

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

215151Orig1s000

PRODUCT QUALITY REVIEW(S)



Title:	NDA IQA Template Title Page- EXEC SUMMARY		
Document ID:	OPQ-ALL-TEM-0040		
Effective Date:	26 Sep 2023	Revision:	00
Total Pages:	5		



Template Revision: 03

Office of Pharmaceutical Quality

New Drug Application (NDA) Integrated Quality Assessment Template

NDA Executive Summary

1. Application/Product Information

NDA Number	215151 Resubmission
Applicant Name	Phathom Pharmaceuticals, Inc.
Drug Product Name	Voquezna® (vonoprazan)
Dosage Form	Tablet
Proposed Strength(s)	10 mg and 20 mg
NDA Classification	Type 9 – New Indication Submitted as Distinct NDA – Consolidated
Route of Administration	Oral
Maximum Daily Dose	40 mg
Rx/OTC Dispensed	Rx
Proposed Indication	• Healing of all grades of erosive esophagitis and relief of heartburn. • Maintenance of healing of all grades of erosive esophagitis and relief of heartburn. • Treatment of Helicobacter pylori (H. pylori) infection.
Drug Product Description	Pharmaceuticals, Inc. has submitted this 505 (b)(1) application for Voquezna® (vonoprazan) Tablets, 10 mg and 20 mg indicated for the treatment of erosive esophagitis and Helicobacter pylori (H. pylori) infection. 10 mg tablets are pale yellow, oval, film-coated tablets debossed with “V10” on one side and plain on the other side. Each Phathom tablet contains 10 mg of vonoprazan provided as 13.36 mg of vonoprazan fumarate as the active ingredient. 20 mg tablets are pale red, oval, film-coated tablets debossed with “V20” on one side and plain on the other side. Each tablet contains 20 mg of vonoprazan provided as 26.72 mg of vonoprazan fumarate as the active ingredient.

	Voquezna[®] tablets also contain the following inactive ingredients: ascorbic acid, croscarmellose sodium, ferric oxide red (only in 20 mg tablets), ferric oxide yellow (only in 10 mg tablets), fumaric acid, hydroxypropyl cellulose, hypromellose, magnesium stearate, mannitol, microcrystalline cellulose, polyethylene glycol 8000, and titanium dioxide. The inactive ingredients used in the tablet composition are all compendial materials. Voquezna[®] tablets are packaged as 30 tablets in high density polyethylene (HDPE) bottles with a (b) (4) Closures. Tablets should be stored at 20°C to 25°C (68°F to 77°F) and excursions permitted to 15°C to 30°C (59°F to 86°F).		
Co-packaged product information	N/A		
Device information	N/A		
Storage Temperature/ Conditions	20°C to 25°C (68°F to 77°F) and excursions permitted to 15°C to 30°C (59°F to 86°F)		
Review Team	Discipline	Primary	Secondary
	Drug Substance	Friedrich Burnett, Ph.D.	Lawrence Perez, Ph.D.
	Drug Product/ Labeling	Hitesh Shroff, Ph.D.	Hamid Shafiei, Ph.D.
	Manufacturing	Mesfin Abdi, Ph.D.	Vaikunth Prabhu, Ph.D.
	Biopharmaceutics	Hansong Chen, Ph.D.	Okponanabofa Eradiri, Ph.D.
	Microbiology	Mesfin Abdi, Ph.D.	Vaikunth Prabhu, Ph.D.
	Other (specify)	N/A	N/A
	RBPM	Megan Nguyen	
	ATL	Hamid Shafiei, Ph.D.	
Consults	N/A		

2. Final Overall Recommendation - Approval

This application was originally submitted on 03/11/2022 which received a Complete Response on 02/07/2023 (b) (4)

(b) (4). The applicant resubmitted this application on 05/19/2023 with adequate information to respond to the deficiencies delineated in the Complete Response Letter dated 02/07/2023.

The resubmission dated 05/19/2023 included updates to the drug substance, reformulation of the drug product (b) (4)

(b) (4) and dissolution data in support of the proposed formulation change.

The drug product specification has also been updated with the test and acceptance criteria for the (b) (4) impurity. The release and stability data provided in this submission show that at 6-month accelerated and long-term stability time point the level of the (b) (4) impurity remains approximately an order of magnitude below the acceptable AI limit (Refer the Drug Product Chapter in IQA). Based on the six-month accelerated and long-term stability data it has been concluded that the level of the (b) (4) will not exceed the acceptable AI limit by the end of the proposed drug product expiration dating period of 24 months.

The labeling negotiations were conduct during the first review cycle and no additional CMC labeling review is performed in this review cycle.

Based the information provided in this resubmission, the OPQ disciplines involved in the review of the resubmission have recommended the approval of this application from their perspective disciplines. Therefore, this application is recommended for approval with an expiration dating period of 24 months.

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

- The applicant of this 505(b)(1) new drug application has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug substance, vonoprazan fumarate and the drug product, Voquezna (vonoprazan) Tablets, 10mg and 20mg.
- The Office Pharmaceutical Manufacturing Assessment has made the overall recommendation of adequate for the facilities involved in this application.
- The CMC issues on labels/labeling have been satisfactorily resolved (refer to the IQA for the first review cycle date 02/06/2023).

- The applicant's request for the categorical exclusion from the preparation of the environmental assessment has been granted (also refer to the IQA for the first review cycle date 02/06/2023).

Therefore, from the OPQ perspective, this NDA is recommended for **approval** with the expiration dating period of **24 months**.

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	-	Adequate

Environmental Assessment: Categorical Exclusion - Adequate
QPA for EA(s): Yes

5. Life-Cycle Considerations

Established Conditions per ICH Q12: No

Comments:

Comparability Protocols (PACMP): No

Comments:

No comparability protocol was submitted in this resubmission. For additional information refer to the original IQA compiled by Dr. Nina Ni Dated 02/06/2023.

Additional Lifecycle Comments:

Continue the review of the stability data to confirm that (b) (4) remains at or below the required AI limit during the proposed expiration dating period (shelf-life).

Application Technical Lead Name and Date:

Hamid Shafiei, Ph.D.
Branch IV/DNDP 2/ONDP/OPQ



Hamid
Shafiei

Digitally signed by Hamid Shafiei

Date: 10/11/2023 11:20:00PM

GUID: 507d824300005f344cf8b5e5989f0057

CHAPTER VI: BIOPHARMACEUTICS

[IQA NDA Assessment Guide Reference](#)

NDA Number	NDA 215151-ORIG-1-RESUB-35
Assessment Cycle Number	02
Drug Product Name/ Strength	VOQUEZNA® (Vonoprazan) tablets 10 mg and 20 mg
Route of Administration	Oral
Applicant Name	Phathom Pharmaceuticals, Inc.
Therapeutic Classification/ OND Division	Acid inhibitory agent /DG
RLD/RS Number	N/A
Proposed Indication	Healing of all grades of erosive esophagitis and relief of heartburn
Primary Reviewer	Hansong Chen, PharmD, Ph.D.
Secondary Reviewer	Okpo Eradiri, Ph.D.

Assessment Recommendation: Adequate

Assessment Summary:

Phathom Pharmaceuticals, Inc. developed VOQUEZNA® (Vonoprazan) tablets 10 mg and 20 mg and submitted the original NDA on 03/11/2022 to seek approval through the 505(b)(1) regulatory pathway. The proposed indication is for healing of all grades of erosive esophagitis and relief of heartburn.

However, a CR was issued to this NDA on 2/7/2023 due to a product quality issue. (b) (4)

(b) (4)
(u) (4) Stability data show that both strengths of vonoprazan tablets cannot consistently meet the acceptance criterion (b) (4). Therefore, the data do not support a viable shelf life for vonoprazan 10 mg and 20 mg tablets. The Applicant was asked to perform a root cause investigation (b) (4)

(b) (4). The Applicant was also requested to revise the acceptance criterion (u) (4) for the drug product release and stability specifications.

To address the above (b) (4) issue, the Applicant reformulated their drug product (b) (4). Before they resubmitted this NDA, they had a type A meeting with FDA on 3/7/2023 to explore the possibility of biowaiver of BA/BE studies for the reformulated drug product. FDA provided the following response:

Your proposed approach appears reasonable. We recommend that you provide detailed justification which may include relevant experimental data (e.g., permeability data using Caco-2 cell) and/or a summary of the literature showing that the (b) (4) amount of (b) (4)

(b) (4) is unlikely to affect intestinal permeability of vonoprazan to support your biowaiver request in your NDA resubmission. The adequacy of your justification to support a biowaiver will be determined at the time of your NDA resubmission.

On 5/19/2023, the Applicant resubmitted this NDA. In this resubmission, the Applicant officially requested a biowaiver for the reformulated drug product.

During the last review cycle, the previous Biopharmaceutics Reviewers concluded that the dissolution method and acceptance criterion had been approved. In this cycle, the Biopharmaceutics review is focused on the evaluation of the biowaiver request for the reformulated VOQUEZNA® (Vonoprazan) tablets, 10 mg and 20 mg.

Key finding of the Biopharmaceutics assessment:

The biowaiver can be granted for the reformulated VOQUEZNA® (Vonoprazan) tablets 10 mg and 20 mg given the following rationale:

- Vonoprazan is a highly soluble drug substance and the drug product is very rapidly dissolving; therefore, vonoprazan tablets have low Biopharmaceutics risk.
- Comparative dissolution testing results demonstrate the original and reformulated drug products exhibit similar dissolution profiles in 0.1 N HCl, pH 4.5 buffer, and pH 6.8 buffer as both of them display very rapid drug release in these three media.
- (b) (4). There is no information or evidence in the scientific literature that (b) (4) impacts absorption of vonoprazan.
- Two BA/BE study results show that significant excipient changes in the formulations of vonoprazan do not affect the absorption of vonoprazan.

Recommendation:

From a Biopharmaceutics perspective, NDA 215151-ORIG-1-RESUB-35 for VOQUEZNA® (Vonoprazan) tablets 10 mg and 20 mg is **ADEQUATE**.

List Submissions being assessed (table):

Document(s) Assessed	Date Received
Sequence 0035 / submission	5/19/2023

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

Concise Description of Outstanding Issues (List bullet points with key information and update as needed): None

B. 13 BIOWAIVER REQUEST

Assessment: adequate

The Applicant requested a biowaiver for the reformulated VOQUEZNA® (Vonoprazan) tablets 10 mg and 20 mg by providing the following supporting data:

1. Solubility of vonoprazan fumarate

Table 1. Solubility of vonoprazan across the physiologic pH range of 1.0-6.8 at 37 °C

pH	Solubility
1.2 (SGF, no enzymes)	19.9
3.6 (citrate)	4.86
4.5 (acetate)	5.02
5.6 (citrate)	4.64
6.8 (SIF, no enzymes)	4.62

The solubility data shown in Table 1 demonstrate that vonoprazan fumarate is highly soluble across the physiologic pH range.

2. Composition comparison between the pre-change and post-change formulations

Table 2 (b) (4) tablet formulation differences for Vonoprazan Tablets 10 mg and 20 mg – original formulation vs reformulation (b) (4)

(b) (4)

--

As shown in Table 2, the Applicant reformulated Vonoprazan Tablets 10 mg and 20 mg (b) (4). All other excipients remain unchanged.

3. In vitro comparative dissolution profile studies

Table 3. Comparative dissolution data of Vonoprazan Tablets 10 mg – original formulation vs (b) (4) reformulation

Batch\time (min)	10	15	20	30	45	60
10 mg Original Lot 4425096 in 0.1 N HCl	97	99	98	99	99	98
10 mg Reformulation Lot 5334249 in 0.1 N HCl	88	89	88	87	87	97
10 mg Original Lot 4425096 in pH 4.5 buffer	93	98	98	98	98	98
10 mg Reformulation Lot 5334249 in pH 4.5 buffer	96	100	100	100	100	100
10 mg Original Lot 4425096 in pH 6.8 buffer	89	95	95	95	95	96
10 mg Reformulation Lot 5334249 in pH 6.8 buffer	92	96	96	96	96	97

Table 4. Comparative dissolution data of Vonoprazan Tablets 20 mg – original formulation vs (b) (4) reformulation

Batch\time (min)	10	15	20	30	45	60
20 mg Original Lot 4425096 in 0.1 N HCl	91	97	98	98	98	98
20 mg Reformulation Lot 5334249 in 0.1 N HCl	93	93	92	90	89	88
20 mg Original Lot 4425096 in pH 4.5 buffer	90	97	98	98	98	98
20 mg Reformulation Lot 5334249 in pH 4.5 buffer	92	98	99	99	99	99
20 mg Original Lot 4425096 in pH 6.8 buffer	90	95	97	96	96	96
20 mg Reformulation Lot 5334249 in pH 6.8 buffer	90	95	95	95	96	95

Figure 1. Comparative dissolution profiles of Vonoprazan Tablets 10 mg – original formulation vs (b) (4) reformulation

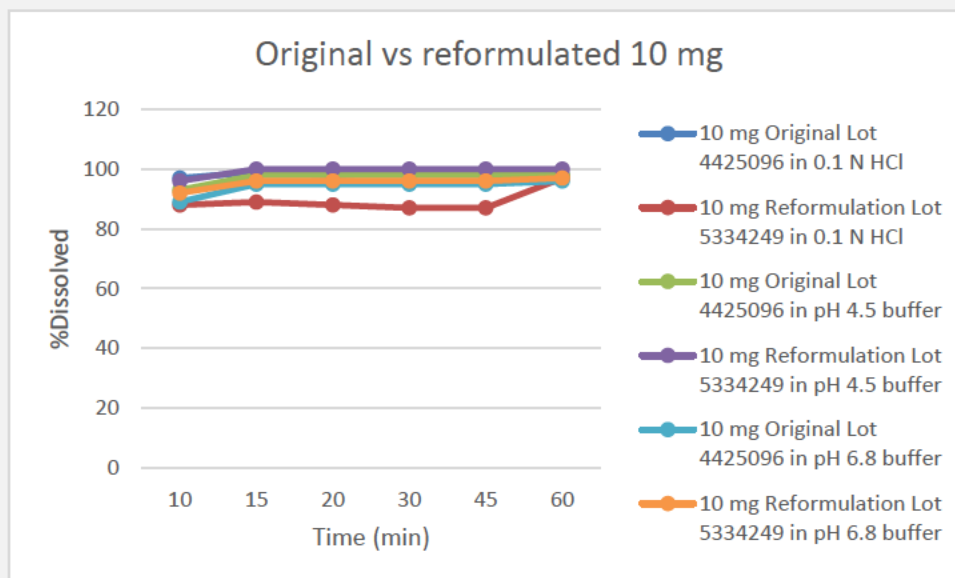
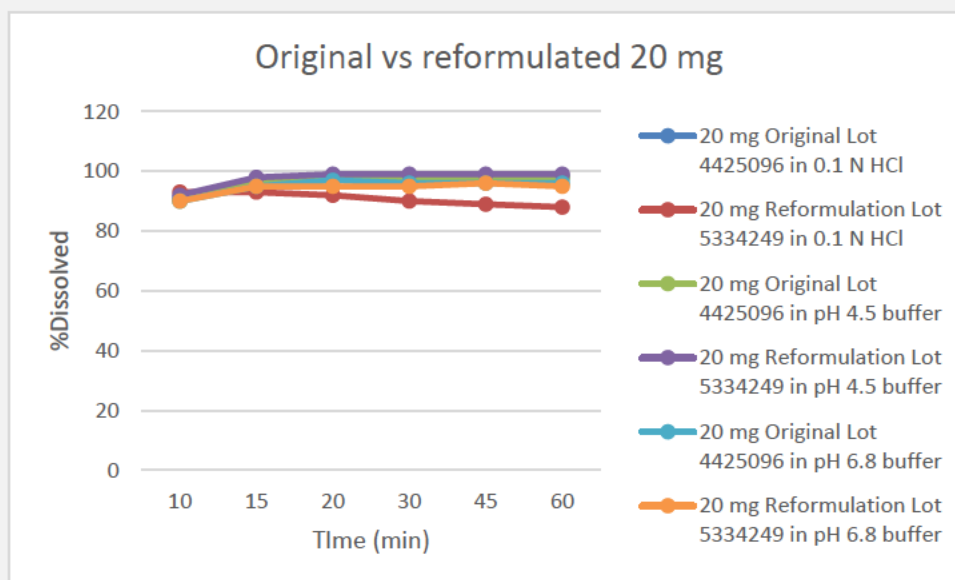


Figure 2. Comparative dissolution profiles of Vonoprazan Tablets 20 mg – original formulation vs (b) (4) reformulation



As shown in Tables 3 and 4, both original and reformulated lots display very rapid dissolution (i.e., >85%) in 0.1 N HCl, pH 4.5 buffer, and pH 6.8 buffer, indicating that the original lot and its respective reformulated lot have similar dissolution profiles in multimedia.

4. (b) (4) impact on absorption of vonoprazan

The Applicant conducted a literature search for evidence of the potential for (b) (4) to impact the absorption of vonoprazan and did not find any published articles directly related to vonoprazan. While there are numerous publications available regarding the addition of (b) (4), the Applicant were unable to identify any published evidence to suggest that (b) (4) in drug product formulations has an impact on the absorption of vonoprazan.

However, the Applicant emphasized that the amount of (b) (4)

(b) (4) which is well within the $\pm 10\%$ requirement for the cumulative difference for excipients that may affect absorption per the FDA Guidance for Industry: M9 Biopharmaceutics Classification System-Based Biowaivers (May 2021).

Reviewer's comment

This Reviewer agrees with the Applicant that the addition of (b) (4) to the formulation does not likely affect the absorption of vonoprazan. In addition, the reformulated drug product tends to have low biopharmaceutics risk as vonoprazan is a highly soluble drug substance.

5. Previous bioequivalence studies

Study TAK-438ODT-1001

Study TAK-438ODT-1001 compared the original vonoprazan 20 mg immediate-release tablet to the vonoprazan 20 mg ODT. These two drug products have different compositions as shown in Table 5; however, the study results show that the pharmacokinetic (PK) profiles of these two drug products were nearly superimposable as shown in Figure 3.

Figure 3. PK profile of Vonoprazan ODT vs Vonoprazan Tablets 20 mg (Study TAK-438ODT-1001)

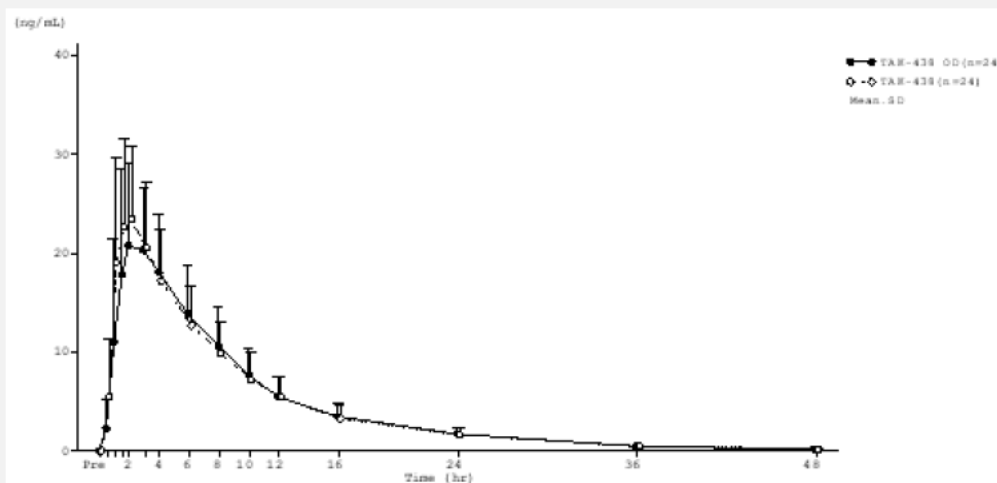


Table 5. Composition of Vonoprazan ODT (10 mg and 20 mg)

Component	10 mg	20 mg
(b) (4)		

Study VPED-101

Study VPED-101 compared the original vonoprazan 20 mg immediate-release tablet to the vonoprazan 20 mg (b) (4) sprinkle capsule formulation. These two formulations have

significantly different compositions as shown in Table 6. However, their PK profiles were also nearly superimposable as shown in Figure 4.

Based on the above two BA/BE studies, the Applicant concluded that vonoprazan formulations with substantial compositional differences perform nearly identically in vivo, indicating that the minor changes to the tablet formulation (b) (4) will not impact absorption profile of the tablets.

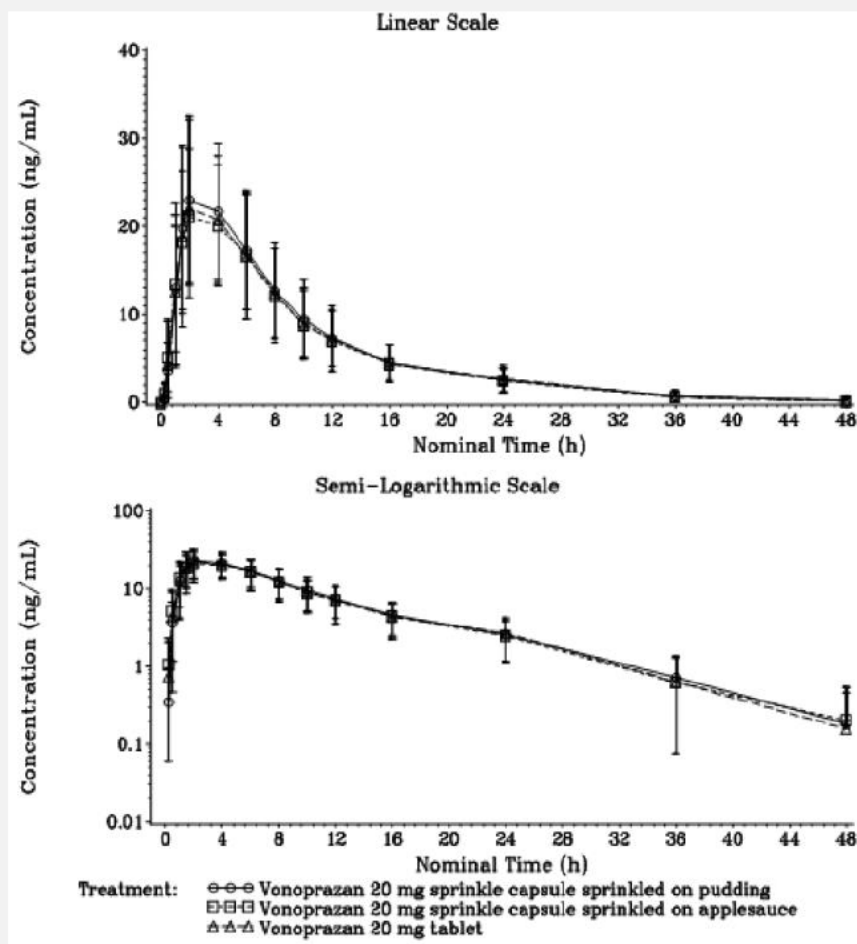
Reviewer's comment:

Although the formulation changes in the above two cases are not directly related (b) (4) two study results clearly show that excipient change in formulations of vonoprazan does not affect the PK profile of vonoprazan. It is expected that the addition of (b) (4) in the formulation of the reformulated drug product will not likely affect the absorption of vonoprazan.

Table 6. Composition of Vonoprazan Pellets in capsule 20 mg

Component	Reference to Quality Standards	Function	Quantity (%)	Quantity (mg/capsule)
(b) (4)				

Figure 4. PK Profile of Vonoprazan Sprinkles 20 mg vs Vonoprazan Tablets 20 mg (Study VPED-101)



6. Relevant Permeability and Absorption Data

The Applicant submitted absorption and permeability data to IND 079212/Sequence No. 0083 as part of the BCS-I Designation Request for the Vonoprazan Tablets 10 mg and 20 mg on 6/03/2021.

Pharmacokinetic Study in Humans: Mass Balance (Study TAK-438_103)

In Study TAK-438_103, the Applicant investigated radiolabeled mass balance and excretion in six healthy male subjects using [^{14}C]-vonoprazan. The excretion and metabolite profiling data from this study demonstrate that nearly 97% of orally administered vonoprazan is absorbed and then excreted as parent drug in the urine and oxidative/conjugative metabolites in the urine and feces.

Reviewer's comment:

The mass balance study results were assessed by Dr. Leah Falade in her Biopharmaceutics review of IND 079212, and it was concluded that this human mass balance study is not sufficient to support the high permeability of vonoprazan as several of the metabolites were labeled as “unknown” and accounted for 35% of the excreted radioactivity in urine and 23% in feces. The Applicant was requested to identify the metabolites grouped under “other” category.

Caco-2 Cell Study (Study PRE-DDA-438-004)

In Study PRE-DDA-438-004, the transcellular transport of [¹⁴C]-vonoprazan (3 µmol/L set to be similar to 0.01 x Dose/250 mL for a 20 mg dose, 2.3 µmol/L) across Caco-2 cell monolayers was investigated compared to 20 model drugs (low permeability, moderate permeability, and high permeability as well as efflux substrates) at pH 7.4.

The apparent permeability (P_{app}) value of [¹⁴C]-vonoprazan (3 µmol/L) from the apical to the basal side was 13.7×10⁻⁶ cm/sec, and that from the basal to the apical side was 22.1×10⁻⁶ cm/sec. The P_{app} value of [¹⁴C]-vonoprazan from the apical to the basal side was approximately 3 times higher than that of [³H]-minoxidil (5.00×10⁻⁶ cm/sec), a high permeability control. Per the Applicant, these results indicate that vonoprazan has high permeability at pH 7.4 and is not a substrate for P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP).

Reviewer’s comment:

This Reviewer is unable to verify the Applicant’s conclusion that vonoprazan has high permeability at pH 7.4 as the applicant did not submit the full study report. However, this Reviewer will assess the high permeability of vonoprazan under IND 079212, which was resubmitted on 7/12/2023.

(b) (4)

(b) (4)

which is currently ongoing.

(b) (4)

(b) (4)

Reviewer’s comment

(b) (4)

this Reviewer will assess the full (b) (4) data of vonoprazan submitted in IND 079212 to make a final determination.

CONCLUSION AND RECOMMENDATION

Based on the above supporting data, this Reviewer concludes that the biowaiver can be granted for the reformulated VOQUEZNA® (Vonoprazan) tablets 10 mg and 20 mg given the following rationale:

- Vonoprazan is a highly soluble drug substance and the drug product is very rapidly dissolving; therefore, vonoprazan tablets have low Biopharmaceutics risk.
- Comparative dissolution testing results demonstrate the original and reformulated drug products exhibit similar dissolution profiles in 0.1 N HCl, pH 4.5 buffer, and pH 6.8 buffer as both of them display very rapid drug release in these three media.
- (b) (4). There is no information or evidence in the scientific literature that (b) (4) impacts absorption of vonoprazan.
- Two BA/BE study results show that significant excipient changes in the formulations of vonoprazan do not affect the absorption of vonoprazan.

BIOPHARMACEUTICS LIST OF DEFICIENCIES

None.



Hansong
Chen

Digitally signed by Hansong Chen

Date: 10/01/2023 11:08:25PM

GUID: 525d7d660003845a197a2e1682433d0d



Okponanabofa
Eradiro

Digitally signed by Okponanabofa Eradiro

Date: 10/01/2023 11:09:14PM

GUID: 50bdfc8d00003559ede66be3fd299f65

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/

HAMID R SHAFIEI
10/12/2023 12:04:15 PM

RECOMMENDATION

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

NDA 215151 Assessment 1

Drug Product Name	Voquezna (vonoprazan) tablets
Dosage Form	Tablet
Strength	10 mg and 20 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Phathom Pharmaceuticals Inc. (Phathom)
US agent, if applicable	NA

Submission(s) Assessed	Document Date	Discipline(s) Affected
Original Submission, eCTD SN 0002	03/11/2022	DS, DP, OPMA, labeling, and Biopharm
Amendment, SN 0008	05/25/2022	DS, DP
Amendment, SN 0011	06/17/2022	DP
Amendment, SN 0012	06/27/2022	DS, DP
Amendment, SN 0014	07/01/2022	OPMA
Amendment, SN 0015	07/15/2022	DP
Amendment, SN 0016	08/02/2022	DP
Amendment, SN 0021	10/05/2022	DS, DP
Amendment, SN 0026	11/14/2022	DS, DP
Amendment, SN 0027	11/28/2022	DP
Amendment, SN 0029	12/12/2022	DP
Amendment, SN 0030	12/22/2022	DP
Amendment, SN 0031	01/23/2023	DP
Amendment, SN 0032	01/24/2023	DP, Labeling



Template Revision: 03

Title:	NDA Executive Summary		
Document ID:	OPQ-ALL-TEM-0013		
Effective Date:	31 May 2022	Revision:	00
Total Pages:	5		



NDA Executive Summary

1. Application/Product Information

NDA Number.	NDA 215151		
Applicant Name	Phathom Pharmaceuticals Inc. (Phathom)		
Drug Product Name	Voquezna (vonoprazan) tablets		
Dosage Form.	Tablet		
Proposed Strength(s)	10 mg and 20 mg		
Route of Administration	Oral		
Maximum Daily Dose	40 mg		
Rx/OTC Dispensed	Rx		
Proposed Indication	For the treatment of healing of erosive esophagitis and relief of heartburn, maintenance of erosive esophagitis and healing of heartburn, and treatment of <i>Helicobacter pylori</i> (<i>H pylori</i>) infection		
Drug Product Description	Vonoprazan tablets are immediate release film coated tablets. Two strengths are available: 10 mg tablets as pale yellow, oval (b) (4), film coated tablets debossed V10 on one side and 20 mg tablets as pale red, oval (b) (4), film coated tablets debossed V20 on one side. The tablets are packaged into HDPE bottles in 30-count as commercial presentation and 5-count as physician samples.		
Co-packaged product information	N/A		
Device information:	N/A		
Storage Temperature/ Conditions	The drug product is proposed to be stored at USP controlled room temperature		
Review Team	Discipline	Primary	Secondary
	Drug Substance	Friedrich Burnett	Lawrence Perez



Title:	NDA Executive Summary		
Document ID:	OPQ-ALL-TEM-0013		
Effective Date:	31 May 2022	Revision:	00
Total Pages:	5		



Template Revision: 03

Template Revision: 03

	<i>Drug Product/ Labeling</i>	Jane Change	Nina Ni
	<i>Manufacturing</i>	Mesfin Abdi	Vaikunth Prabhu
	<i>Biopharmaceutics</i>	Kamrun Nahar	Tapash Ghosh
	<i>Microbiology</i>	N/A	N/A
	<i>Other (specify):</i>	N/A	N/A
	<i>RBPM</i>	Melinda Bauerlien/Grafton Adams	
	<i>ATL</i>	Nina Ni	
Consults	N/A		

2. Final Overall Recommendation - Complete Response

3. Deficiencies

(b) (4)



Title:	NDA Executive Summary		
Document ID:	OPQ-ALL-TEM-0013		
Effective Date:	31 May 2022	Revision:	00
Total Pages:	5		

Template Revision: 03

(b) (4)

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

The proposed drug product, voquezna (vonoprazan) tablets are intended to be supplied as two dosage strengths: 10 mg of vonoprazan (equivalent to 13.36 mg of vonoprazan fumarate) and 20 mg of vonoprazan (equivalent to 26.72 mg of vonoprazan fumarate) for oral administration. This NDA cross-references NDAs 215152 and 215153 for the drug substance and 20 mg strength tablets, including development pharmaceuticals and analytical methods that are applicable to both the 10 mg and 20 mg tablets. The formulation of 20 mg strength vonoprazan tablets is identical to that of NDAs 215152 and 215153.

(b) (4)

The proposed commercial product presentation for this NDA is 30-count per bottle. The presentation of 5-count per bottle is for professional use only, not for resale.

*Based on OPQ evaluation of the available information, the applicant has **not** provided sufficient information to support an approval recommendation from the product quality perspective (21 CFR 314.125(b)(1)). The applicant has **not** provided adequate chemistry, manufacturing, and controls (CMC) information to ensure the identity, strength, purity, and quality of the proposed drug product although the overall manufacturing inspection recommendation remains approval for all the facilities associated with this application per email from Mesfin Abdi, Ph. D., dated 02/06/2023. The proposed labeling and labels submitted in the Amendment, SDN 0032, dated 01/24/2023 also include adequate information to meet the regulatory requirements.*

In a recent submission to NDA 215152 (Supplement 2, Manufacturing (CMC), submitted 05-Oct-2022),

(b) (4)

The applicant proposed (b) (4) acceptable intake (AI) (b) (4) as well as (b) (4) acceptance criterion of NMT (b) (4) ppm in the drug

(b) (4)



Title:	NDA Executive Summary		
Document ID:	OPQ-ALL-TEM-0013		
Effective Date:	31 May 2022	Revision:	00
Total Pages:	5		



Template Revision: 03

substance specification and (b) (4) in the drug product specifications. The Pharm/Tox team (b) (4) have concluded that the proposed (b) (4) acceptable intake (AI) (b) (4) is acceptable. However, the applicant's proposed (b) (4) acceptance criteria (b) (4) for the drug product specifications are not acceptable because the daily intake (b) (4), if present, at both limits exceeds the acceptable intake (b) (4). Thus, based on AI (b) (4), the (b) (4) limit for the drug product specification is (b) (4) based on a maximum daily intake of 40 mg of vonoprazan. The AI limit (b) (4) was communicated to the applicant on 12/19/2022 and the (b) (4) acceptance criterion of (b) (4) for the drug product specification was communicated to the applicant via General Advice letter, dated 12/23/2022.

Based on limited available (b) (4) stability data for the drug substance, the applicant agrees to assign a retest period of (b) (4) months for the drug substance to ensure that the (b) (4) limit of NMT (b) (4) ppm in the drug substance is met. Apart from (b) (4) data, although the applicant provided 12 months drug product stability data under long term condition and 6 months stability data under accelerated condition for vonoprazan tablets, 10 and 20 mg while stored in HDPE bottles, the applicant only provided limited (b) (4) stability data for the drug product. Even though other stability data are acceptable, the limited stability data (b) (4) cannot consistently meet the (b) (4) acceptance criterion (b) (4). Thus, neither the applicant's proposed drug product expiration dating period of 24 months nor a viable drug product expiration dating period can be granted.

OTR considers the analytical procedure for quantitation (b) (4) adequate for quality purpose. Therefore, OTR will not conduct laboratory verification.

Note: Information in the eCTD-0031 Amendment dated 1/23/2023 submitted to this NDA, e.g., the proposed plan to submit data in the future for six reformulated batches (three batches each for each strength) (b) (4) in the reformulated product, is not covered in this (Integrated Quality Assessment (IQA) review since the information provided in the Amendment does not address the deficiencies identified in this IQA review. Thus, information on the proposed reformulation will be assessed during future resubmission of this NDA.

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



Title:	NDA Executive Summary		
Document ID:	OPQ-ALL-TEM-0013		
Effective Date:	31 May 2022	Revision:	00
Total Pages:	5		



Template Revision: 03

Recommendation by Subdiscipline:

Drug Substance	-	Adequate
Drug Product	-	Inadequate
Quality Labeling	-	Adequate
Manufacturing	-	Adequate
Biopharmaceutics	-	Adequate
Microbiology	-	N/A

Environmental Assessment: Categorical Exclusion - Adequate
QPA for EA(s): Yes

5. Life-Cycle Considerations

Established Conditions per ICH Q12: No
Comments:

Comparability Protocols (PACMP): Yes

Comments: The applicant submitted a Comparability Protocol for the addition of Evonik Operations GmbH for manufacture of vonoprazan fumarate drug substance post-approval via CBE-30.

Additional Lifecycle Comments: None



Nina
Ni

Digitally signed by Nina Ni

Date: 2/06/2023 05:44:15PM

GUID: 502d1ab500002afbbe642f8f37136920

61 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

MEMORANDUM

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

DATE: February 3, 2023

TO: Addendum of Assessment #1 of NDA 215151 Quality Assessment - Drug Product

FROM: Jane Chang, Ph.D.
Master Chemistry Reviewer, OPQ/ONDP/DNDP II

THROUGH Nina Ni, Ph.D.
Senior Pharmaceutical Quality Assessor, OPQ/ONDP/DNDP II/Branch 4

SUBJECT: Final Recommendation on Quality Assessment - Drug Product

SUMMARY

The previous Quality Assessment – Drug Product, Assessment Cycle #1 dated 21-Oct-2022, concluded inadequate because of insufficient stability data (b) (4) to assure the drug product purity throughout the proposed 24 months shelf life (see [NDA 215151 DP R01](#)). In addition, a final decision on the proposed acceptable intake (AI) (b) (4) was pending. On 12/19/2022, FDA informed the applicant that the proposed AI (b) (4) is acceptable. The AI (b) (4) corresponds to a (b) (4) acceptance criterion of (b) (4) in the drug product. Thus, the proposed acceptance criteria (b) (4) are not acceptable. The stability data to date show that (b) (4) cannot consistently meet the (b) (4) acceptance criterion (b) (4). Therefore, the CMC data in NDA 215151 do not support a viable shelf life for vonoprazan 10 mg and 20 mg tablets.

OTR considers the analytical procedure for quantitation (b) (4) adequate for quality purpose. Therefore, OTR will not conduct laboratory verification.

Information in the eCTD-0031 amendment dated 1/23/2023 submitted to this NDA, e.g., the proposed plan to submit data in the future for six reformulated batches (three batches each for each strength) (b) (4) in the reformulated product, is not covered in this addendum since the deficiencies identified in LIST OF DEFICIENCIES AND RECOMMENDATIONS TO ADDRESS THE DEFICIENCIES have not been addressed in this amendment. Information on the proposed reformulation will be assessed in the future.

RECOMMENDATION

This application is not ready for approval in its present form from the drug product quality assessment perspective.

LIST OF DEFICIENCIES AND RECOMMENDATIONS TO ADDRESS THE DEFICIENCIES

(b) (4)

As the levels (b) (4) in your drug products are above the AI limit, we recommend that you perform a root cause investigation (b) (4)

Submit long term, accelerated data, and where appropriate, intermediate data for at least three batches for each strength (i.e., 10 mg and 20 mg tablets) representative of the to-be-marketed product per ICH Q1A(R2) demonstrating that the data meet the updated specifications, including acceptance criterion (b) (4).

Assessment Notes

Assessor Comment: A drug product deficiency was identified in Assessment Cycle #1 dated 21-Oct-2022 (see [NDA 215151 DP R01](#)). Subsequently, amendments were submitted to this NDA and the cross-referenced NDA 215152. These amendments, as listed below, are the subject of this addendum.

List of submissions being reviewed:

Document Reviewed (eCTD #)	Date Received	Information
NDA 215152 (eCTD-0061, SDN-100)	11/14/2022	Response to NDA 215152-Suppl-2 Information Request dated 11-02-2022*
NDA 215152 (eCTD-0064, SDN-104)	11/28/2022	Response to NDA 215152-Suppl-2 Information Request dated 11-02-2022*
NDA 215151 (eCTD-0028, SDN-28)	12/2/2022	Response to NDA 215151 Information Request dated 11-29-2022
NDA 215152 (eCTD-0068, SDN-108)	12/12/2022	Response to NDA 215152-Suppl-2 Information Request dated 12-06-2022*
NDA 215152 (eCTD-0070, SDN-110)	12/22/2022	Response to NDA 215152-Suppl-2 Information Request dated 12-06-2022*

*This NDA cross-references NDA 215152. The information assessed was provided only to NDA 215152. See NDA 215151, [SDN-25](#), [SDN-27](#), [SDN-29](#), and [SDN-30](#).

1.0 DRUG PRODUCT

The following issues regarding (b) (4) were not resolved at the conclusion of the previous Drug Product Quality Assessment, Assessment Cycle #1 dated 21-Oct-2022.

(b) (4)

In [NDA 215152, SDN-100](#), the applicant provided a response for Information Request dated 11/2/2022 for NDA 215152-Suppl-2, which is listed below.



Nina
Ni

Digitally signed by Nina Ni
Date: 2/03/2023 01:32:15PM
GUID: 502d1ab500002afbbe642f8f37136920



Jane
Chang

Digitally signed by Jane Chang
Date: 2/03/2023 01:33:32PM
GUID: 5034f819000053b21e2574590781f330

CHAPTER IV: LABELING

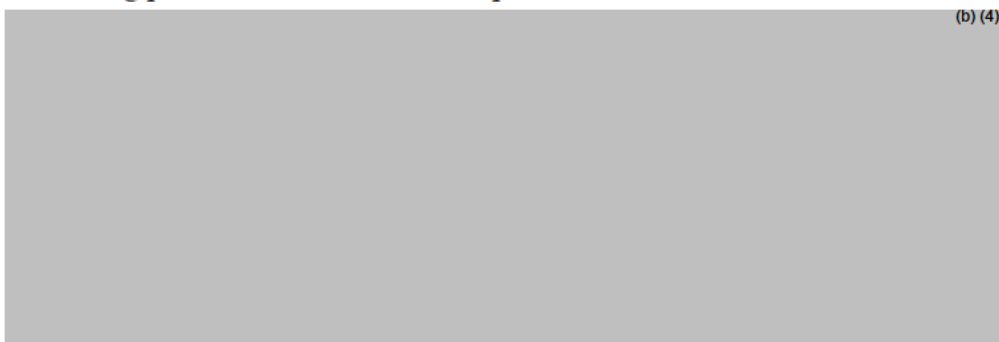
See [Chapter IV \(Labeling\) of the NDA IQA Guide](#)

List Submissions being reviewed:

Document Reviewed (eCTD #)	Date Received	Information Provided
eCTD-0003 (SDN-3)	03/17/2022	Container Labels, Carton Labeling, and Prescribing Information Labeling
eCTD-0008 (SDN-8)	05/25/2022	Prescribing Information Labeling
eCTD-0022 (SDN-22)	10/14/2022	Container Labels and Carton Labeling

1.0 PRESCRIBING INFORMATION

(refer to [Labeling Review Tool \(LRT\)](#) on the Labeling Development Team's website)
Labeling provided in eCTD-0008 is provided below.



Items	Items in Proposed Labeling	Assessor's Comments
Drug name [201.57(a)(2)]		
Established name ¹	Inadequate	(b) (4) should be revised to "(vonoprazan) tablets" based on the revised container labels and carton labeling in SDN-22.
Dosage form, route of administration	Adequate	"tablets" as the dosage form and "oral" as route of administration
Controlled drug substance symbol (if applicable)	N/A	N/A
Initial U.S. Approval	Inadequate	Vonoprazan as a new molecular entity was first approved in May 2022. Therefore, "2022" should be listed.
Dosage Forms and Strengths [201.57(a)(8)]		
Dosage Forms and Strengths in metric system	Adequate	"tablets" as the dosage form and the strengths "10 mg and 20 mg" are provided.
If the drug product contains an active ingredient that is a salt, clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of	Inadequate	Include the active moiety for the strengths, i.e., 10 mg and 20 mg of vonoprazan.

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

drug-x) or active ingredient (e.g., Tablets: 10 mg of drug-x hydrochloride).		
Whether the drug product is scored. If product meets guidelines and criteria for a scored tablet, state “functionally scored”.	N/A	The product is not scored.

Conclusion: *Unsatisfactory*

The recommended revisions are shown below:

VOQUEZNA (vonoprazan) tablets), for oral use

Initial U.S. Approval: (b) (4) 2022

Tablets: 10 mg and 20 mg of vonoprazan

(b) (4)

Items	Information in Proposed Labeling	Assessor's Comments
Available dosage forms	Adequate	“tablets” provided
Strengths in metric system.	Adequate	“10 mg” and “20 mg” provided
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance. Clearly state whether the strength is based on the active moiety.	Inadequate	The active moiety as the basis of strengths should be provided.
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, and color and clarity of the solution, when applicable.	Adequate	Color, shape, film coating, debossing information provided.
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state “functionally scored”	N/A	The product is not scored.

Conclusion: *Unsatisfactory*

The recommended revisions are shown below:

(b) (4) **Tablets:**

- 10 mg **of vonoprazan**: pale yellow, oval, film-coated tablet debossed V10 on one side and plain on the other side.
- 20 mg **of vonoprazan**: pale red, oval, film-coated tablet debossed V20 on one side and plain on the other side.

(b) (4)

Items	Information in Proposed Labeling	Assessor's Comments
Proprietary name and established name [21 CFR 201.57(c)(12)(i)(A)]	Inadequate	Established name is not provided. Per 201.10(g)(1), the established name shall accompany the proprietary name. The established name shall be used at least once in the running text in association with such proprietary name or designation.
Dosage form and route of administration [21 CFR 201.57(c)(12)(i)(B)]	Inadequate	"tablets" provided, but not the route of administration.
Active moiety expression of strength with equivalence	Inadequate	Salt equivalence statements are provided. However, the statement

statement (if applicable) per 21 CFR 201.100(b)(4)		should follow each respective strength.
Inactive ingredient information [21 CFR 201.57(c)(12)(i)(C)] [quantitative, if injectables 21CFR201.100(b)(5)(iii), listed by USP/NF names (if any) in alphabetical order]. Not required for oral use, except for colorant. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect. If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol at 60 °F (15.56 °C) per 21 CFR 201.10(d)(2).	Inadequate	Inactive ingredients are provided using the respective established names in alphabetical order. However, clarification on ferric oxide red (only in 20 mg tablets) and ferric oxide yellow (only in 10 mg tablets) is needed.
Sterility statement [if applicable, 21 CFR 201.57(c)(12)(i)(D)]	N/A	Not a sterile product.
Pharmacological/ therapeutic class [21 CFR 201.57(c)(12)(i)(E)]	Adequate	“a potassium-competitive acid blocker (PCAB)” provided.
Chemical name, structural formula, molecular weight [21 CFR 201.57(c)(12)(i)(F)]	Inadequate	The stereochemistry should be included in the chemical name of fumarate.
If radioactive, statement of important nuclear characteristics [21 CFR 201.57(c)(12)(i)(G)]	N/A	Not a radioactive product.
Other important chemical or physical properties (such as pKa or pH) [21 CFR 201.57(c)(12)(ii)]	Adequate	Solubility of the drug substance is provided.
For oral prescription drug products, include gluten statement if applicable	N/A	Not applicable
Remove statements that may be misleading or promotional (e.g., “synthesized and developed by Drug Company X,” “structurally unique molecular entity”	N/A	No misleading or promotional statements.
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled. Note the labeling requirement may be applicable	N/A	There is no USP monograph for the drug product.

to another section of the PI (e.g., Section 2).		
--	--	--

Conclusion: *Unsatisfactory*

In the Highlights of Prescribing Information, “tablets” is included in the parenthesis for the product title, which suggests that the proprietary name includes the dosage form. The applicant should clarify whether they intend to use the proprietary name VOQUEZNA for only one dosage form (see page 11). Meanwhile, the dosage form is included in the parenthesis (see the revisions below for Sections 11 and 16) to be consistent with the product title.

The recommended revisions are shown below:

Vonoprazan (as the fumarate), is a potassium-competitive acid blocker (PCAB). Chemically, it is 1*H*-~~P~~pyrrole-3-methanamine, 5-(2-fluorophenyl)-*N*-methyl-1-(3-pyridinylsulfonyl)-, (*2E*)-2-butenedioate (1:1). Its empirical formula is C₁₇H₁₆FN₃O₂S•C₄H₄O₄ with a molecular weight of 461.5. Vonoprazan **fumarate** has the following structure:

Vonoprazan fumarate is white to nearly white crystals or crystalline powder which melts at 194.8°C. Vonoprazan fumarate is soluble in dimethyl sulfoxide; sparingly soluble in *N,N*-dimethylacetamide, slightly soluble in *N,N*-dimethylformamide, methanol and water; very slightly soluble in ethanol (99.5%); and practically insoluble in 2-propanol, acetone, 1-octanol, and acetonitrile.

VOQUEZNA (**vonoprazan**) tablets are available in two dosage strengths: 10 mg **of vonoprazan (equivalent to 13.36 mg of vonoprazan fumarate)** and 20 mg **of vonoprazan (equivalent to 26.72 mg of vonoprazan fumarate) for oral administration-** (b) (4)

(b) (4) the following inactive ingredients: croscarmellose sodium, ferric oxide red (**only in 20 mg tablets**), ferric oxide yellow (**only in 10 mg tablets**), fumaric acid, hydroxypropyl cellulose, hypromellose, magnesium stearate, mannitol, microcrystalline cellulose, polyethylene glycol 8000, and titanium dioxide.

(b) (4)

Items	Information in Proposed Labeling	Assessor's Comments
Dosage form	Adequate	"tablets" provided. Per Labeling Review Tool , consider including proprietary name and established name.
Strength(s) in metric system. If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance. Clearly state whether the strength is based on the active moiety.	Inadequate	Strengths in metric system are provided. However, the active moiety as the basis of strengths should be added.
Available units (e.g., bottles of 100 tablets)	Adequate	Each bottle contains 30 tablets. Per Labeling Review Tool , do not list professional samples.
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable, NDC number. Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	Adequate	Color, shape, film coating, debossing information and NDC number provided. Tablets are not scored.
Special handling (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g. to protect from light or moisture, to maintain stability, etc.) For hazardous drugs, state "DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures.x" with x numerical citation to "OSHA Hazardous Drugs."	N/A	No special handling is required.
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	The product does not contain any desiccant.
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Adequate	Minor formatting edits are recommended.
Latex: If product does not contain latex and manufacturing of product and container did not	N/A	Not applicable

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."		
--	--	--

(b) (4)

Conclusion: *Unsatisfactory*

Per [Labeling Review Tool, Revised March 2022 \(page 70 of 93\)](#), consider including the proprietary name (if any) and the nonproprietary name in section 16. The recommended revisions are shown below:

VOQUEZNA (vonoprazan) tablets:

10 mg of vonoprazan: pale yellow, oval, film-coated tablets debossed V10 on one side and plain on the other side. Bottles of 30 (NDC 81520-100-30).

(b) (4)

20 mg of vonoprazan: pale red, oval, film-coated tablets debossed V20 on one side and plain on the other side. Bottles of 30 (NDC 81520-200-30).

(b) (4)

Store between 20°C and 25°C (68°F and 77°F); excursions permitted between: (b) (4)
 15°C (b) (4) and 30°C (59°F (b) (4) and 86°F (b) (4) [see USP Controlled Room Temperature].

(b) (4)

Item	Information in Proposed Labeling	Assessor's Comments
Name and location of business (street address, city, state, and zip code) of the manufacturer, distributor, and/or packer [21 CFR 201.1(h)(5)]	Inadequate	VOQUEZNA is manufactured for and distributed by Phathom. Per Labeling Review Tool , the street address is not required if the address is shown in a current city or telephone directory. Per Google search, Phathom's street address in Buffalo Grove, IL is: 2150 E. Lake Cook Road, Suite 800

Conclusion: *Unsatisfactory*

The recommended revision is shown below.

VOQUEZNA is manufactured **for** and distributed by Phathom Pharmaceuticals, Inc., Buffalo Grove, IL, 60089, U.S.A.

2.0 CONTAINER LABELS AND CARTON LABELING

Labels provided in eCTD-0003 (SDN-3) are shown below.

2.1 CONTAINER LABEL

Items	Items in Proposed Labeling	Assessor's Comments
Proprietary name, established name [FD&C Act 502(e)(1)(A)(i)] [font size at least half as large as the proprietary name, and prominence per FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2)]	Inadequate	The established name should be presented in parenthesis on the same line.
Route of administration, if it is not for oral use [21 CFR 201.100(b)(3)]	N/A	Not required for oral drugs
Strength(s) in metric system	Inadequate	10 mg and 20 mg provided. The strength of professional samples is recommended to be expressed as (b) (4) "20 mg* per tablet".
Active moiety expression of strength with equivalence statement (if applicable) [FD&C Act 502(e)(1)(ii), 21 CFR 201.10(d)(1); 21 CFR 201.100(b)(4), USP <1121>]	Inadequate	Strengths based on the active moiety vonoprazan. An equivalence statement is provided on the side panel. However, the format is recommended to follow the recommendation in FDA guidance entitled <i>Naming of Drug Products Containing Salt Drug Substances</i> (Appendix 2).
Net content [FD&C Act 502(b)(2), 21 CFR 201.51(a)]	Adequate	Retail: 30 Tablets per bottle Sample: 5 Tablets per bottle
Name of all inactive ingredients, in alphabetical order required for OTC drugs [FD&C Act 502(e)(1)(A)(iii), 21 CFR 201.10(a)] [except for oral drug per 21 CFR 201.100(b)(5) or limited space per 21 CFR 201.10(i)(2)]; [Quantitative ingredient information is required for injectables per 21 CFR 201.100(b)(5)(iii)]	N/A	Not required for oral drugs
"Rx only" displayed on principal display [21 CFR 201.100(b)(1)]	Adequate	Provided
NDC number [per 21 CFR 201.2, requested, but not required for all labels or labeling, also see 21 CFR 207.35(b)(3)(i)]	Adequate	10 mg: 81520-100-30 (b) (4) 20 mg: 81520-200-30 20 mg sample: 81520-200-05
Lot number (21 CFR 201.18) and expiration date (21 CFR 201.17)	Adequate	Space allocated

Storage conditions	Adequate	Minor edits recommended as shown below: “excursions permitted between 15°C and 30°C (59°F and 86°F) [see USP Controlled Room Temperature]”
Bar code [21CFR 201.25(c)(2)]	Adequate	Bar code provided in a vertical orientation for retail bottles. The bar code requirement does not apply to prescription drug samples [21 CFR 201.25(b)(1)(i)(A)].
Adequate directions for use [FD&C Act 502(f)(1), 21 CFR 201.5] or “Recommended Dosage: See Prescribing Information” (21 CFR 201.55)	Inadequate	The following revision for (b) (4) is recommended: “Recommended Dosage: See Prescribing Information”
Name of manufacturer/distributor [502(b)(1), 21 CFR 201.1(a), 21 CFR 201.1(h)(5)]	Adequate	Information provided
And others, if space is available	Adequate	Do not accept if seal over bottle is broken or missing.

Conclusion: *Unsatisfactory*

In an email communication dated 8/9/2019 with a DMEPA assessor for labeling of another NDA, the DMEPA assessor stated that based on DMEPA management’s involvement with the Labeling Workgroup, it was determined that the usual dosage statement be changed from “See package insert for dosage information” to “Recommended Dosage: See Prescribing Information”.

The following issues should be addressed:

1. Regarding the container labels:
 - a. Whether the established name includes the dosage form “tablets” is not clearly indicated. No parenthesis is used for the established name. Revise the established name such that the active moiety and the dosage form are on the same line and the established name is in the parenthesis. That is, present the proprietary name and established name as one of the following:

VOQUEZNA
(vonoprazan tablets)

or

VOQUEZNA
(vonoprazan) tablets
 - b. The strength of professional samples is expressed as (b) (4) “20 mg*”. Per FDA guidance entitled *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors*, the strength of professional samples is recommended to be expressed as (b) (4) “20 mg* per tablet”.

- c. Follow the recommendation in FDA guidance *entitled Naming of Drug Products Containing Salt Drug Substances* (Appendix 2) for the format of salt equivalence statement. Revise the salt equivalence statement, including the line format for the text, as the following:
- Each tablet contains:
Vonoprazan.....10 mg
(equivalent to 13.36 mg Vonoprazan Fumarate)
- Each tablet contains:
Vonoprazan.....20 mg
(equivalent to 26.72 mg Vonoprazan Fumarate)
- d. The terminology used for storage statement is not consistent with USP <659>. Revise the storage statement to “Store between 20°C and 25°C (68°F and 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) [see USP Controlled Room Temperature]”.
- e. Replace the statement (b) (4) with “Recommended Dosage: See Prescribing Information”.

In SDN-22, updated container labels were provided.



(b) (4)

Items	Items in Proposed Labeling	Assessor's Comments
Proprietary name, established name [FD&C Act 502(e)(1)(A)(i)] [font size at least half as large as the proprietary name, and prominence per FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2)]	Adequate	“VOQUEZNA (vonoprazan) tablets” provided.
Route of administration, if it is not for oral use [21 CFR 201.100(b)(3)]	N/A	Not required for oral drugs
Strength(s) in metric system	Adequate	10 mg and 20 mg provided for retail products. The strength of professional samples is expressed as (b) (4) “20 mg* per tablet” per FDA guidance entitled <i>Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors</i> .
Active moiety expression of strength with equivalence statement (if applicable) [FD&C Act 502(e)(1)(ii), 21 CFR 201.10(d)(1); 21 CFR 201.100(b)(4), USP <1121>]	Adequate	Strengths based on the active moiety vonoprazan. An equivalence statement is provided on the side panel, following the format recommended in FDA guidance entitled <i>Naming of Drug Products Containing Salt Drug Substances</i> (Appendix 2).
Net content [FD&C Act 502(b)(2), 21 CFR 201.51(a)]	Adequate	Retail: 30 Tablets per bottle Sample: 5 Tablets per bottle
Name of all inactive ingredients, in alphabetical	N/A	Not required for oral drugs

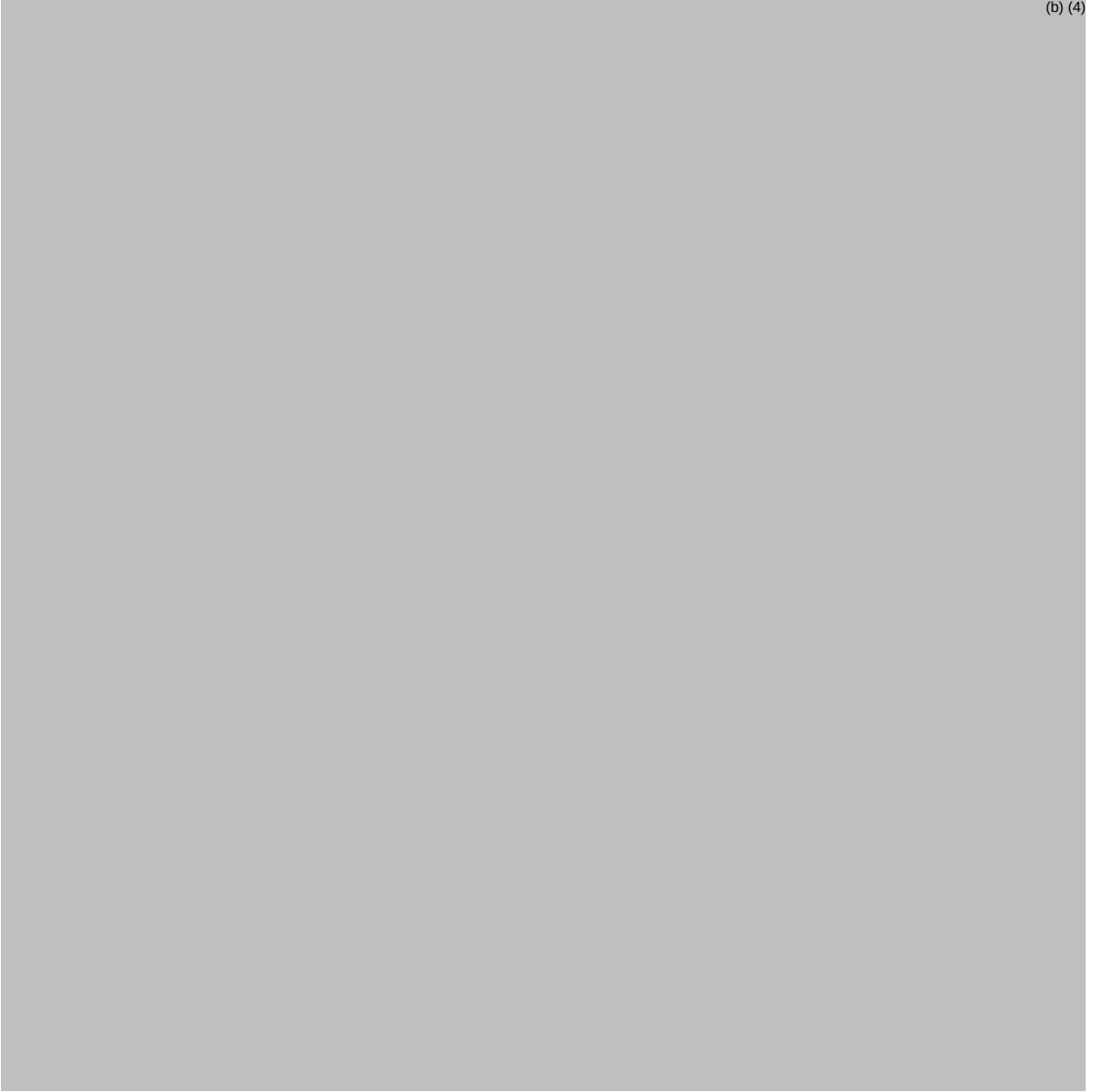
order required for OTC drugs [FD&C Act 502(e)(1)(A)(iii), 21 CFR 201.10(a)] [except for oral drug per 21 CFR 201.100(b)(5) or limited space per 21 CFR 201.10(i)(2)]; [Quantitative ingredient information is required for injectables per 21 CFR 201.100(b)(5)(iii)]		
“Rx only” displayed on principal display [21 CFR 201.100(b)(1)]	Adequate	Provided
NDC number [per 21 CFR 201.2, requested, but not required for all labels or labeling, also see 21 CFR 207.35(b)(3)(i)]	Adequate	10 mg: 81520-100-30 (b) (4) 20 mg: 81520-200-30 20 mg sample: 81520-200-05
Lot number (21 CFR 201.18) and expiration date (21 CFR 201.17)	Adequate	Space allocated
Storage conditions	Adequate	“Store between 20°C and 25°C (68°F and 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) [see USP Controlled Room Temperature]” provided.
Bar code [21CFR 201.25(c)(2)]	Adequate	Bar code provided in a vertical orientation for retail bottles. The bar code requirement does not apply to prescription drug samples [21 CFR 201.25(b)(1)(i)(A)].
Adequate directions for use [FD&C Act 502(f)(1), 21 CFR 201.5] or “Recommended Dosage: See Prescribing Information” (21 CFR 201.55)	Adequate	“Recommended Dosage: See Prescribing Information” provided.
Name of manufacturer/distributor [502(b)(1), 21 CFR 201.1(a), 21 CFR 201.1(h)(5)]	Adequate	“Distributed by Phathom PHARMACEUTICALS Buffalo Grove, IL 60089, U.S.A.” provided.
And others, if space is available	Adequate	Do not accept if seal over bottle is broken or missing.

Conclusion: *Satisfactory*

The information provided on the container labels as provided in SDN-22 meets the regulatory requirements.

2.2 CARTON LABELING

(b) (4)



(b) (4)

Items	Items in Proposed Labeling	Assessor's Comments
Proprietary name, established name [FD&C Act 502(e)(1)(A)(i)] [font size at least half as large as the proprietary name, and prominence per FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2)]	Inadequate	The established name should be presented in parenthesis on the same line.
Strength(s) in metric system	Inadequate	10 mg and 20 mg provided. The strength of professional samples is recommended to be expressed (b) (4) "20 mg* per tablet".

Route of Administration [not required for oral, 21 CFR 201.100(b)(3)]	N/A	Not required for oral drug
Active moiety expression of strength with equivalence statement (if applicable) [FD&C Act 502(e)(1)(ii), 21 CFR 201.10(d)(1); 21 CFR 201.100(b)(4), USP <1121>]	Adequate	Strengths based on the active moiety vonoprazan. Equivalence statements provided on the back panel.
Net content [FD&C Act 502(b)(2), 21 CFR 201.51(a)]	Adequate	Sample: 5 tablets
Name of all inactive ingredients, in alphabetical order required for OTC drugs [FD&C Act 502(e)(1)(A)(iii), 21 CFR 201.10(a)] [except for oral drug per 21 CFR 201.100(b)(5) or limited space per 21 CFR 201.10(i)(2)]; [Quantitative ingredient information is required for injectables per 21 CFR 201.100(b)(5)(iii)]	N/A	Not required for oral drugs
“Rx only” displayed on principal display [21 CFR 201.100(b)(1)]	Adequate	Provided
NDC number [per 21 CFR 201.2, requested, but not required for all labels or labeling, also see 21 CFR 207.35(b)(3)(i)]	Adequate	(b) (4) 20 mg Samples: 81520-200-05
Lot number (21 CFR 201.18) and expiration date (21 CFR 201.17)	Adequate	Space allocated
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new beyond-use-date (BUD).	Adequate	Provided on the right panel. Minor edits recommended as shown below: “excursions permitted between 15°C and 30°C (59°F and 86°F) [see USP Controlled Room Temperature]”
Bar code [21 CFR 201.25(c)(2)]	Adequate	Provided on the right panel
Adequate directions for use [FD&C Act 502(f)(1), 21 CFR 201.5] or “Recommended Dosage: See Prescribing Information” (21 CFR 201.55)	Inadequate	The following revision for (b) (4) is recommended: “Recommended Dosage: See Prescribing Information”
If there is a Medication Guide, must include a statement about dispensing a Medication Guide to each patient.	N/A	No Medication Guide
“Keep out of reach of children” (Required for OTC in CFR. Optional for Rx drugs)	Adequate	Provided on the left side panel

Name of manufacturer/distributor [502(b)(1), 21 CFR 201.1(a), 21 CFR 201.1(h)(5)]	Adequate	Provided on the left side panel
And others, if space is available	Adequate	“PROFESSIONAL SAMPLE – NOT FOR RESALE”
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled.	N/A	There is no USP monograph for the drug product.
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

Conclusion: *Unsatisfactory*

Items 1a, 1b, 1c, 1d, and 1e identified under Container Labels section (see page 11) are also applicable to the carton labeling. In addition, the following issue should be addressed:

- Regarding the carton labeling, replace the statement (b) (4) with “Recommended Dosage: See Prescribing Information”.

In SDN-22, updated carton labeling was provided.

(b) (4)

Items	Items in Proposed Labeling	Assessor's Comments
Proprietary name, established name [FD&C Act 502(e)(1)(A)(i)] [font size at least half as large as the proprietary name, and prominence per FD&C Act 502(e)(1)(B) , 21 CFR 201.10(g)(2)]	Adequate	"VOQUEZNA (vonoprazan) tablets" provided.
Strength(s) in metric system	Adequate	10 mg and 20 mg provided for retail products. The strength of professional samples is expressed as (b) (4) "20 mg* per tablet" per FDA guidance entitled

		<i>Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors.</i>
Route of Administration [not required for oral, 21 CFR 201.100(b)(3)]	N/A	Not required for oral drug
Active moiety expression of strength with equivalence statement (if applicable) [FD&C Act 502(e)(1)(ii), 21 CFR 201.10(d)(1); 21 CFR 201.100(b)(4), USP <1121>]	Adequate	Strengths based on the active moiety vonoprazan. An equivalence statement is provided on the back panel, following the format recommended in FDA guidance entitled <i>Naming of Drug Products Containing Salt Drug Substances</i> (Appendix 2).
Net content [FD&C Act 502(b)(2), 21 CFR 201.51(a)]	Adequate	Sample: 5 tablets
Name of all inactive ingredients, in alphabetical order required for OTC drugs [FD&C Act 502(e)(1)(A)(iii), 21 CFR 201.10(a)] [except for oral drug per 21 CFR 201.100(b)(5) or limited space per 21 CFR 201.10(i)(2)]; [Quantitative ingredient information is required for injectables per 21 CFR 201.100(b)(5)(iii)]	N/A	Not required for oral drugs
“Rx only” displayed on principal display [21 CFR 201.100(b)(1)]	Adequate	Provided
NDC number [per 21 CFR 201.2, requested, but not required for all labels or labeling, also see 21 CFR 207.35(b)(3)(i)]	Adequate	(b) (4) 20 mg Samples: 81520-200-05
Lot number (21 CFR 201.18) and expiration date (21 CFR 201.17)	Adequate	Space allocated
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new beyond-use-date (BUD).	Adequate	Provided on the right panel: Store between 20°C and 25°C (68°F and 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) [see USP Controlled Room Temperature]
Bar code [21 CFR 201.25(c)(2)]	Adequate	Provided on the right panel
Adequate directions for use [FD&C Act 502(f)(1), 21 CFR 201.5] or “Recommended Dosage: See Prescribing Information” (21 CFR 201.55)	Adequate	“Recommended Dosage: See Prescribing Information” provided.
If there is a Medication Guide, must include a statement about	N/A	No Medication Guide

dispensing a Medication Guide to each patient.		
“Keep out of reach of children” (Required for OTC in CFR. Optional for Rx drugs)	Adequate	Provided on the left side panel
Name of manufacturer/distributor [502(b)(1), 21 CFR 201.1(a), 21 CFR 201.1(h)(5)]	Adequate	Provided on the left side panel: “VOQUEZNA is distributed by Phathom Pharmaceuticals, Inc. (b) (4)
And others, if space is available	Adequate	“PROFESSIONAL SAMPLE – NOT FOR SALE”
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled.	N/A	There is no USP monograph for the drug product.
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

Conclusion: *Satisfactory*

The information provided on the carton labeling as provided in SDN-22 meets the regulatory requirements.

3.0 LIST OF DEFICIENCIES:

A. Regarding PI

a) Highlight Section

1. Revise the proprietary name and established name from (b) (4) to “VOQUEZNA (vonoprazan) tablets” based on the revisions of container labels and carton labeling in SDN-22.
2. List the year for Initial U.S. Approval as “2022”.
3. Include the active moiety vonoprazan as the basis of strengths under Dosage Forms and Strengths.

b) Full Prescribing Information

Section 3: Dosage Forms and Strengths

4. Include the active moiety vonoprazan as the basis of strength.

Section 11: Description

5. Include “(2E)” in the chemical name of fumarate.
6. Include the established name in conjunction with the proprietary name.

Section 16: How Supplied/Storage and Handling

7. Include the active moiety vonoprazan as the basis of strength.

Section 17: Patient Counseling Information

8. Replace (b) (4) with “manufactured for and distributed by”. VOQUEZNA is manufactured by Catalent Pharma Solutions, LLC, not by Phathom.

B. Regarding the Container/Carton Labels

All issues on the container labels and carton labeling have been addressed satisfactorily in SDN-22.

OVERALL ASSESSMENT:

Issues on the container labels and carton labeling have been satisfactorily resolved. The container labels and carton labeling provided in SDN-22 are acceptable. Issues on the Prescribing Information labeling have been identified and recommended revisions have been provided to the review team. As of the date of this assessment, discussions for other (i.e., non-quality) sections of Prescribing Information labeling are still ongoing. Once the recommended revisions as shown in Sections 1.1 and 1.2 of this assessment are adopted, the Prescribing Information labeling will be adequate.

RECOMMENDATION:

Other than some revisions for the Prescribing Information labeling to be negotiated with the applicant, from the ONDP perspective, labeling of this NDA is adequate.

Primary Labeling Assessor Name and Date:

Jane Chang, Ph.D.
Master Chemistry Reviewer
OPQ/ONDP/DNDP II/Branch 4
10/18/2022

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

Nina Ni, Ph.D.
Senior Pharmaceutical Quality Assessor
OPQ/ONDP/DNDP II/Branch 4
10/18/2022



Jane
Chang

Digitally signed by Jane Chang
Date: 10/18/2022 06:05:07PM
GUID: 5034f819000053b21e2574590781f330



Nina
Ni

Digitally signed by Nina Ni
Date: 10/18/2022 06:32:03PM
GUID: 502d1ab500002afbbe642f8f37136920

BIOPHARMACEUTICS**NDA:** NDA 215151**Drug Product Name / Strength:** Vonoprazan tablets, 10 mg, and 20 mg**Route of Administration:** Oral**Applicant Name:** Phathom Pharmaceuticals, Inc.**Indication:** Healing of all grades of erosive esophagitis and relief of heartburn**Submission date:** 03/11/2022**Primary Reviewer:** Kamrun Nahar, Ph.D.**Secondary Reviewer:** Tapash Ghosh, Ph.D.**Recommendation:** Adequate**BACKGROUND:**

The Applicant is seeking approval under 505(b)(1) regulatory pathways for Vonoprazan tablets, 10 mg, and 20 mg, for oral administration, indicated for the healing of all grades of erosive esophagitis and relief of heartburn, and maintenance of healing of all grades of erosive esophagitis and relief of heartburn.

Vonoprazan tablets 20 mg was submitted by Phathom as a part of a convenience pack (Vonoprazan Tablets 20 mg, Clarithromycin Tablets, 500 mg, and Amoxicillin Capsules, 500 mg) for the treatment of Helicobacter pylori (H pylori) infection and was approved under the NDA# 215152. This application cross-references NDA 215152 for the drug substance and 20 mg strength tablets, including development pharmaceuticals and analytical methods that are applicable to both the 10 mg and 20 mg tablets.

REVIEW SUMMARY:

The Biopharmaceutics review was focused on the evaluation of the adequacy of the overall information/data supporting: 1) the proposed dissolution method and acceptance criteria, 2) formulation bridging throughout product development, and 3) BCS based biowaiver request. Summary of the key findings are presented below, based on the review of the provided information/data:

1) Dissolution Method and Acceptance Criteria: Acceptable

The approved dissolution method and acceptance criterion for quality control and stability testing of the proposed Vonoprazan tablets, 10 mg, and 20 mg:

Apparatus	Rotation Speed (rpm)	Medium	Volume (mL)	Temperature	Acceptance Criterion
USP Apparatus 2 (Paddle)	50	Acetate buffer, pH 4.5	900	37±0.5°C	$Q = \frac{(Q)}{(Q)}$ % in 15 minutes

2) Bridging of Formulations: Acceptable

The Applicant developed four formulations, denoted as Formulation T1, T2, T3, and T4 that were used throughout development. The Applicant adequately bridged the formulations— a. used in clinical development phase, i.e., T1, T2, T3 and T4 formulations, b. Over-encapsulated Tablet to unencapsulated tablet; c. formulations manufactured at different sites (b) (4); and d. Phathom commercial tablets vs (b) (4) commercial tablets.

III) BCS (b) (4) based waiver for in vivo studies: Not applicable

(b) (4) the assessment outcome is still pending as of 10/25/2022. In NDA 215152 (b) (4) TRIPLE PAK Vonoprazan tablets 20 mg/Amoxicillin capsules 500 mg, USP/Clarithromycin tablets, 500 mg, a formal request for BCS (b) (4) based biowaiver for conducting bioequivalence studies for the formulation changes during clinical development for the formulations T1 to T4 was requested; however, the request was accepted by the Biopharmaceutics reviewer¹ not via BCS based biowaiver but due to the fact that the change was within acceptable limit which could be supported via dissolution profiles comparison. In the current NDA, the Applicant (Phathom) is asking for the approval of the Vonoprazan tablet, 10 mg and 20 mg and cross-referenced NDA 215152 for bridging among the formulations.

Like NDA 215152, the BCS (b) (4) designation is not needed for the approval of this NDA, since the excipients changes between the T1 and T2, T2 and T3 and T2 and T3 for both strengths 10 mg and 20 mg, and T3 to T4 formulations for Vonoprazan tablet, 20 mg are within $\pm 10\%$, the formulated 10 mg and 20 mg of T4 formulation are compositionally proportional (b) (4). Therefore, T1 to T4 formulation can be bridged by dissolution profile comparison and a BCS (b) (4) based waiver for in vivo studies is not required for the approval of the NDA.

CONCLUSION AND RECOMMENDATION:

Form a Biopharmaceutics perspective, NDA 215151 Voquenza (vonoprazan) tablets, 10 mg and 20 mg is **adequate** for approval.

¹ <https://panorama.fda.gov/task/view?ID=61942b1a0091dbf58f925e3eafca6406>

BIOPHARMACEUTICS ASSESSMENT:**List Submissions being reviewed:**

1. 0001 08/26/2022 Original submission

Solubility:

(b) (4)

Table 1: Solubility data of vonoprazan across the physiological pH range 1.0-6.8

Solubility (37°C)	pH	Solubility (mg/mL)
	1.2 (SGF, no enzymes)	19.9
	3.6 (citrate)	4.83
	4.5 (acetate)	5.02
	5.6 (citrate)	4.64
	6.8 (SIF, no enzymes)	4.62

Note: SGF stands for simulated gastric fluid; SIF stands for simulated intestinal fluid

Dissolution Method:

The Applicant developed a dissolution method for vonoprazan immediate-release Tablets, 10 mg, and 20 mg for quality control (QC) at release and stability using the standard dissolution conditions. The Approved dissolution conditions are as follows- paddle apparatus, 50 rpm, 0.05 mol/L acetate buffer pH 4.5, 900 mL at 37±0.5°C which was approved by the Agency as a part of IND submission. The review of the complete dissolution method development report finalized on 10/19/2021) can be found at the following link:

<https://dartrts.fda.gov/dartrts/ViewDocument?documentId=090140af8061ece7>.

Dissolution acceptance criterion:

The Applicant proposed dissolution acceptance criterion as “Q= ^{(b) (4)}% in 15 minutes”. Based on the dissolution data provided for the clinical formulations, the proposed dissolution acceptance criterion is deemed adequate.

Formulations used in clinical studies:

The Applicant used four formulations, designated as T1, T2, T3 and T4 formulations in the development of Vonoprazan tablets, 10 mg, and 20 mg (Table 2). The Applicant adjusted the excipients in T1, T2 and T3 formulations. (Table 3). The T4 formulation represents the final 10 and 20 mg commercial formulations approved in Japan. The T4 formulation was used in further Phase 1, 2 and 3 studies conducted by Takeda, and was also used in Phase 1 Studies VONO-101, VONO-103 and pivotal Phase 3 Studies HP-301 and EE-301 conducted by Phathom. that the tablets were blinded by over-encapsulation for the Takeda Study Vonoprazan-2001 and the

Phathom pivotal Phase 3 Studies HP-301 and EE-301. T4 tablets consist of the same (b) (4) tablet excipients as the T3 formulation. (b) (4)

The equivalence of the T2 to T3, and T3 and T4 formulations (10 mg and 20 mg) were demonstrated by comparative dissolution profile testing in 3 different media (pH 1.2, pH 3.0 and pH 6.8) and water. Dissolution data showed very rapid drug release in all pH conditions.

Table 2: Summary of formulations used in clinical studies

Formulation	Film-coated Tablet Strengths	Study
T1	1 mg, 10 mg, 40 mg	Phase 1: TAK-438/CPH-001, TAK-438_101
T2	5 mg, 10 mg, 20 mg	Phase 1: TAK-438/CPH-002, TAK-438/CPH-003, TAK-438_107, TAK-438_109, TAK-438_110 Phase 2: TAK-438/CCT-001
T3	10 mg, 20 mg, 40 mg	Phase 1: TAK-438_111, TAK-438_112, TAK-438_113, TAK-438/CPH-401 Phase 2: Vonoprazan-2001 (40 mg) Phase 3: TAK-438/CCT-002, TAK-438/OCT-001, TAK-438/CCT-003, TAK-438/CCT-101, TAK-438/CCT-102, TAK-438/CCT-301, TAK-438/OCT-301, TAK-438/CCT-302, TAK-438/OCT-302, TAK-438/OCT-303, TAK-438/OCT-304, TAK-438/CCT-401, TAK-438/CCT-201, TAK-438/OCT-002
T4	10 mg, 20 mg	Phase 1: TAK-438/CPH-007, TAK-438_114, TAK-438_115, TAK-438/CPH-010, TAK-438ODT-1001, VONO-101 and VONO-103 Phase 2: Vonoprazan-2001 (20 mg) Phase 3: TAK-438_303, HP-301, EE-301, Vonoprazan-3001, TAK-438_305, TAK-438_304, and TAK-438_302 The T4 formulation is approved in Japan (10 and 20 mg). The 10 and 20 mg tablets are proposed in this application for commercialization. The only difference is that the Japanese-approved tablets include printing while the proposed US commercial tablets will be debossed.

Table 3: Composition of a. T1, b. T2, c. T3 and d. T4 formulations

a. T1 formulation:

(b) (4)



b. T2 formulation:

(b) (4)



c. T3 formulation:

(b) (4)

d. T4 formulation:

Component	Function	10 mg tablet (mg)	20 mg tablet (mg)
Vonoprazan fumarate		13.36	26.72
(Vonoprazan)	Active	(10)	(20)
(b) (4) (4) Mannitol	(b) (4)	(b) (4)	(b) (4)
Microcrystalline cellulose ^a			
Hydroxypropyl cellulose			
Fumaric acid			
Croscarmellose sodium			
Magnesium stearate			
Hypromellose ^b			
(b) (4)			
Titanium dioxide			
Red ferric oxide			
Yellow ferric oxide			
Total			
			(b) (4)

Tablets manufactured at different sites (b) (4):

All clinical tablet formulations T1 through T4 were manufactured at pilot-scale (b) (4)

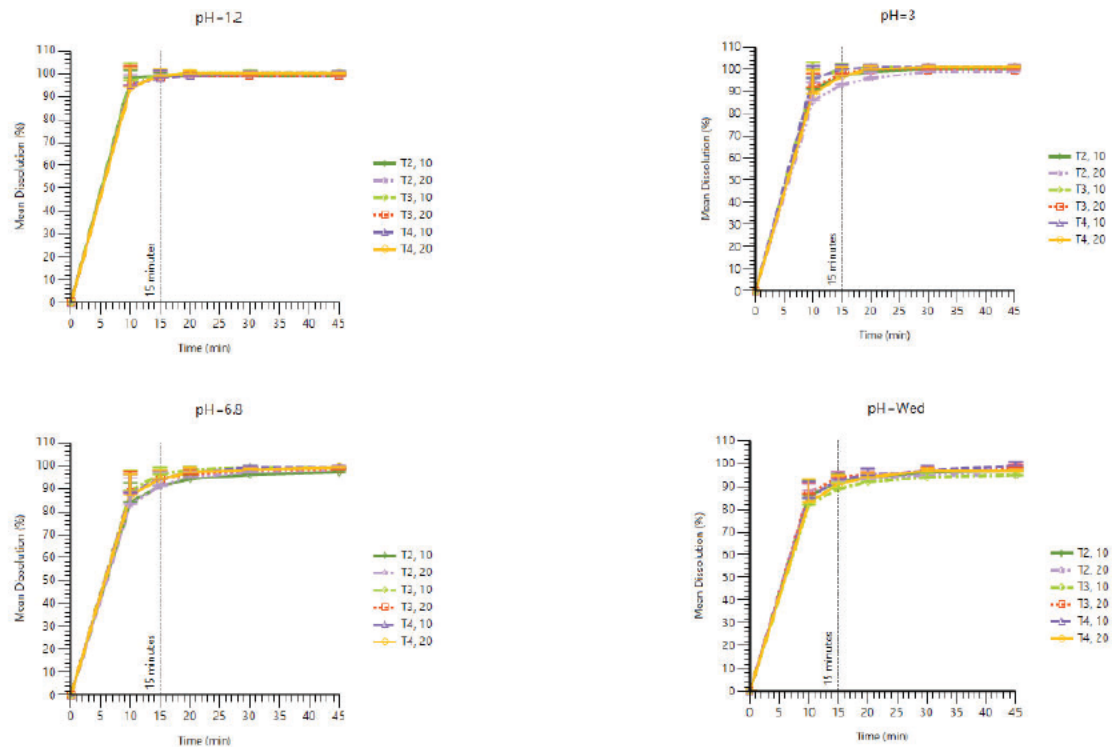
The 20 mg tablets used in the Phathom Phase 1 Studies VONO-101, VONO-103 and pivotal Phase 3 Studies HP-301 and EE-301 were manufactured (b) (4). The equivalence of tablets (10 and 20 mg) from both sites was demonstrated by comparative dissolution profile testing in 3 different media (pH 1.2, pH 4.5 and pH 6.8). Dissolution profiles showed very rapid drug release from both strengths of the tablets (b) (4).

Over-encapsulated and unencapsulated tablets:

During the pivotal Phase 3 Study HP-301, T4 formulation (20 mg) and study EE-301, T4 formulations (10 mg and 20 mg) were over-encapsulated for blinding purposes. The Applicant conducted comparative dissolution profiles of over-encapsulated and unencapsulated tablets using the QC dissolution method. Dissolution data showed very rapid dissolution rate from both over-encapsulated and unencapsulated tablets (Figure 3)

Debossed vs printed tablets

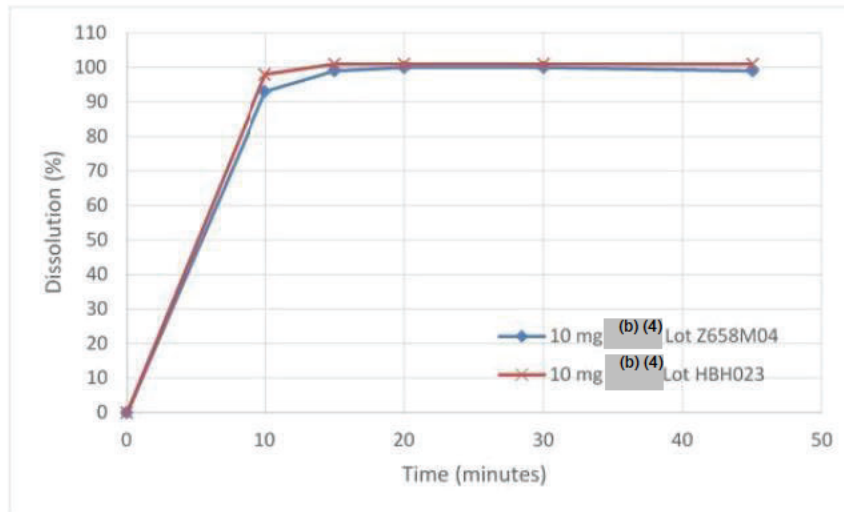
Phathom's 10 and 20 mg strengths commercial tablets will be debossed (b) (4) compared to Takeda's tablets which is printed, and 20 mg tablet is scored. The proposed manufacturing site for Phathom's commercial tablets is Phathom Contract Manufacturing Organization (CMO) site, Catalent in Winchester, Kentucky, US. The Applicant submitted comparative dissolution profiles of Takeda commercial tablets (b) (4) and Phathom commercial tablets (manufactured at Catalent) using QC dissolution method. Dissolution data showed very rapid dissolution rate, i.e., >85% in 15 minutes for both tablet image and manufacturing site (Figure 4).

Dissolution data:**Figure 1: Dissolution profiles of T1, T2, T3, and T4 formulation at multi pH 1.2, 4.5, 6.8 and water**

Abbreviations: Wed = Water (Japanese Pharmacopoeia 16th Edition Purified Water)

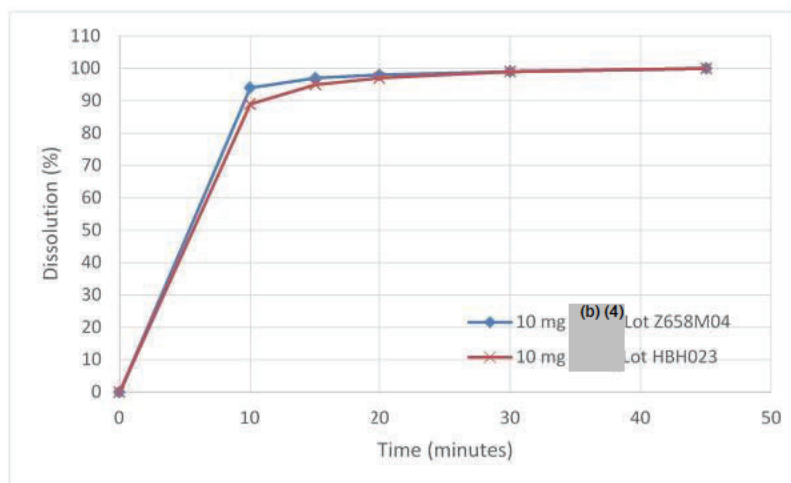
Figure 2: Dissolution profiles of Vonoprazan Tablets, 10 mg and 20 mg manufactured at different sites (b) (4) at multi pH 1.2, 4.5, 6.8 and water

Dissolution profiles of Vonoprazan Tablets, 10 mg in simulated gastric fluid (SGF) without enzymes, pH 1.2

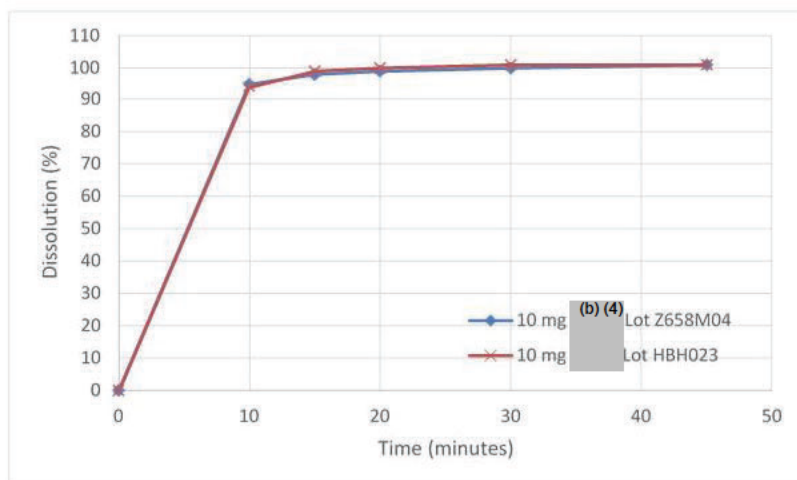


Abbreviations: SGF = simulated gastric fluid

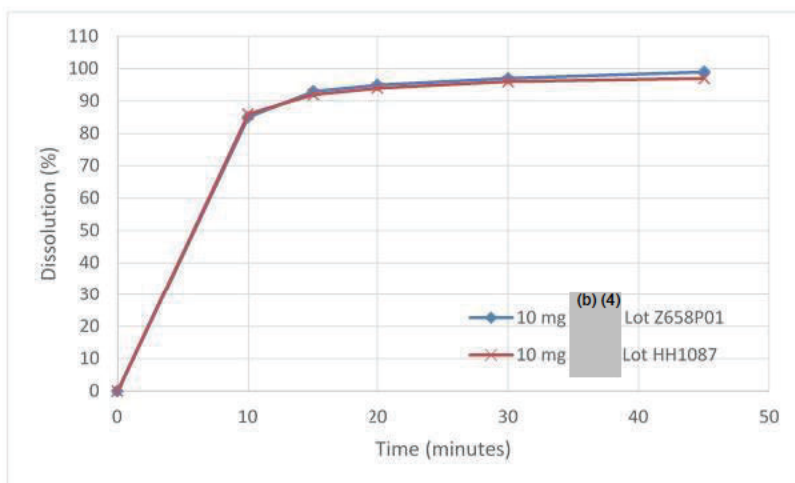
Dissolution Profile of Vonoprazan Tablets (10 mg) in acetate buffer solution (pH 4.5)



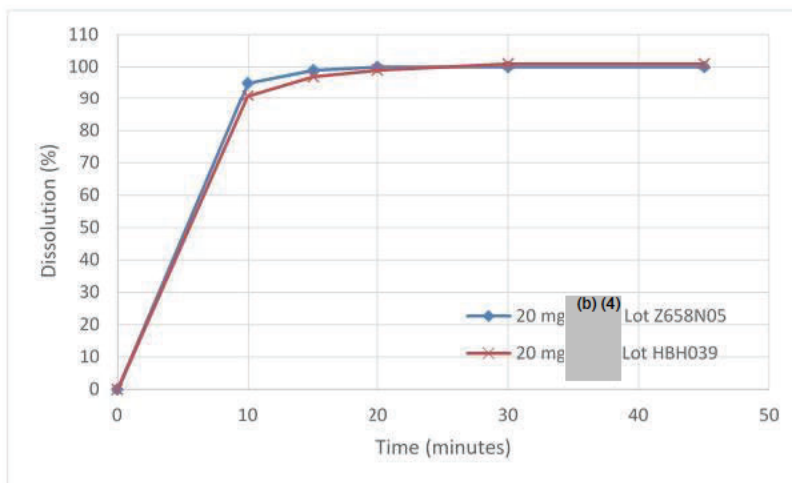
Dissolution Profile of Vonoprazan Tablets (10 mg) in SIF Without Enzymes (pH 6.8)



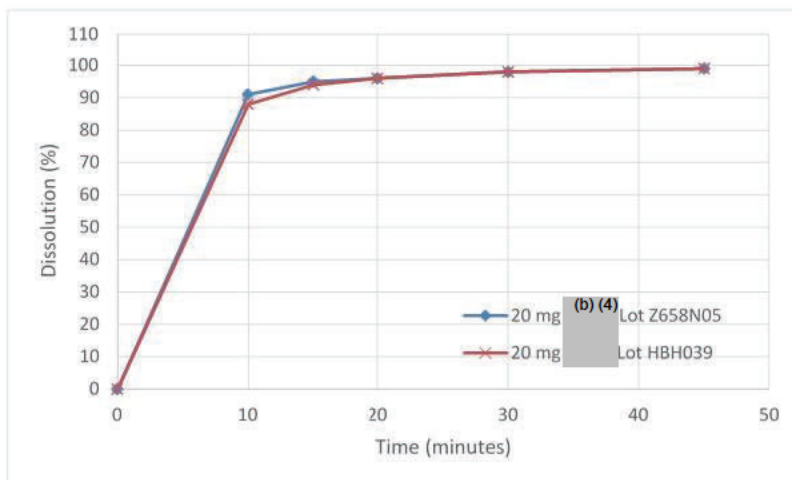
Dissolution Profile of Vonoprazan Tablets (10 mg) in Water



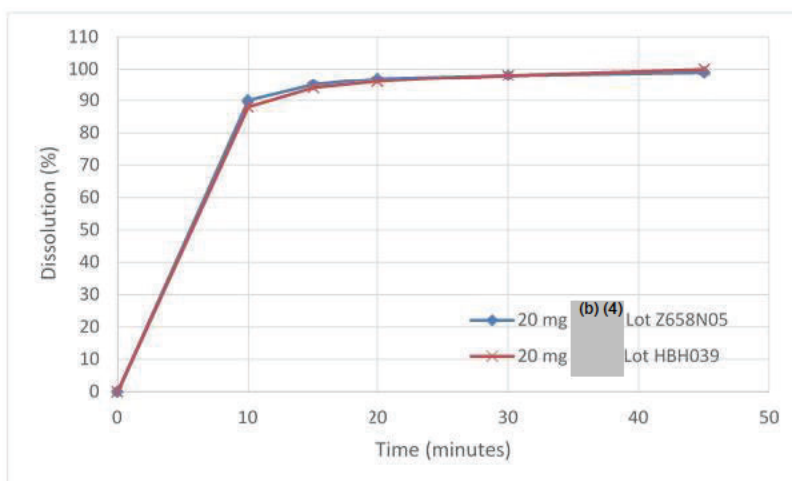
Dissolution Profile of Vonoprazan Tablets (20 mg) in SGF Without Enzymes (pH 1.2)



Dissolution Profile of Vonoprazan Tablets (20 mg) in Acetate Buffer Solution (pH 4.5)



Dissolution Profile of Vonoprazan Tablets (20 mg) in SIF Without Enzymes (pH 6.8)



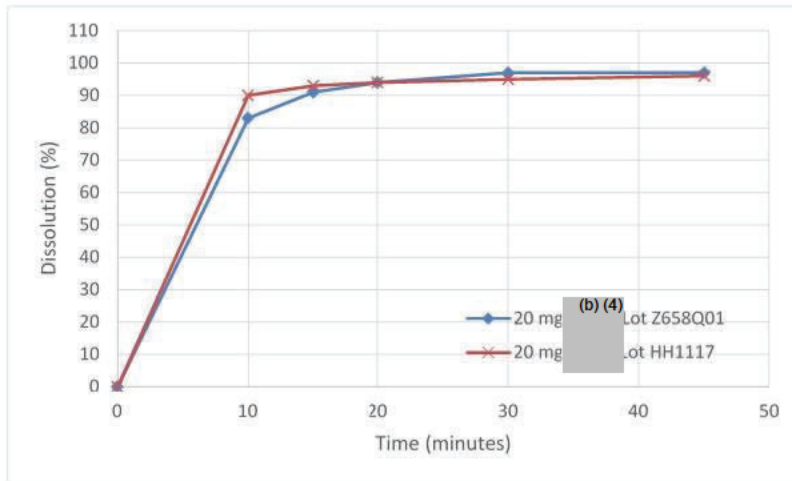
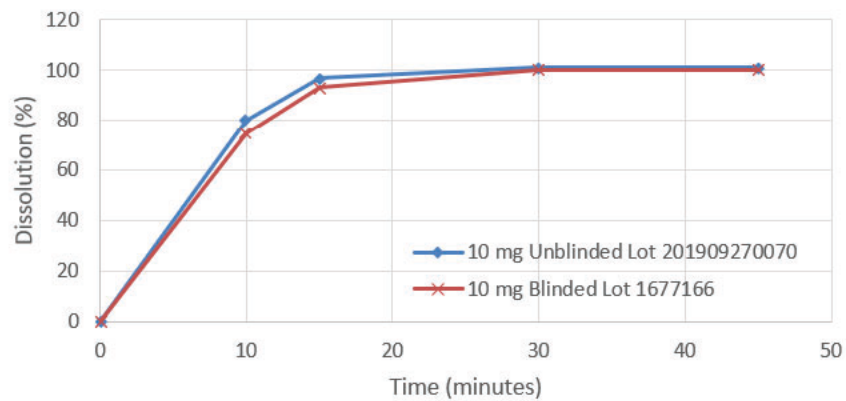
Dissolution Profile of Vonoprazan Tablets (20 mg) in Water

Figure 3: Comparative Dissolution Profiles of Vonoprazan Tablets 10 mg and 20 mg for Unblinded and Over-encapsulated Vonoprazan Tablets 10 mg in QC method (pH 4.5 Media), a. 10 mg; and b. 20 mg

a. Vonoprazan Tablets 10 mg**b. Vonoprazan Tablets 20 mg**

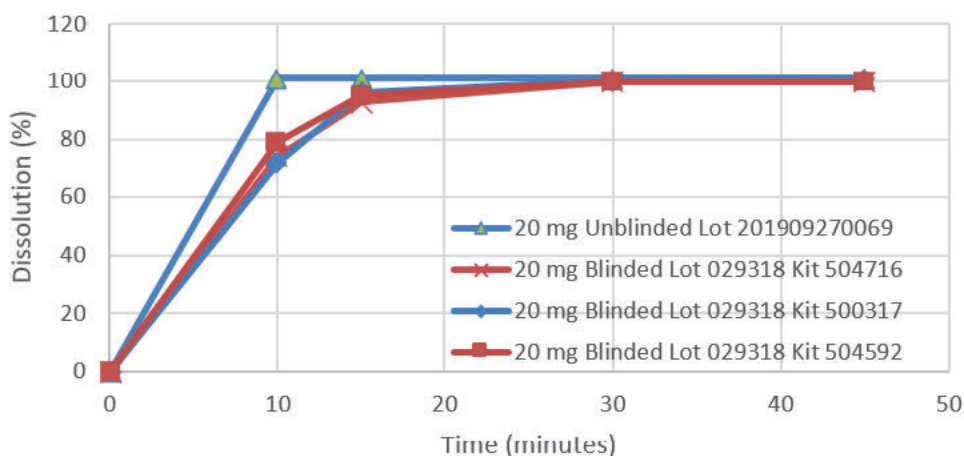
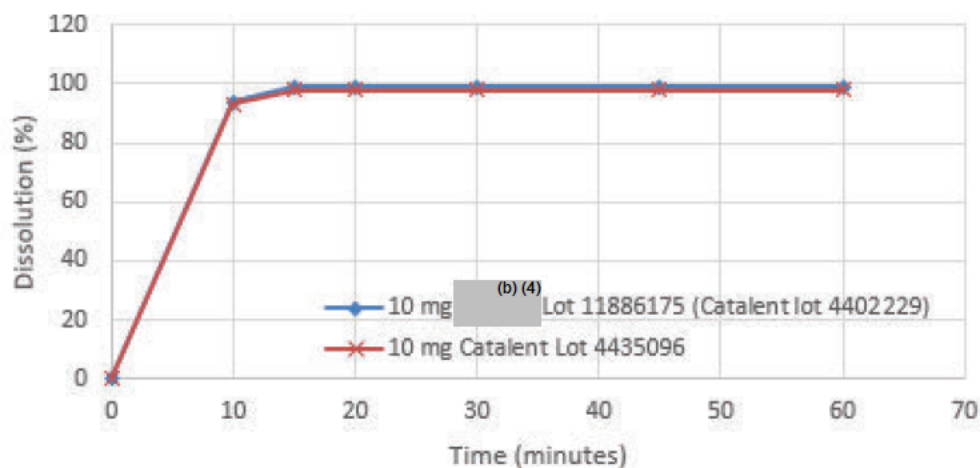
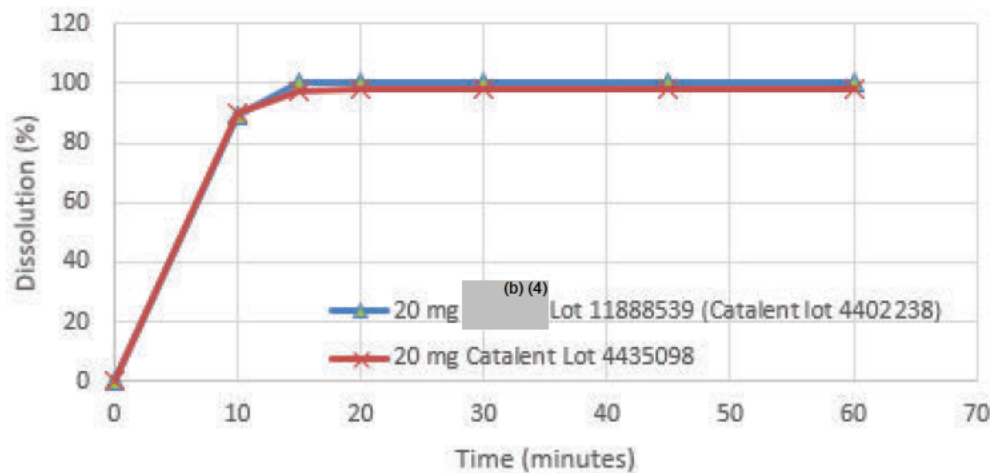


Figure 4: Comparative Dissolution Profiles of Vonoprazan Tablets 10 mg and 20 mg manufactured at (b) (4) vs Catalent, Winchester, Kentucky US in QC method (pH 4.5 Media), a. 10 mg; and b. 20 mg

a. Vonoprazan Tablets 10 mg



b. Vonoprazan Tablets 20 mg

**Compatibility protocol: Adequate**

The Applicant is planning to add Evonik (Dossenheim) site as an alternate manufacturing site for vonoprazan fumarate (TAK-438) drug substance via Change Being Effected in 30 days (CBE-30) supplement in future. (b) (4)

The compatibility protocol is adequate.

Appendix 1. Dissolution Data

Dissolution data: [\\CDSESUB1\EVSPROD\nda215151\0002\m2\27-clin-sum\summary-biopharm-ee.pdf](#) (page 51)

Compatibility protocol: [\\CDSESUB1\EVSPROD\nda215151\0012\m3\32-body-data\32r-reg-info\regional-information-comparability-protocol-qual-0001714.pdf](#)



Kamrun
Nahar

Digitally signed by Kamrun Nahar

Date: 11/14/2022 10:59:53AM

GUID: 57b38236009c032e2a84627cd295a5cd



Tapash
Ghosh

Digitally signed by Tapash Ghosh

Date: 11/14/2022 11:20:19AM

GUID: 508da7230002a2433ddcef616ca190df

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/

NINA NI
02/06/2023 07:24:30 PM