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APPLICATION NUMBER:

204655Orig1s000

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

ONDQA BIOPHARMACEUTICS REVIEW

NDA#:	204655/N-000
Submission Date:	05/30/13, 09/27/13, and 02/20/14 (commitment)
Brand Name:	Nexium 24HR
Generic Name:	Esomeprazole magnesium trihydrate
Formulation:	Delayed release (DR) oral capsule
Strength:	20 mg (One strength)
Applicant:	AstraZeneca
Type of submission:	Original, prescription to OTC (over-the-counter) switch
Reviewer:	Tien-Mien Chen, Ph.D.

SYNOPSIS

Background

AstraZeneca's Nexium (Esomeprazole magnesium) DR capsule under NDA 21153 was approved on 02/20/01 for two strengths (20 and 40 mg). Esomeprazole is the S-^{(b) (4)} isomer of the approved Omeprazole (S+R racemate), a proton pump inhibitor (PPI). The OTC Nexium 24HR DR 20 mg capsule under development by AstraZeneca is proposed for the indication of the treatment of frequent heartburn occurring 2 or more days a week.

The Applicant reported that

- 1). The manufacture and composition/formulation of the proposed OTC Nexium 24HR DR 20 mg capsule is ^{(b) (4)} the OTC Nexium 24HR DR 20 mg capsule is required to be sealed by a tamper band.
- 2). The gelatin band will be colored differently from the capsule shell to provide visual differentiation between the Rx capsule and the OTC capsule.

The Applicant requested a meeting on 01/15/11 for the development of the proposed OTC Nexium 24HR DR 20 mg capsule. FDA's preliminary comments were sent to the Applicant prior to the meeting and the Applicant then cancelled the 01/15/11 meeting. Please see the FDA's preliminary comments for the above meeting in DARRTS for details.

Current Submission

On 05/30/13, AstraZeneca submitted original NDA 204655 for Nexium 24HR DR 20 mg caps for OTC use. As agreed upon, the Applicant submitted 1). Comparative dissolution profile/data (with f2 calculations), 2). A biowaiver request, and 3). An IVIVC simulation/prediction for plasma PK profiles based on *in vitro* comparative dissolution profiles. The Applicant proposes to market Nexium 24HR DR 20 mg capsules for the OTC treatment of frequent heartburn occurring 2 or more days a week and the proposed treatment regimen is one capsule QD for 14 days every 4 months.

On 09/27/13, the Applicant submitted additional IVIVC parameter per Agency's information request.

Biopharmaceutics Review

The Biopharmaceutics review is focused on the evaluation and acceptability of the comparative dissolution profile/data, biowaiver request, and IVIVC prediction to support the biowaiver for a BE (bioequivalence) study requirement.

Reviewer's Comments:

1. The comparative dissolution profile/data show similarity between the Rx Nexium DR 20 mg capsule (without tamper band) and the proposed OTC Nexium 24HR DR 20 mg capsule (with tamper band). The similarity factor (f2) is calculated to be >50 indicating that the dissolution of Nexium DR capsules is not affected by the tamper band.
2. The results of the IVIVC prediction of the plasma profiles between the Rx Nexium DR 20 mg capsule and the proposed OTC Nexium 24 HR DR 20 mg capsule showed that the predicted difference between the PK parameters of interests are all within the 10% predicted errors allowed per FDA IVIVC guidance.

The IVIVC prediction is reassessed by the Biopharmaceutics team and the results are found comparable. Therefore, the IVIVC prediction is acceptable which supports the biowaiver for the proposed OTC Nexium 24HR DR 20 mg capsules.

3. Finally, the Applicant's proposed dissolution acceptable criterion of $Q = \frac{(b)}{(4)}\%$ at 30 min is NOT acceptable since esomeprazole dissolved $\frac{(b)}{(4)}\%$ at 30 min in the buffer stage. The Agency's recommendation of $Q = \frac{(b)}{(4)}\%$ at 30 min should be implemented. On 02/18/14, an information request was sent to the Applicant to request tightening the dissolution specification from $Q = \frac{(b)}{(4)}\%$ at 30 min to $Q = \frac{(b)}{(4)}\%$ at 30 min.

With further clarification, the Applicant accepted on 02/20/14 the Agency's recommendation and committed to 1). Tightening the dissolution acceptance criterion from $Q = \frac{(b)}{(4)}\%$ at 30 min to $\frac{(b)}{(4)}\%$ at 30 min and 2). Updating the Drug Product Specification section by 02/26/14.

RECOMMENDATION

From the Biopharmaceutics perspective, since the Applicant made a commitment on 02/20/14 to tightening the dissolution acceptance criterion from $Q = \frac{(b)}{(4)}\%$ at 30 min to $\frac{(b)}{(4)}\%$ at 30 min and to updating the Drug Product Specification section by 02/26/14, this NDA is recommended for approval. No further comments are to be sent to the Applicant at this time.

Tien-Mien Chen, Ph.D.
ONDQA Biopharmaceutics Reviewer

02/20/14

Date

John Duan, Ph.D.
ONDQA Biopharmaceutics Acting Team Leader

02/20/14

Date

CC: DARRTS/NDA No.204655/N000/RLostritto

PRODUCT QUALITY - BIOPHARMACEUTICS ASSESSMENT

BACKGROUND

AstraZeneca's Nexium (Esomeprazole magnesium) DR capsule under NDA 21153 was approved on 02/20/01 for two strengths (20 and 40 mg). Esomeprazole is the S-^{(b) (4)} isomer of Omeprazole (S+R racemate), an approved PPI. Nexium DR 20 and 40 mg capsules are indicated for the following:

- Treatment of gastroesophageal reflux disease (GERD),
- Risk reduction of NSAID (non-steroid-anti-inflammatory-drug)-associated gastric ulcer,
- *H. pylori* eradication to reduce the risk of duodenal ulcer recurrence, and
- Pathological hypersecretory conditions, including Zollinger-Ellison syndrome

The OTC Nexium 24HR DR 20 mg capsule under development is proposed for the indication of the treatment of frequent heartburn occurring 2 or more days a week. The proposed treatment regimen is one capsule QD for 14 days every 4 months.

The Applicant requested a meeting on 01/15/11 for the development of the proposed OTC Nexium 24HR DR 20 mg capsule. The Applicant planned to

- Use the same composition/formulation as the currently marketed Nexium DR 20 mg capsule for Rx use, ^{(b) (4)},
- Conduct two clinical trials to support the proposed OTC indication using the currently marketed Nexium DR 20 mg caps ^{(b) (4)}.
- Obtain the same label claim as that of the currently approved OTC PPIs, while continuing to market all currently available Rx Nexium products.

The Applicant reported that

- 1). The proposed OTC Nexium 24 HR DR 20 mg capsule is also a two-piece hard gelatin capsule formulation, except that the OTC Nexium 24 HR DR 20 mg capsule is required to be sealed by a tamper band.
- 2). The gelatin band will be colored differently from the capsule shell to provide visual differentiation between the Rx capsule and the OTC capsule. .

FDA's preliminary comments were sent to the Applicant and the Applicant then cancelled the 01/15/11 meeting. Please see FDA's preliminary comments for the above meeting in DARRTS for details. Biopharmaceutics responses related to the Applicant's question Nos.8 and 9 are highlighted here:

Question 8

Does the Agency agree that the banding, and use of a band with a color different from the capsule, will provide sufficient visual differentiation between the Rx capsule and the OTC capsule, as both would be available on the market concurrently provided approval for the OTC indication is granted?

FDA Preliminary Response:

It is difficult to compare the products without visual examination. However, your proposal appears that it could be acceptable. From a quality perspective, the detailed manufacturing process for banding needs to be included in the application.

Question 9

In principle, does the Agency agree that the proposed OTC capsule, with the minor change of banding the capsule for tamper resistance/evidence, is eligible for a bioequivalence waiver?

FDA Preliminary Response:

Yes, you may submit a bioequivalence waiver request. A multipoint-dissolution profile comparison will be needed. Since a Level A IVIVC is reportedly established, the similarity assessment should be based on the prediction of the in vivo performance. The predicted C_{max} and AUCs of the proposed OTC delayed release 20 mg capsule should not differ by more than 20% from the currently marketed Nexium 20 mg delayed release capsule.

Please submit: 1) The biowaiver request; 2) Mean and individual dissolution data (n=12 capsules/batch) and mean comparative dissolution profiles; 3) The results of the IVIVC similarity assessment to the NDA for review.

CURRENT SUBMISSION

On 05/30/13, AstraZeneca submitted original NDA 204655 for Nexium 24HR DR 20 mg caps for OTC use. As agreed upon, the Applicant submitted 1). Comparative dissolution profile/data (with f2 calculations), 2). A biowaiver request, and 3). An IVIVC prediction for plasma PK profiles based on *in vitro* comparative dissolution profiles. On 09/27/13, the Applicant submitted additional IVIVC parameter per Agency’s information request.

BIOPHARMACEUTICS REVIEW

The Biopharmaceutics review is focused on the evaluation and acceptability of the comparative dissolution profile data and IVIVC prediction for plasma PK profiles to support the biowaiver for a BE study requirement.

FORMULATION COMPARISONS

The composition/formulation of proposed Nexium DR 20 mg cap for OTC use is exactly the same as the currently marketed Nexium DR 20 mg cap except for a gelatin band for tamper resistance purposes. The currently marketed Nexium DR 20 cap (b) (4) as shown below for the manufacturing of the proposed OTC Nexium 24HR DR 20 mg capsules.

Table 1 Composition

Components	Quantity per unit	Function	Standard
Esomeprazole delayed-release capsules 20 mg (as esomeprazole magnesium trihydrate 22.3 mg) (b) (4)	1 capsule	(b) (4)	AstraZeneca
Gelatin	(b) (4)	(b) (4)	NF
Ferric oxide			NF
Titanium dioxide (b) (4)			USP USP

^a The amount of (b) (4) may vary, the amount given is typical.
(u) (4)

DISSOLUTION METHODOLOGY AND ACCEPTANCE CRITERION

The currently FDA approved USP dissolution method is shown below:

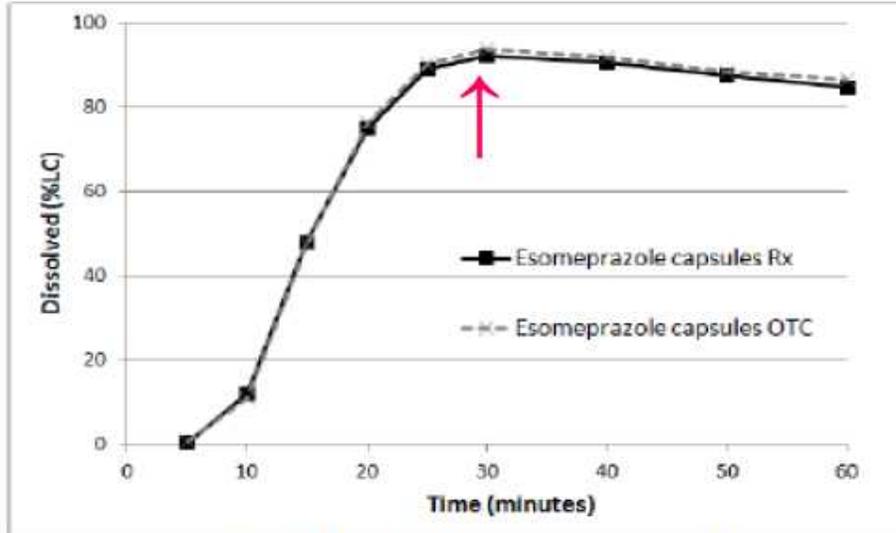
Acid Stage: USP Apparatus 2 (Paddle) with 100 rpm in 0.1N HCl (pH 1.2) medium for 2 hours

Buffer Stage: USP Apparatus 2 (Paddle) with 100 rpm in 1000 mL pH 6.2 medium

Proposed Acceptance Criterion: Q= $\frac{(b)}{(4)}$ % at 30 min

1. Comparative Dissolution Profile Data

Figure 1. Comparative Mean Dissolution Profiles of Esomeprazole from the Currently Approved Nexium DR 20 mg Capsules Rx (Batch No. 2259) and the Proposed Nexium 24HR DR 20 mg Capsules OTC (Batch No. 11) (Mean Data, n = 12)



USP Apparatus 2 at 100 rpm, 1000 ml pH 6.2 buffer after 2 hour pre-exposure to 0.1 M HCl.

The similarity factor (f_2) is calculated to be 93.6 indicating similarity in the above dissolution profile comparison. Please see mean and individual dissolution data in Appendix 1 for details.

2. Proposed Dissolution Acceptance Criterion:

The Applicant proposed $Q = \frac{(b)}{(4)}\%$ at 30 min which is NOT acceptable by the Biopharmaceutics/ONDQA because Esomeprazole dissolved in buffer stage $\frac{(b)}{(4)}\%$ at 30 min (as the red arrow indicated).

PREDICTION BASED ON THE APPROVED IVIVC RELATIONSHIP

1. Biowaiver using the previously approved IVIVC:

The IVIVC was accepted upon the approval of NDA21153 for Rx Nexium DR 40 and 20 mg capsules. An equation of the *in vivo* time vs. *in vitro* time was obtained as shown below.

(b) (4)

Based on the comparative dissolution profiles (Figure 1) and the approved IVIVC relationship, a simulation/prediction for the plasma profile of the proposed OTC Nexium 24HR DR 20 mg capsule is made and compared with that of the Rx Nexium DR capsules to support the biowaiver for a BE study.

2. Prediction of PK Profiles and Data between the Rx Nexium DR Capsules and the Proposed OTC Nexium 24HR DR Capsules

Their predicted mean plasma profiles/PK parameters were shown below (Figure 2 and Table 2).

Figure 2. Predicted Plasma Concentration-Time Profiles for the Currently Approved Rx Nexium DR 20 mg Capsules and the Proposed OTC Nexium 24HR DR 20 mg Capsules

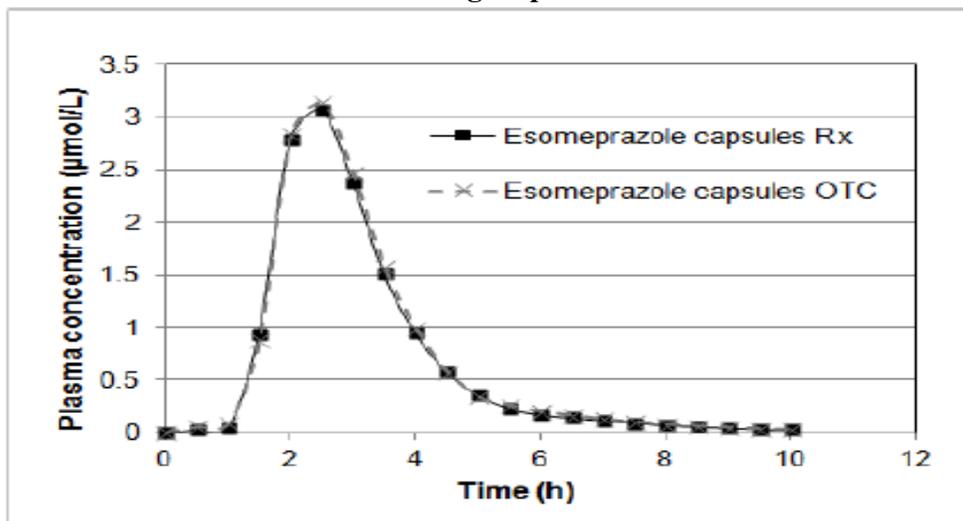


Table 2. Estimated PK Parameters for Rx Nexium DR 20 mg Capsules and the Proposed OTC Nexium 24HR DR 20 mg Capsules

Pharmacokinetic parameter	Esomeprazole capsules Rx (reference)	Esomeprazole capsules OTC (test)	Ratio of test/reference
C_{max} (µmol/L)	3.07	3.14	1.02
AUC (h*µmol/L)	6.81	7.01	1.03

Reviewer’s Overall Comments:

1. The comparative dissolution profile/data showed similarity between the Rx Nexium DR 20 mg capsule (without tamper band) and the proposed OTC Nexium 24HR DR 20 mg capsule (with tamper band). The similarity factor (f_2) is calculated to be >50 indicating that the dissolution of Nexium DR capsules is not affected by the tamper band.
2. The results of the IVIVC prediction of the plasma profiles between the Rx Nexium DR 20 mg capsule and the proposed OTC Nexium 24HR DR 20 mg capsule showed that the predicted difference between the PK parameters of interests are all within the 10% predicted errors allowed per the FDA IVIVC guidance.

The IVIVC simulation/prediction is reassessed by the Biopharmaceutics team and the results are found comparable. Please see Appendix 2 for details. Therefore, the Applicant’s IVIVC simulation/prediction is acceptable which supports the biowaiver for the proposed OTC Nexium 24HR DR 20 mg capsules.

3. Finally, the Applicant’s proposed dissolution acceptable criterion of $Q = \frac{(b)}{(4)}\%$ is NOT acceptable since esomeprazole dissolved $\frac{(b)}{(4)}\%$ at 30 min in the buffer stage. The

Agency recommendations $Q = \frac{(b)}{(4)}\%$ at 30 min should be implemented. The above information request on tightening the dissolution specification from $Q = \frac{(b)}{(4)}\%$ at 30 min to $Q = \frac{(b)}{(4)}\%$ at 30 min was conveyed to the Applicant on 02/18/14.

With further clarification, the Applicant accepted on 02/20/14 the Agency's recommendation and committed to 1). Tightening the dissolution acceptance criterion from $Q = \frac{(b)}{(4)}\%$ at 30 min to $\frac{(b)}{(4)}\%$ at 30 min and 2). Updating the Drug Product Specification section by 02/26/14.

**NDA 204655 (N-000) for Nexium 24 HR
DR 20 mg Capsules for OTC Use**

Appendix 1

Comparative Dissolution Profile/Data

Table 1 Dissolution^a of esomeprazole from Esomeprazole capsules Rx and Esomeprazole capsules OTC

Product description	Time (min)	1	2	3	4	5	6	7	8	9	10	11	12	Mean	RSD (%)
Esomeprazole capsules Rx (Batch 2259)		(b) (4)												0	34.7
		(b) (4)												12	39.8
		(b) (4)												48	18.7
		(b) (4)												75	10.9
		(b) (4)												89	6.4
		(b) (4)												92	4.9
		(b) (4)												90	3.8
		(b) (4)												87	3.9
Esomeprazole capsules OTC (Batch 11)		(b) (4)												85	4.0
		(b) (4)												1	160.0
		(b) (4)												11	26.5
		(b) (4)												48	11.4
		(b) (4)												76	5.4
		(b) (4)												90	3.2
		(b) (4)												94	2.6
	(b) (4)												92	2.7	
	(b) (4)												88	3.3	
	(b) (4)												87	3.3	

^a USP Apparatus 2 at 100 rpm, 1000 ml pH 6.2 buffer following 2 hour pre-exposure to 0.1 M HCl.

**NDA 204655 (N-000) for Nexium 24 HR
DR 20 mg Capsules for OTC Use**

Appendix 2

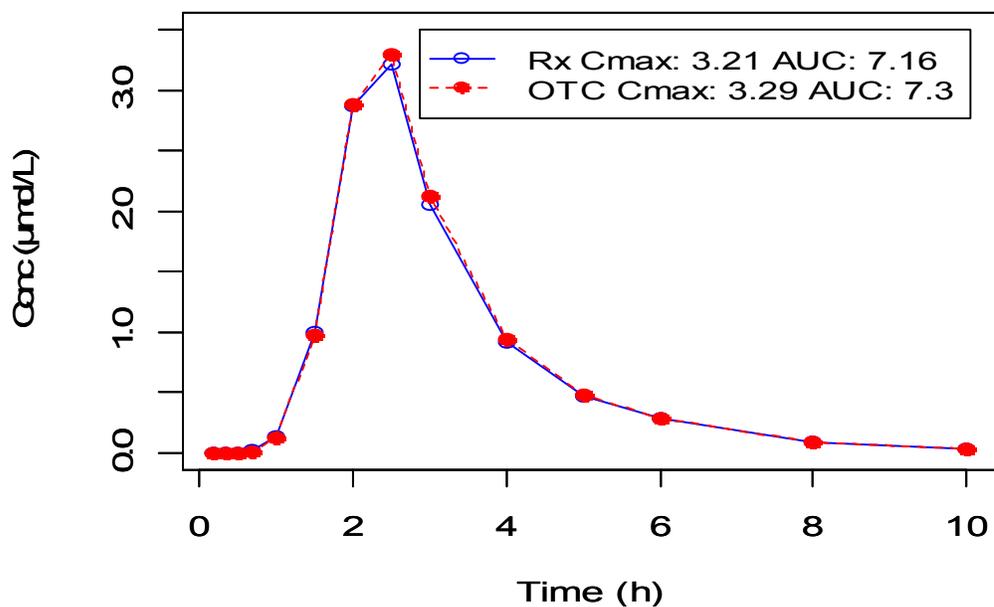
IVIVC Simulation/Prediction

To confirm the similarity between the proposed OTC formulation and the approved prescription formulation, the IVIVC model was used to predict the *in vivo* drug concentrations for both formulations. The following procedure was used.



4. The predicted plasma concentration obtained from the convolution results are plotted against time for both formulations and the C_{max} and AUC were calculated. The results are shown in the following figure and table.

Formulation	C _{max} (μmol/L)	AUC (h·μmol/L)
Rx	3.21	7.16
OTC	3.29	7.3
Ratio (OTC/Rx)	1.03	1.02



The predictions based on IVIVC model indicate that the mean concentration profile for the OTC is almost overlapped with that of the Rx formulation. The AUC and Cmax ratios (OTC/Rx) are 1.02 and 1.03, respectively, well within the bioequivalence limits and are comparable with the IVIVC prediction results obtained from the Applicant. Therefore, the biowaiver request can be granted based on the IVIVC model.

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/s/

TIEN MIEN CHEN
02/20/2014

JOHN Z DUAN
02/20/2014

PRODUCT QUALITY - BIOPHARMACEUTICS FILING REVIEW

NDA Number	204655
Product name, generic name of the active, and dosage form and strength	Nexium 24 HR, Esomeprozole Magnesium, Delay Release (DR) Capsule, 20 mg
Submission date	05/30/13
Applicant	AstraZeneca
Medical Division	DGEIP
Type of Submission	Original NDA
Biopharmaceutics Reviewer	Tien-Mien Chen, Ph.D.
Biopharmaceutics Team Leader	Angelica Dorantes, Ph.D.

The following parameters from the ONDQA Quality (CMC and Biopharmaceutics) joint filing checklist are necessary in order to initiate a full Biopharmaceutics review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. BIOPHARMACEUTICS				
	Parameter	Yes	No	Comment
1.	Does the application contain dissolution data?	X		The FDA approved dissolution method and acceptance criterion for Nexium DR 40 and 20 mg capsules are proposed to use for this OTC Nexium 24 HR DR 20 mg capsules as shown below: Acid stage: USP Apparatus 2 with 100 rpm in 0.1 N HCl medium, 300 ml at 37°C for 2 hours Buffer stage: USP Apparatus 2 with 100 rpm in Sodium Phosphate Buffer, pH 6.8 medium, 1000 mL at 37°C Acceptance Criterion: Q= $\frac{(b)(4)}{(4)}$ % at 30 min
2.	Is the dissolution test part of the DP specifications?	X		
3.	Does the application contain the dissolution method development report?		X	The same, currently approved dissolution method for Nexium DR capsules is proposed for this OTC Nexium 24 HR DR 20 mg Caps.
4.	Is there a validation package for the analytical method and dissolution methodology?		X	Since the approved dissolution method is being proposed, there is no need to submit this information. The same analytical method is used for the proposed batch of Nexium 24 HR DR 20 mg capsules with tamper band (Batch No. 11 ; $\frac{(b)(4)}{(4)}$ capsules) obtained from a part $\frac{(b)(4)}{(4)}$ % of the commercial batch of Nexium capsules without tamper band (Batch No. 2259; $\frac{(b)(4)}{(4)}$ capsules).

**PRODUCT QUALITY - BIOPHARMACEUTICS
FILING REVIEW**

5.	Does the application include a biowaiver request?	X		A BA/BE waiver is requested for the proposed lower strength (20 mg) of Nexium DR capsule, which is proposed for OTC switch
6.	Does the application include an IVIVC model?	X		IVIVC was previously reviewed and accepted in the original NDA.
7.	Does the application include information/data on in vitro alcohol dose-dumping potential?		X	Not applicable
8.	Is there any in vivo BA or BE information in the submission?		X	There is no BA/BE data. Note that two clinical trials were conducted to support the proposed indication/claim.
B. filing conclusion				
	Parameter	Yes	No	Comment
9.	IS THE PRODUCT QUALITY AND BIOPHARMACEUTICS SECTIONS OF THE APPLICATION FILEABLE?	X		The NDA is fileable from the Biopharmaceutics Perspective
10.	If the NDA is not fileable from the biopharmaceutics perspective, state the reasons and provide filing comments to be sent to the Applicant.			No Applicable
11.	Are there any potential review issues identified?		X	Note: A Pre-NDA agreement was reached between the Applicant and ONDQA on the usage of the currently approved Nexium DR capsules (without (b)(4)) in the clinical trials (Preliminary meeting minutes dated 05/13/11 under IND 111185). The established Level A IVIVC and the predicted comparative plasma PK profile/data are provided in Appendix 1 of M271.
12.	Are there any comments to be sent to the Applicant as part of the 74-Day letter?	X		<i>The following comment needs to be sent to the Applicant in the 74-Day letter: Please submit the information on the unit impulse response (UIR) of your IVIVC model (information obtained previously). Note that we need the UIR information to verify the IVIVC model used to generate the Cmax and AUC data supporting your biowaiver request.</i>

**PRODUCT QUALITY - BIOPHARMACEUTICS
FILING REVIEW**

{See appended electronic signature page}

Tien-Mien Chen, Ph.D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

07/05/13
Date

{See appended electronic signature page}

Angelica Dorantes, Ph.D.
Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

07/08/13
Date

cc. R. Lostritto

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/s/

TIEN MIEN CHEN
07/09/2013

ANGELICA DORANTES
07/10/2013