CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214410Orig1s000
210854Orig1s004,s010

PRODUCT QUALITY REVIEW(S)

U.S. FOOD & DRUG ADMINISTRATION

RECOMMENDATION

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

NDA 214410
Assessment # 1-addendum

Drug Product Name	Xofluza® (baloxavir marboxil) for oral suspension
Dosage Form	Granules for suspension
Strength	40 mg/20 mL (2mg /mL)
Route of Administration	Oral and enteral
Rx/OTC Dispensed	Rx
Applicant	Genentech
US agent, if applicable	NA

Submission(s) Assessed	Document Date	Discipline(s) Affected
eCTD 0052	11/05/2020	Quality

QUALITY ASSESSMENT TEAM, RELATED/SUPPORTING DOCUMENTS, Consults, risk table- See Review #1

EXECUTIVE SUMMARY

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

The NDA, as amended, has provided adequate CMC information to assure the identity, strength, purity, and quality of the proposed drug product. The manufacturing and testing facilities for this NDA are deemed acceptable and an overall “Approve” recommendation was entered into Panorama on August 18, 2020. Therefore, this NDA is recommended for approval by the Office of Pharmaceutical Quality (OPQ).

II. SUMMARY OF QUALITY ASSESSMENTS

A. **Product Overview-** See review #1

B. Quality Assessment Overview

Drug Substance: Adequate

See Review #1

Drug Product: Adequate

As captured in review #1, the applicant previously implemented analytical methods for the tests of the content of baloxavir marboxil in 20 mL of the constituted suspension, and quantitative homogeneity of the constituted suspension. The 11/05/2020 amendment provided additional validation data for these methods and were found adequate.

This NDA is recommended for approval from a drug product perspective. For additional details, refer to the memorandum by Sheena (Hailin) Wang, Ph.D.

Labeling: Adequate

Labeling recommendations were communicated to the OND project manager. The labeling was found adequate.

Manufacturing: Adequate

See Review #1

Biopharmaceutics: Adequate

The NDA was recommended for approval from a Biopharmaceutics perspective in review #1. The Biopharmaceutics team had recommended the use of 25 rpm as the agitation speed in the dissolution method. This was accepted, implemented, and the relevant section in the NDA were updated on 08/07/2020, as described in review #1. That review captured that the applicant committed to provide additional validation of the 25 rpm agitation speed post-approval, which was found adequate. The 11/05/2020 addendum to the NDA indicated that the validation of analytical procedures- dissolution method, will be provided post-approval. Since this was previously agreed to, no additional Biopharmaceutics review was necessary for this response.

The NDA is still recommended for approval from a Biopharmaceutics perspective.

Microbiology (if applicable): Adequate

See Review #1

D. List of Deficiencies for Complete Response

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

None

Application Technical Lead Name and Date:

Erika E. Englund, 11/10/2020

Erika Englund

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MEMORANDUM

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

DATE: November 06, 2020

TO: Review #1 of NDA 214410 Product Quality Assessment

FROM: Hailin (Sheena) Wang, Ph.D.
Chemist, CDER/OPQ/ONDP/DNDPI/NDPB2

THROUGH Thomas F. Oliver, Ph.D.
Division Director
CDER/OPQ/ONDP/DNDPI

SUBJECT: **Updates on analytical method validation**

SUMMARY

The applicant has previously implemented two new methods (in SD 26 and SD36) for the tests of content of baloxavir marboxil in 20 mL of constituted suspension (UHPLC-3), and quantitative homogeneity of the constituted suspension (UHPLC-4) as recommended by the review division in FDA IRs on 06/07/2020 and 08/17/2020 respectively. Since these two methods use the same chromatographic conditions and sample concentrations as that used for the content of baloxavir marboxil in granules method (UHPLC-1) except for differences in sample preparation, the aspects of the validation of method UHPLC-1, i.e., specificity, linearity, accuracy, range, and robustness with respect to chromatographic conditions are considered applicable to the new methods for the constituted suspension. Therefore, a partial validation, including the precision (repeatability), and intermediate precision and robustness (with respect to the sample preparation) has been provided in this amendment (SD52) to confirm the validity of the two new methods, especially with respect of sample preparation. All acceptance criteria established for the validation of the UHPLC for content in 20 mL of suspension method (UHPLC-3) and the quantitative homogeneity method (UHPLC-4) have been met, which supports the suitability of these two methods for its intended purposes.

RECOMMENDATION:
This application is still recommended for **Approval** from the Product Quality perspective.

Assessment Notes

A new Section 3.2.P.5.3 Validation of Analytical Procedures: Ultra-High- Performance Liquid Chromatography Method for Content of Constituted Suspension (UHPLC-3) and Quantitative Homogeneity (UHPLC-4) is provided.

The results for the other aspects of validation (specificity, linearity, accuracy, robustness of chromatographic conditions, and stability in solution) are taken from the validation for the content of baloxavir content in the granules for oral suspension (UHPLC-1), as the chromatographic conditions are the same for both methods.

A summary of the partial validation results for both methods is provided below.

Table P.5.3-1 Summary of Validation Parameters and Results

Parameter	Acceptance Criteria	Results
Precision (repeatability) for quantitative homogeneity	(b) (4)	0.84%
Precision (repeatability) for content in constituted suspension		0.87%
Intermediate Precision for quantitative homogeneity		0.68%
Intermediate Precision for content in constituted suspension		0.70%
Robustness (sample standing time for quantitative homogeneity)		0.72% for a standing time of up to 1 minute

Abbreviations: RSD = relative standard deviation.

Sheena Hailin Wang

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Thomas Oliver

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/s/

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U.S. FOOD & DRUG ADMINISTRATION

RECOMMENDATION

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

NDA 214410
Assessment # 1

Drug Product Name	Xofluza® (baloxavir marboxil) for oral suspension
Dosage Form	Granules for suspension
Strength	40 mg/20 mL (2mg /mL)
Route of Administration	Oral and enteral
Rx/OTC Dispensed	Rx
Applicant	Genentech
US agent, if applicable	NA

Submission(s) Assessed	Document Date	Discipline(s) Affected
eCTD 0001	1/23/2020	All
eCTD 006	2/20/2020	Quality
eCTD 0010	3/20/2020	Quality
eCTD 0015	5/12/2020	Quality
eCTD 0022	6/3/2020	Quality
eCTD 0026	7/6/2020	Quality
eCTD 0027	7/16/2020	Quality
eCTD 0030	8/4/2020	Quality
eCTD 0031	8/7/2020	Quality
eCTD 0033	8/13/2020	Quality
eCTD 0034	8/13/2020	Quality
eCTD 0036	8/24/2020	Quality
eCTD 0038	8/28/2020	Quality
eCTD 0045	9/30/2020	Quality
eCTD 0046	10/08/2020	Labeling
eCTD 0048	10/22/2020	Labeling

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessment	Secondary Assessment
Drug Substance	Karina Zuck	Ali Al Hakim
Drug Product	Hailin (Sheena) Wang	Thomas Oliver
Manufacturing	Abdollah Koolivand	Bo Jiang

Microbiology	Daniel Schu	Erika Pfeiler
Biopharmaceutics	Mathew John	Elsbeth Chikhale
Regulatory Business Process Manager	Anh-Thy Ly	
Application Technical Lead	Erika E. Englund	
Laboratory (OTR)	NA	
Environmental	NA	

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)	IV	(b) (4)		Adequate	9/10/2020	Reviewed by Hailin (Sheena) Wang
	III	Refer to container closure assessment.				

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

Document	Application Number	Description
NDA	210854	Baloxavir marboxil tablets
IND	126653	Baloxavir marboxil

2. CONSULTS

Discipline	Status	Recommendation	Date	Assessor
Biostatistics	NA			
Pharmacology/Toxicology	adequate	Deacquinita Diggs, Ph.D. confirmed there was sufficient information to support		

		the safety qualification of the strawberry flavor		
CDRH-ODE	NA			
CDRH-OC	NA			
Clinical	NA			
Other	NA			

EXECUTIVE SUMMARY

IQA NDA Assessment Guide Reference

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

The NDA, as amended, has provided adequate CMC information to assure the identity, strength, purity, and quality of the proposed drug product. The manufacturing and testing facilities for this NDA are deemed acceptable and an overall "Approve" recommendation was entered into Panorama on August 18, 2020. Therefore, this NDA is recommended for approval by the Office of Pharmaceutical Quality (OPQ).

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

NDA 210854 for Xofluza (Baloxavir marboxil) tablets was approved 10/24/2018. The proposed commercial product described in this NDA is Xofluza (baloxavir marboxil) for oral suspension. When NDA 214410 was originally submitted on January 23, 2020, the proposed indication was for the post-exposure prophylaxis and treatment of acute uncomplicated influenza in otherwise healthy patients 1 years of age and older. However, following the review by OND, the labeled indication was changed to the treatment of acute uncomplicated influenza in patients **12 years** of age and older. (b) (4) . With the updated indication, a patient is either prescribed 40 mg (if patient is less than 80 kg) or 80 mg (if patient is at least 80 kg). This corresponds to either one bottle (40 mg/20 mL) or two separate bottles (40 mg/20 mL x2).

This product was developed under IND 126653, and pre-NDA meeting comments were sent to the sponsor on 10/03/2019. NDA 210854 efficacy supplements 4 (b) (4) are under review concurrently with NDA 214410.

Proposed Indication(s) including Intended Patient Population	For prophylaxis of influenza and treatment of acute uncomplicated influenza in patients twelve years of age and older. (Note: the originally proposed indication in the NDA was for patients one years of age and older).
Duration of Treatment	A single dose
Maximum Daily Dose	80 mg
Alternative Methods of Administration	Oral or enteral

B. Quality Assessment Overview

Drug Substance: Adequate

Baloxavir marboxil, the active ingredient in XOFLUZA, is a prodrug of baloxavir . All drug substance information was referenced to the approved NDA 210854 (baloxavir marboxil tablets (Xofluza)). The current drug substance information in NDA 210854 was found adequate to support NDA 214410.

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

Drug Product: Adequate

Baloxavir marboxil, granules for oral suspension, 40 mg/20 mL (2 mg/mL), consists of white to light yellow granules for oral suspension. The product is supplied in an amber glass bottle with a child-resistant screw cap. Each bottle contains 40 mg (nominal) of baloxavir marboxil and the granules must be constituted with 20 mL of drinking water or sterile water to yield a 2 mg/mL oral suspension. All excipients are either USP or NF grade, except for the strawberry flavor which uses an in-house specification.

There's no overage, but a (b) (4) % overfill was justified based on volume of expansion in order to yield the labeled concentration of 2 mg/mL. Extractable studies were also performed to confirm that at least 20 mL could be withdrawn from the bottle.

(b) (4)

Following the microbiological reviewer assessment of results from an additional redesigned microbial challenge study, the in-use time was assigned as 10 hours at 20-25°C in either

drinking water or sterile water. Refer to the microbiology review and drug product review addendum for additional details.

18 months of stability was submitted to support the 30 month shelf life of the product at USP controlled room temperature.

The claim of categorical exclusion was evaluated in the drug product review, and also found acceptable.

After the original drug product review was finalized on 09/09/2020, the CMC team was informed that the product would not be approved for patients under 12 years of age. A drug product review addendum was written to capture the modified maximum daily dose of 80 mg and the results of the microbial challenge study to support the in-use time (refer to microbiology review for further details).

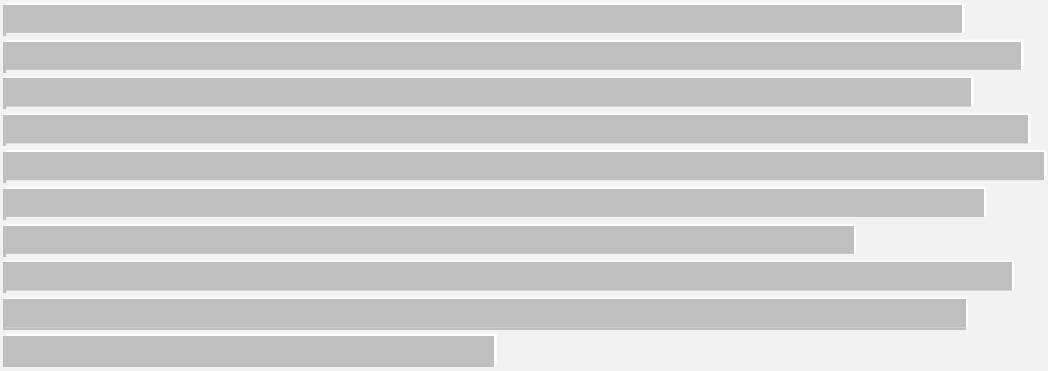
This NDA is recommended for approval from a drug product perspective. For additional details, refer to the review by Sheena (Hailin) Wang, Ph.D.

Labeling: Adequate

Labeling recommendations were communicated to the OND project manager. The labeling was found adequate.

Manufacturing: Adequate

The manufacturing process for the granules uses (b) (4)



The registration batches were manufactured at the proposed commercial batch size (b) (4) and there were (b) (4) in the manufacturing process.

All facilities including drug substance and drug product manufactures, lab facilities and packaging site have compliant status and experience with proposed responsibilities. Therefore, no PAI request was issued during

the review cycle. The Overall Manufacturing Inspection Recommendation was entered into Panorama as “approve” on 8/18/2020.

This NDA is recommended for approval from an OPMA perspective. For additional details, refer to the review by Abdollah Koolivand, Ph.D.

Biopharmaceutics: Adequate

The Biopharmaceutics assessment evaluated the data supporting the proposed dissolution method, dissolution acceptance criterion and need for bridging between the drug product used in phase 1 clinical studies (2 % w/w granules (20 mg/g) packaged inside a sachet (administered directly to the mouth of the subject with a glass (200 mL) of water)) and the to be marketed formulation (2 g of granules containing 40 mg of baloxavir marboxil (20 mg /g) inside a bottle to be constituted with 20 mL water to make it an oral suspension before administration).

The acceptance criterion of NLT (b) (4)% (Q) at 20 minutes was found acceptable for the dissolution of the 2 grams of granules as the sample. Based on the submitted PK data, (BE and relative BA studies reviewed by OCP), and the similarity in the in-vitro dissolution data, the bridging between the Tablets, Granules, and Granules for Oral Suspension is established. Therefore, it is justified that NDA 214410 (granules for oral suspension) relies in part on clinical studies using tablets (and clinical studies using granules). Based on the totality of the submitted information, no significant difference in BE performance between the two different modes of administration is expected. The bridging between tablets, granules, and granules for suspension, is supported by the data and information and is found to be adequate.

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

Microbiology (if applicable): Adequate

The original NDA included an (b) (4)hour in-use storage period for the product when constituted with sterile water. (b) (4) the applicant described on 7/26/2020 that microbial growth began to occur at 10 hours in a microbial challenge study.

(b) (4). The microbiology team was consulted for this study.

A microbiology IR was sent on August 10, 2020 with a request that the microbiological study be repeated with the recommended conditions. The applicant provided updated data on September 30, 2020. Based on the results from the studies, the microbiology reviewer concluded that the overall trend in the data suggests that the drug product constituted in sterile water or drinking water was not significantly growth promoting. In addition, based on the oral route of administration, the drug product is relatively low risk from a microbiology perspective. The provided microbiological challenge studies support the proposed post-constitution hold time of 10 hours at 20-25°C when prepared with drinking water or sterile water.

For additional details, refer to the memo by Daniel Schu, 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**
Assay, stability		2		Acceptable	
Physical Stability		36		Acceptable	(b) (4)
Content Uniformity		36		Acceptable	
Microbial Limits		6	Microbial control found acceptable	Acceptable	

			in OPMA review		
Dissolution		18	Dissolution acceptance criteria and data found acceptable in biopharmaceutics review	Acceptable	
Constitution Time		24		Acceptable	(b) (4)

D. List of Deficiencies for Complete Response

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

None

2. Drug Substance Deficiencies

N/A

3. Drug Product Deficiencies

N/A

4. Labeling Deficiencies

5. Manufacturing Deficiencies

6. Biopharmaceutics Deficiencies

7. Microbiology Deficiencies

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

Application Technical Lead Name and Date:

Erika E. Englund, 10/27/2020

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MEMORANDUM

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

DATE: October 07, 2020

TO: Review #1 of NDA 214410 Product Quality Assessment

FROM: Hailin (Sheena) Wang, Ph.D.
Chemist, CDER/OPQ/ONDP/DNDPI/NDPB2

THROUGH Thomas F. Oliver, Ph.D.
Division Director
CDER/OPQ/ONDP/DNDPI

SUBJECT: **Update on MDD and microbial challenge study**

SUMMARY

The previous Product Quality Review #1 dated 09/16/2020 used a Maximum Daily Dose (MDD) of (b) (4) for the evaluation of the excipients and impurity qualifications (see N214410 IQA Drug Product R1). (b) (4) The product labeling has been updated to include the adult indication only with a MDD of 80 mg, the same as the previously approved XOFLUZA® tablet formulation. The quality review outcome remains the same based on a MDD of 80 mg.

In addition, Dr. Daniel Schu from OPMA/DMA has reviewed the microbial challenge study submitted on 09/30/2020 and concluded in his memo on 10/02/2020 that the study results "*support the proposed post-constitution hold time of 10 hours at 20-25°C when prepared with drinking water or sterile water*". Based on this information, a longer hold-time of the constituted suspension in sterile water (10 hours vs previously proposed (b) (4) hours) and alternative preparation with drinking water will be recommended for the dose and administration. Recommended labeling revisions in the PI and Container & Closure labels related to the hold-time of the constituted suspension has been conveyed to the applicant.

RECOMMENDATION:
This application is still recommended for **Approval** from the Product Quality perspective.

Assessment Notes

Excipients (remains adequate)

Based on an MDD of 80 mg, the levels of all compendial excipients are still within FDA's IIG data base. While for the non-compendial excipient, strawberry flavor, its safety qualification is confirmed based on input from Pharm/Tox reviewer Deacqunita Diggs.

Related Substance (remains adequate)

MDD: 80 mg, IT= (b) (4)%, QT = (b) (4)% or (b) (4)µg

Impurity specification proposed in NDA214410

Related Substances by HPLC (b) (4)	HPLC-UV Section P.5.2 *Analytical Procedures—Related Substances by High-Performance Liquid Chromatography*

Impurity specification in approved NDA 210854 for XOFLUZA tablets

Related substances by HPLC (b) (4)	3.2.P.5.2.4	Not more than (b) (4) Not more than Not more than Not more than Not more than

With MDD at 80 mg, the impurity qualification threshold (b) (4)%. However, the proposed limits of all known impurities are still considered justified based on approved NDA 210854 and the active metabolite rationale provided in the original DP review for (b) (4).

Elemental Impurity (remains adequate)

Based on an 80 mg maximum daily dose, the total daily exposure of each elemental impurity of concern is still estimated to be below (b) (4)% of the PDE limits defined in ICH Q3D. The proposed control strategy of elemental impurities is still considered adequate.

Thomas Oliver

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Sheena Hailin Wang

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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

XOFLUZA® (baloxavir marboxil) tablets, for oral use
XOFLUZA® (baloxavir marboxil) for oral suspension
Initial U.S. Approval: 2018

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	**XOFLUZA**	**Adequate**
Established name(s)	(baloxavir marboxil) for oral suspension	**Adequate** Established name is based on active ingredient
Route(s) of administration	oral	**Adequate**
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	For suspension: 40 mg/20 mL when constituted for final concentration of 2 mg/mL	**Adequate** Consistent with FDA dosage form SPL acceptable term
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	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	N/A

1.2 FULL PRESCRIBING INFORMATION
1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

2.1 Dosage and Administration Overview

XOFLUZA is available in two dosage forms:

- XOFLUZA tablets
- XOFLUZA for oral suspension. This granule formulation is intended for patients who are unable to or have difficulty swallowing tablets, or those who require enteral administration *[see Dosage and Administration (2.3)]*.

XOFLUZA should be taken as soon as possible after influenza symptom onset or exposure to influenza and may be taken with or without food. However, coadministration of XOFLUZA with dairy products, calcium-fortified beverages, polyvalent cation-containing laxatives, antacids, or oral supplements (e.g., calcium, iron, magnesium, selenium, or zinc) should be avoided *[see Drug Interactions (7.1) and Clinical Pharmacology (12.3)]*.

2.2 Recommended Dosage (Not copied here as it does not pertain to CMC)

2.3 Preparation of XOFLUZA for Suspension for Oral (b) (4) by Healthcare Provider

Prior to dispensing to the patient, constitute XOFLUZA for suspension with 20 mL of drinking water or sterile water. After constitution, each bottle of XOFLUZA suspension contains 40 mg of baloxavir per 20 mL of volume for a final concentration of 2 mg/mL.

Constituting XOFLUZA for Suspension for Oral (b) (4)

Prepare the suspension at the time of dispensing. **Administration must occur within 10 hours after constitution because the product does not contain a preservative.**

1. Gently tap the bottom of the bottle to loosen the granules.
2. Constitute XOFLUZA granules with 20 mL of drinking water or sterile water.
3. Gently swirl the suspension to ensure that the granules are evenly suspended. Do not shake.
4. Write the expiration time and date on the bottle label in the space provided (10 hours from constitution time).

Important Information for the Healthcare Provider

- Provide caregiver or patient with a measuring device (e.g. oral syringe, measuring cup) to deliver the prescribed dose of the suspension for oral use. For enteral administration (i.e., feeding tube), draw up suspension with an enteral syringe. Flush with 1 mL of water before and after enteral administration.
- Instruct the caregiver or patient that the total prescribed dose of XOFLUZA for suspension may require more than one bottle (e.g., for adults and adolescents weighing at least 80 kg).

Item	Information Provided in the NDA	Assessor's Comments
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)	Prepare the suspension at the time of dispensing. Administration must occur within 10 hours after constitution because the product does not contain a preservative. 1.Gently tap the bottom of the bottle to loosen the granules. 2.Constitute XOFLUZA granules with 20 mL of drinking water or sterile water. 3.Gently swirl the suspension to ensure that the granules are evenly suspended. Do not shake. 4.Write the expiration time and date on the bottle label in the space provided (10 hours from constitution time).	**Adequate from DP perspective** Supported by a diluent compatibility study and microbial challenge study.

2.1.1 Section 3 (DOSAGE FORMS AND STRENGTHS)

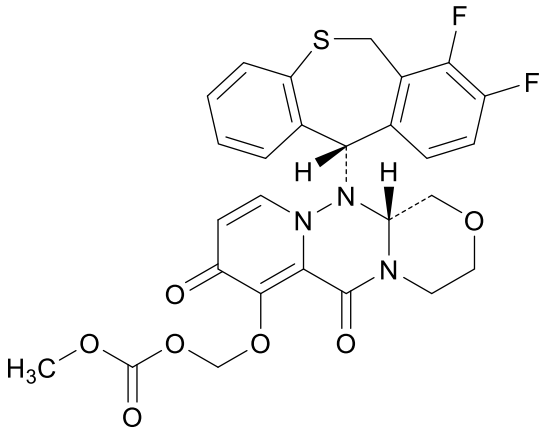
For Suspension, for Oral or Enteral Use:
XOFLUZA oral suspension contain 40 mg/20 mL or 2 mg/mL baloxavir marboxil after constitution with 20 mL of drinking water or sterile water. The granules are white to light yellow. The constituted product is a white to light yellow opaque suspension with strawberry flavor.

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	(b) (4)	**Adequate** Minor recommended edits "For Oral Suspension: (b) (4) " to be consistent with the revised product title/established name
Strength(s) in metric system	40 mg/20 mL or 2 mg/mL	**Adequate**
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	N/A	**N/A**
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	The granules are white to light yellow. The constituted product is a white to light yellow opaque suspension with strawberry flavor.	**Adequate**
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	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.	N/A	N/A

2.1.3 Section 11 (DESCRIPTION)

XOFLUZA (baloxavir marboxil) is an antiviral PA endonuclease inhibitor.

The active component of XOFLUZA is baloxavir marboxil. The chemical name of baloxavir marboxil is ({(12aR)-12-[(11S)-7,8-Difluoro-6,11-dihydrodibenzo[b,e]thiepin-11-yl]-6,8-dioxo-3,4,6,8,12,12a-hexahydro-1H-[1,4]oxazino[3,4-c]pyrido[2,1-f][1,2,4]triazin-7-yl}oxy)methyl methyl carbonate. The empirical formula of baloxavir marboxil is $C_{27}H_{23}F_2N_3O_7S$, and the chemical structure is shown below.



Baloxavir marboxil has a molecular weight of 571.55 and a partition coefficient (log P) of 2.26. It is freely soluble in dimethylsulfoxide, soluble in acetonitrile, slightly soluble in methanol and ethanol, and practically insoluble in water.

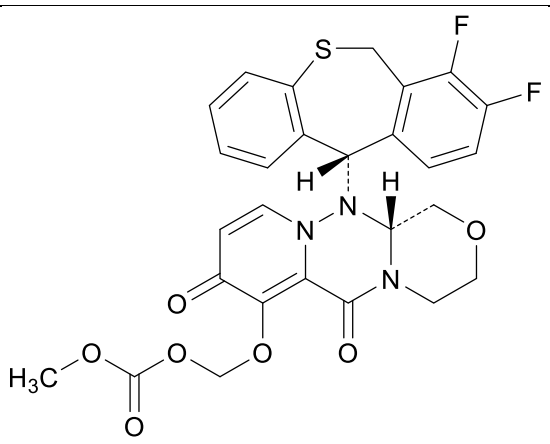
XOFLUZA is supplied as tablets and as granules for suspension:

XOFLUZA tablets are white to light yellow, film-coated tablets for oral administration. The inactive ingredients of XOFLUZA tablets are: croscarmellose sodium, hypromellose, lactose monohydrate, microcrystalline cellulose, povidone, sodium stearyl fumarate, talc, and titanium dioxide.

XOFLUZA for oral suspension are white to light yellow granules supplied in an amber glass bottle. Each bottle contains 40 mg (nominal) of baloxavir marboxil. The granules must be constituted with 20 mL of drinking water or sterile water to yield a 2 mg/mL suspension with strawberry flavor. The inactive ingredients are: hypromellose, maltitol, mannitol, povidone K25, sodium chloride, strawberry flavor, sucralose and talc.

Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s)	XOFLUZA (baloxavir marboxil) for oral suspension	**Adequate**
Dosage form(s) and route(s) of administration	for oral suspension	**Adequate**

If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	N/A	N/A
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	The inactive ingredients are: hypromellose, maltitol, mannitol, povidone K25, sodium chloride, strawberry flavor, sucralose and talc.	**Adequate from CMC perspective** Includes all excipients used for granule formulation. Inactive ingredients are 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	N/A
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	N/A
Statement of being sterile (if applicable)	N/A	N/A
Pharmacological/ Therapeutic class	antiviral PA endonuclease inhibitor	Pharmacological/Therapeutic class is included.
Chemical name, structural formula, molecular weight	({(12aR)-12-[(11S)-7,8-Difluoro-6,11-dihydrodibenzo[b,e]thiepin-11-yl]-6,8-dioxo-3,4,6,8,12,12a-hexahydro-1H-[1,4]oxazino[3,4-c]pyrido[2,1-f][1,2,4]triazin-7-yl}oxy)methyl methyl carbonate. The empirical formula of baloxavir marboxil is $C_{27}H_{23}F_2N_3O_7S$, and the chemical structure is shown below.	**Adequate** Consistent with information provided in 3.2.S.

		
If radioactive, statement of important nuclear characteristics.	N/A	N/A
Other important chemical or physical properties (such as pKa or pH)	Baloxavir marboxil has a molecular weight of 571.55 and a partition coefficient (log P) of 2.26. It is freely soluble in dimethylsulfoxide, soluble in acetonitrile, slightly soluble in methanol and ethanol, and practically insoluble in water.	**Adequate** Consistent with information provided in 3.2.S. and for XOFLUZA tablet

Section 11 (DESCRIPTION) Continued

Item	Information Provided in the NDA	Assessor's Comments
For oral prescription drug products, include gluten statement if applicable	N/A	N/A
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity"	N/A	N/A

2.1.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

XOFLUZA for Oral Suspension

How Supplied

XOFLUZA for oral suspension 40 mg/20 mL (2 mg/mL) are white to light yellow granules and are supplied in an amber glass bottle with a child-resistant cap. When constituted with drinking

water or sterile water, the usable volume of suspension is 20 mL, equivalent to 40 mg of baloxavir marboxil. XOFLUZA for oral suspension are available as:

- 40 mg/20 mL (2 mg/mL) for oral suspension: NDC 50242-583-01

Handling

The product contains no preservative and **must be administered within 10 hours after constitution**.

Storage

Store granules at room temperature 20°C to 25°C (68°F to 77°F) and keep in the original bottle; excursions are permitted between 15°C and 30°C (59°F and 86°F).

Store constituted suspension no longer than (b) (4) hours at room temperature 20°C to 25°C (68°F to 77°F) when constituted with sterile water. The suspension must be discarded if not used within (b) (4) hours of preparation or if suspension has been stored above 25°C (77°F).

Item	Information Provided in the NDA	Assessor's Comments
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	for oral suspension	**Adequate** Minor recommended edits as shown in yellow highlights above
Strength(s) in metric system	40 mg/20 mL (2 mg/mL)	**Adequate**
Available units (e.g., bottles of 100 tablets)	N/A	**N/A**
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	white to light yellow granules and are supplied in an amber glass bottle with a child-resistant cap. NDC 50242-583-01	**Adequate**
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	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	N/A

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

Item	Information Provided in the NDA	Assessor's Comments
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.)	N/A	**N/A**
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	N/A
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Store granules at room temperature 20°C to 25°C (68°F to 77°F) and keep in the original bottle; excursions are permitted between 15°C and 30°C (59°F and 86°F). Store constituted suspension no longer than 10 hours at room temperature 20°C to 25°C (68°F to 77°F) when constituted with drinking water or sterile water. The suspension must be discarded if not used within 10 hours of preparation or if suspension has been stored above 25°C (77°F).	**Adequate** Storage condition is supported by long term and in-use stability data.
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.	N/A	N/A

Avoid statements such as "latex-free."		
Include information about child-resistant packaging	child-resistant closure	Adequate

2.1.5 Other Sections of Labeling

None

2.1.6 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	Distributed by: **Genentech USA, Inc.** A Member of the Roche Group 1 DNA Way South San Francisco, CA 94080-4990 Manufactured by: **Shionogi Pharma Co., Ltd.** 2-5-1 Mishima, Settsu Osaka 566-0022, Japan	**Adequate**

2.0 PATIENT LABELING

The patient labeling comply with all regulatory requirements from a CMC perspective.

3.0 CARTON AND CONTAINER LABELING

3.1 Container Label

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

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Proprietary name, established name, and dosage form (font size and prominence	Xofluza® (baloxavir marboxil) for oral suspension	**Adequate** The font of the Established name appears to be at least half as large as the letters comprising the proprietary name. Both propriety name and established name have the same font color and appear to have same prominence.
Dosage strength	40 mg/20 mL (2 mg/mL)	**Adequate**
Route of administration	Oral	**Adequate**
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	**N/A**	**N/A**
Net contents (e.g. tablet count)	N/A	**N/A**
"Rx only" displayed on the principal display	Yes	**Adequate**
NDC number	NDC 50242-583-01	**Adequate**
Lot number and expiration date	Yes	**Adequate**
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	**Store granules** at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) **Store suspension** no longer than 10 hours at room temperature 20°C to 25°C (68°F to 77°F) when constituted with drinking water or sterile water. Take before the suspension expires.	**Adequate from DP perspective** Consistent with PI and supported by long term and in-use stability data.
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	N/A	N/A

Other package terms include pharmacy bulk package and imaging bulk package which require “Not for direct infusion” statement.	N/A	N/A
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	N/A
Bar code	Yes	Adequate

Item	Information Provided in the NDA	Assessor’s Comments about Carton Labeling
Name of manufacturer/distributor	Distributed by: Genentech USA, Inc.	**Adequate**
Medication Guide (if applicable)	N/A	N/A
No text on Ferrule and Cap overseal	None	**Adequate**
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	N/A	N/A

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

The drug name listed on container and carton labels, as of this review comply with all regulatory requirements from a CMC perspective

ITEMS FOR ADDITIONAL ASSESSMENT

None

Overall Assessment and Recommendation:

Adequate

Primary Labeling Assessor Name and Date: Hailin (Sheena) Wang, Ph.D. 10/23/2020

Secondary Assessor Name and Date:

Sheena Hailin Wang

Digitally signed by Sheena Hailin Wang
Date: 10/26/2020 08:25:14AM
GUID: 5203a2110001f7235a14cac1b60d05c4

Thomas Oliver

Digitally signed by Thomas Oliver
Date: 10/26/2020 08:21:39AM
GUID: 508da71f00029ed4697700cee3d31ca0
Comments: Sheena: It doesn't look like you signed yet?

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CHAPTER VI: BIOPHARMACEUTICS

Product Information	
NDA Number	214410
Assessment Cycle Number	01
Drug Product Name/ Strength	Xofluza® (baloxavir marboxil) granules for oral suspension / 2mg /mL
Route of Administration	Oral
Applicant Name	Genetech Inc
Therapeutic Classification/ OND Division	DAI
RLD/RS Number	N/A
Proposed Indication	For prophylaxis of influenza and treatment of acute uncomplicated influenza in patients one year of age and older.
Primary Assessors	Mathew John, Ph.D.
Secondary Assessors	Elsbeth Chikhale, Ph.D.
Assessment	**Adequate**
Recommendation	Recommended for Approval from a Biopharmaceutics perspective.

Background:

This is a 505 b (1) application of Xofluza® (baloxavir marboxil) granules for oral suspension, 2 mg/mL, indicated for prophylaxis of influenza and the treatment of acute uncomplicated influenza in patients one year of age and older. The Applicant has conducted a Phase 3 pediatric study (CP40563) to support the safety and efficacy of the proposed drug product. The Applicant has also performed a BE study in adults (1703T081G) between the approved Baloxavir marboxil tablets, 20 mg (NDA 210854 from the same Applicant) and Baloxavir marboxil granules (2 % w/w) packaged inside a sachet, which have the same formulation as the proposed drug product, but were administered as granules with a glass of water (200 mL), instead of suspended in 20 mL water before administration.

Biopharmaceutics Assessment Summary:

The Biopharmaceutics assessment of this Application evaluates the data supporting the proposed dissolution method, dissolution acceptance criterion and need for bridging between the drug product used in phase 1 clinical studies (2 % w/w granules (20 mg/g) packaged inside a sachet (administered directly to the mouth of the subject with a glass (200 mL) of water)) and the to be marketed formulation (2 g of granules containing 40 mg of baloxavir marboxil (20 mg /g) inside a bottle to be constituted with 20 mL water to make it an oral suspension before administration).

Dissolution Method and Acceptance Criterion:
The following revised dissolution method and acceptance criterion are acceptable as QC method for drug product batch release and stability testing:

Sample for Dissolution Study	USP Apparatus	Rotation Speed	Medium	Volume / Temperature	Cumulative % of Drug Dissolved (Label Claim)
2g Granules	II (Paddle)	25 rpm	0.16% CTAB (w/v) in phosphate buffer, pH 6.8.	900 mL /37°C ± 0.5°C	NLT (b) (4)% (Q) at 20 minutes

Highlight Key Issues from Last Cycle and Their Resolution: N/A, this is the first review cycle.

Concise Description of Outstanding Issues: None

B.1 DRUG SUBSTANCE SOLUBILITY

The solubility data of baloxavir marboxil at 37 °C submitted in NDA 210854 are as follows[1],

Solvent	Solubility of API (µg/mL) at 37°C
Water	18.4
Hydrochloric acid buffer solution, pH 1.2	20.6
Diluted MacIlvaine buffer solution, pH 3.0	20.2
Diluted MacIlvaine buffer solution, pH 4.0	19.3
Diluted phosphate buffer solution, pH 6.8	18.9

Table 1: Solubility of baloxavir marboxil in phosphate buffer pH 6.8 with different surfactant concentrations at 37°C[2]

Surfactant	Concentration of Surfactant (%)	Solubility (mg/L)
No Surfactant Added		18.9
Polysorbate 20	0.9	76.8
	1.0	82.0
	1.1	90.8
Sodium Dodecyl Sulfate (SDS)	0.07	59.9
	0.08[a]	70.9
	0.09[a]	112.5
n-Hexadecyltrimethylammonium Bromide (CTAB)	0.14	120.7
	0.16	135.5
	0.18	150.6
Cetyltrimethylammonium Chloride (CTACl)	0.06	69.0
	0.07	78.5
	0.13	133.5

[a] Aggregated substance was observed.

The Applicant claims that the particle size of drug substance is controlled ((b) (4) and that the particle size acceptance criteria in place ensures satisfactory drug dissolution.

Reviewer's Assessment: Based on the pH solubility data, the drug substance has a pH independent low solubility across the physiologic pH. The drug substance exhibits the highest observed solubility in phosphate buffer pH 6.8 with a surfactant concentration of

[1] http://panorama.fda.gov/PanoramaDocMgmt/webhooks/viewdownload?id=090026f881bf5a56
[2] \\cdsesub1\evsprod\nda214410\0001\m3\32-body-data\32p-drug-prod\baloxavir-marboxil-granules-for-oral-suspension\32p2-pharm-dev\pharmaceutical-development-formul-development.pdf
[3] \\cdsesub1\evsprod\nda214410\0006\m2\23-qos\drug-product.pdf

0.18 % CTAB. The drug substance particle size is adequately controlled (refer to the assessment of the dissolution method below for details).

B.2 DISSOLUTION METHOD

The Applicant provided data and justifications for the selection of the dissolution methodology a iscussed below:

(b) (4)

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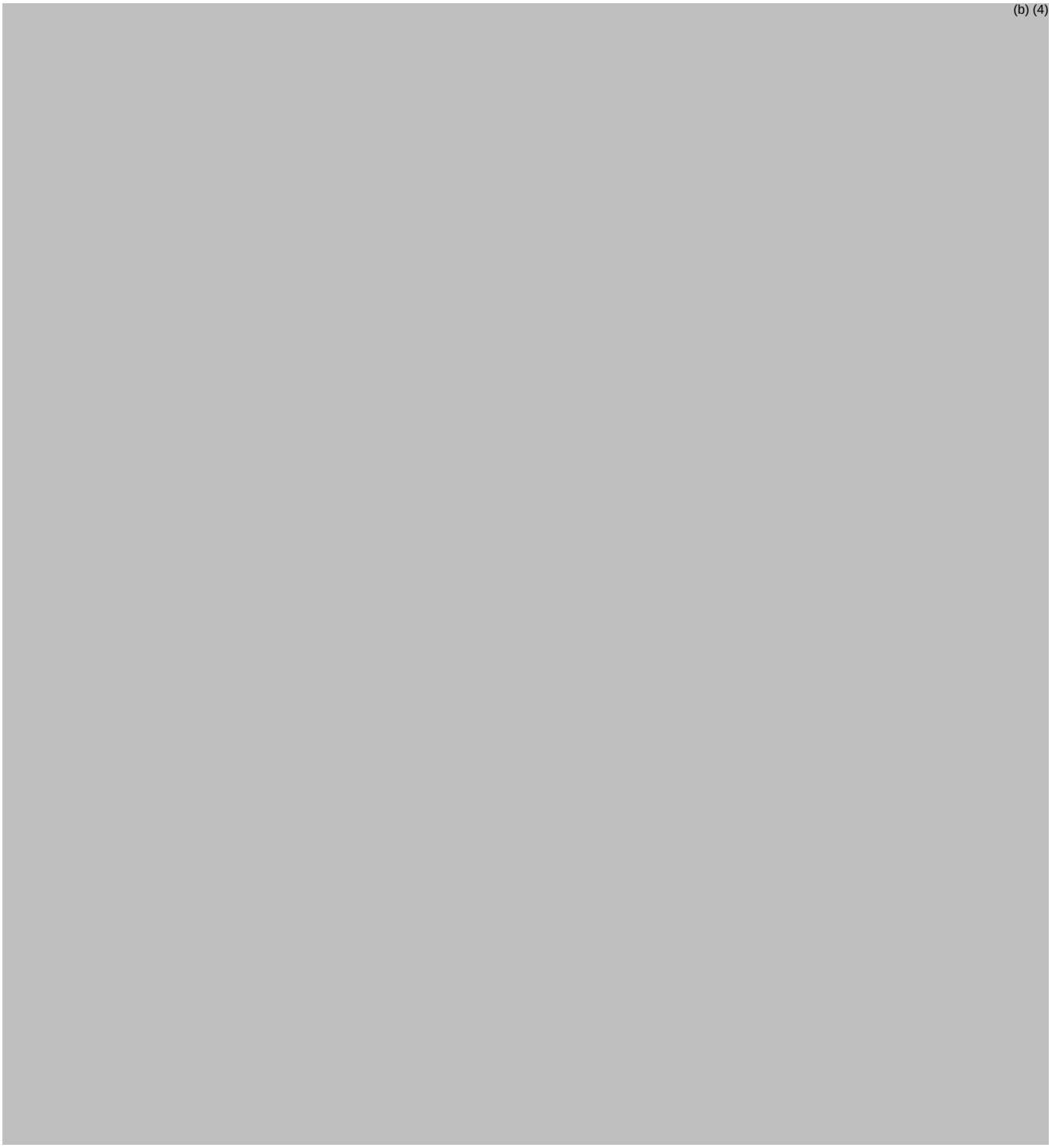
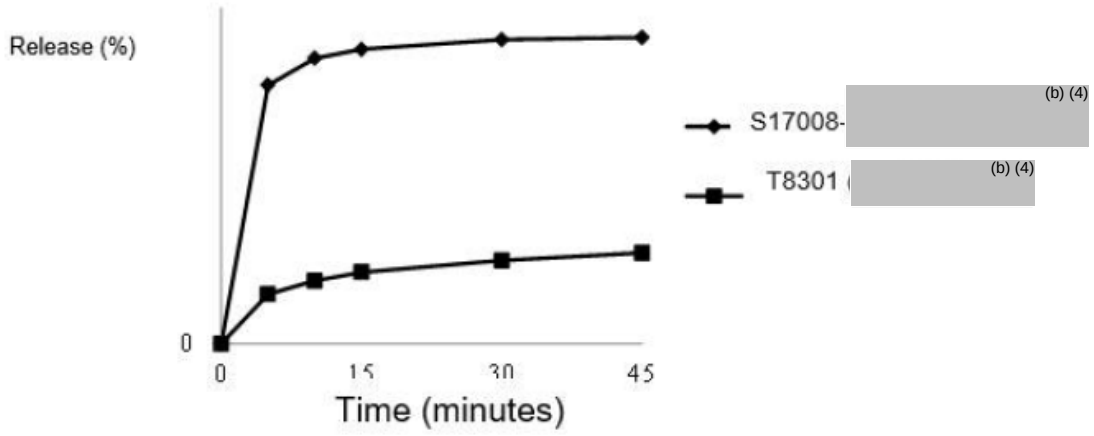


Discriminatory ability of the proposed dissolution method:

The Applicant investigated the discriminating ability of the originally proposed dissolution method ((b) (4) in terms of critical material attributes such as drug substance particle size using different drug substance particle size ((b) (4)) and the dissolution profiles for granules are as follows,

Figure P.2.2-3 **Dissolution Profile of Baloxavir Marboxil Granules with Different Particle Sizes of Drug Substance**

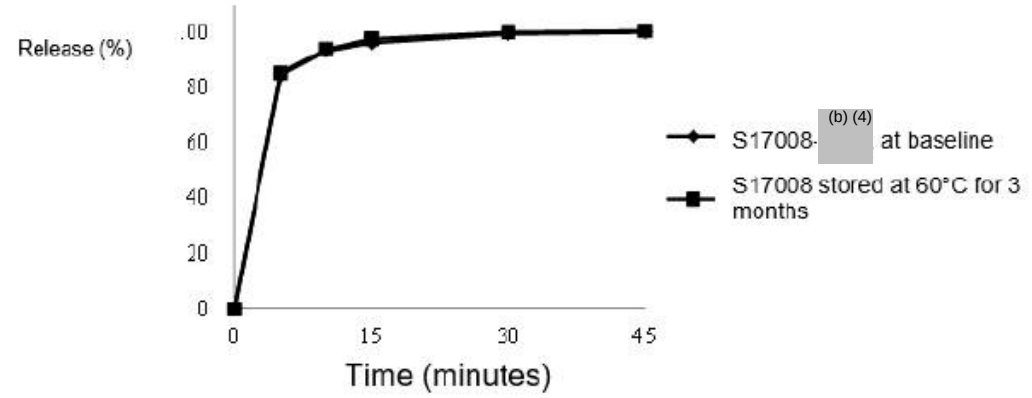
(b) (4)



The Applicant evaluated the impact of accelerated storage on the drug product and submitted the dissolution profiles of the drug product at baseline and after storage at 60°C for 3 months as follows,

Figure P.2.2-4 **Dissolution Profile of Baloxavir Marboxil Granules at Baseline and After Storage at 60°C For 3 Months**

(b) (4)



Reviewer's Assessment of the Discriminatory Ability: The Applicant has demonstrated the discriminating ability of the originally proposed dissolution method ((b) (4)) in terms of a critical material attribute, i.e. the particle size of the drug substance (drug substance with (b) (4) and has controlled the particle size of the drug substance (b) (4) . The revised dissolution method with 25 rpm instead of (b) (4) is expected to have more discriminating ability than the originally proposed dissolution method.

B.3 DISSOLUTION ACCEPTANCE CRITERION

Batch S17009-(b) (4) was used in the BE study T081G (primary packaging batch CF7013[4] of bulk batch S17009) and in the Phase 3 post-exposure prophylaxis (PEP) study T0834 conducted in Japan (CF8024 of bulk batch S17009). The Applicant submitted dissolution data at the (b) (4) minute time point[5] using the original dissolution method ((b) (4) for bulk batches S-17008(b) (4), S17009-(b) (4) and S17010-(b) (4) of the drug product (granules 2% in sachet) and proposed a dissolution acceptance criterion of '(b) (4). The dissolution data for the clinical / supportive stability batch (Batch GMP0358-02) using the revised dissolution method (25 rpm) are shown in Table 2.

Table 2: Dissolution Data (% Dissolved) of clinical / supportive stability batch (Batch GMP0358-02) using the revised dissolution method (25 rpm, using 2 g granules as the dissolution sample)

	Sampling/Min						
Unit	5	10	15	20	30	45	60
1	(b) (4)						
2							
3							
4							
5							
6							
7							
8							
9							
10							
11							
12							
Average	59	76	86	91	95	97	98
Min	(b) (4)						
Max							
SD (%)	4.7	5.0	4.5	4.0	3.4	2.6	2.2

Abbreviations: SD = standard deviation.

Reviewer's Assessment: The Applicant proposed dissolution acceptance criterion of '(b) (4) is permissive. Based on the dissolution data of the clinical / supportive stability batch (Batch # GMP0358-02) and registration batches (Batch #s GMP0378, GPR0131, GPR0132) (Appendix 1), an acceptance criterion of '(b) (4) (Q) in (b) (4) minutes' was recommended if the Applicant intend to use (b) (4) as the sample for dissolution studies or, an acceptance criterion of 'NLT (b) (4)% (Q) in 20 minutes' was recommended if the Applicant intend to use 2 g Granules as the sample

[4] \\cdsesub1\evsprod\nda214410\0001\m3\32-body-data\32p-drug-prod\baloxavir-marboxil-granules-for-oral-suspension\32p5-contr-drug-prod\32p54-batch-analys\batch-analyses.pdf (Page # 3)

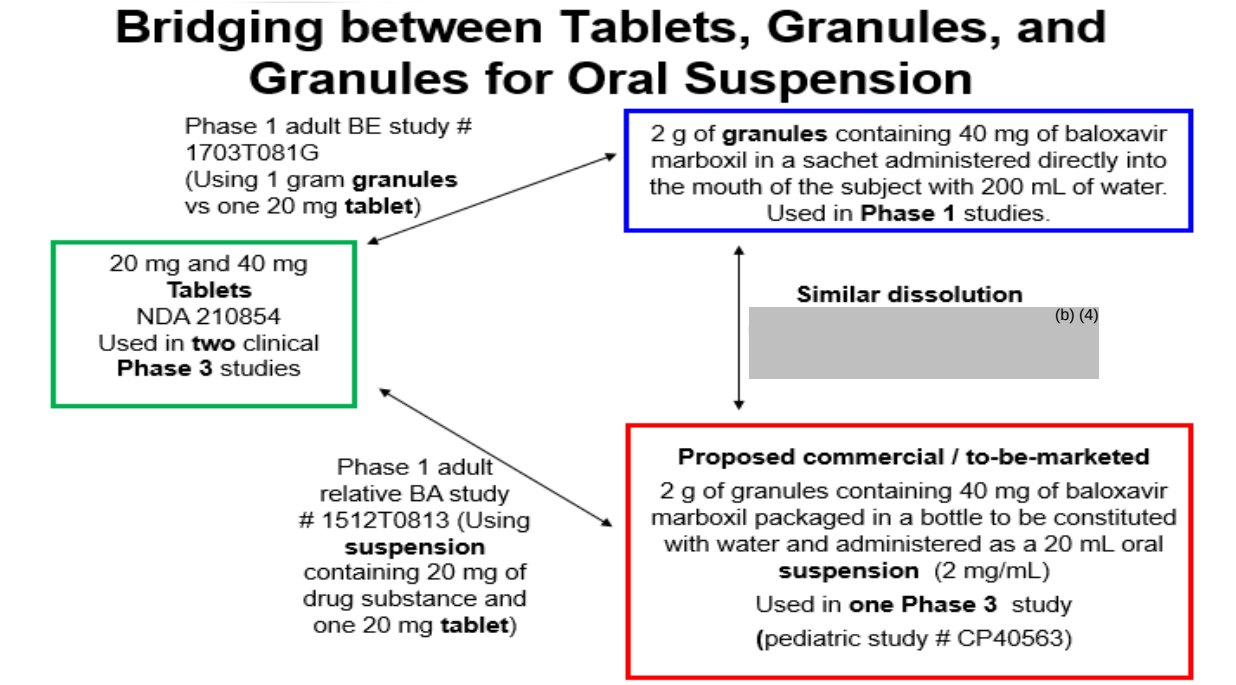
[5] \\cdsesub1\evsprod\nda214410\0001\m3\32-body-data\32p-drug-prod\baloxavir-marboxil-granules-for-oral-suspension\32p2-pharm-dev\pharmaceutical-development-formul-development.pdf (**page # 29**)

for dissolution studies (see Biopharmaceutics IR 4 in Appendix 1). In the response dated 08/24/2020, the Applicant accepted FDA recommendation to implement 2g Granules as the sample for dissolution testing and a dissolution acceptance criterion of NLT (b) (4)% (Q) at 20 minutes and updated relevant sections of the Application. Therefore, the revised dissolution acceptance criterion is adequate.

B.4 STABILITY

There is no significant trend in dissolution values at (b) (4) minutes for the proposed drug product after 6 months accelerated storage and 12 months long term storage using the originally proposed dissolution method. The Applicant also confirmed that there was no agglomerate observed after constitution of the oral suspension. The Applicant has submitted additional stability data which meets the revised specifications.

B.5 BRIDGING



As depicted in the diagram above, the BE study (1703T081G) was conducted between granules that are packaged in a sachet and were administered directly into the mouth with a glass of water and the previously approved tablets. However, in the phase 3 pediatric study (CP40563) and for the proposed commercial drug product, the granules are packaged in a bottle which must be constituted with water to make an oral suspension before administration. There is no change in the qualitative and quantitative composition of the granules used in the BE study (1703T081G) and in the pediatric study (CP40563). The Applicant also conducted a relative BA study (#1512T0813) to support the administration of a suspension instead of the granules with a glass of water. To further support the bridge between these two modes of administration, the Applicant was requested to submit comparative dissolution data between the granules and the suspension.

Reviewer's Assessment: The to-be-marketed drug product (granules for oral suspension) is the same drug product as the drug product used in the pivotal pediatric clinical studies (granules for oral suspension used in CP40563). The Applicant has conducted a phase 1 adult BE study # 1703T081G using 1g granules Vs one 20 mg tablet (which was bioequivalent as reviewed by OCP) and a phase 1 relative bioavailability study # 1512T0813 using suspension containing 20 mg of drug substance Vs one 20 mg tablet (which had comparable bioavailability as per the OCP assessment). (b) (4) The comparative PK information will be evaluated by the Office of Clinical Pharmacology (OCP). An IR was sent to the Applicant on 06/05/2020 to submit comparative individual and mean (n=12) dissolution data between 2-gram granules (containing 40 mg baloxavir marboxil) Vs. samples consisting of 20 mL oral suspension (2 mg/mL). The comparative dissolution data (please refer Appendix 1) for 2-gram granules (containing 40 mg baloxavir marboxil) Vs. samples consisting of 20 mL

oral suspension of all three registration batches GPR0131, GPR0132 and GMP0378 at 25 rpm is similar as it satisfies one criterion of dissolution similarity which is (b) (4)% of the drug is dissolved in (b) (4) minutes. Therefore, based on the submitted PK data, (BE and relative BA studies reviewed by OCP), and the similarity in the in-vitro dissolution data, the bridging between the Tablets, Granules, and Granules for Oral Suspension is established. Therefore, it is justified that NDA 214410 (granules for oral suspension) relies in part on clinical studies using tablets (and clinical studies using granules). Based on the totality of the submitted information, no significant difference in BE performance between the two different modes of administration is expected. The bridging between tablets, granules, and granules for suspension, as depicted in the diagram above, is supported by the data and information and is found to be adequate.

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Mathew John

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Elsbeth Chikhale

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Date: 9/02/2020 08:22:57AM
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M E M O R A N D U M

DATE: 02 October 2020

TO: Anh-Thy Ly, Pharm. D.
Regulatory Business Process Manager
CDER/OPQ/OPRO

FROM: Daniel J. Schu, Ph.D.
Microbiologist
CDER/OPQ/OPMA/DMA/B3

THROUGH: Erika Pfeiler, Ph.D.
Supervisory Microbiologist
CDER/OPQ/OPMA/DMA/B6

SUBJECT: Product Quality Microbiology Review Consult for NDA 214410
Consult Request Date: 06 August 2020
Drug Product: Baloxavir marboxil, 2 mg/mL (proposed: XOFLUZA)
Applicant: Genentech, Inc.
Consult Review Goal Date: 10/02/2020

REVIEW DECISION: The provided microbiological challenge studies support the proposed post-constitution hold time of 10 hours at 20-25°C when prepared with drinking water or sterile water.

Background: The Product Quality Microbiology review consult request was to seek input on the adequacy of a microbiological challenge study to support proposed post-constitution hold times for baloxavir marboxil, 2 mg/mL. The subject drug product is indicated for the treatment of influenza and post-exposure prophylaxis of influenza in pediatric patients (i.e., one year of age and older). Baloxavir marboxil, 2 mg/mL is provided as non-sterile granules for oral suspension at a 2 mg/mL dose. Each 50 mL glass bottle contains 40 mg (nominal) of baloxavir marboxil. Table P.1.1 was provided in *Description and Composition of Drug Product* (Seq 0001, Section 3.2.P.1) for the composition of the subject drug product, which has been reproduced below.

Table P.1-1 Composition of Baloxavir Marboxil, Granules for Oral Suspension, 2 mg/mL

Component	Reference to Standards	Function	Quantity per Unit Dose (mg/bottle)	Concentration in Suspension per Bottle (mg/mL)
Baloxavir Marboxil	In-house standard	Active ingredient	40	2.0
Mannitol	USP/Ph. Eur./JP	(b) (4)		(b) (4)
Maltitol	NF/Ph. Eur./JPE			
Sodium Chloride	USP/Ph. Eur./JP			
Hypromellose	USP/Ph. Eur./JP			
Povidone (K value: 25)	USP/Ph. Eur./JP			
Colloidal Silicon Dioxide	NF/Ph. Eur./JP			
Sucralose	NF/Ph. Eur./JPE			
Talc	USP/Ph. Eur./JP			
Strawberry Flavor[a]	In-house standard			
(b) (4)			(b) (4)	
Total Weight[c]	—	—		100.0

(b) (4)

The drug product is tested for Microbial Limits at release per USP <61> and USP<62>. The Microbial Limits acceptance criteria are consistent with USP <1111> acceptance criteria for non-aqueous preparations for oral use. The drug product will also be tested for Microbial Limits at the end of shelf-life as part of the post-approval stability protocol.

The following instructions for preparation of the drug product for administration to a patient are provided in the package insert:

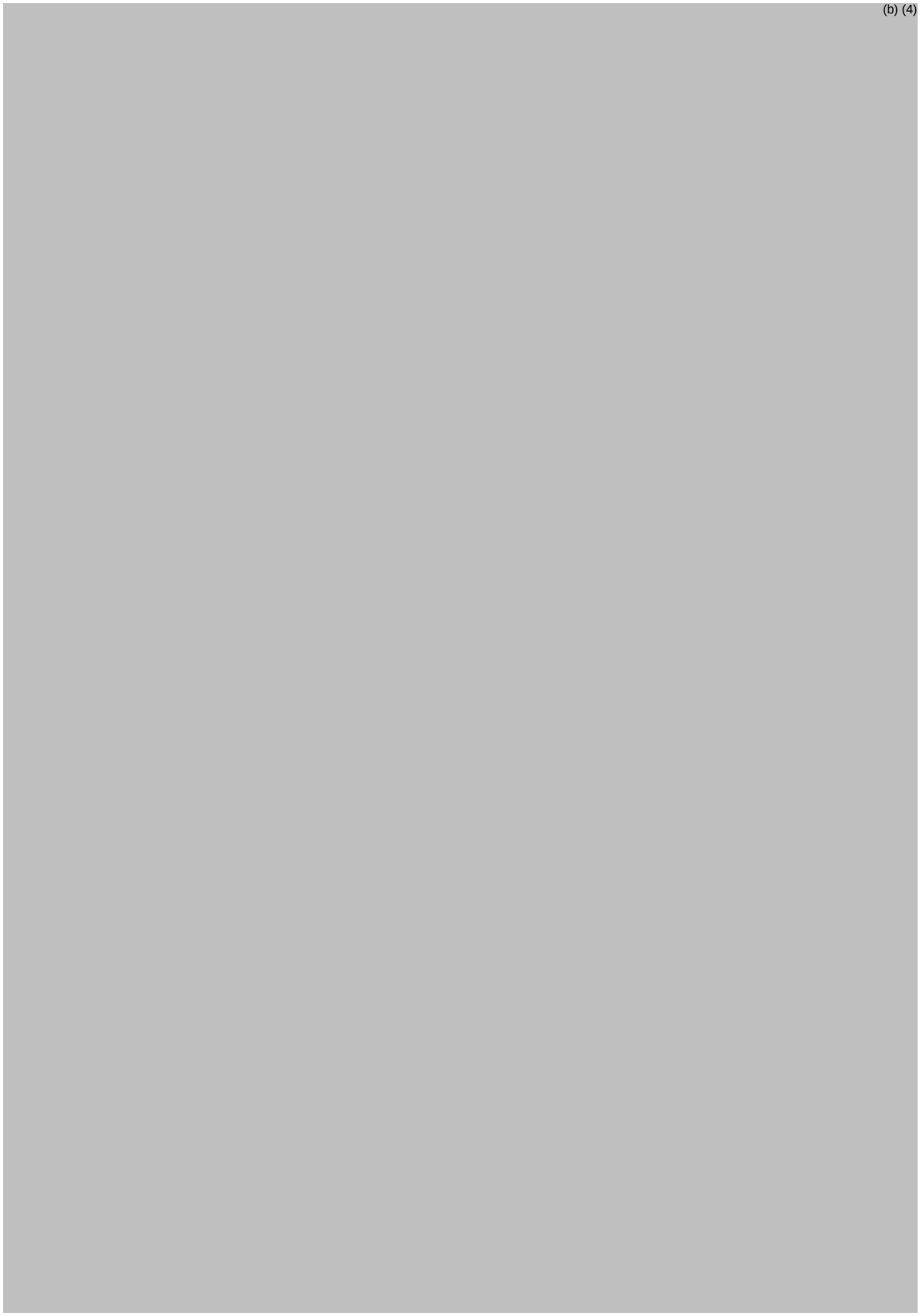
> *Prior to dispensing to the patient, constitute XOFLUZA for suspension with 20 mL of sterile water. After constitution, each bottle of XOFLUZA suspension contains 40 mg of baloxavir per 20 mL of volume for a final concentration of 2 mg/mL.*
>
> *Administration must occur within* (b) (4) *hours after constitution because the product does not contain a preservative.*

(b) (4)

The 04 August 2020 submission is a response to a 27 July 2020 Information Request by the CMC reviewer regarding a proposed (b) (4) hour post-constitution hold time. The original CMC Information Request and subject applicant response are

summarized below.

(b) (4)



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Although these results and the results from the recent study with sterile water may not be completely accurate and/or precise, the overall trend in the data suggests that the subject drug product constituted in sterile water or drinking water was not significantly growth promoting at 20-25°C up to 10 hours. Additionally, based on the route of administration (i.e., oral administration), the subject drug product is relatively low microbiological risk to patients. The following justifications were also provided by the applicant and taken into consideration by this reviewer in support of this hold time: 1) drinking water is expected to be free of *E. coli* as per regulations (21CFR129.35 and National Primary Drinking Water Regulations), 2) the product is to be constituted by the pharmacist and therefore the water to be used for constitution at the pharmacy should fulfill the requirements for drinking water in the US, and 3) the subject drug product is tested for microbial limits on release, which confirms the absence of *E. coli*. Therefore, the applicant has provided sufficient data along with their justifications to support the newly proposed post-constitution hold time for the subject drug product of 10 hours at 20-25°C when constituted in drinking water or sterile water.

Conclusion: The provided microbiological challenge studies support the proposed post-constitution hold time of 10 hours at 20-25°C when prepared with drinking water or sterile water.

END

Daniel Schu

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Erika Pfeiler

Digitally signed by Erika Pfeiler
Date: 10/02/2020 01:25:17PM
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