking Force and Dissolution

Drug substance				Drug product		
Type	d_{10} (µm)	d_{50} (µm)	d_{90} (µm)	Formulation	(b) (4)	Dissolved at 30 min (%)
(b) (4)				Tablet II		96
				Tablet IV		75
				Tablet IV		98
				Tablet IV		96
				Tablet IV		96

USP Apparatus 2 with 50 RPM paddle speed in 900 mL of 0.1 N HCl at 37°C
Source: Module 3, Section 3.2.P.2.1.

Validation of Dissolution Method

An HPLC assay method is used to quantify the drug in the dissolution samples. The Applicant reported that the HPLC method was validated with regard to system suitability, linearity, specificity, accuracy, repeatability (mean result at 30 minutes 90.9% and a % RSD of 6.3%), precision (mean result at 30 minutes 94.7% and a % RSD of 5.9%), filter compatibility, solution stability, and robustness with respect to HPLC system changes and dissolution method parameter by varying the normality of the dissolution media from the target value of 0.10 N HCl [0.09 N HCl: mean result at 30 minutes 98.9% and a % RSD of 4.0%; 0.11 N HCl: mean result at 30 minutes 93.8% and a % RSD of 5.2%].

Refer to the Drug Product Review, for the evaluation of the adequacy of the analytical method validation (HPLC method used for dissolution testing).

- Dissolution Acceptance Criterion

A dissolution acceptance criterion of Q= (b) (4)% at 30 minutes is proposed by the Applicant based on the multi-point dissolution profiles from batch release (Table 9) and long-term stability data (refer to Module 3, Section 3.2.P.8.3) for the clinical and registration stability batches, including

i) batch release and long-term stability data up to 36 months data for four batches used in the phase 2 studies (SHP620-202 and SHP620-203 using Tablet II) manufactured at the clinical site, (b) (4).
ii) batch release data for three batches used in the phase 3 study (SHP620-303 studies using Tablet IV) and long-term stability data up to 36 months data for one phase 3 batch (STDH) manufactured at (b) (4).
iii) batch release and long-term stability data up to 18 months for three primary stability batches (L073414, L073412 and L0703411) manufactured at the commercial site, (b) (4).
iv) batch release and long-term stability data up to 9 months for the supportive stability batch (4047053) and two rejected lots 4101273 and 4101278 at batch release manufactured at (b) (4).

Table 9. Summary of Dissolution Data at Batch Release for Clinical and Registration Batches

Use	Bulk drug product lot	N	Dissolution (%)								
			15 min			30 min			45 min		
			Mean	Min	RSD	Mean	Min	RSD	Mean	Min	RSD
Phase 2	PD123M-001	12	85	(b) (4)	8	93	(b) (4)	4	95	(b) (4)	3
	PD123M-002	12	72		6	89		7	92		6
	PD123M-003	12	71		11	84		8	89		6
	GGPT	12	91		9	95		5	97		5
Phase 3	STDH	12	97		3	99		2	100		2
	XXVG	12	80		13	91		9	94		6
	CDHNX	12	84		10	95		7	96		6

Use	Bulk drug product lot	N	Dissolution at 30 min (%)		Q=(b)(4)%, S_2 required?	Q=(b)(4)%, S_2 required?
			Mean	Min		
Phase 2	PD123M-001[a]	12	94	(b) (4)	(b) (4)	Yes
	PD123M-002	6	83			Yes
	PD123M-003	6	89			Yes
	GGPT	6	96			No
Phase 3	STDH	6	99			No
	XXVG	6	96			No
	CDHNX	6	96			No
Primary	L0703411	6	96			Yes
	L0703412	6	95			No
	L0703414	6	87			Yes
Supportive	4047053	6	98			No
	4101273[b]	6	75			Yes
	4101278[b]	6	76			Yes

S_2: Stage 2

[a] Batch release testing was performed using dissolution medium of 0.01 N hydrochloric acid; data from initial stability time point in 0.1 N hydrochloric acid is shown.

[b] Batches were rejected due to a deviation associated with the tablet hardness tester. Due to rejection, lots were not placed on stability.

USP Apparatus 2 with 50 RPM paddle speed in 900 mL of 0.1 N HCl at 37℃
Source: Module 3, Section 3.2.P.5.6.

Based on the submitted dissolution data, the Applicant's proposed Q value of (b) (4)% at 30 minutes is permissive and not acceptable. This Reviewer recommended a dissolution acceptance criterion of Q=(b)(4)% at 30 minutes (IR dated 07/01/2021). On 7/15/2021, the Applicant proposes to maintain Q=(b)(4)% at 30 minutes because

1 (b) (4)

2

The Applicant's response is not acceptable, and the following IR comments were conveyed to the Applicant on 7/25/2021:

"After reviewing your response dated 7/15/2021 to the FDA's recommendation of "Q=(b)(4)% at 30 minutes" and the overall information and data submitted, we have determined that your proposed dissolution acceptance criterion of NLT (b)(4)% (Q) at 30 minutes is not justified for the following reasons:

- *The provided dissolution data for the three phase 3 clinical batches and one supportive registration stability batch (4047053) (representative of the proposed commercial product) at batch release, showed the dissolution achieved 91-99% and can pass Stage 1 testing using the recommended dissolution acceptance criteria of "NLT (b)(4)% (Q) in 30 minutes". As for the four phase 2 batches and the three primary stability batches, the mean dissolution values were more than 85% (except one batch PD123M-002 having 83% dissolution), and all the batches can pass the dissolution test in Stage 1 or Stage 2 with the recommended dissolution acceptance criteria of "NLT (b)(4)% (Q) in 30 minutes".*
- *The discriminating power of the dissolution method toward product critical attributes (e.g., tablet hardness) could be lost if Q of (b)(4)% is set at 30 minutes. The two rejected registration lots 4101273 and 4101278 with incorrect hardness would fail the dissolution test with the recommended Q=(b)(4)% at 30 minutes, however; they would pass the proposed Q=(b)(4)% at 30 minutes in Stage 2 testing.*
- *The acceptance criterion should be primarily set based on, and reflective of, the data from the pivotal clinical batches, as well as the ability to reject drug product batches with unacceptable quality attributes and/or in vivo performance. The stability data are considered supportive, as these data are expected to comply with the proposed acceptance criterion throughout the proposed shelf-life, which ensures the drug product quality and clinical performance. If the dissolution characteristics of the drug product change with time during its shelf-life, or high variability is observed in dissolution, the source of the change/variability must be identified and resolved.*

Therefore, the recommendation to set the acceptance criterion of "NLT (b)(4)% (Q) in 30 minutes" for the proposed maribavir tablet 200 mg remains. Update the drug product specifications and other sections of the NDA accordingly.

Alternatively, you could consider submitting in vivo PK data, if available, or PBPK and PBBM modeling demonstrating that the batches (e.g., two rejected lots 4101273 and 4101278) representing the dissolution profile of your proposed dissolution acceptance criterion have equivalent exposure compared to the pivotal clinical batch."

In an amendment (Seq. 0009 dated 08/03/2020), the Applicant acknowledged the FDA's feedback and recommendation, and revised the dissolution acceptance criteria to "NLT (b)(4)% (Q) at 30 minutes" based on the analysis of data from the pivotal clinical batches and the ability to reject drug product batches with unacceptable quality attributes. The Applicant updated Section 3.2.P.5.1 to include the new proposed specification, and Section 3.2.P.5.6 to reflect the

justification for the acceptance criterion of Q= (b) (4)% at 30 minutes. The Applicant's response is adequate.

Qi Zhang

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Elsbeth Chikhale

Digitally signed by Elsbeth Chikhale
Date: 8/13/2021 09:01:37AM
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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/

ANAMITRO BANERJEE
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