CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

217188Orig1s000

PRODUCT QUALITY REVIEW(S)

OPQ Joint Review Addendum (Review #3)

Application	NDA 217188		
Regulatory Pathway	505(b)(1)		
Applicant Name	Pfizer, Inc.		
Drug Product Name	PAXLOVID (nirmatrelvir tablets and ritonavir tablets) copackaged, for oral use		
Dosage Form	Tablets		
Proposed Strength(s)	150 mg nirmatrelvir tablets and 100 mg ritonavir tablets		
Indication	Treatment of mild-to-moderate COVID-19 in adult patients		
Assessment Cycle Number	1		
Clearance History	S. Anand 05/08/2023; E Chikhale 05/08/2023; G Gieser 5/8/2023		
Review Team	**Discipline**	**Primary**	**Secondary**
	Drug Substance	Katherine Windsor	Paresma Patel
	Drug Product/Labeling	Shalini Anand	David Claffey
	OPMA	Abdollah Koolivand	Hang Guo
	Biopharmaceutics	Gerlie Gieser	Elsbeth Chikhale
	Environmental Assessment	Xiaoqin Wu	James Laurenson
	RBPM	Erica Keafer and Musse Olani	
	ATL	David Claffey	

Assessment Recommendation: Adequate

Updated drug product stability data were provided representing several drug product manufacturing sites. The data continue to support the proposed 24 month drug product expiry period.

Document(s) Assessed	Date Received
Seq. 0158	May 01, 2023

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

Drug product:

Assessment Recommendation: Adequate

Assessment Summary:

<u>Drug Product Stability and Shelf Life-</u>

In the SN-158 amendment, Pfizer submitted the 18-month long-term (25°C/60%RH) and intermediate (30°C/75% RH) stability data for 3 primary stability batches (nirmatrelvir tablets packaged in (b) (4) *blister, manufactured at Freiburg site, lots FG9131, FJ1399 and FJ1400). The data met the proposed regulatory specifications.*

In addition, Pfizer submitted the 12 months of long-term and intermediate stability data for four batches of nirmatrelvir tablets manufactured at the Newbridge site (FT3310, FT3301, FT3313, FT3659, packaged in the (b) (4) *blister). The 6-month long term, intermediate and accelerated stability data for 3 PAXLOVID batches (containing nirmatrelvir tablets manufactured at Ascoli site, packaged with Hetero ritonavir tablets in the child resistant blister, lots- GE5412, GE5413 and GE5414) were also submitted. The Applicant also submitted the 6-weeks long-term, intermediate and accelerated stability data for 3 PAXLOVID batches (with nirmatrelvir tablets manufactured at* (b) (4) *site and packaged with child resistant blister pack, lot no-3225150, 3225512, 3225154). The data met the proposed regulatory specifications and demonstrate that the change in drug nirmatrelvir tablets manufacturing site has no impact on drug product stability profile.*

As captured in drug product review-1, the provided data still support the proposed 24-month shelf life for PAXLOVID at controlled room temperature.

Biopharmaceutics:

Assessment Recommendation: *Adequate*

Assessment Summary:

SN-158 includes the updated dissolution on stability data of seven [child-resistant (CR) [redacted] *blister] co-packaged Paxlovid lots from three nirmatrelvir tablet manufacturers (Pfizer-Freiburg, Pfizer-Ascoli and* [redacted]*). Specifically, the dissolution dataset is updated to include 12-month individual dissolution data for nirmatrelvir & ritonavir (Hetero) batch FX3846, 6-month nirmatrelvir & ritonavir (Hetero) individual dissolution data for batches GE5412, GE5413, GE5414 and 6-week nirmatrelvir & ritonavir (Abbvie) individual dissolution data for batches 3225150, 3225152 and 3225154.*

During up to 12 months of long-term (25°C 60%RH), up to 12 months of intermediate and up to 6 months of accelerated stability testing, these PAXLOVID lots were able to conform to the proposed/recommended nirmatrelvir dissolution acceptance criterion (Q = [redacted]*% at 30 min) by USP Stage 1 (n=6) testing, as well as to the approved ritonavir dissolution acceptance criterion by USP Stage 1 (n=6) or USP Stage 2 (n=12) testing.*

Additionally, based on this Reviewer's modeling using the "Stability Test" feature of the JMP software (version 16), the nirmatrelvir and ritonavir dissolution data [i.e., from the Paxlovid lot (FX3846) with at least 12 months of long-term (25°C 60%RH) stability data] continue to support the proposed PAXLOVID expiration dating period of 24 months.

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/

SHALINI ANAND
05/08/2023 04:25:55 PM

DAVID J CLAFFEY
05/08/2023 04:27:11 PM

OPQ Joint Review Addendum (Review #2)

Application	NDA 217188		
Regulatory Pathway	505(b)(1)		
Applicant Name	Pfizer, Inc.		
Drug Product Name	PAXLOVID (nirmatrelvir tablets and ritonavir tablets) copackaged, for oral use		
Dosage Form	Tablets		
Proposed Strength(s)	150 mg nirmatrelvir tablets and 100 mg ritonavir tablets		
Indication	Treatment of mild-to-moderate COVID-19 in adult patients		
Assessment Cycle Number	1		
Clearance History	K.Windsor 04/11/2023; P. Patel 4/11/2023; E. Chikhale 04/12/2023;S.Anand 04/13/2023		
Review Team	**Discipline**	**Primary**	**Secondary**
	Drug Substance	Katherine Windsor	Paresma Patel
	Drug Product/Labeling	Shalini Anand	David Claffey
	OPMA	Abdollah Koolivand	Hang Guo
	Biopharmaceutics	Gerlie Gieser	Elsbeth Chikhale
	Environmental Assessment	Xiaoqin Wu	James Laurenson
	RBPM	Erica Keafer and Musse Olani	
	ATL	David Claffey	

Assessment Recommendation: Adequate

Information was provided in this amendment to update the drug substance and drug product stability data and provide updates to the dissolution and ritonavir polymorph testing. The data continue to support overall approval recommendation and the drug

substance retest and drug product expiry periods in OPQ Review #1. Refer to the review notes below for more details.

Document(s) Assessed	Date Received
Seq. 0142	March 10, 2023

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

UPDATE SUMMARY

Drug substance:

Assessment Recommendation: Adequate.

Assessment Summary: *This addendum provides an assessment of the following drug substance information submitted since the original drug substance review (06-FEB-2023): 9-month stability data for (b) (4) nirmatrelvir drug substance.*

At the time of original drug substance review, long-term (30 °C/75% RH or 30 °C/65% RH) and accelerated (40 °C/75% RH) stability data were provided for 18 batches of (b) (4) drug substance: 9 batches through six months and 9 batches through 3 months. Supportive stability data were provided for three batches of (b) (4) drug substance through 6 months and one batch each of (b) (4) drug substance through 12 months. The totality of the information provided at that time was evaluated and found acceptable to support a (b) (4) retest period for nirmatrelvir drug substance for commercial supply stored at either (b) (4)

Updated long-term (30 °C/75% RH) stability data for the (b) (4) drug substance manufactured at Pfizer Ireland were provided through the 9-month timepoint (data submitted on 10-MAR-2023). No significant changes were noted. (b) (4) ; however, all stability data remained well within specification. The updated supporting stability data for (b) (4) drug substance support the proposed (b) (4) retest period for nirmatrelvir drug substance for commercial supply.

Drug product:

Assessment Recommendation: Adequate

Assessment Summary:

<u>Drug Product Stability and Shelf Life-</u>

In the SN-142 amendment, Pfizer submitted the 12-month long-term stability data for 3 EUA supply batches (FL4516, FL4517, FR7229) of PAXLOVID (nirmatrelvir tablets manufactured at Freiburg site and packaged with AbbVie ritonavir tablets in the child resistant blister pack). As discussed in drug product review #1, only nirmatrelvir tablets were tested for these batches beyond 6 months' time points for the long-term (25°C/60%RH) stability studies, due to availability of limited samples of these batches. However, for two of these EUA batches I.e., FL417 and FR7229, Pfizer submitted 12-month intermediate (30°C/ 75%RH) stability data for both ritonavir tablets and nirmatrelvir tablets. The 9-month stability data for the three non-US EUA supply batches of PAXLOVID (nirmatrelvir tablets from Freiburg site and ritonavir batches from Hetero, packaged in (b) (4) *blister, lots FX2130, FX2131 and FX3846) were also submitted. In this submission, Pfizer also submitted the 6-month stability data for two PAXLOVID batches (containing nirmatrelvir tablets from Freiburg site and ritonavir tablets from AbbVie –lots 1910752A and 285897) packaged in the proposed child resistant blister pack. The provided data of all these batches met the proposed regulatory specifications. The primary stability batches of nirmatrelvir tablets alone (packaged in the* (b) (4) *blister pack) were also manufactured at the Freiburg site, the 12-month long term and 6-month accelerated stability data of these batches was found acceptable (Refer drug product review-1 for additional details).*

The Applicant also submitted 9-month long term and intermediate stability data for four nirmatrelvir tablets batches (FT3310, FT3301, FT3313 and FT3659) manufactured at the Newbridge site and packaged in (b) (4) *blister pack. The 6-month stability data for one PAXLOVID batch containing nirmatrelvir tablets manufactured at the Newbridge site, packaged with ritonavir tablets from AbbVie in* (b) (4) *blister pack is also submitted. The data met the proposed regulatory specifications and demonstrate that the change in drug product manufacturing site do not impact the quality of the drug product.*

In addition, initial time point data for three PAXLOVID batches (3225150, 3225152, 3225154) containing nirmatrelvir tablets manufactured at the (b) (4) *site and packaged ritonavir tablets from AbbVie in the proposed commercial child resistant*

blister pack were submitted. The data met the proposed regulatory specifications. Pfizer agreed to a post marketing commitment and will submit the 3-month stability data for these three batches via a CBE-0 supplement.

Pfizer submitted the documentation to demonstrate that the (b) (4) *and child resistant blister pack are equivalent in providing protection from moisture and thus stability testing in* (b) (4) *blister pack is representative of child resistant (proposed commercial packaging) blister pack. (Refer to drug product review-1 for additional details). As captured in drug product review-1, the provided data still support the proposed 24-month shelf life for PAXLOVID at controlled room temperature conditions.*

(b) (4) ***Testing of Ritonavir Tablets-***

Pfizer previously submitted the updated release and stability specifications for Hetero and AbbVie ritonavir tablets with inclusion of (b) (4) test on 01-31-2023. The detailed analytical method and validation report are provided in this amendment. The (b) (4) This test is validated as a limit test for impurities and validated for specificity, limit of detection (LOD) and repeatability, as per the FDA guidance- Text on Validation of Analytical Procedures. The proposed LODs for (b) (4) are (b) (4) of the API load, respectively. The proposed LODs were found acceptable by the Drug Product and Biopharmaceutics review teams.

OPMA: NAI

Biopharmaceutics:

Assessment Recommendation: Adequate

Assessment Summary: An updated dissolution on stability dataset was provided in SN-142. During up to 12 months of long-term (25°C 60%RH), up to 12 months of intermediate and up to 6 months of accelerated stability testing, the PAXLOVID lots (consisting of nirmatrelvir 150 mg tablets from various manufacturers and the Abbvie-sourced or Hetero-sourced ritonavir 100 mg tablets co-packaged in child-resistant and (b) (4) foil/foil blisters) were able to conform to the proposed/recommended nirmatrelvir dissolution

acceptance criterion (Q = (b) (4)% at 30 min) by USP Stage 1 (n=6) testing, as well as to the approved ritonavir dissolution acceptance criterion by USP Stage 1 (n=6) or USP Stage 2 (n=12) testing.

Additionally, based on this Reviewer's modeling using the "Stability Test" feature of the JMP software (version 16), the nirmatrelvir and ritonavir dissolution data during up to 6 to 12 months of long-term (25°C 60%RH) storage continue to support the proposed PAXLOVID expiration dating period of 24 months.

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/

DAVID J CLAFFEY
04/17/2023 03:17:58 PM

NDA Executive Summary

1. Application/Product Information

NDA Number.	217188		
Applicant Name	Pfizer		
Drug Product Name	PAXLOVID (nirmatrelvir tablets and ritonavir tablets) copackaged, for oral use		
Dosage Form.	Tablets		
Proposed Strength(s)	150 mg nirmatrelvir tablets and 100 mg ritonavir tablets		
Route of Administration	Oral		
Maximum Daily Dose	Two nirmatrelvir tablets and one ritonavir tablet – twice daily for five days.		
Rx/OTC Dispensed	Rx		
Proposed Indication	Treatment of mild-to-moderate COVID-19 in adult patients		
Drug Product Description	Co-packaged Immediate Release Tablets		
Co-packaged product information	Dose packs of either one or two nirmatrelvir tablets and one ritonavir tablet. 10 Dose packs are contained within a carton.		
Storage Temperature/ Conditions	20ºC to 25ºC (68ºF to 77 ºF); excursions permitted between 15ºC to 30ºC (59ºF to 86ºF)		
Review Team	**Discipline**	**Primary**	**Secondary**
	Drug Substance	Katherine Windsor	Paresma Patel
	Drug Product/ Labeling	Shalini Anand	David Claffey
	Manufacturing	Abdollah Koolivand	Hang Guo

	Biopharmaceutics	Gerlie Geiser	Elsbeth Chikhale
	EA	Xiaoqin Wu	James Laurenson
	RBPM	Erica Keafer and Musse Olani	
	ATL	David Claffey	

2. Final Overall Recommendation - *Approval*

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

PAXLOVID is a co-packaged oral antiviral drug indicated for the treatment of mild-to-moderate COVID-19 in adult patients. The product is currently authorized for emergency use (EUA 105). The drug product blisters contain immediate release tablets of nirmatrelvir, 150 mg and ritonavir,100 mg. The marketing of two dosage presentations is proposed – they differ only in having either one or two nirmatrelvir tablets in each dose pack. The blister packs have been updated since the EUA to contain single doses – instead of the daily dose packs in the EUA product. Nirmatrelvir tablets are manufactured by the Applicant whereas the ritonavir tablets are sourced from two previously approved sources – AbbVie (NDA 22417) and Hetero (ANDA 204587). The NDA contains many updates from the EUA in terms of manufacturing sites, processes and controls. The data provided support the quality and labeling of the proposed product including a (b) (4) retest period for nirmatrelvir and a 24-month expiry period for both nirmatrelvir tablets and ritonavir tablets. The PAXLOVID co-packaged drug product expiry date will reflect the shorter expiry of the two components. Additional site-specific ((b) (4)) confirmatory nirmatrelvir tablets stability data are subject to a Post Marketing Commitment together with additional Environmental Assessment data.

b. Is the overall recommendation in agreement with the individual discipline recommendations? Yes

Recommendation by Subdiscipline:

Drug Substance - Adequate
Drug Product - Adequate
Quality Labeling - Adequate
Manufacturing - Adequate

Biopharmaceutics - Adequate
Microbiology - N/A

Environmental Assessment: Categorical Exclusion - Adequate
QPA for EA(s): Choose Yes or No.

5. Life-Cycle Considerations

Established Conditions per ICH Q12: No
Comments:

Comparability Protocols (PACMP): Yes
Comments: Three Comparability Protocols were found acceptable (b) (4) all CBE-30 supplements.

Additional Lifecycle Comments: Pfizer committed to submit CBE-0 supplement with the three-month long-term and accelerated stability data for three nirmatrelvir tablets batches manufactured at (b) (4) by 31 JUL 2023. Pfizer also committed to submit additional supporting assay data for the environmental assessment as a CBE-0 submission by 15 DEC 2023. PMC numbers for both commitments remain pending at completion of this assessment document.

95 Pages have been Withheld in Full as b4 (CCI/TS) immediately following this page

CHAPTER IV: LABELING

IQA NDA Assessment Guide Reference

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information:

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	PAXLOVID (nirmatrelvir tablets; ritonavir tablets), co-packaged for oral use	Adequate
Established name(s)	Nirmatrelvir tablets; Ritonavir tablets	Adequate.
Route(s) of administration	For oral use	Adequate.
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	Tablets: nirmatrelvir 150 mg Tablets: ritonavir 100 mg	Adequate
Controlled drug substance symbol (if applicable)	N/A	
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	Tablet: N/A	

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

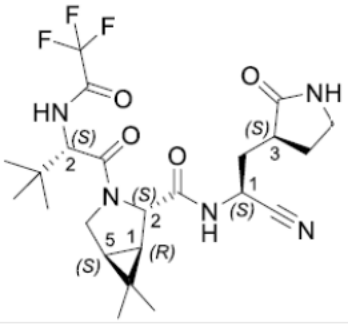
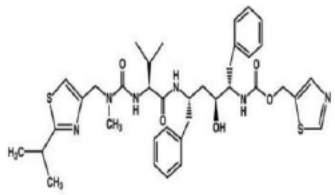
Item	Information Provided in the NDA	Assessor's Comments
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	PAXLOVID (both nirmatrelvir and ritonavir tablets) should be swallowed whole and not chewed, broken, or crushed.	Adequate The USPI of Norvir tablets (Abbvie, NDA 022417) include the following statement – 'Norvir tablets should be swallowed whole and not chewed, broken, or crushed'. The statement included in section 2 of the PAXLOVID USPI is in accordance with USPI of Norvir tablets.

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

Item	Information Provided in the NDA	Assessor's Comments
Available dosage form(s)	[PAXLOVID is nirmatrelvir tablets co-packaged with ritonavir tablets	Adequate.
Strength(s) in metric system	• Nirmatrelvir Tablet- Each tablet contains 150 mg of nirmatrelvir. • Ritonavir Tablet- Each tablet contains 100 mg of ritonavir.	Adequate
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	N/A	Adequate
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	• Nirmatrelvir is supplied as oval, pink immediate-release, film-coated tablets debossed with "PFE" on one side and "3CL" on the other side. Each tablet contains 150 mg of nirmatrelvir. • Ritonavir is supplied as white or white to off-white film-coated tablets uniquely identified by the color, shape, and debossing. Each tablet contains 100 mg of ritonavir.	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	Adequate
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	Adequate

1.2.3 Section 11 Description

Item	Information Provided in the NDA	Assessor's Comments
Proprietary and established name(s)	PAXLOVID is nirmatrelvir tablets co-packaged with ritonavir tablets.	Adequate
Dosage form(s) and route(s) of administration	Nirmatrelvir tablets co-packaged with ritonavir tablets.	Adequate
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	N/A	Adequate
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	Each nirmatrelvir tablet contains following inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, lactose monohydrate, microcrystalline cellulose, and sodium stearyl fumarate. The following are the ingredients in the film coating: hydroxy propyl methylcellulose, iron oxide red, polyethylene glycol, and titanium dioxide. Each ritonavir tablet contains following inactive ingredients: anhydrous dibasic calcium phosphate, colloidal silicon dioxide, copovidone, sodium stearyl fumarate, and sorbitan monolaurate. The film coating may include the following ingredients: colloidal anhydrous silica, colloidal silicon dioxide, hydroxypropyl cellulose, hypromellose, polyethylene glycol, polysorbate 80, talc, and titanium dioxide.	Adequate Hetero and AbbVie ritonavir tablets contain similar inactive ingredients, other than slight difference in the coating material inactive ingredients. The inactive materials of both Hetero and AbbVie tablets coating material are included in section 11.
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	Adequate
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Statement of being sterile (if applicable)	N/A	

Pharmacological/ therapeutic class	Nirmatrelvir is a SARS-CoV-2 main protease (Mpro) inhibitor, and ritonavir is an HIV-1 protease inhibitor and CYP3A inhibitor.	Pharm/ tox team confirmed the accuracy of the therapeutic class (commented in the PI)
Chemical name, structural formula, molecular weight	Nirmatrelvir- The chemical name is: 1R,2S,5S)-N-((1S)-1-Cyano-2-((3S)-2-oxopyrrolidin-3-yl) ethyl)-3-((2S)-3,3-dimethyl-2-(2,2,2 trifluoroacetamido) butanoyl)-6,6-dimethyl-3-azabicyclo [3.1.0]hexane-2-carboxamide] It has a molecular formula of C23H32F3N5O4 and a molecular weight of 499.54. Its structural formula is:  Ritonavir- The chemical name is: 10-Hydroxy-2-methyl-5-(1-methylethyl)-1- [2-(1 methylethyl)-4-thiazolyl]-3,6-dioxo-8,11-bis(phenylmethyl)-2,4,7,12- tetraazatridecan-13-oic acid, 5-thiazolylmethyl ester, [5S-(5R*,8R*,10R*,11R*)]. Its molecular formula is C37H48N6O5S2, and its molecular weight is 720.95. Its structural formula is: 	Adequate
If radioactive, statement of important nuclear characteristics.	N/A	

Other important chemical or physical properties (such as pKa or pH)	N/A	

1.2.4 Section 16 HOW SUPPLIED/STORAGE AND HANDLING section

Item	Information Provided in the NDA	Assessor's Comments
Available dosage form(s)	Tablets	Adequate.
Strength(s) in metric system	Supplied in two different dose packs- • 300 mg nirmatrelvir; 100 mg ritonavir • 150 mg nirmatrelvir; 100 mg ritonavir	Adequate.
Available units (e.g., bottles of 100 tablets)	• 300 mg/100 mg dose pack - Each blister card contains: 2 nirmatrelvir tablets (150 mg each) and 1 ritonavir tablets (100 mg each) - Each carton contains: 30 tablets divided in 10 blister cards • 150 mg/100 mg dose pack- - Each blister card contains: 1 nirmatrelvir tablets (150 mg each) and 1 ritonavir tablets (100 mg each) - Each carton contains: 20 tablets divided in 10 blister cards	Adequate.

Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Nirmatrelvir tablets: Oval, pink immediate-release, film-coated tablets debossed with "PFE" on one side and "3CL" on the other side. Ritonavir tablets: White film-coated ovaloid tablets debossed with the “a” logo and the code NK. (AbbVie tablets) Or White film-coated ovaloid tablets debossed with “NK” on one side. (AbbVie tablets) Or White to off-white, capsule-shaped, film-coated tablets debossed with “H” on one side and “R9” on the other side. (Hetero tablets)	Adequate - Pfizer proposed separate NDC number for PAXLOVID dose packs packed with Hetero or AbbVie ritonavir tablets. - Separate NDC numbers are proposed for PAXLOVID 150 mg/ 100 mg and 300 mg/100 mg dose packs. - Per the submission dated 02/08/2023, Pfizer intend to pack AbbVie ritonavir tablets for 150 mg/100mg dose pack. - In the submission dated 01-31-2023, Pfizer included additional description of AbbVie ritonavir tablets without ‘a’ logo (debossed with only NK on one side). Pfizer proposed different NDC codes for AbbVie ritonavir tablets with and without ‘a’ logo. Refer to DP review for additional details about this.
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.	Tablet: N/A	Adequate
Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to “Dispense in original container,” provide reason why (e.g. to protect from light or moisture, to maintain stability, etc.)	Tablet: None	Adequate
If the product contains a desiccant, ensure the size and shape differ	N/A	Adequate: Tablets are packaged in blister pack.

from the dosage form and desiccant has a warning such as "Do not eat."		
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Store at USP controlled room temperature 20ºC to 25ºC (68ºF to 77 ºF); excursions permitted between 15ºC to 30ºC (59ºF to 86ºF).	Adequate Up to 12-month of supporting stability data for nirmatrelvir tablets and 24-month of ritonavir tablets (in HDPE bottles) supports the proposed storage conditions.
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	Adequate
Include information about child-resistant packaging	Nirmatrelvir tablets and ritonavir tablets are supplied in separate blister cavities within the same child-resistant blister card.	Adequate

1.2.3 Other Sections of Labeling

1.2.4 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: Pfizer Labs, Division of Pfizer Inc., New York, NY 10017	Adequate.

Reviewer's Assessment of Package Insert: Acceptable

The CMC sections of the USPI are acceptable from DP perspective.

2.0 CARTON AND CONTAINER LABELING

IMAGES OF LABEL AND LABELING RECEIVED ON DEC 20, 2022

2.1 Container/Blister Label

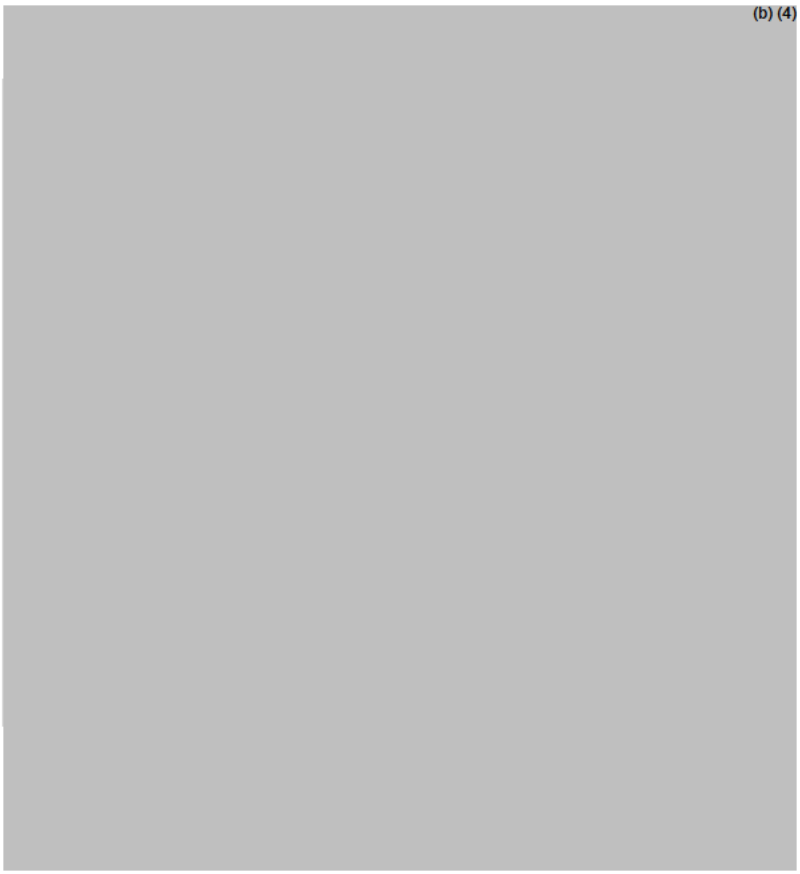
3 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Item	Information provided in the AbbVie 300 mg/100 mg blister label	Information provided in the Hetero 300 mg/100 mg blister label	Information provided in the AbbVie 150mg/100 mg blister label
Proprietary name, established name, and dosage form (font size and prominence	PAXLOVID™ (nirmatrelvir tablets; ritonavir tablets), co-packaged for oral use	PAXLOVID™ (nirmatrelvir tablets; ritonavir tablets), co-packaged for oral use	PAXLOVID™ (nirmatrelvir tablets; ritonavir tablets), co-packaged for oral use
Dosage strength	300 mg; 100 mg	300 mg; 100 mg	150 mg; 100 mg
Route of administration	For oral use	For oral use	For oral use
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	N/A	N/A	N/A
Net contents (e.g. tablet count)	3 Tablets	3 Tablets	2 Tablets
"Rx only" displayed on the principal display	Yes	Yes	Yes
NDC number	NDC 0069-5001-06 Or NDC 0069-5321-03 (Blister pack with AbbVie Ritonavir tablets debossed with NK' only)	NDC 0069-5045-06	NDC 0069-5017-04 Or NDC 0069-5317-02 (Blister pack with AbbVie Ritonavir tablets debossed with 'NK' only)
Lot number and expiration date	Yes	Yes	Yes
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	Not Included	Not Included	Not Included
Bar code	Yes	Yes	Yes
Name of manufacturer/distributor	Pfizer Labs, Division of Pfizer Inc., New York, NY 10017	Pfizer Labs, Division of Pfizer Inc., New York, NY 10017	Pfizer Labs, Division of Pfizer Inc., New York, NY 10017
Medication Guide (if applicable)	N/A	N/A	N/A
No text on Ferrule and Cap overseal	N/A	N/A	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	N/A	N/A
And others, if space is available	Take these 3 tablets together	Take these 3 tablets together	Take these 2 tablets together

2.2 Carton Labeling

(b) (4)



3 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Item	Information provided in the AbbVie 300 mg/100 mg Carton label	Information provided in the Hetero 300 mg/100 mg Carton label	Information provided in the AbbVie 150mg/100 mg Carton label
Proprietary name, established name, and dosage form (font size and prominence	PAXLOVID™ (nirmatrelvir tablets; ritonavir tablets), co-packaged for oral use	PAXLOVID™ (nirmatrelvir tablets; ritonavir tablets), co-packaged for oral use	PAXLOVID™ (nirmatrelvir tablets; ritonavir tablets), co-packaged for oral use
Dosage strength	300 mg; 100 mg Dose Pack	300 mg; 100 mg Dose Pack	150 mg; 100 mg Dose Pack
Route of administration	For oral use	For oral use	For oral use
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	N/A	N/A	N/A
Net contents (e.g. tablet count)	Each carton contains 30 tablets in 10 blister cards Each blister card contains 3 tablets: • 2 nirmatrelvir tablets (150 mg each) • 1 ritonavir tablet (100 mg each)	Each carton contains 30 tablets in 10 blister cards Each blister card contains 3 tablets: • 2 nirmatrelvir tablets (150 mg each) • 1 ritonavir tablet (100 mg each)	Each carton contains 20 tablets in 10 blister cards Each blister card contains 2 tablets: • 1 nirmatrelvir tablet (150 mg each) • 1 ritonavir tablet (100 mg each)
"Rx only" displayed on the principal display	Yes	Yes	Yes
NDC number	NDC 0069-5001-30 Or NDC 0069-5321-30	NDC 0069-5045-30	NDC 0069-5017-20 Or NDC 0069-5317-20
Lot number and expiration date	Yes	Yes	Yes
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	Store at room temperature 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F).	Store at room temperature 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F).	Store at room temperature 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F).
Bar code	Yes	Yes	Yes
Name of manufacturer/distributor	Pfizer Labs, Division of Pfizer Inc., New York, NY 10017	Pfizer Labs, Division of Pfizer Inc., New York, NY 10017	Pfizer Labs, Division of Pfizer Inc., New York, NY 10017
Medication Guide (if applicable)	N/A	N/A	N/A
No text on Ferrule and Cap overseal	N/A	N/A	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	N/A	N/A
And others, if space is available	Take all 3 tablets from one blister card together, twice daily (in morning and at bedtime) for 5 days.	Take all 3 tablets from one blister card together, twice daily (in morning and at bedtime) for 5 days.	Take both tablets from one blister card together, twice daily (in morning and at bedtime) for 5 days.

Assessment of Carton and Container Labeling: Adequate

The CMC information on the blister and carton labels are in accordance with information provided in quality sections of the NDA. The provided information is acceptable.

ITEMS FOR ADDITIONAL ASSESSMENT

N/A

Overall Assessment and Recommendation:

Refer to discussion above and recommendations in OND labeling.

Primary Labeling Reviewer Name and Date:

Shalini Anand, PhD, Branch 1; ONDP Division of New Drug Products I; OPQ

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

David Claffey, PhD, Branch Chief; ONDP Division of New Drug Products I; OPQ

Shalini Anand

Digitally signed by Shalini Anand
Date: 2/13/2023 11:44:15AM
GUID: 52795e43000905f07ea0803d93709d84

David Claffey

Digitally signed by David Claffey
Date: 2/13/2023 11:50:52AM
GUID: 508da71e00029e20b201195abff380c2

103 Pages have been Withheld in Full as b4 (CCI/TS) immediately following this page

CHAPTER VI: BIOPHARMACEUTICS

Product Information	
NDA Number	NDA 217188* (Associated with EUA 105 & IND 153517)
Drug Product Name/ Strength	PAXLOVID® [Nirmatrelvir Film-Coated Tablets/150 mg, co-packaged with externally sourced Norvir® or Hetero (Ritonavir) Film-Coated Tablets/100 mg]
Route of Administration	Oral
Applicant Name	Pfizer, Inc.
Therapeutic Classification/ OND Division	Nirmatrelvir: SARS-CoV-2 main protease inhibitor; Ritonavir: PK boosting agent of nirmatrelvir / Division of Antivirals
Indication	Treatment of mild-to-moderate COVID-19 in adult patients who are at high risk for progression to severe COVID-19, including hospitalization or death
Dosage	Nirmatrelvir/Ritonavir 300 mg/100 mg twice daily for 5 days, with or without food Swallow tablets whole; do not chew or crush. For patients with moderate renal impairment: Nirmatrelvir/Ritonavir 150 mg/100 mg twice daily, with or without food
*PAXLOVID was previously *authorized* for emergency use under EUA-000105 on 12/20/2021; this NDA requests FDA *approval* for US marketing. Letters of authorization (LOAs) to cross-reference the technical information in Abbvie's NDA 022417 for Norvir® Tablets 100 mg and in Hetero's ANDA 204587 for Ritonavir Tablets 100 mg were provided to the NDA Applicant. This Biopharmaceutics assessment focuses mainly on the nirmatrelvir component of the co-packaged drug product.	

Assessment Recommendation: APPROVAL

Assessment Summary:

Based on the available *in vitro* and *in vivo* data, nirmatrelvir (previously known as PF-07321332) exhibits the characteristics of a low solubility and low permeability drug substance, per BCS criteria.

Based mainly on the submitted *in vitro* dissolution profile data and *in vivo* PK data of target and variant nirmatrelvir 150 mg tablet lots investigated in Relative Bioavailability Study C4671008, the proposed QC dissolution method and acceptance criterion (as tabulated below) are considered adequate for the routine QC of Nirmatrelvir Film-Coated Tablets/150 mg at batch release and during shelf-life/stability testing.

USP Apparatus	Speed	Medium/Temperature	Volume	Acceptance criterion
II (Paddle)	75 rpm	0.05 M Sodium Phosphate, pH 6.8 with 0.2% Sodium Dodecyl Sulfate (SDS); 37 ± 0.5 ℃	900 mL	Q = (b) (4) % at 30 min

There were no formulation and manufacturing process-type changes to the nirmatrelvir tablets after initiation of the main part of the pivotal clinical trial (Study C4671005) that would have necessitated *in vivo* bridging data. Overall, for purposes of bridging to the final commercial nirmatrelvir 150 mg tablet drug product, the provided comparative *in vitro* nirmatrelvir dissolution profile data, additional CMC data and clinical information were deemed adequate to support the minor CMC changes that were introduced after conducting the pivotal clinical trial (specifically those related to the nirmatrelvir 150 mg tablet appearance/manufacturing sites/manufacturing process steps, and the nirmatrelvir drug substance manufacturing process/manufacturing sites, as well as related to the co-packaging of the nirmatrelvir tablets and ritonavir tablets). To support the Applicant's proposal to add suppliers for three nirmatrelvir tablet excipients, no additional dissolution data apart from those generated from routine QC testing are needed, since per the CMC reviewer's assessment there is no corresponding change in the technical grades of the excipients.

Additionally based on the *in vitro* ritonavir dissolution profile data/information provided in the Paxlovid® NDA, as well as the cross-referenced *in vivo* bioequivalence (BE) information that supported the approval of ANDA 204587, the nirmatrelvir PK-boosting performance of the externally sourced Norvir® (ritonavir 100 mg) Tablets (from Abbvie) and Hetero Lab's Ritonavir 100 mg Tablets is expected to be comparable/equivalent. Of note, Hetero's ritonavir tablets were co-administered with the nirmatrelvir tablets in the (double-blinded) pivotal clinical trial (Study C4671005) that supported Paxlovid®'s EUA, and Abbvie's Norvir® tablets was used as the Reference Standard/RLD in the BE study conducted to support the approval of Hetero's ritonavir tablets (ANDA 204587).

Per FDA recommendation, the originally submitted Comparability Protocols (CPs) for post-approval changes (b) (4)

List of Submissions Assessed and Relevant Documents in NDA 217188:

Documents	Date Received
SN-001 Original NDA	6/29/2022
SN-005 (QT Evaluation Report/TQT Waiver Request)	7/29/2022
SN-006 (includes CMC Wave 2)	7/29/2022
SN-012 (Response to Quality Information Request)	8/19/2022
SN-035 (CMC Wave 3)	9/30/2022
SN-053 (Quality IR Response)	10/26/2022
SN-054 (Response to Drug Product IR)	10/25/2022
SN-059 (Response to Biopharm IR)	11/3/2022
SN-063 (Response to Drug Product IR)	11/8/2022
SN-066 (Single Dose Blister Presentation)	11/10/2022
SN-073 (Response to Quality IR – including Biopharm)	11/23/2022
SN-089 (Response to Quality IR)	12/16/2022
SN-091 (CMC Wave 5 - includes dissolution datasets)	12/19/2022
SN-121 (Response to Quality IR – including dissolution)	1/31/2023

B.1 BCS DESIGNATION

Assessment:
This Reviewer agrees with the Applicant's classification of nirmatrelvir as a BCS IV (low solubility, low permeability) drug substance.

Solubility: *Low*
Based on the pH-solubility data in Table 3.2.P.2.2-15, the equilibrium total solubility (b) (4) of nirmatrelvir (b) (4) is pH-independent and low (0.98 to 1.21 mg/mL) across the physiologic pH range of 1.02 – 6.96. As reported in 3.2.S.1.3, the final pH values after 72 hours of solubility testing were all within 0.10 units of the initial pH values. Note that the standard clinical dosage of nirmatrelvir is 300 mg (two 150 mg tablets) when concomitantly administered with 100 mg ritonavir (one 100 mg tablet) taken orally twice daily for 5 days, with or without food.

(b) (4)

(b) (4)

Permeability: *Low*
Note that nirmatrelvir is a substrate of the CYP3A4 metabolizing enzyme and the P-glycoprotein (P-gp) drug efflux transporter. Co-administration with ritonavir (a CYP3A4 and P-gp inhibitor) is required to increase nirmatrelvir plasma concentrations to therapeutic levels.

Based on the results of the human Mass Balance study (Study 4671001/Part 4), it appears that <85% of the administered dose of nirmatrelvir was systemically absorbed following a single 300 mg dose of an oral suspension (*boosted* with four ritonavir 100 mg doses separated by 12 hours) in six healthy subjects. Per the Applicant, 27.5% of the administered dose was recovered in the feces potentially representing unabsorbed drug. The absolute oral bioavailability of nirmatrelvir 150 mg tablets has not been determined.

In vitro, the apparent passive permeability of nirmatrelvir from the apical to basolateral direction in Madin-Darby Canine Kidney (MDCK) cell line is low (i.e., $P_{app, A \rightarrow B} = 1.71 \times 10^{-6}$ cm/sec). Additionally, nirmatrelvir is a substrate of the P-glycoprotein efflux transporter in the Multidrug Resistance Mutation-1 (MDR1) - MDCK cell line. *In vitro* Caco-2 permeability data for nirmatrelvir were not provided.

Dissolution: *Not Rapid in Various pH Media Without Surfactant*
Within 30 minutes, approximately 55% to 60% of nirmatrelvir from the 150 mg tablet dissolves in 900 mL volumes of pH 1.2, pH 4.5 and pH 6.8 media, (USP Apparatus 2 at 75 rpm); refer to Figure 3.2.P.2.2-11.

Per the Applicant, *in vitro* and *in vivo* dissolution of nirmatrelvir (b) (4) is (b) (4)

B.2 DISSOLUTION METHOD AND ACCEPTANCE CRITERIA

Assessment:

DISSOLUTION METHOD - *ADEQUATE*

The proposed commercial QC dissolution method parameters for nirmatrelvir tablets are shown in excerpted Table 3.2.P.2.2-18.

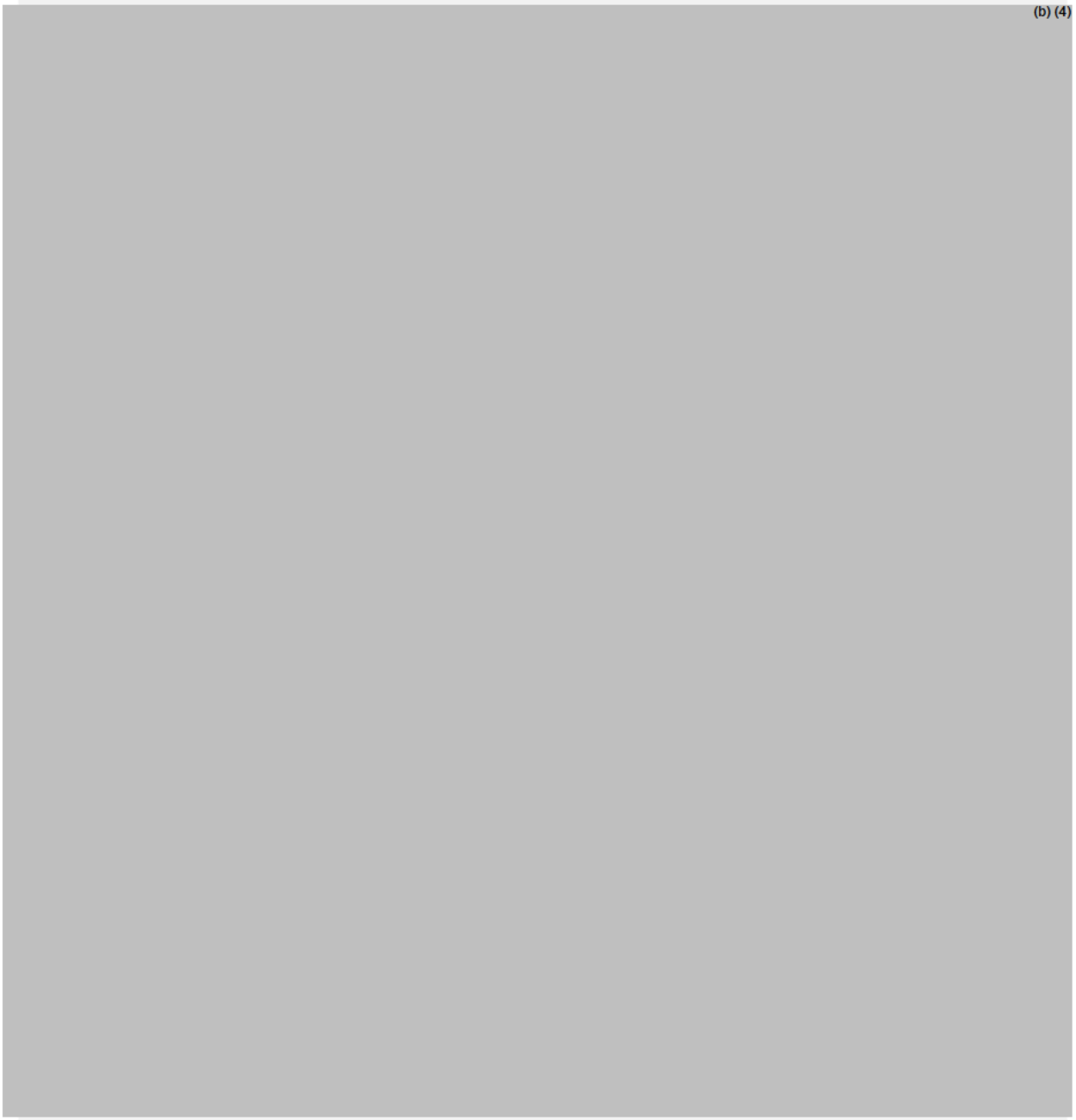
Table 3.2.P.2.2-18. Proposed Dissolution Method for Nirmatrelvir Tablets

Apparatus	USP Apparatus 2 (paddles)
Medium	0.05M Sodium Phosphate, pH 6.8 with 0.2% (w/v) Sodium Dodecyl Sulfate (SDS)
Volume	900 mL
Agitation rate	75 rpm
Temperature	37 °C
Analytical End Analysis	HPLC with UV detection at (b) (4) nm

Method TM-9379A

(b) (4)

1 Page has been Withheld in Full as b4 (CCI/TS) immediately following this page



Analytical Method Validation

HPLC with UV detection (b) (4) is used for quantification of nirmatrelvir in the dissolution samples. Analytical method validation included specificity, linearity, accuracy, precision, filter suitability, and analytical solution stability. Per the Applicant, the dissolution method was robust with respect to the following studied dissolution method parameter ranges: Paddle rate: 75 (b) (4) rpm; Medium % SDS: 0.20 (b) (4) %; Medium volume: 900 (b) (4) mL; Medium

Temperature: 37 (b) (4) °C (refer to Table 3.2.P.5.3-46). Per the Drug Product Reviewer (Dr. Shalini Anand), the analytical method validation for dissolution is acceptable.

(b) (4)

DISSOLUTION ACCEPTANCE CRITERION – *Acceptable (for routine QC testing of the target drug product)*

The proposed dissolution acceptance criterion for Nirmatrelvir Film-Coated Tablets/150 mg of "not less than (b) (4) % (Q) of the label claim is dissolved in 30 minutes" is acceptable based mainly on the following supporting data/information:

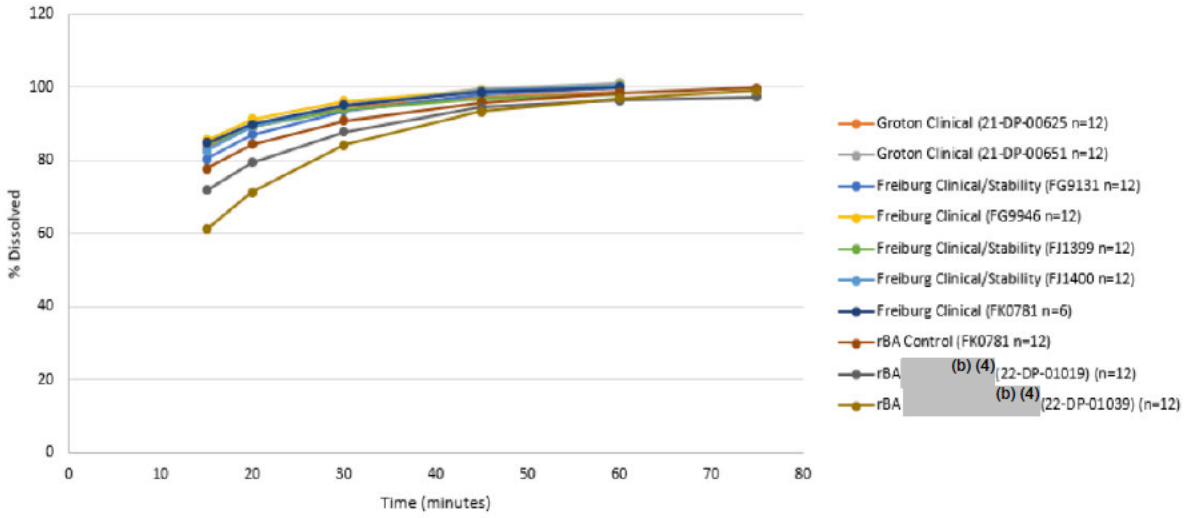
1. The results of completed Relative BA (rBA) Study 1008 that found comparable nirmatrelvir PK following single dose administrations of the target product and its (b) (4) variant, along with the dissolution profile data of these target/reference and variant tablet lots

(b) (4)

1 Page has been Withheld in Full as b4 (CCI/TS) immediately following this page

2. The dissolution profile data of the pivotal clinical trial lots, as shown in excerpted Figure 3.2.P.5.6-2 below.

Figure 3.2.P.5.6-2. Mean Dissolution Profile of Nirmatrelvir Film-Coated Tablet Clinical Batches at Release*



*rBA study supplies tested within 30 days of study C4671008 dosing

Although nirmatrelvir is a low solubility drug substance per BCS criteria, this Reviewer determines that a 2nd/early dissolution specification time point is not required (i.e., specifically to guard against premature drug release) based on the following considerations:

(1) As shown in the excerpted Figure above, the clinical lots were rapidly to very rapidly dissolving (i.e., ≥85% within 30 minutes). Note: The (b) (4) variant lot (**Batch 22-DP-01039**) that exhibited comparable PK to the target product in rBA Study 1008 exhibited a mean (range) dissolution of 84% (b) (4) at 30 min.
(2) The proposed drug product is intended for immediate drug release.
(3) Based on the analysis of the ECG data from the supratherapeutic dose cohort of PK Study C467001 and the ECG data from the sentinel cohort of COVID-19 patients in Study C4671005 and Study C4671002, as well as based on the results of nonclinical studies, the Applicant concluded (and the CDER-QT-IRT Team confirmed) that the combination of nirmatrelvir 300 mg and ritonavir 100 mg does not have a clinically meaningful effect on QT; refer to 2.7.4.4.2, as well as SN-5 of the NDA, as well as the CDER QT-IRT Review. Thus,

nirmatrelvir 150 mg tablet lots with significantly faster dissolution rate are not anticipated to pose a relative safety hazard, based on currently available nonclinical and clinical safety data.

(4) Based on the FDA recommended labeling edits, it appears that the major clinical safety concern related to PAXLOVID is drug-drug interaction potential associated with the ritonavir component. Since anti-COVID efficacy relies upon the nirmatrelvir component, assurance of adequate nirmatrelvir bioavailability (through attainment of a minimum dissolution rate) appears critical.

Dissolution on Stability

Co-Packaged Nirmatrelvir/Ritonavir Tablets in Child-Resistant (CR) Foil/Foil Blister:

Based on up to 9 months of long-term (25°C/60% RH), intermediate (30°C/75% RH) and up to 6 months of accelerated (40°C/75% RH) stability data, the three US EUA supply CR foil/foil blister packaged PAXLOVID Lots FL4516, FL4517, and FR7229 (consisting of Pfizer Freiburg-manufactured nirmatrelvir 150 mg tablets using (b) (4) /Ringaskiddy nirmatrelvir drug substance, and Abbvie's ritonavir 100 mg tablets), demonstrated ability to conform to the proposed nirmatrelvir dissolution acceptance criterion (Q = (b) (4) % at 30 min) and the approved Norvir® dissolution acceptance criterion (Q = % at 120 min) both by USP Stage 1 (n=6) testing. The packaging of these three lots is consistent with that described in Section 3.2.P.7.1 Container Closure System; refer also to Table 3.2.P.8.1-1 in SN-73.

- Using the "Stability Test" analysis feature of JMP 15, this Reviewer's modeling suggests that based on the nirmatrelvir dissolution (at 30 minute) data onbtained during 9 months long-term stability storage of US EUA Supply PAXLOVID (copackaged nirmatrelvir tablets and ritonavir) Lots FL4516, FL4517, and FR7229, the earliest crossing time of the 95% confidence intervals with the nirmatrelvir dissolution tolerance limit of "(b) (4) % at 30 min" is approximately 33.8 months (refer to Reviewer Figure 2A below). Using the dissolution data obtained over 7 months of intermediate testing, the earliest crossing time is 44.2 months (refer to Reviewer Figure 2B below). Thus, it appears that the proposed PAXLOVID expiration dating period of 24 months at room temperature storage is supported by the nirmatrelvir dissolution stability modeling results for these three US EUA Supply PAXLOVID lots. Note that modeling could not be performed for the ritonavir component of PAXLOVID because only Month 0 (initial) ritonavir dissolution on long-term stability data were available. However, using ritonavir dissolution data obtained during 6 months intermediate stability storage, the model-predicted an earliest crossing time with the ritonavir dissolution tolerance limit of "Q = (b) (4) % at 120 min" at 85.5 months with 95% confidence. *The final determination of the product's shelf-life is deferred to the Drug Product Reviewer.*

Reviewer Figure 2A PAXLOVID Shelf-life Determination Based on Predicted Nirmatrelvir Dissolution at 30 min Data During Long-Term Storage (Per ICH Q1E Guidelines)	Reviewer Figure 2B PAXLOVID Shelf-life Determination Based on Predicted Nirmatrelvir Dissolution at 30 min Data During Intermediate Stability Storage (Per ICH Q1E Guidelines)
(b) (4)	

Based on 3 months of long-term and accelerated stability data, the co-packaged "Stability" PAXLOVID CR foil/foil co-packaged tablet lot [2858974] consisting of nirmatrelvir tablets manufactured by Freiburg/Germany using (b) (4) nirmatrelvir drug substance, and ritonavir 100 mg tablets supplied by Abbvie, conforms to the approved Norvir® dissolution acceptance criterion (Q = (b) (4)% at 120 min) by USP Stage 1 (n=6) testing.

Three (3) months nirmatrelvir and ritonavir (long-term and accelerated) stability data were submitted for three additional CR foil/foil co-packaged tablet lots [GE5412, GE5413, GE5414] consisting of nirmatrelvir tablets manufactured by Ascoli using (b) (4) nirmatrelvir drug substance, and Hetero Ritonavir 100 mg tablets. Based on up to 3 months dissolution on stability data of these three lots, the nirmatrelvir tablets are able to conform to Q = (b) (4)% at 30 min by USP Stage 1 (n = 6) testing whereas the ritonavir tablets are able to conform to Q = (b) (4)% at 90 min by USP Stage 2 (n = 12) testing.

Co-Packaged Nirmatrelvir/Ritonavir Tablets in (b) (4) Foil/Foil Blister:
Based on up to 6 months of long-term, intermediate, and accelerated stability data for three Non-US emergency supply PAXLOVID (b) (4) foil/foil co-packaged tablet lots [FX2130, FX2131, FX3846] consisting of nirmatrelvir tablets manufactured by Freiburg using (b) (4) nirmatrelvir drug substance, and ritonavir 100 mg tablets supplied by Hetero, the nirmatrelvir tablets in PAXLOVID Lots FX2130, FX2131, FX3846 were able to conform to the proposed dissolution acceptance criterion (Q = (b) (4)% at 30 min) by USP Stage 1 testing. As well, the co-packaged

Hetero Ritonavir 100 mg Tablets were able to conform to the approved dissolution acceptance criterion [NLT (b) (4)% (Q) at 90 min] by USP Stage 1 testing.

Based on 3 months of long-term, intermediate, and accelerated stability data, the co-packaged "Stability" PAXLOVID (b) (4) foil/foil co-packaged tablet lot [FY1865] consisting of nirmatrelvir tablets manufactured by Newbridge/Ireland using (b) (4) nirmatrelvir drug substance, and ritonavir 100 mg tablets supplied by Abbvie,
demonstrated ability to conform to the proposed nirmatrelvir tablets dissolution acceptance criterion (Q= (b) (4)% at 30 min) and the approved Norvir® dissolution acceptance criterion (Q = % at 120 min), both by USP Stage 1 (n=6) testing.

Per the Applicant, the stability data observed to date for the co-packaged nirmatrelvir 150 mg tablets and ritonavir 100 mg tablets are consistent with those observed for the separately commercially foil/foil blister packaged nirmatrelvir tablets.

The proposed expiration dating period of the PAXLOVID® (nirmatrelvir 150 mg tablets and ritonavir tablets packaged in a common aluminum/aluminum foil blister card) is 24 months when stored under USP Controlled Room Temperature conditions. *Refer to the Drug Product Review for the assessment of the acceptability of the proposed expiration dating period of 24 months for the proposed commercial product.*

B.4 APPLICATION OF DISSOLUTION/IVIVC IN QbD

Assessment: *Adequate*

Dissolution and Nirmatrelvir Drug Substance Particle Size Distribution
The proposed drug substance particle size distribution acceptance criteria (d_{90} NMT (b) (4) µm, d_{50} NMT (b) (4) µm) is supported by the *in vitro* dissolution and *in vivo* PK results of completed rBA Study 1008 that included "(b) (4)" variant nirmatrelvir tablet lots using input (b) (4) drug substance lot (22-AP-00733) manufactured by Pfizer-Groton/USA. For the CMC information of nirmatrelvir DS Lot 22-AP-00733, refer to Table 3.2.S.4.5-4.

The proposed API d_{50} and d_{90} acceptance criteria encompass the particle size of the nirmatrelvir (b) (4) drug substance lots from Pfizer Sandwich/UK that were used to manufacture 150 mg tablets for the pivotal Phase 3 clinical trial, as well as the historical batch ranges as reported by the Applicant (at the time of NDA submission) particularly for those produced using the proposed final nirmatrelvir drug substance manufacturing process (b) (4) by Pfizer Ringaskiddy/Ireland, (b) (4)

Drug Substance Synthetic Process	Nirmatrelvir Drug substance Lot Number	Nirmatrelvir Drug Substance Particle Size Distribution[a]		
		API d_{90} (um)	API d_{50} (um)	API d_{50} (um)
(b) (4)	21-AP-00640	(b) (4)		-
	21-AP-00642			-
	21-AP-00581			-
	21-AP-00594			-
	(e.g., 22-AP-00733)			-

[a] measured by (b) (4)
[b] 3.2.S.4.4. Batch Analyses
Refer to the DS review for further details and evaluation of the particle size distribution acceptance criteria.

B. 12 BRIDGING

Assessment: *Adequate*

Majority (~98%) of the non-hospitalized COVID-19 patients in the pivotal clinical trial (Study C4671005; EPIC-HR) were administered the 150 mg nirmatrelvir tablets manufactured using the final proposed commercial formulation/process, or placebo treatment. Nirmatrelvir pharmacokinetic (PK) and/or pharmacodynamic (PD) data from healthy subjects and/or mild-to-moderate COVID-19 patients (enrolled in EPIC-HR and other Phase 2/3 clinical trials) when coadministered with ritonavir are also available. Thus, additional *in vivo* clinical PK/PD/efficacy/safety data/information are not needed to establish the bridge from the final pivotal clinical trial product to the proposed commercial EUA formulation/process product. [For the comparison of the formulation compositions and other quality attributes of the immediate release nirmatrelvir tablets that were used during clinical development, refer to Table 3.2.P.2.2-4 and Table 3.2.P.2.2-5. For the comparison of the manufacturing process/site details of the pivotal clinical, registration stability and proposed 150 mg nirmatrelvir tablets, refer to Table 3.2.P.2.3-1. For details regarding the available PK and PD data/information for the final pivotal clinical/commercial nirmatrelvir 150 mg tablet formulation and prior clinical development formulations, refer to the 'Reviewer Note 1' section below.]

As shown in excerpted Table 3.2.P.2.2-5, two of three 150 mg nirmatrelvir tablet lots evaluated in the pivotal Phase 3 clinical trial were manufactured by Pfizer Groton/USA; the third Phase 3 clinical trial lot (which is also 1 of 3 primary registration/stability lots) was manufactured by the final proposed (EUA-stage) drug product manufacturing site, Pfizer Freiburg/Germany, at a similar batch size range

((b) (4) ; Lot FG9131). All three primary registration/stability lots were manufactured at the Freiburg site (b) (4) using nirmatrelvir API from the clinical supplier (Pfizer Sandwich/UK) synthesized using either drug substance (b) (4) (clinical process) or (b) (4) (1 of 2 final proposed drug substance processes at the time of authorization of PAXLOVID for emergency use).

For the minor CMC changes that were made to the 150 mg nirmatrelvir tablet at the post-pivotal clinical trial stage, i.e., including changes in the drug product manufacturing site, drug substance synthetic route, tablet appearance, and/or changes/differences in drug product manufacturing (b) (4) step or batch size, comparative *in vitro* dissolution profile data (especially as generated by a QC dissolution method that is clinically relevant) and/or CMC data are deemed sufficient for bridging from the clinical/primary stability product to the commercial product. The dissolution profile data of the nirmatrelvir tablet batches that provide support to these minor CMC changes are discussed in more detail below.

Table 3.2.P.2.2-5. Nirmatrelvir Drug Product Clinical Lot Genealogy Table

Drug Product Description	Drug Product Batch Number	Drug Product Manufacturing Site	Drug Substance Batch Number	Drug Substance Synthetic Route	Drug Substance Manufacturing Site	Clinical Study Number
EP oral suspension	N/A	PCRU [a] New Haven, USA and Brussels, BE	21-AP-00525	(b) (4)	(b) (4)	C4671001, C4671015
250 mg IR tablet core	21-PN-00103	Groton, USA	21-AP-00525			C4671001
100 mg film-coated tablet	21-DP-00508	Groton, USA	21-AP-00521			C4671005 [b], C4671010, C4671011, C4671012, C4671013
150 mg film-coated tablet	21-DP-00625	Groton, USA	21-AP-00581		Pfizer Sandwich, UK	C4671005
150 mg film-coated tablet	21-DP-00651	Groton, USA	21-AP-00581		Pfizer Sandwich, UK	C4671002, C4671005, C4671006, C4671014
150 mg film-coated tablet	FG9131 [c]	Freiburg, Germany	21-AP-00594		Pfizer Sandwich, UK	C4671005, C4671006
150 mg film-coated tablet	FG9946	Freiburg, Germany	21-AP-00594		Pfizer Sandwich, UK	C4671002, C4671006
150 mg film-coated tablet	FJ1399 [d]	Freiburg, Germany	21-AP-00640		Pfizer Sandwich, UK	C4671006, C4671026
150 mg film-coated tablet (debossed)	FJ1400 [e]	Freiburg, Germany	21-AP-00642		Pfizer Sandwich, UK	C4671016
150 mg film-coated tablet (debossed)	FK0781	Freiburg, Germany	21-AP-00640 & 21-AP-00642		Pfizer Sandwich, UK	C4671006, C4671008, C4671019, C4671024, C4671026
150 mg film-coated tablet (b) (4)	22-DP-01019	Groton, USA	22-AP-00733		Pfizer Sandwich, UK	C4671008
150 mg film-coated tablet (b) (4)	22-DP-01039	Groton, USA	22-AP-00733		Pfizer Sandwich, UK	C4671008
PF-07321332 500 mg/g (b) (4)	21-PN-00132	Bend, USA	21-AP-00594		Pfizer Sandwich, UK	C4671008
PF-07321332 200 mg/g (b) (4)	22-DP-01036	Groton, USA	21-AP-00707		Pfizer Sandwich, UK	C4671024

a. Pfizer Clinical Research Unit (PCRU)
b. Used in the C4671005 sentinel cohort only.
c. 1st registration stability batch.
d. 2nd registration stability batch.
e. 3rd registration stability batch. Debossed with PFE and 3CL.

Note that (as shown in Reviewer Figure 1 above) all the nirmatrelvir 150 mg tablet lots manufactured with these minor CMC changes (as well as additional post-clinical lots manufactured to date) exhibited nirmatrelvir dissolution profiles (at batch release

or initial time point) that are higher than the dissolution profile of rBA Study 1008's [redacted] (**22-DP-01039**) [redacted].

1) Change in Nirmatrelvir 150 mg Tablet (Drug Product) Manufacturing Site (Pfizer Groton → Pfizer Freiburg + Pfizer Newbridge + Pfizer Ascoli → … + [redacted]:

At the time of the EUA request, the only proposed commercial nirmatrelvir 150 mg tablet manufacturing site was Pfizer, Freiburg/Germany.

- Since a 150 mg nirmatrelvir tablet lot (FG9131) produced by the Freiburg/Germany site was introduced into the pivotal clinical trial (Study 1005, as confirmed by the Applicant in the EUA/SN-006 IR Response) and in registration stability studies, *in vitro* bridging to the 150 mg tablets produced by the original pivotal clinical trial drug product manufacturer (Pfizer, Groton/USA) is not necessary. Nevertheless, the comparable *in vitro* dissolution profile data of Pivotal Clinical Study 1005 (EPIC-HR) Lot 21-DP-00625 (Groton/USA) and Supportive Phase 2/3 Clinical Study 1006 (EPIC-PEP) Lot FG9946 (Freiburg/Germany) in various pH media (without surfactant) and using the proposed QC dissolution method (with surfactant) confirm the equivalence of the two drug product manufacturing sites, and further supports the use of both Groton- and Freiburg- manufactured 150 mg nirmatrelvir tablets in the pivotal Phase 3 clinical trial (Study 1005). For the supporting comparative dissolution profiles, refer to Figure 3.2.P.2.2-24 through Figure 3.2.P.2.2-27.

- More recently, additional Freiburg-manufactured nirmatrelvir 150 mg tablet lots have been used in other clinical studies [e.g., Phase 2/3 Study C4671002 (EPIC-SR), rBA Study C4671008, Food-Effect Study C4671019, rBA Study C4671024, Phase 2/3 Study C4671026 (EPIC-Peds)], as shown in excerpted Table 3.2.P.2.2-5 above.

Since the granting of the EUA request, three additional nirmatrelvir 150 mg tablet manufacturers/manufacturing sites, i.e., Pfizer/Newbridge (Ireland), [redacted] and Pfizer Ascoli/Italy have also been authorized.

- Adequate evidence of comparable *in vitro* dissolution profile data to the Freiburg-manufactured nirmatrelvir 150 mg tablet lots in various pH media (without surfactant) and using the proposed QC dissolution method were provided to support the post-EUA addition of these three additional nirmatrelvir 150 mg tablet manufacturing sites; refer to the Biopharmaceutics (bridging) assessments for EUA-105/SN-63, SN-117, and SN-140,

respectively, and Section 3.2.P.2.2.8.4 and Section 3.2.P.2.2.8.5, as well as Reviewer Figure 1 above.

After the original NDA (217188) submission, the addition of [redacted] as an alternate nirmatrelvir 150 mg tablet manufacturing site was proposed.

- Adequate evidence of comparable *in vitro* dissolution profile data to the reference nirmatrelvir 150 mg tablet lot (manufactured by Pfizer Freiburg using input nirmatrelvir drug substance from [redacted]) in various pH media (without surfactant) and using the proposed QC dissolution method were provided to support addition of [redacted] as alternative nirmatrelvir 150 mg tablet manufacturing site, i.,e., when using input nirmatrelvir drug substance from one of the already authorized manufacturers [redacted] Refer to Section 3.2.P.2.2.1.6.

- Relative to the slowest dissolving nirmatrelvir 150 mg tablet Lot 22-DP-01039 in rBA Study 1008, the [redacted] batches exhibited higher mean dissolution profiles and higher minimum individual unit values for dissolution at 30 minutes (refer to Reviewer Figure 1 above).

2) Change in Drug Substance Synthetic Process and Manufacturing Site [redacted]

At the time of the EUA request, the proposed commercial drug substance synthetic routes were [redacted] the proposed commercial drug substance manufacturing sites were Pfizer Ringaskiddy/Ireland and [redacted]

- Nirmatrelvir Drug Substance Manufacturing Process. The comparable *in vitro* dissolution profile data of Primary Registration/Phase 3 Clinical Drug Product Lot # FG9131 (DS Process [redacted] and Primary Registration/Clinical Lot # FJ1399 (DS Process [redacted] (using the proposed QC dissolution method) supports the conclusion that change in drug substance synthetic process from [redacted] is not anticipated to impact drug product performance. Note that these two compared lots were manufactured by Pfizer Freiburg at the same commercial scale using input drug substance from the same supplier, and are both [redacted] tablet lots. [Additionally, evidence of superimposable *in vitro* dissolution profiles in various pH media (without surfactant) and using the proposed QC dissolution method were provided for Freiburg-manufactured [redacted] tablet Lot FG9946 and [redacted] tablet Lot FJ1400 (which used 'Process [redacted] and 'Process [redacted] input drug substance

lots, respectively); refer to Section 3.2.P.2.2.8.2. As discussed in more detail below further evidence is available to enable this Reviewer to conclude that the presence/absence of (b) (4) did not significantly impact the observation of comparable dissolution profiles between these two tablet lots despite the difference in the ingoing drug substance synthetic routes (i.e., (b) (4)] Furthermore, notwithstanding the (b) (4) differences, the evidence of superimposable *in vitro* dissolution profiles in various pH media (without surfactant) provided for both Freiburg-manufactured tablet lots (FJ1400 and FP4796) both using ingoing Pfizer Sandwich-sourced drug substance produced via "Process (b) (4) and "Process (b) (4), respectively, supports extension of the bridge to the final commercial drug substance synthetic route (b) (4); refer to Table 3.2.P.2.2-75 and the associated Tables and Figures. [Note that earlier drug substance Processes (b) (4) were not used to produce lots for the pivotal clinical trial or primary stability studies; Process (b) (4) was used to manufacture the 100 mg nirmatrelvir tablet formulation evaluated in the sentinel cohort of Study 1005 and in one of the (first generation) 150 mg tablet supportive stability batches.]

- Nirmatrelvir Drug Substance Manufacturer/Manufacturing Sites For Route (b) (4) and Other Routes used for Pivotal Clinical Trial Supply. Pfizer, Sandwich/UK supplied the ingoing Process (b) (4) or Process (b) (4) drug substance lots for the Phase 3 clinical trial (Study 1005) and prim ry registration/stability studies. Per the Drug Substance Reviewer, the provided drug substance batch analysis data were adequate to support the EUA manufacturing sites (i.e., Pfizer Ringaskiddy/Ireland and (b) (4)) and the two proposed synthetic routes (b) (4)

Since the granting of the EUA request, the additions of (b) (4) as alternative drug substance manufacturers have been authorized; refer to the Drug Substance Review for EUA-105/SN-60, and Drug Substance Review for EUA-105/SN-134, respectively.

- As shown in excerpted Table 3.2.P.2.2-5 above, drug substance lots using *'Route (b) (4) /Pfizer Sandwich* have since emergency authorization of Paxlovid been used to manufacture two nirmatrelvir tablet lots (22-DP-01019 and **22-DP-01039**) that were demonstrated to have comparable PK to the reference (commercial EUA) nirmatrelvir 150 mg tablet lots (based on the results of completed Relative BA Study 1008).

- Note that the already authorized additions of Pfizer Newbridge/Ireland, (b) (4) and Pfizer Ascoli/Italy as drug product manufacturers (via EUA-105/SN-63, SN-117, and SN-140, respectively) were supported in part by the *in vitro* dissolution profile data of Pfizer Newbridge-manufactured,

(b) (4)-manufactured and Pfizer Ascoli-manufactured drug product lots using input (b) (4) drug substance batches supplied by (b) (4) (b) (4) Refer to Table 3.2.P.2.2-37 of the NDA for details regarding the ingoing drug substance routes and suppliers used to manufacture the pre-change/reference and post-change/test nirmatrelvir 150 mg tablet lots used in these comparative *in vitro* dissolution studies. For example, the evidence of superimposable *in vitro* dissolution profiles in various pH media (without surfactant) provided for Newbridge-manufactured debossed tablet Lots FR2906 and FR3678 versus reference Freiburg-manufactured debossed tablet Lot FP4796, (all using ingoing (b) (4) drug substance) supports use of (b) (4) as final commercial drug substance suppliers, in addition to Pfizer Sandwich which (as mentioned above) provided input drug substance for the manufacture of the pivotal clinical and other clinical lots; refer to Table 3.2.P.2.2-75 and the associated tables and figures.

- Additionally as provided in SN-6, the comparative *in vitro* dissolution profile data in various pH media of the nirmatrelvir 150 mg tablet lot (GD4172) produced by Pfizer Freiburg using input nirmatrelvir (b) (4) *Pfizer Ringaskiddy* drug substance were comparable to those for the reference Freiburg-manufactured lot (FR6824) using input nirmatrelvir (b) (4) drug substance, thereby providing further support for the addition of the Ireland site as a nirmatrelvir (b) (4) drug substance manufacturing site. Refer to Figures 3.2.P.2.2-54, -55, and -56. Note also that (as shown in Reviewer Figure 1 above) the mean dissolution profile data and the minimum individual dissolution at 30 min value of Lot GD4172 are both higher than those for rBA Study's (b) (4) tablet lot (**22-DP-01039**). Note that nirmatrelvir tablet Lots FR6824 and GD4172 differ in terms of (b) (4) and the manufacturing batch sizes; however, as stated above, this Reviewer determined that (b) (4) did not contribute to significant nirmatrelvir tablet dissolution changes, and it is noted that the batch size difference is less than 10-fold (i.e., (b) (4) kg versus (b) (4) kg). Note that per 3.2.P.3.2, the proposed commercial batch size range is (b) (4) kg to (b) (4) kg).

- In SN-6, evidence was provided that the *in vitro* dissolution profiles in various pH media from nirmatrelvir 150 mg tablet lot (3209523R) produced by (b) (4) using input (b) (4) nirmatrelvir drug substance sourced from (b) (4) were comparable to those from the reference drug product lot (i.e., with f_2 >50 values). Additionally, evidence was provided that the average dissolution profile data and the minimum individual unit dissolution at 30 min value of Lot 3209523R using the proposed QC

dissolution method was not lower than rBA Study 1008's slowest dissolving tablet Lot **22-DP-01039**.

The NDA proposes the addition of [redacted] as a [redacted] nirmatrelvir drug substance manufacturer.

- In SN-35, the dissolution profile data (in various pH media without surfactant and using the QC dissolution method) of Pfizer-Freiburg nirmatrelvir film-coated debossed tablet lot (GH5539) using ingoing drug substance lot sourced from [redacted] were shown to be comparable to those from the reference Pfizer-Freiburg [redacted] tablet lot (FR6824) using ingoing [redacted] drug substance lot sourced from [redacted] [As explained above, data suggest that the [redacted] on the tablet does not significantly influence nirmatrelvir dissolution data.] For the data/information that supported the addition of [redacted] as a "[redacted] nirmatrelvir drug substance manufacturer, refer to Table 3.2.P.2.2-117, the comparative multi-pH dissolution profile data in Figure 3.2.P.2.2-57, Figure 3.2.P.2.2-58, and Figure 3.2.P.2.2-59, as well as the comparative QC dissolution profile data in Reviewer Figure 1. Additionally, at batch release, tablet lot GH5539 was reported to conform to the dissolution acceptance criterion (Q = [redacted]% at 30 min) by USP Stage 1 (n=6) testing. Of note, per the Drug Substance Reviewer, the batch analyses data of the ingoing drug substance lot (0030008161) were not submitted; nevertheless, the data available for three commercial batches of [redacted] drug substance showed that those lots are comparable to those for previously authorized nirmatrelvir DS manufacturers.

3) Changes in Drug Product Appearance and Packaging Presentation:

A summary of the proposed labeling's description of the co-packaged nirmatrelvir tablets and ritonavir tablets is as follows:

Nirmatrelvir is supplied as oval, pink immediate-release, film-coated tablets debossed with "PFE" on one side and "3CL" on the other side. Each tablet contains 150 mg of nirmatrelvir.

Ritonavir is supplied as white [redacted] *Each tablet contains 100 mg of ritonavir.* [redacted]

PAXLOVID® Tablets are supplied in separate cavities within the same blister card. (b) (4)

- Based on the comparable dissolution profile data of Primary Registration Drug Product Lots # FJ1399 ((b) (4) and # FJ1400 (debossed), it can be concluded that the change in tablet appearance at the post-clinical stage is not anticipated to impact drug product performance. Note that these two compared lots were manufactured at the Freiburg site using (b) (4) drug substance.
- The proposal to revise the CR-blister packaging presentations (b) (4) to a single dose pack and the introduction of the reduced dose packs, i.e., in order to remediate concerns of medication errors related to dosing of the wrong tablet combination or wrong dose, is acceptable from the Biopharmaceutics perspective. No dissolution profile data are specifically required to support these packaging presentation changes, provided these changes do not result in significant blister material and packaging process changes (per the evaluation of the Drug Product and Process Reviewers), and DMEPA finds the revised blister pack and carton labels/labeling acceptable.

4) Change in Drug Product Manufacturing Step (b) (4) (b) (4)

(b) (4)

5) Change in Supplier of Excipients (Lactose Monohydrate, Microcrystalline Cellulose, Croscarmellose Sodium)

Note that the Applicant claims (and the Drug Product Reviewer confirmed) that the proposed changes in the suppliers of lactose monohydrate, microcrystalline cellulose, and croscarmellose sodium do not involve a change in technical grades of these three excipients.

- Since there are no excipient technical grade changes involved, in line with the SUPAC-IR Guidance recommendations, evidence that the finished drug product is able to conform to the approved dissolution specifications is considered sufficient to support the proposed change in excipient supplier.

Reviewer Note 1:
Clinical PK of Final Commercial Nirmatrelvir Tablet (150 mg) Formulation, and Bridging to the Earlier Clinical Development Nirmatrelvir Liquid and Solid Oral Formulations

Intensive nirmatrelvir PK data of the proposed commercial 150 mg nirmatrelvir film-coated tablet formulation (when co-administered with ritonavir) in healthy subjects are available mainly via Carbamazepine Drug Interaction Study C4671014 using batch 21-DP-00651; refer to Table 4 of the proposed labeling, and Food-Effect Study 1019 (using Pfizer Freiburg batch FK0781). Nirmatrelvir pharmacokinetics/PK (predicted by population analysis) and nirmatrelvir pharmacodynamics/PD (i.e., changes from baseline viral RNA levels) in mild-to-moderate COVID-19 patients

treated with PAXLOVID are also summarized in the proposed labeling's Table 5 and Table 2, respectively. Per the Clinical Pharmacology Reviewer (Dr. Cristina Miglis), the nirmatrelvir PK data provided for the final commercial drug product formulation is adequate.

Intensive nirmatrelvir PK data of the 100 mg film-coated nirmatrelvir tablet (co-administered with ritonavir) in healthy subjects are available via PK (in Renal Impairment) Study C4671011 should *in vivo* PK bridging to this earlier developmental nirmatrelvir tablet formulation be needed. Note that the earlier 100 mg tablet and the final 150 mg tablet formulations of nirmatrelvir that were used in Study 1005 do not have the same excipients, so *in vitro* bridging is not considered appropriate. The Applicant reported that the observed plasma nirmatrelvir concentrations in the pivotal clinical trial (Study 1005) were comparable between the sentinel cohort patients who received the 100 mg nirmatrelvir tablet and the non-sentinel cohort patients who received the 150 mg nirmatrelvir tablet (both at the recommended dosage of 300 mg nirmatrelvir and 100 mg ritonavir twice daily for 5 days), as depicted in Figure 2 of the final Population PK study report. Refer to the Clinical Pharmacology Review for the assessment of the sparse nirmatrelvir PK data collected in Study 1005 and the PopPK modeling study report.

PK data are also available for additional earlier pre-EUA stage nirmatrelvir formulations including an extemporaneously prepared nirmatrelvir oral suspension and an uncoated 250 mg nirmatrelvir immediate release tablet formulation (via First in Human Study C4671001/Part 3), as well as a post-EUA investigational nirmatrelvir 500 mg/g (b) (4) formulation administered as an extemporaneous oral suspension in Relative BA Study 1008. [Note that unlike the immediate release oral tablet and suspension dosage forms of nirmatrelvir evaluated during clinical development (pre-EUA) which used (b) (4) of the drug substance, the (b) (4) formulation contains (b) (4) of the nirmatrelvir drug substance in a (b) (4) which enhances oral bioavailability relative to the commercial nirmatrelvir 150 mg tablet (when both are co-administered with ritonavir 100 mg tablets).] Refer to the Clinical Pharmacology Review should it be necessary to compare the PK of these various nirmatrelvir formulations to the commercial nirmatrelvir 150 mg tablet.

Reviewer Note 2:

Ritonavir Over-encapsulation in Pivotal (Double-Blinded) Clinical Trial, and Dissolution Testing of Co-Packaged Norvir® (Ritonavir) 100 mg Tablets and Hetero Ritonavir 100 mg Tablets

Previously in SN-29 of IND 153517 (Figure 1), the Applicant provided comparative *in vitro* ritonavir dissolution profile data (generated using the USP monograph dissolution test for ritonavir tablets) to demonstrate that over-encapsulation of the 100 mg ritonavir tablets for clinical trial blinding purposes did not alter the dissolution

performance of the commercially/externally sourced ritonavir tablets (manufactured by Hetero Labs, distributed by Camber Pharmaceuticals, Inc). Specifically, the over-encapsulated Hetero ritonavir tablets were still able to meet the dissolution acceptance criterion (i.e., Q = (b) (4)% at 90 min) and dissolution method parameters ([redacted]) as approved by FDA for ANDA 204587.

For commercial supply, Norvir® (ritonavir) tablets, 100 mg was initially authorized to be co-packaged with nirmatrelvir 150 mg film-coated tablets in a common foil/foil blister. Per 3.2.P.5.1 and 3.2.P.5.2 of cross-referenced NDA 22417, the dissolution test and acceptance criterion of the externally sourced Norvir® tablets [redacted]

refer to the Biopharmaceutics assessment of EUA-105/SN-95. It was noted that ANDA 204587 was approved based on demonstration of *in vivo* bioequivalence between Hetero Labs Limited's Ritonavir 100 mg Tablets and Abbvie's Norvir® 100 mg Tablets, and satisfactory *in vitro* dissolution profile data using a suitable dissolution method. It was also noted that commercially available Hetero Ritonavir 100 mg tablets (distributed by Camber Pharmaceuticals in the US) were used in the pivotal clinical studies that supported the granting of the EUA of PAXLOVID. Additionally, the externally sourced Hetero ritonavir 100 mg tablets (to be used for co-packaging with nirmatrelvir 150 mg tablets) will continue to use for QC testing the same dissolution specifications as previously approved by FDA for ANDA 204587.

Note that in SN-121, per the Drug Product Reviewer's recommendation, the Applicant included [redacted] Per the Drug Product Reviewer, the Applicant's proposal (in SN-89) to perform release testing of nirmatrelvir bulk tablets only (not the co-packaged tablets) at the nirmatrelvir drug product manufacturing site (prior to shipping the bulk tablets to the packaging site) is acceptable.

B. 13 BIOWAIVER REQUEST

Assessment: *Not Applicable*

The Applicant did not submit a biowaiver request. There is only one strength (150 mg) of the nirmatrelvir tablet proposed for emergency use authorization and this strength was also used by a majority of the patients (who received 300 mg nirmatrelvir with 100 mg ritonavir twice daily for 5 days) in the pivotal

clinical trial (as well as for primary registration/stability studies). Thus, a biowaiver for additional strengths not studied clinically was not requested nor required.

B. R. REGIONAL INFORMATION

Comparability Protocols – *ADEQUATE*

(b) (4)

[redacted]

3 Pages have been Withheld in Full as b4 (CCI/TS) immediately following this page

General Note Regarding The Proposed Comparability Protocols:
Also in SN-53, the Applicant agreed to update to the CBE-30 filing category the comparability protocols (b) (4) The Applicant also acknowledged the possibility that the CBE-30 submission may be elevated to a Prior-Approval NDA Supplement based on FDA determination upon submission receipt.

BIOPHARMACEUTICS LIST OF DEFICIENCIES

None

Primary Biopharmaceutics Assessor's Name and Date:
Gerlie Gieser, Ph.D., 02/01/2023

Secondary Assessor Name and Date:
Elsbeth Chikhale, Ph.D., 02/03/2023

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/

DAVID J CLAFFEY
02/24/2023 02:53:42 PM