CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207920Orig1s000

CHEMISTRY REVIEW(S) /

NDA 207920
Review # 1

Drug Name/Dosage Form	Nexium® 24 HR (esomeprazole magnesium) Delayed Release 20 mg tablets
Strength	20 mg
Route of Administration	Oral
Rx / OTC Dispensed	OTC
Applicant	AstraZeneca 1800 Concord Pike P. O. Box 8355 Wilmington, DE 19803-8355
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original	06-Feb-2015	ONDP/OPF
Amendment	15-May-2015	ONDP
Amendment	28-July-2015	OPF
Amendment	06-Oct-2015	OPF
Amendment	14-Oct-2015	ONDP
Amendment	21-Oct-2015	OPF

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Ravindra K. Kasliwal, Ph.D.	ONDP/DNDP-II/ Branch VI
Drug Product	Ravindra K. Kasliwal, Ph.D.	ONDP/DNDP-II/ Branch VI
Process	Daniel (Yingxu) Peng, Ph.D.	OPF/DPAII/BranchVI
Microbiology	Daniel (Yingxu) Peng, Ph.D.	OPF/DPAII/BranchVI
Facility	Juandria Williams, Ph.D.	OPF/DIA/B3
Biopharmaceutics	Peng Duan, Ph.D.	ONDP/DB/BBII
Regulatory Business Process Manager	Thao, Vu	OPRO/DRBPMI/RBPMBI
Application Technical Lead	Swapan K. De, Ph.D.	ONDP/DNDP-II/ Branch VI
Laboratory (OTR)	NA	NA
ORA Lead	Paul Perdue	ORA/OMPTO/DMPTPO/MDTP
Environmental Assessment (EA)	Ravindra K. Kasliwal, Ph.D.	ONDP/DNDP-II/ Branch VI

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS[1]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	Type- IV	(b) (4)	(b) (4)	Adequate		Sufficient data in the application.
	Type -III			Adequate	13-Feb-2003	The DMF and the components have been reviewed in detail by Dr. Jean Salemme, PhD. (13-Feb-2003), and were found to be adequate.
	Type- III			N/A		Sufficient data in the application.
	Type-III			N/A		Sufficient data in the application.
	Type-III			N/A		Sufficient data in the application.
	Type-III			N/A		Sufficient data in the application.
	Type-III			N/A		Sufficient data in the application.
	Type-III			N/A		Sufficient data in the application.
	Type-II			Adequate	Reviewed by Swapan K De On 10/21/2015	(b) (4)
	Type-III			N/A		application.

[1] Adequate h Information Request, Deficient, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	204655	Esomeprazole Magnesium Delayed – Release Capsule
PIND	118964	NEXIUM® (esomeprazole magnesium) Delayed-Release Tablets
NDA	021153	Nexium (esomeprazole magnesium) Delayed-Release Capsules, 20 mg and 40 mg and Nexium (esomeprazole magnesium) Delayed-Release Oral Suspension, 2.5 mg, 5 mg, 10 mg, 20 mg, and 40 mg.
IND	053733	NEXIUM® (esomeprazole magnesium) Delayed-Release Capsules

2. CONSULTS:

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	NA			
Pharmacology/Toxicology	NA			
CDRH	NA			
Clinical	NA			
Office of Surveillance/OPQ	Complete	Acceptable	10/21/15	Alex Viehmann

Table of Contents

Executive Summary (NDA-207920)

I. Recommendations

Regarding Chemistry Manufacturing and Controls, the application may be approved.

A. Recommendation and Conclusion on Approvability

Regarding quality aspects of the application the drug substance, drug product, quality biopharmaceutics, microbiology, process and facility sections are reviewed and found adequate to support the approval of the application. The drug product has been granted a shelf life of 24 months under controlled room temperature storage conditions. Following comment should be included in the action letter:

"The testing protocol (sampling plan for (b) (4) uniformity) for intra-batch variability is acceptable for post-approval implementation and collected data to be submitted in the Annual Report as agreed with OPQ on 10/06/2015 and 10/20/2015."

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

The applicant has provided a testing protocol (sampling plan for (b) (4) uniformity) to address the intra-batch variability on 10/6/2015. The sampling protocol is reviewed by Alex Viehmann on 10/21/2015 (see review at the end of process review section) and found to be adequate. The applicant committed to submit the (b) (4) uniformity data resulting from the protocol in the Annual Report (1st Annual Report). The CMC post-approval agreement with the applicant was discussed in an internal meeting (entire NDA review team including clinical) held on 10/09/2015 and finalized within the OPQ team on 10/20/2015. Following comment should go to action letter.

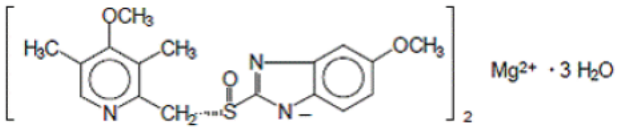
The testing protocol (sampling plan for (b) (4) uniformity) for intra-batch variability is acceptable for post-approval implementation and collected data to be submitted in the Annual Report as agreed with OPQ on 10/06/2015 and 10/20/2015.

II. Summary of Quality Assessments;

Drug substance information is referred to Applicant's previously approved NDA 21-153. Since the current NDA (NDA-207920) is from the same applicant, (b) (4) tablet formulation is proposed in place of previously approved capsule formulation, the level of information provided in support of the drug substance quality is acceptable. Some basic information is shown below.

1. Drug Substance [USAN Name] Quality Summary

Chemical Name or IUPAC Name/Structure:
N Bis (1H-Benzimidazole,5-methoxy-2-[(S)-[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl)
sulfinyl]),magnesium salt,trihydrate
Formula: $(C_{17}H_{18}N_3O_3S)_2Mg \times 3H_2O$.
CAS Number 217087-09-7
MW= 767.2 g/mol (trihydrate) and 713.1 g/mol (anhydrous basis)



Esomeprazole is the S-isomer of Omeprazole, which is a mixture of the S- and R-isomers. The drug substance (b) (4) magnesium salt of S-Omeprazole i.e. "Esomeprazole magnesium trihydrate". The molecule contains one asymmetrically substituted sulphoxide moiety, which makes the molecule chiral. In esomeprazole the sulphur atom has the *S*-configuration. (b) (4) (b) (4) (b) (4) (b) (4) The (b) (4) magnesium salt is a white to slightly colored (b) (4) It is slightly soluble in water (approx. 1.5 mg/mL with a pH of 10.0). The stability of Esomeprazole magnesium is a function of pH; it rapidly degrades in acidic media, but it has acceptable stability under alkaline conditions. At pH 6.8 (buffer), the half-life of the magnesium salt is about 19 hours at 25°C and about 8 hours at 37°C.

(b) (4)

A. Drug Product [Established Name] Quality Summary

1. Strength: 20 mg

2. Description/Commercial Image:

Esomeprazole magnesium delayed release tablet for over-the-counter (OTC) use provides a 20 mg dose of esomeprazole as 22.3 mg esomeprazole magnesium trihydrate. The drug product (b) (4) containing the active ingredient into a (b) (4) purple, oblong, biconvex, (b) (4) tablet engraved "20 mG" on one side and "N" on the other side. The theoretical tablet weight is approximately 420 mg based on a yield corresponding to 100%.

***3.* Summary of Product Design**

This application proposes an additional dosage form to the 20 mg Esomeprazole delayed release capsule. The new dosage form will be 20 mg Esomeprazole delayed release tablet. Currently, capsule form is approved for the US OTC market. (b) (4) The delayed release Rx tablet has been approved in the EU market for more than 10 years. The tablet and the manufacturing process for the proposed US product (b) (4)

(b) (4)

The final esomeprazole magnesium tablets are oblong, 7 x 14 mm, biconvex tablets with (b) (4) purple color. The (b) (4) tablets are engraved "20 mG" on one side and "N" on the other side. The theoretical tablet weight is approximately 420 mg.

4. List of Excipients:

Corn starch, crospovidone, D&C red no. 27 aluminum lake, FD&C blue no. 2 aluminum lake, FD&C red no. 40 aluminum lake, glyceryl monostearate, hydroxypropyl cellulose,

hypromellose, magnesium stearate, methacrylic acid copolymer, mica, microcrystalline cellulose, paraffin, polyethylene glycol, polysorbate 80, sodium stearyl fumarate, sucrose, talc, titanium dioxide, triethyl citrate.

5. Process Selection (Unit Operations Summary)

The manufacturing process for Esomeprazole delayed release tablets 20 mg was developed and validated to support commercialization of a prescription product in the European Union. The prescription product has been on the market for more than 10 years. The manufacturing process for the proposed US product [redacted] (b) (4)

6. Container Closure:

The drug product is packaged in high density polyethylene (HDPE) bottles with an induction sealed closure [redacted] (b) (4) The bottle contains a [redacted] (b) (4) desiccant.

7. Expiration Date & Storage Conditions

Proposed expiration date of the drug product of 24 months is acceptable and supported by statistical analysis provided from the real time stability data obtained from 12-month study at long-term storage conditions (25°C/60% RH) and 6-month study at accelerated conditions (40°C/75% RH).

The storage statement will be written as "Store at 20°C – 25°C (68°F - 77°F)". This reflects the numerical value of the controlled room temperature [stored at 25°C (77°F) with excursions permitted to 15°C-30°C (59°F-86°F)], and is a modified version of the wording requested by the FDA, but aligns with the currently approved storage statement for Nexium 24HR Capsules.

8. List of co-packaged components: None

B. Summary of Drug Product Intended Use

Proprietary Name of the Drug Product	Nexium®24HR
Non Proprietary Name of the Drug Product	esomeprazole [redacted] (b) (4)
Non Proprietary Name of the Drug Substance	esomeprazole magnesium trihydrate
Proposed Indication(s) including Intended Patient Population	Treats frequent heartburn (occurs 2 or more days a week)
Duration of Treatment	One tablet a day; 14-Day course of Treatment; May repeat a 14-Day Courses every 4 months; Adults 18years of age and older.
Maximum Daily Dose	20 mg
Alternative Methods of Administration	None

C. Biopharmaceutics Considerations

1. BCS Classification: Not applicable (BCS class is determined only when applicant proposed the product as BCS Class I.

- Drug Substance:
- Drug Product:

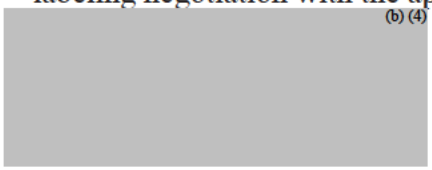
2. Biowaivers/Biostudies (For NDA only)
   - Biowaiver Requests: No
   - PK studies: Yes
   - IVIVC: No

D. Novel Approaches

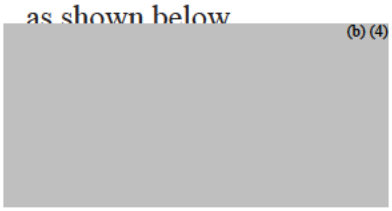
E. Any Special Product Quality Labeling Recommendations

Established name of the drug product is still under discussion and will be finalized during labeling meetings through OND. There are two options under discussion as shown below.

1. To keep the PDP (principal display panel) panel consistent with Rx and other generic products, the established name of the drug product will remain as Esomeprazole magnesium, 20 mg. However, this is scientifically incorrect because amount of Esomeprazole active ingredient alone is 20 mg. The 22.3 mg represents total weight of final drug product esomeprazole magnesium (without trihydrate). This is still under discussion with OND and will be finalized during labeling negotiation with the applicant.



2. To keep the PDP panel as Esomeprazole, 20 mg, that will represent actual weight of the active pharmaceutical ingredient, Esomeprazole. The PDP will look like as shown below



F. Life Cycle Knowledge Information (see table below)

Risk Assessment:

Product attribute/CQA	Factors that can impact the CQA	Probability (O)	Severity of Effect (S)	Detectability (D)	FMECA RPN Number	Comment
Assay, stability	• Formulation • Raw materials • Process parameters • Scale/equipments	2	2	2	8	Similar assay method as approved for capsule dosage form. Impurities

	• Site					are monitored.
Physical stability (API)	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	2	2	2	8	Stable based on limited data provided.
Content uniformity	• Formulation • Raw materials • Process parameters •Scale/equipment • Site	3	2	2	12	(b) (4)
Microbial Limits	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	2	2	2	8	Controlled with specifications.
Dissolution	• Formulation • Raw materials • Process parameters •Scale/equipments • Site • Exclude major reformulations • Alcohol dose dumping	2	2	2	8	

OVERALL ASSESSMENT AND SIGNATURES: EXECUTIVE SUMMARY

Application Technical Lead Signature:

Swapan K. De -S

Digitally signed by Swapan K. De -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Swapan K. De -S, 0.9.2342.19200300.100.1.1=1300132497
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ASSESSMENT OF THE BIOPHARMACUETICS

1. Are the in-vitro dissolution test and acceptance criteria adequate for assuring quality control and consistent bioavailability of the drug product?

Applicant's Response:

The proposed dissolution method is per USP monograph method; the same for the approved Nexium DR capsules:

USP apparatus: 2
Stage 1(acid stage):
0.1 HCl pretreated for 2 hrs
Stage 2 (buffer stage):
Phosphate buffer (pH 6.8)
Rotation: 100 rpm
Specifications: NLT (b) (4)% at 30 min

Reviewer's Assessment:

1. Dissolution method

The proposed drug product is esomeprazole magnesium delayed release (DR) tablets, which is cross-referenced to the Nexium (esomeprazole magnesium 22.3 mg) DR capsules approved on Mar 28, 2014 under NDA 204655 for OTC use. The Applicant conducted a bioequivalence (BE) trial (study B5141002) to demonstrate BE of the proposed esomeprazole DR tablets 20 mg to the reference product under fast and fed conditions. Table 1 shows the composition comparison of the proposed drug product compared to that of OTC reference product, Nexium DR capsules. Due to the similarity between the (b) (4) proposed esomeprazole magnesium DR tablets, the Applicant proposed to adopt the dissolution method described in the USP monograph for Nexium DR capsules. The Applicant's proposal is acceptable.

	Reference Product	Comparator
Batch Number	1569-0001-003	1587-0003-004
Manufacturing Batch #	BAAS	BDLK
Description	20 mg purple capsule	20 mg purple tablet
Shape	#4 capsule with gelatin band	Oblong biconvex (b) (4) tablet, engraved
Esomeprazole magnesium trihydrate	22.3	22.3
Inactive Ingredients		
Cellulose, microcrystalline	n/a	(b) (4)
Crospovidone (b) (4)	n/a	
(b) (4)	n/a	n/a
Gelatin	(b) (4)	n/a
Ferric oxide		n/a
Titanium dioxide		n/a
(b) (4)		n/a
Glyceryl monostearate		(b) (4)
Hard gelatin capsules, amethyst (size 4)		n/a
Hydroxypropyl cellulose		(b) (4)
Hypromellose		
Magnesium stearate		
Methacrylic acid co polymer (b) (4)		
(b) (4)		
(b) (4)	n/a	
D&C Red No. 27 Aluminum Lake	*n/a*	
FD&C Blue No. 2 Aluminum Lake	*n/a*	
FD&C Red No. 40 Aluminum Lake	*n/a*	
(b) (4)	*n/a*	
Hypromellose	*n/a*	
(b) (4)	*n/a*	
Polyethylene glycol	*n/a*	
Titanium dioxide	*n/a*	
Polysorbate 80	(b) (4)	
Sodium stearyl fumarate	n/a	
(b) (4)	(b) (4)	
(b) (4) Paraffin	n/a	
Talc	(b) (4)	
Triethyl citrate		
(b) (4)		
(b) (4)		

The proposed specification by the Applicant is per the specification in USP. In the filling review, we conveyed the following advice to the Applicant on April 22, 2015:

The proposed dissolution acceptance criterion in buffer stage, Q= (b) (4) % at 30 min, needs to be revised. A minimum of Q= (b) (4) % at X time point should be employed. The final decision on the acceptance criterion, however, will be made after reviewing the totality of the dissolution profile data in the NDA submission.

On May 15, 2015, the Applicant responded:

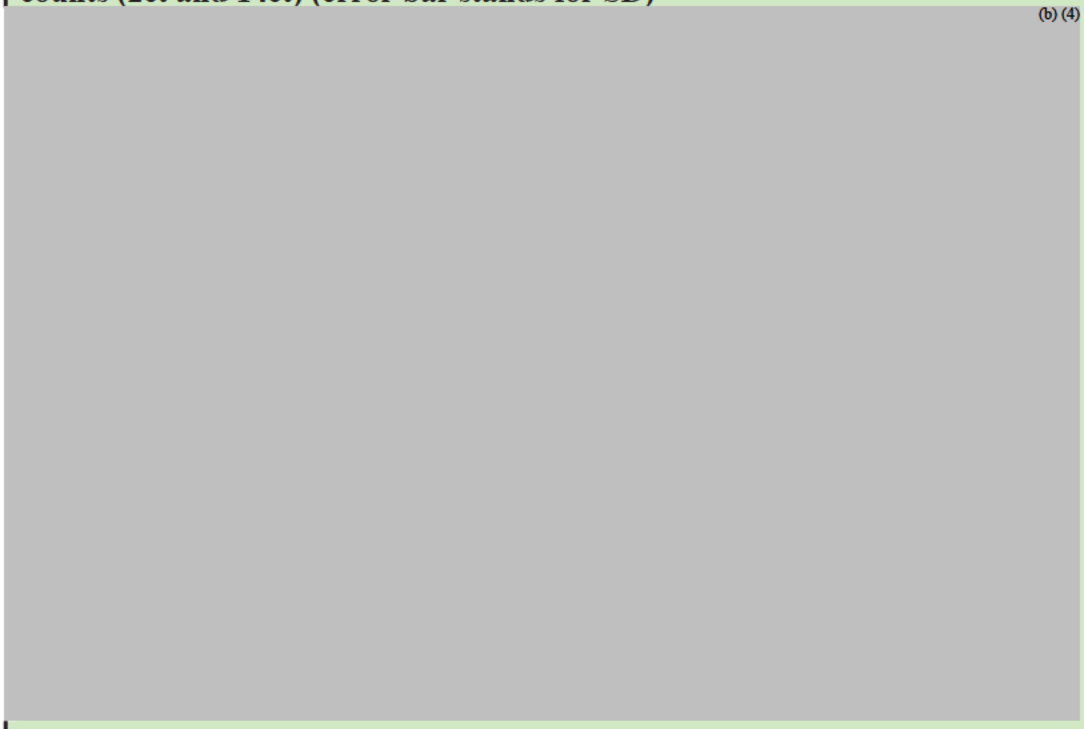
The available data for the drug product supports tightening the specification to Q (b) (4) % at 30 minutes as requested. This limit should also be reviewed against the commercial process capability as additional manufacturing experience gained with this drug product.

The lowest value obtained in the currently available dissolution data for esomeprazole magnesium DR tablets is (b) (4)% at 30 minutes (b) (4) This result would require stage 2 testing with a specification of Q= (b) (4)%.

An updated Section 3.2.P.5.1, incorporating the revised acceptance criterion of Q= (b) (4)% at 30 minutes for dissolution in the buffer stage, is provided as part of this response. Additionally, Sections 3.2.P.5.4, 3.2.P.5.6, 3.2.P.8.1 and 3.2.P.8.3 have been revised to reflect the new proposed specifications and replacement versions are provided as part of this response.

The Applicant's response is acceptable. Dissolution test was conducted with three commercial scale stability batches. One of the primary stability batches was used in BE study. Figure 1 shows the release of three stability batches at room temperature storage condition up to 12 months.

Figure 1. Comparative dissolution profiles for primary stability and clinical batches at initial room temperature condition (0M) and after 12 month (12M) for 2 different counts (2ct and 14ct) (error bar stands for SD)



The three primary batches are lot 1587-0003-004-AZ lot BDLK (004), 1587-0003-005-AZ lot BDLD (005), and 1587-0003-006-AZ lot BDLG (006). Batch No. 004 was also used in the BE trial. As Figure 1 shows, the dissolution profiles of all batches are similar, and there is no fluctuation in the drug release during the room temperature storage up to 12 months. The release of labeled drug in buffer stage is higher than (b) (4)% at (b) (4) min and it

seems to reach plateau. The Applicant claimed that the lowest value obtained in the currently available dissolution data for esomeprazole delayed release tablets is (b) (4)% at 30 minutes. After checking the stability data submitted to the NDA, the lowest rel se of (b) (4)% is only found in the stability test of lot 1587-0003-004 at 6 months under 25°C/60% RH storage condition. A Stage-2 testing could be conducted if necessary. Therefore, the proposed specification Q (b) (4)% at 30 min as revised is acceptable.

The Applicant provided the validation report for the dissolution method. The validation includes the parameters for linearity and range, precision, accuracy, robustness (stability of sample and solutions, influence of chromatographic parameters) and specificity. The validation report is reviewed and found acceptable.

2. Alcohol dose-dumping study

For modified released formulation, evaluation of the impact of alcohol induced dose dumping in vitro has been recommended. However, in the current NDA submission, the Applicant request to waive the alcohol dumping study with following justifications:

- The proposed formulation for Esomeprazole magnesium DR tablets contains a DR component (b) (4) but does not contain an extended release component.
- The delayed release component of the proposed drug product (b) (4), which is labile in the acid environment of the stomach.
- Esomeprazole, the active ingredient, is highly unstable in acid conditions. Due to the rapid degradation of esomeprazole in acid media, it is not possible to determine the amount released to the medium so either sampling during acid exposure or testing the acidic media for the presence of the active ingredient after 2 hours is not meaningful.
- In the buffer stage (pH 6.8) the drug product of esomeprazole behaves similar to an immediate release product, typically showing dissolution of (b) (4)% of the esomeprazole in (b) (4) minutes.

Esomeprazole is not stable under acid condition, therefore, if alcohol dose-dumping study is needed, the release of esomeprazole in the presence of alcohol could only be conducted in the Buffer Stage. The purpose of conducting an in vitro alcohol dose-dumping study is to see if there is an unexpectedly quick release of entire drug contents, thereby leading to safety concerns. However, for the current proposed esomeprazole delayed release tablets, in the Buffer Stage, it behaves similarly to an IR product rather than an extended release formulation, and more than (b) (4)% of the drug releases as early as at (b) (4) min. Furthermore, the proposed DR tablet (b) (4), which has been available on the market for years, therefore, the safety and/or efficacy issue on the in vitro alcohol dose-dumping is determined not to be

pursued. Overall, the Applicant's justification is considered acceptable.

3. Bioequivalence study B5141002

3.1 Review of statistical analysis

Study B514002 was an open label, randomized, partial replicate cross-over study to investigate if the proposed 20 mg DR tablet (the Test) and the reference, 20 mg DR capsule are bioequivalent following a single-dose administration under fasting conditions. The other primary objective is to demonstrate bioequivalence of Nexium banded OTC capsule compared to the Nexium (b) (4) tablet under fed conditions. The secondary objective is to assess the effect of co-administration with a high fat meal on the relative bioavailability of esomeprazole when administered as the approved Nexium banded OTC capsule or the proposed esomeprazole DR tablet (b) (4) tablet).

42 subjects was estimated to ensure at least 80% power, and approximately 54 subjects were enrolled to account for dropouts. The treatments were as follows:

Treatment A: 20 mg esomeprazole delayed-release capsule (Ref) in the fasted state (administered in 2 treatment periods)
Treatment B: 20 mg esomeprazole delayed-release tablet (Test) in the fasted state
Treatment C: 20 mg esomeprazole delayed-release capsule (Ref) with a high fat meal (administered in 2 treatment periods)
Treatment D: 20 mg esomeprazole delayed-release tablet (Test) with a high-fat meal

Due to the high variability of the pharmacokinetics (PK) of esomeprazole, the Applicant conducted the BE study (No. B5141002) using the reference-scaled bioequivalence (RSAB) approach as described in the **FDA 2011 Draft Guidance on Progesterone**. It was a 6-period cross-over partial replicate design and the 6-study periods were listed as below:

1. B-A-C-D-A-C
2. A-D-B-C-C-A
3. D-C-A-A-B-C
4. C-A-D-C-A-B
5. A-C-C-B-D-A
6. C-B-A-A-C-D

On Mar 26, 2015, a consul request was sent to Office of Biostatistics for additional statistical analysis on this BE study by Dr. Sungwoo Choi, Ph.D. Based on the data submitted, the Applicant concluded that:

- For the comparison between the proposed esomeprazole DR tablet (Nexium (b) (4) tablet) and the referenced Nexium banded OTC capsule under the fasted condition:
  a. Statistical analysis of AUC_{inf} supports a demonstration of bioequivalence because the 90% confidence interval of the mean difference is (0.891,1.011) which is completely covered by the Agency's BE acceptance criteria of (0.80, 1.25) as well as for AUC_{last} (0.919, 1.034);
  b. Statistical analysis of C_{max} supports a demonstration of bioequivalence because the 95% upper confidence limit -0.050 is less than the acceptance limit of 0 using the reference-scaled average bioequivalence test (RSAB);
- For the comparison between proposed esomeprazole DR tablet (Nexium (b) (4) tablet) and the Nexium banded OTC capsule under the fed condition:
  a. Statistical analysis of AUC_{inf} and AUC_{last} supports a demonstration of bioequivalence because the 95% upper confidence limits of the mean difference are -0.061 and -0.411, respectively, which is less than the acceptance limit of 0 using RSAB;
  b. C_{max} does not establish bioequivalence because the point estimate of the Test/Reference geometric mean ratio is 1.341, which is outside (0.80, 1.25).
- Regarding the food effect, for AUC_{last}, AUC_{inf}, and C_{max}, their mean values under the fed condition are much smaller than their means under the fasted condition for both Nexium (b) (4) tablet and Nexium banded OTC capsule.

Table 1 shows the results for the Bioequivalence tests.

Table 1. Summary of the statistical bioequivalence tests

Comparison	Parameter	Swr	Ratio (Test/Reference)	90% CI	95% Upper Confidence bound	Method
B vs A (fasted)	AUC_{inf}	0.202	0.948	(0.890,1.010)	--------	Unscaled
	AUC_{last}	0.206	0.975	(0.919,1.034)	--------	Unscaled
	C_{max}	0.304	1.009	--------	-0.050	Scaled
D vs C (fed)	AUC_{inf}	0.351	0.994	--------	-0.061	Scaled
	AUC_{last}	0.886	1.128	--------	-0.411	Scaled
	C_{max}	0.763	1.341	--------	-0.156	Scaled

For the reported primary PK parameters, AUC_{inf} and C_{max}, as well as the secondary PK endpoint AUC_{last}, the within-subject standard deviations for the reference formulations (A and C) denoted by Swr were calculated.

- If Swr≥0.294, RSAB approach was used. Test and reference formulations are considered as bioequivalent if the 95% upper confidence bound for $(\mu T-\mu R)^2-\theta S^2_{wr}$ is not greater than 0, and the point estimate of the Test/Reference geometric mean ratio is within (0.80, 1.25). Here, μT and μR are the population

average response of log- transformed measure for the test and the reference formulations, respectively, and $\theta = \left(\frac{\ln 1.25}{0.25}\right)^2$.

- If $s_{wr} < 0.294$, the unscaled average bioequivalence approach was used. If 90% confidence interval of $\mu_T - \mu_R$ is within (0.80, 1.25), test and reference formulations are considered as bioequivalent.

As Table 1 shows, while comparing the proposed Nexium (b) (4) tablet (B, the Test) to the reference Nexium Branded OTC capsule (A, the Ref) in the fasted condition, the BE analysis on AUC_{inf} and AUC_{last} was unscaled since Swr was less than 0.294, the ratio and 90% CI were fall within BE criterion. The BE analysis on Cmax was scaled because of Swr as 0.304, and mean ratio was within 0.80-1.25, with 95% upper CI less than 0. Therefore, it was concluded that the proposed product and the reference drug are bioequivalent at fast state.

While comparing the bioavailability between proposed product esomeprazole DR tablet (Nexium (b) (4) tablet) and the reference drug Nexium Branded OTC capsule under fed state, they were bioequivalent in terms of AUC_{inf} and AUC_{last}, but not on C_{max} because of mean ratio were out of the criterion (0.80-1.25), and C_{max} increased ~34%.

Table 2 shows the Applicant's analysis on food effect.

Table 2: Summary of the statistical comparisons for food effect

Comparison	Parameter	Ratio(Test/Reference)
Fed vs Fasted (Nexium OTC capsule)	AUC_{inf}	0.539
	AUC_{last}	0.435
	C_{max}	0.255
Fed vs Fasted (Nexium (b) (4) tablet)	AUC_{inf}	0.563
	AUC_{last}	0.476
	C_{max}	0.317

The intake of high fat meal affects the bioavailability of both the reference drug (Nexium OTC capsule) and proposed drug product (Nexium (b) (4) tablet). Since the ratio of mean AUC_{inf}, AUC_{last}, and C_{max} between (fed and fasted) are less than 1, therefore, mean AUC_{inf}, AUC_{last}, and C_{max} at fed state are smaller than that at fasted condition for both proposed drug esomeprazole DR tablet (Nexium (b) (4) tablet), and the reference drug Nexium OTC capsule.

FDA biostatistics reviewer conducted his own analysis based on submitted data from the Applicant. As described in the statistical consult report finished by Dr. Sungwoo Choi, the Applicant's crossover design was acceptable because this design allows unbiased estimate of formulation effects under both fasted and fed condition.

Table 3 shows the reviewer's own analysis on primary PK parameters for the Applicant's

results shown on Table 1.

Table 3. Summary of Bioequivalence Test from FDA Statistics Reviewer's Independent Analysis using All Available Data

Comparison	Parameter	Ratio(Test/Reference)	90% CI	95% Upper Confidence Bound	Method
B vs A	AUC_{inf}	0.949	(0.891,1.011)	-----	Unscaled
	C_{max}	1.022	-----	-0.048	Scaled
D vs C	AUC_{inf}	0.983	-----	-0.056	Scaled
	C_{max}	1.270	-----	-0.197	Scaled

There are slightly different in the values of mean ratios or CI between the Applicant's results and the analysis conducted by the FDA reviewer, however, the conclusions are the same. Furthermore, the reviewer's analysis on food effect is consistent with the Applicant's results shown in Table 2. The AUC_{last}, AUC_{inf}, and C_{max} under the fed state are much smaller than that under fasted condition for both reference drug and proposed drug product esomeprazole DR tablet (Nexium (b) (4) tablet).

The reference drug Nexium OTC capsule is OTC drug widely used for a long time. In the User Direction of the Nexium OTC capsule, it is advised that one capsule should be taken before eating in the morning. The Applicant follows the same User Direction as the reference drug in their proposed label, i.e., (b) (4) Furthermore, as Tables 2 and 3 above, Cmax ratio of 1.27 between Test((b) (4) tablet)/Reference(OTC capsule), the decrease in Cmax with food intake is slightly less in proposed esomeprazole DR tablet product (b) (4) tablet) compared to the reference, OTC Nexium capsule (0.317 (~68% decreased) vs 0.255 (~75% decreased)). Therefore, if there is an efficacy concern with the reduced C_{max} in fed state, the proposed drug is slightly better than the reference drug.

Overall, the proposed drug achieved bioequivalence with reference drug under fast condition, and it has similar food effect as the reference drug with the AUCs met the bioequivalence with reference drug at fed state.). The result of BE study B5141002 is acceptable.

3.2 Review of Bioanalytical method

The bioanalytical method of BE study B5141002 was validated by (b) (4) The validation summary for omeprazole and its metabolite are as follows:

QUALITY ASSESSMENT

Omeprazole			
Internal Standard (IS)	Omeprazole-d_3		
Regression, Weighting	Quadratic, 1/concentration^2		
Average Recovery of Drug (%)	83.2%		
Average Recovery of IS (%)	82.0%		
Standard Curve Concentrations	1.00 to 1000 ng/mL		
QC Concentrations	1.00, 3.00, 7.50, 30.0, 120, and 750 ng/mL		
QC Intra-assay Statistics (%)	Conc. (ng/mL)	Precision	Accuracy
	1.00	3.67 to 12.5%	-3.84 to 13.9%
	3.00	1.94 to 4.51%	-1.63 to 5.01%
	7.50	2.41 to 4.71%	-4.60 to 2.45%
	30.0	1.20 to 2.53%	-5.20 to 0.279%
	120	1.39 to 4.37%	-5.40 to 2.25%
	750	1.94 to 2.98%	-9.57 to 1.85%
QC Inter-assay Statistics (%)	Conc. (ng/mL)	Precision	Accuracy
	1.00	11.0%	1.86%
	3.00	4.21%	2.17%
	7.50	4.48%	-0.636%
	30.0	3.01%	-1.39%
	120	3.81%	-0.965%
	750	5.40%	-1.22%
Thawed Matrix Stability (hrs)	24 hours at room temperature and on ice		
Solution Stability (days)	Omeprazole	91 days at -20 °C in 50:50:0.05 methanol/water/triethylamine	
	Omeprazole-d_3	1091 days at -20 °C in 50:50:0.05 methanol/water/triethylamine *	
Solution Stress Stability (hours)	Omeprazole	6 hours at room temperature in 50:50:0.05 methanol/water/triethylamine	
	Omeprazole-d_3	6 hours at room temperature in 50:50:0.05 methanol/water/triethylamine	
Extract Stability (hrs)	127 hours at 2 to 8 °C		
Freeze-thaw Stability (cycles)	Five cycles thawed at room temperature		
Frozen Matrix Storage Stability (days)	87 days at -20 °C and -70 °C		

Omeprazole	
Whole Blood Stability	Two hours at room temperature and on ice
Dilutional Linearity	30.0 ng/mL diluted four-fold 2000 ng/mL diluted ten-fold
Selectivity	No significant interfering peaks noted in blank plasma samples
Hemolysis	No effect from hemolysis on the quantitation of omeprazole
Lipemia	No effect from lipemia on the quantitation of omeprazole

* [redacted] (b) (4). Data are stored on file there.

5-Hydroxyomeprazole			
Internal Standard (IS)	5-Hydroxyomeprazole-d_3		
Regression, Weighting	Quadratic, 1/concentration^2		
Average Recovery of Drug (%)	127%		
Average Recovery of IS (%)	129%		
Standard Curve Concentrations	1.00 to 1000 ng/mL		
QC Concentrations	1.00, 3.00, 7.50, 30.0, 120, and 750 ng/mL		
QC Intra-assay Statistics (%)	Conc. (ng/mL)	Precision	Accuracy
	1.00	2.46 to 3.71%	-4.02 to 5.14%
	3.00	1.77 to 2.15%	-3.88 to 3.25%
	7.50	2.34 to 6.55%	-8.78 to -0.256%
	30.0	1.45 to 2.87%	-8.03 to -1.52%
	120	1.74 to 5.55%	-6.55 to 0.218%
	750	2.08 to 4.07%	-9.68 to -0.532%
QC Inter-assay Statistics (%)	Conc. (ng/mL)	Precision	Accuracy
	1.00	4.63%	1.01%
	3.00	3.18%	-0.0631%
	7.50	5.03%	-3.48%
	30.0	3.43%	-3.97%
	120	4.16%	-2.74%
	750	4.78%	-3.40%
Thawed Matrix Stability (hrs)	24 hours at room temperature and on ice		
Solution Stability (days)	5-hydroxyomeprazole	91 days at -20 °C in 50:50:0.05 methanol/water/triethylamine	
	5-Hydroxyomeprazole-d_3	87 days at -20 °C in 50:50:0.05 methanol/water/triethylamine *	
Solution Stress Stability (hours)	5-hydroxyomeprazole	6 hours at room temperature in 50:50:0.05 methanol/water/ triethylamine	
	5-Hydroxyomeprazole-d_3	6 hours at room temperature in 50:50:0.05 methanol/water/ triethylamine	
Extract Stability (hrs)	127 hours at 2 to 8 °C		
Freeze-thaw Stability (cycles)	Five cycles thawed at room temperature		
Frozen Matrix Storage Stability (days)	87 days at -20 °C and -70 °C		

5-Hydroxyomeprazole	
Whole Blood Stability	Two hours at room temperature and on ice
Dilutional Linearity	30.0 ng/mL diluted four-fold 2000 ng/mL diluted ten-fold
Selectivity	No significant interfering peaks noted in blank plasma samples
Hemolysis	No effect from hemolysis on the quantitation of 5-hydroxy-omeprazole
Lipemia	No effect from lipemia on the quantitation of 5-hydroxy-omeprazole

* Established following the validation

To demonstrate reproducible quantitation of incurred subject samples, approximately 10% of the study samples were re-assayed. The incurred sample reproducibility (ISR) values were used for comparison purposes and are included in the analytical report but not used in determining the final reported value. 98.3% of samples were within ± 20% of original values. The result of bioanalytical report is reviewed and found acceptable.

2. Are the changes in the formulation, manufacturing process, manufacturing sites during the development appropriately bridged to the commercial product?

Applicant's Response:

The Applicant used one of the three primary stability batches (#004) for the clinical bioequivalence study (B5141002). To bridge the stability batch and clinical batch, the Applicant conducted the comparative dissolution test. As Figure 1 and Figure 2 (from the submission) show, the dissolution of clinical batch lot 004 is similar to the dissolution of other stability batches.

Figure 2. Comparative Dissolution Profiles for Primary Stability and Clinical Batches of Esomeprazole Magnesium Delayed Release Tablets

* Clinical batch used in Bioequivalence study B5141002.

Reviewer's Assessment:

Because of the instability of esomeprazole in the acid condition, the proposed drug product (b) (4) delayed release tablet, (b) (4) (b) (4). In the buffer stage, the release of drug is similar as an immediate release formulation. From Figure 1 and Figure 2, the release of clinical batch and three stability batches is similar; therefore, the stability batches are appropriately bridged to clinical batches.

OVERALL ASSESSMENT AND SIGNATURES: BIOPHARMACUETICS

Reviewer's Assessment and Signature:

1. The applicant follows the dissolution method described in USP monograph, and the revised dissolution acceptance criterion Q= (b) (4)% at 30 min is acceptable.

2. The justification from the Applicant on waiver of in vitro alcohol dose dumping study is acceptable.
3. The results from the bioequivalence study B5141002 are acceptable. The proposed drug product, esomeprazole DR tablet, is bioequivalent to the reference drug, Nexium OTC capsule under fasted condition and the proposed drug product has similar food effect as the reference drug product.

From Biopharmaceutics perspective, NDA 207920 is recommended for approval.

Peng Duan -S

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Secondary Review Comments and Concurrence:

Concur

Tien-Mien Chen

Tienmien Chen -S

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ASSESSMENT OF MICROBIOLOGY

1. Are the tests and proposed acceptance criteria for microbial burden adequate for assuring the microbial quality of the drug product?

Applicant's Response:

Test/Method Type	Analytical Procedure	Acceptance Criteria (Release)	Acceptance Criteria (Stability)
Microbiological Quality [d]	USP <61> and <62>		
Total Aerobic Microbial Count (TAMC)		N/A	(b) (4) CFU/g
Total combined Yeasts/Molds Count (TYMC)		N/A	(b) (4) CFU/g
Escherichia coli		N/A	(b) (4)
Salmonella sp.		N/A	

[d] Testing not routinely performed at release. Microbiological Quality will be monitored on annual maintenance batches at initial and end of shelf life time points.

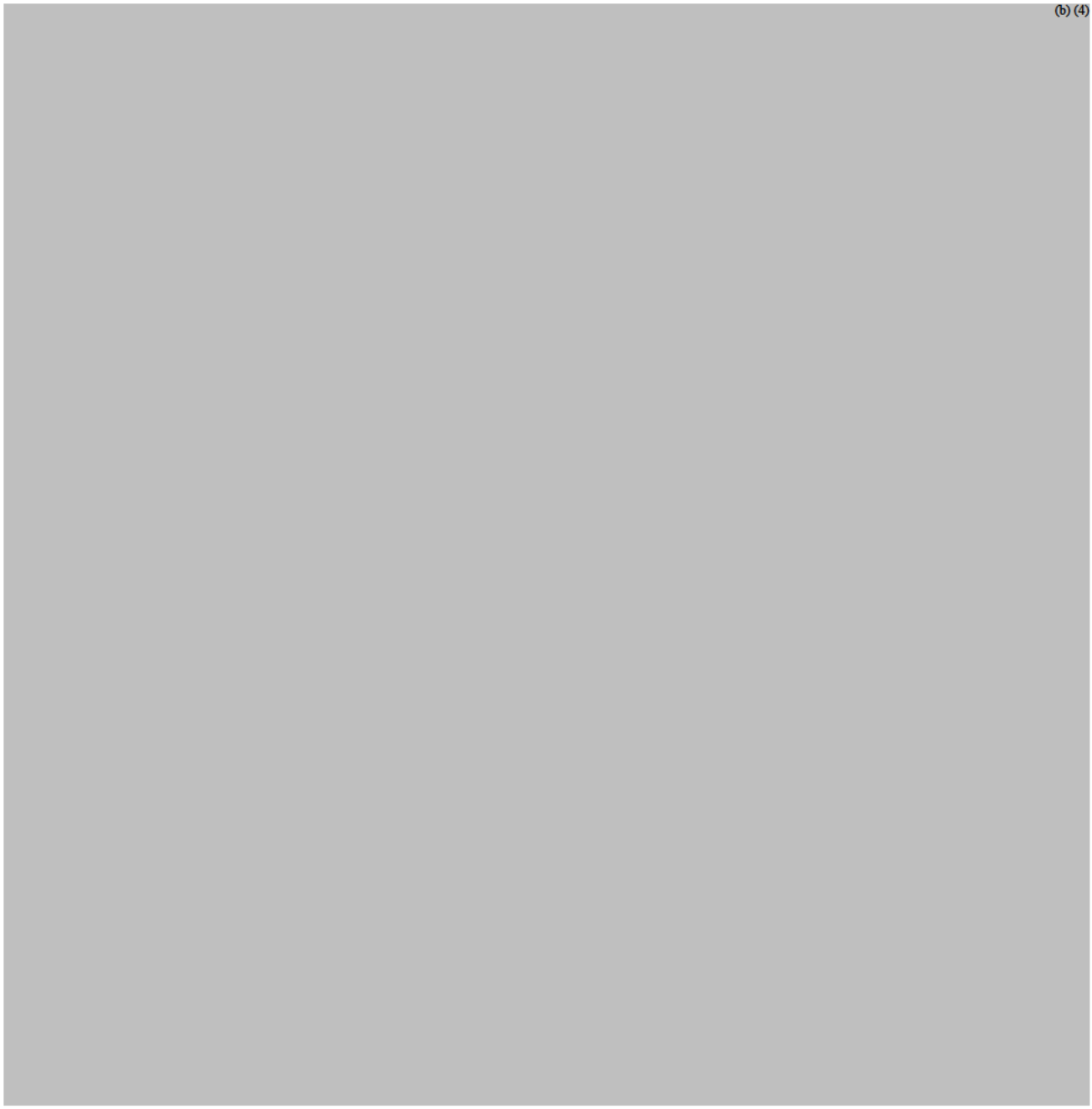
Reviewer's Assessment: Adequate

The firm established microbial limit test per USP <61> and <62> and the results obtained comply with microbiological acceptance criteria for Non-aqueous preparations for oral use in USP (currently USP<1111>)

The firm also follows CGMP to ensure that the microbiological quality of the product is not compromised during manufacture of the drug product. This includes appropriate monitoring of process and cleaning water and the control of the environment in the tablet manufacturing area. Microbiological testing to pharmacopoeial standards is also routinely performed for (b) (4) excipients used in the manufacture of the esomeprazole delayed release tablets.

(b) (4) is being monitored in the ongoing formal stability study for Esomeprazole delayed release tablets stored at 25°C/60% RH in HDPE bottles. Pharmaceutical products with (b) (4) are identified by USP as good candidates for reduced Microbial Limits testing at release and on stability. Test results through the 12 month time point are at (b) (4) %.

Microbiological quality is also being monitored in the ongoing formal stability study for Esomeprazole delayed release tablets stored at 25°C/60% RH in HDPE bottles. The total aerobic microbial count, total combined yeasts/molds count and the absence of E. coli will be determined annually until the end of this study. The results obtained so far in the study (up to 12 months) comply with the USP acceptance criteria.



2.3.P.7 Container/Closure System

2. Is the proposed container/closure system for the drug product validated to function as a barrier to microbial ingress? What is the container/closure design space and change control program in terms of validation?

Applicant's Response:

Esomeprazole delayed release tablets are packaged in high density polyethylene (HDPE) bottles with an induction sealed closure (b) (4) The bottle contains (b) (4) desiccant in an HDPE (b) (4)

For distribution to packaging sites, bulk tablets are [redacted]

Table 3.2.P.7.1-1. Packaging Systems for Esomeprazole Delayed Release Tablets

HDPE Bottle/Closure System				
Strength	**Count**	**Bottle Size (mL)**	**Closure Size (mm)**	**Desiccant**
20 mg	2	45	33	[redacted]
20 mg	14	45	33	

HDPE Containers
The HDPE containers have been tested in accordance with USP <661> Containers Polyethylene Containers, [redacted]

Bulk Package For Storage And Shipping
The bulk tablets are packed in [redacted]

Reviewer's Assessment: Adequate

The proposed container/closure system for the drug product is validated to function as a barrier to microbial ingress. The HDPE bottle has been tested in accordance with USP <661> [redacted] and meets the established acceptance criteria therein.

There is no container/closure design space and change control program in this application.

A APPENDICES

A.2 Adventitious Agents Safety Evaluation

3. Are any materials used for the manufacture of the drug substance or drug product of biological origin or derived from biological sources? If the drug product contains material sourced from animals, what documentation is provided to assure a low risk of virus or prion contamination (causative agent of TSE)?

Applicant's Response:

Reviewer's Assessment: Adequate
None of the starting materials or excipients used in the manufacture of Esomeprazole magnesium delayed release tablets [redacted] This section is not applicable.

4. If any of the materials used for the manufacture of the drug substance or drug product are of biological origin or derived from biological sources, what drug substance/drug product processing steps assure microbiological (viral) safety of the component(s) and how are the viral inactivation/clearance capacity of these processes validated?

Applicant's Response:

Reviewer's Assessment: N/A

OVERALL ASSESSMENT AND SIGNATURES: MICROBIOLOGY

Reviewer's Assessment and Signature: Adequate (Daniel Peng, 06/11/2015)

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Secondary Review Comments and Concurrence:

Concur with primary reviewer assessment; Ubrani V. Venkataram, 10/15/15.

Ubrani V. Venkataram -S

QUALITY ASSESSMENT

ASSESSMENT OF THE FACILITIES

2.3.S DRUG SUBSTANCE

2.3.S.2 Manufacture

S.2.1 Manufacturer(s)

1. Are the manufacturers in conformity with current good manufacturing practice to assure that the drug meets the requirements of the FD&C Act as to safety and has the identity and strength, and meets the quality and purity characteristics which it purports?

Establishment name	FEI Number	Responsibilities and profile codes	Current status	Initial Risks Identified	Final Recommendation
(b) (4)			No PAI recommended	Low risk	Acceptable based on inspectional history and experience

Applicant's Response:

Reviewer's Assessment:

(b) (4)

The firm proposes to manufacture and test the esomeprazole magnesium trihydrate bulk API. The firm was previously owned and managed by AstraZeneca (b) (4) (b) (4) purchased the firm in (b) (4) Thus, the firm's inspectional history is very limited under the current quality systems. Nevertheless, the firm does have manufacturing experience, since 2000, with the proton pump inhibitor drug class, including esomeprazole magnesium, both under (b) (4) and AstraZeneca quality systems.

The initial risk assessment revealed that the individual process and product profiles each yielded a "low" risk. An assessment of the facility profile yielded a medium risk, primarly due to just one year's worth of inspectional history. While it *could* appear that such limited history would not be substantive enough to provide a high degree of

confidence of the firm's manufacturing abilities, the previous inspections under the (b) (4) and AstraZeneca quality systems suggest that the firm has maintained a remarkable state of control – all inspections were classified NAI. As such, the overall facility risk assessment is determined to be "low".

The firm's inspectional history and related experience with similarly classed bulk APIs preclude the need for a pre-approval inspection as reflected by the "low" risk across all individual profiles. The overall risk for this facility is thus considered "low" risk, although the initial risk assessment worksheet yielded an overall "medium" risk - this is due to the risk bin threshold assigned to the overall risk category. **This facility is considered acceptable to manufacture the esomeprazole magnesium trihydrate bulk API to support NDA 207920.**

2.3.P DRUG PRODUCT

2.3.P.3 Manufacture

P.3.1 Manufacturer(s)

2. Are the manufacturers in conformity with current good manufacturing practice to assure that the drug meets the requirements of the FD&C Act as to safety and has the identity and strength, and meets the quality and purity characteristics which it purports?

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OVERALL ASSESSMENT AND SIGNATURES: FACILITIES

Reviewer's Assessment and Signature:

There appear to be no significant or outstanding risks to the manufacturing process or final product based on the individual and composite evaluation of the listed facility's inspection results, inspectional history, and relevant experience. The facilities are determined acceptable to support approval of NDA 207920.

Post-approval coverage during the next inspection is recommended for the following facilities:

- **AstraZeneca AB**
- **Wyeth Pharmaceutical Company (for testing)**
- **Pfizer Consumer Healthcare**

Juandria Williams, PhD, OPF/DIA/B3
October 15, 2015

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Secondary Review Comments and Concurrence:

I concur.
Grace E. McNally, Acting Branch Chief, OPF/DIA/B3
October 15, 2015

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