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APPLICATION NUMBER:

207920Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	November 3, 2015
From	Francis E. Becker, M.D., F.A.C.P
Subject	Cross-Discipline Team Leader Review
NDA/BLA # **Related IND**	207920 118964
Applicant	AstraZeneca/Pfizer
Date of Submission	February 6, 2015
PDUFA Goal Date	December 4, 2015
Proprietary Name / Established (USAN) names	Nexium 24 HR/esomeprazole magnesium trihydrate
Dosage forms / Strength	Delayed-release tablets/20 mg
Proposed Indication(s)	1. Treats frequent heartburn (occurs 2 or more days a week) 2. Not intended for immediate relief of heartburn; this drug may take 1 to 4 days for full effect
Recommended:	*Approval contingent on satisfactory labeling*

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1. Introduction

Pfizer Inc. (Pfizer), on behalf of AstraZeneca, submitted a 505 b(1) New Drug Application (NDA) for Nexium 24HR (esomeprazole magnesium) delayed-release tablets, 20 mg, for the Over-the-Counter (OTC) treatment of frequent heartburn in patients 18 years of age and older. The proposed tablet dosage form contains 22.3 mg esomeprazole magnesium which is equivalent to 20 mg esomeprazole. The application includes a Letter of Authorization from AstraZeneca Pharmaceuticals authorizing Pfizer to serve as its agent, pursuant to 21 CFR 314.50 (a)(5), for submitting and executing all matters relating to this NDA. This includes cross-reference to **NDA 204655** for Nexium 24HR (esomeprazole magnesium) capsules where Pfizer is also the sponsor agent.

The application is based primarily on bridging to data submitted under **NDA 204655** through Study **B5141002**, an open-label, randomized, partial replicate crossover study to investigate if the test 20 mg delayed-release tablet and the reference 20 mg delayed-release capsule are bioequivalent following single dose administration under fed and fasted conditions. This is the only new study conducted for this application.

In writing this summary review, I have considered the following primary FDA reviews:

Table 1: Primary Reviews

Material Reviewed	***Name of Discipline Primary Reviewer***
DNDP Medical Officer Review	Elizabeth A. Donohoe, M.D.
DNDBE/OSIS Inspection Report	Shila S. Nkah, Consumer Safety Officer
DMEPA/OMEPRM/OSE Proprietary Name Review	Grace P. Jones, PharmD, BCPS
ONDQA Biopharmaceutics Review	Tien-Mien Chen, Ph.D
OTS/OB/DBIV Consultative Review	Andrew J. Shiber, Pharm D.
DNRD/ODE IV Labeling Review	Mary R. Vienna, RN, MHA
DNDP Pharmacology/Toxicology Review	Wafa Harouk, Ph.D.
ONDP/DNDP-II/Branch VI Quality Assessment	Swapan K. De, Ph.D.
Office of Surveillance/OPQ Review	Alex Viehmann
Office of Clinical Pharmacology Review	Dilara Jappar, Ph.D.
Biometrics Review	Sungwoo Choi, Ph.D.

DNDP=Division of Nonprescription Drug Products
DNDBE=Division of New Drug Bioequivalence Evaluation
DNRD=Division of Nonprescription Regulation
DMEPA=Division of Medication Error and Prevention
DBIV=Division of Biometrics IV
OSIS=Office of Study Integrity and Surveillance
OMEPRM=Office of Medication Error Prevention and Risk Management
ONDQA= Office of New Drug Quality Assessment
ONDP=Office of New Drug Products
OTS=Office of Translational Sciences
OB=Office of Bioequivalence
OPQ=Office of Pharmaceutical Quality

In addition, I considered the following Discipline Reports which were submitted as part of the Quality Review Team Assessments:

Table 2: 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/DMPTI
Environmental Assessment (EA)	Ravindra K. Kasliwal, Ph.D.	ONDP/DNDP-II/ Branch VI

OPF= Office of Process and Facilities
DPAII=Division of Process Assessment II
DIA/B3=Division of Inspectional Assessment/Branch III
OPRO = Office of Program and Regulatory Operations
DRBPMI=Division of Regulatory Business Process Management I
RBPMBI=Regulatory Business Process Manager Branch I
ORA=Office of Regulatory Affairs
OMPTO=Office of Medical Products and Tobacco Operations
DMPTPO= Division of Medical Products and Tobacco Program Operations
DMPTI=Division of Medical Products and Tobacco Inspections

2. Background

Esomeprazole is a proton pump inhibitor (PPI) and was first approved for oral use in Sweden in 2000. It was approved for prescription use in the United States (Nexium®) in 2001. It is currently approved in more than 125 countries for various acid-related disorders. Nexium Control was approved for OTC use in Europe in 2013.

In the United States, prescription esomeprazole (Nexium®) is indicated in adults for the treatment of gastroesophageal reflux disease (GERD), risk reduction of NSAID-associated gastric ulcers, H. pylori eradication, and hypersecretory conditions including Zollinger-Ellison syndrome (**NDA 21153**). Prescription labeling allows for adult oral doses ranging from 20 mg once daily to 40 mg twice daily.

The pediatric indications for prescription esomeprazole (Nexium®) are:

- 12 to 17 year old: treatment of symptomatic GERD, healing of erosive esophagitis
- 1 to 11 years old: short-term treatment of symptomatic GERD, healing of erosive esophagitis
- 1 month old to < 1 year old: erosive esophagitis

PPIs and the proposed OTC indication are familiar to U.S. consumers. OTC omeprazole (Prilosec OTC) and lansoprazole (Prevacid 24HR) were approved in 2003 and 2009,

respectively. In March 2014, Nexium® 24HR (esomeprazole magnesium) delayed-release capsules, 20 mg, were approved for OTC use in the treatment of frequent heartburn in adults 18 years of age and older. This indication is consistent with the other OTC PPI labels. FDA has taken the position that symptoms of heartburn in children should be evaluated by a healthcare provider for safety reasons. In contrast, the prescription labeling for Nexium provides pediatric dosing for the GERD indication down to 1 month of age.

The intended indication for OTC marketing of Nexium 24HR tablets is "treatment of frequent heartburn (occurs 2 or more days a week)." The proposed dosing regimen is 20 mg daily for 14 days, with an option for a repeat 14-day course no sooner than 4 months. Thus, the proposed indication and dosing are identical to currently approved OTC Nexium 24HR capsules.

A face-to-face Type B Pre-NDA Meeting was held with the sponsor on January 28, 2014 (**PIND 118964**). At the meeting, the following important points were discussed:

- FDA confirmed to the sponsor that a new bioequivalence (BE) study between the proposed OTC delayed-release (DR) 20 mg tablet and the OTC DR capsule is required (contingent on approval of the capsule, which was under review at the time of the meeting). FDA recommended a 2-way crossover design under fasting conditions. The sponsor agreed to submit the protocol for review.
- FDA also requested that the sponsor provide data characterizing the effect of food on the pharmacokinetics of the proposed OTC 20 mg DR tablet.
- FDA recommended that the sponsor conduct an in vitro alcohol dose-dumping study. However, upon further discussion, FDA agreed that the sponsor has the option to submit a justification for why such a study would not be feasible for this product.
- FDA agreed that the safety and efficacy data submitted for approval of the OTC esomeprazole DR capsule may be supportive of the NDA for the OTC 20 mg tablet, provided that the tablet formulation is demonstrated to be bioequivalent to the capsule formulation.
- FDA agreed that it was acceptable for the sponsor to reference the Integrated Summary of Safety (ISS) submitted in **NDA 204655** (OTC esomeprazole magnesium 20 mg capsules) and provide an interim safety update from AstraZeneca's safety database, the BE study, and a literature review from May 1. 2013 up to a cut-off date as close as possible to the filing date of the OTC tablet.
- Agreement was reached that a waiver request for pediatric studies would be appropriate for the NDA submission and FDA review.

On April 15, 2014, the sponsor submitted the proposed BE protocol (**B51410002**) for FDA review. However, at that time, the sponsor also notified FDA that the BE study was initiated on April 5, 2014. In ONDQA Biopharmaceutics Review dated September 18, 2014 (**IND 118964**), Dr. Tien-Mien Chen wrote that since the BE protocol had already been initiated, the protocol "would not be reviewed at this time." Biopharmaceutics review would be conducted upon formal submission of the NDA.

3. CMC/Device

Drug Formulation

Esomeprazole magnesium delayed release tablet for 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 with "20 mg" on one side and "N" on the other side.

(b) (4)

(b) (4)

Esomeprazole degrades rapidly at low pH (as encountered in stomach), so it needs to be protected during exposure to gastric juice. The formulation has been developed (b) (4) containing the active ingredient (b) (4) tablet along with

necessary excipients. In the stomach while the tablet may disintegrate into the constituent [redacted] (b) (4)

Site Inspections and Recommendations

DNDP requested site inspections at the following two sites:

1) [redacted] (b) (4) the analytical site [redacted] (b) (4)
2) Bio-Kinetic Clinical Applications: the clinical site in Springfield, Missouri

However, the Division of New Drug Bioequivalence Evaluation (DNDBE) within Office of Study Integrity and Surveillance (OSIS) recommended accepting data without inspection, because OSIS had recently inspected the two sites. The inspectional outcome from the inspections was classified as No Action Indicated (NAI).

Assessment of the proposed manufacturing facility (Minakem Dunkerque; Dunkerque, France) was performed by Juandria Williams, PhD, OPF/DIA/B3. In her review (October 15, 2015), Dr. Williams concluded that, "There appear to be no significant 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."

I concur with DNDBE and OPF recommendations.

Quality Assessment Review

Quality Assessment Review Memo (October 23, 2015) was completed by Dr. Swapan De, Application Technical Lead, ONDP/DNDP-II/ Branch IV. In his Review, Dr. De stated that "drug substance, drug product, quality biopharmaceutics, microbiology, process and facility sections are reviewed and found adequate to support the approval of the application." Dr, De continued, "The drug product has been granted a shelf life of 24 months under controlled temperature storage conditions." However, Dr. De noted that the real time stability data was obtained from the 12-month study at long-term storage conditions (25°C/60% RH [relative humidity]). Therefore, the storage statement should be written as, "Store at 20°C - 25°C (68°F - 77°F)" as 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 aligns with the currently approved storage statement for Nexium 24HR Capsules.

CDTL Comment: The sponsor's proposed DFL for Nexium 24HR tablets states, [redacted] (b) (4) *Therefore, I agree that the DFL should be revised to include Dr, De's recommendation (see* ***Section 12****).*

During the review cycle, FDA sent an Information Request to the sponsor regarding manufacturing process pertaining to intra-batch variability [redacted] (b) (4) uniformity IPC, and

sampling plan. The sponsor requested a teleconference (t-con) with FDA CMC which was held on September 30, 2015 to discuss and clarify these issues. At the t-con, the sponsor agreed to submit a testing protocol (sampling plan for (b) (4) uniformity) to address intra-batch variability. The testing protocol was submitted on October 6, 2015. In addition, the sponsor agreed to a post-approval commitment that the testing protocol would be implemented on commercial batches to perform additional testing of content uniformity on bulk tablets for a specified number of batches. It was agreed that the (b) (4) uniformity data generated from the post-approval testing would be provided in the first Annual Report. The sponsor also submitted a proposed sampling plan which will be used to demonstrate content uniformity. The plan was reviewed by Alex Viehmann (Office of Surveillance/OPQ) who found the plan acceptable. An internal meeting of the entire NDA review team was held on October 9, 2015 to discuss the CMC post-approval agreement, and the agreement was finalized within the OPQ team on October 20, 2015. Therefore, Dr. De recommends that the 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 10/6/2015 and 10/20/2015.

CDTL Comments: I have discussed this recommendation with the Quality Assessment team and agree with the above proposal.

The established name of the drug product was under discussion and will be finalized during labeling meetings. Dr. De proposes two options:

1) To keep the principal display panel (PDP) consistent with the Rx and other generic products, the established name of the drug product would remain as "Esomeprazole magnesium, 20 mg." However, this is scientifically incorrect because the amount of esomeprazole active ingredient alone is 20 mg. The 22.3 mg represents the total weight of the final drug product esomeprazole magnesium (without trihydrate). In this scenario (consistent with the Rx label), the PDP would be as follows:

(b) (4)

2) To keep the PDP as "Esomeprazole, 20 mg," which would represent the actual weight of the active pharmaceutical ingredient, esomeprazole. The PDP would be as follows:

(b) (4)

CDTL Comments: *During the review cycle, there has been much internal discussion regarding the proper approach to this issue. The sponsor's proposed PDP (see* ***Appendix I****) is as follows:*

(b) (4)

(b) (4) *but is clearly confusing to consumers, because it implies that the product is a higher dose and therefore stronger than Nexium 20 mg products. To add to the confusion, the proposed PDP includes a picture of the tablet on which is imprinted "20 mg." Furthermore, as noted by Dr. De, the proposed PDP is scientifically inaccurate because the amount of esomeprazole active ingredient alone is 20 mg. In my opinion, the best option is to ensure scientific accuracy and reduce consumer confusion. Therefore, I recommend using the established name, "Esomeprazole 20 mg."*

Dissolution Method

Due to (b) (4) in the approved Nexium DR capsules and the (b) (4) used in the proposed esomeprazole magnesium DR tablets, the sponsor proposed to adopt the dissolution method described in the USP monograph for Nexium DR capsules. Dr. Peng Duan, Office of Biopharmaceutics, reviewed the proposal and concluded that the proposal was acceptable, except that the proposed dissolution acceptance criterion in buffer stage, Q= (b) (4) %, should be revised to a minimum of Q= (b) (4) % at X time point should be employed. This information was conveyed to the sponsor and the sponsor complied. The Dissolution test was conducted in three commercial scale stability batches, one of which was used in the BE study. The dissolution profiles of all batches were similar, and there is no fluctuation in the drug release during the room temperature storage up to 12 months.

Alcohol Dose Dumping

For modified release formulation, evaluation of the impact of alcohol induced dose dumping in vitro has been recommended. However, in the current submission, the sponsor requested to waive the alcohol dose dumping for the following reasons:

- 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) of esomeprazole, which is acid labile in 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 similarly to an immediate release product, typically showing dissolution of (b) (4) of the esomeprazole in (b) (4) minutes.

Dr. Peng Duan, Office of Biopharmaceutics, reviewed the sponsor's waiver request and in his review (October 15, 2015), wrote the following:

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 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 (b) (4)min. Furthermore, the proposed DR tablets (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.

I concur with the recommendations of Dr. Duan.

Microbiology Assessment

Dr. Xingxu Ping (OPF/DPAII/Branch VI) performed the microbiology assessment and found it to be acceptable.

Environmental Assessment (EA)

Dr. Ravindra Kasliwal (ONDP/DNDP-II/ Branch VI) assessed the environmental analysis. The sponsor claims a categorical exclusion to the environmental assessment requirements in compliance with categorical exclusion criteria 21 CFR Part 25.31 (a) applicable for action on an NDA when the action does not increase the use of the active moiety. Dr Kasliwal confirmed that the EA staff "has looked at this claim and stated the claim is acceptable."

4. Nonclinical Pharmacology/Toxicology

Dr. Wafa Harouk, DNDP, performed the Pharmacology/Toxicology (pharm/tox) review and recommended approval from a pharm/tox perspective. No new nonclinical studies were conducted under this NDA. The sponsor cross-referenced the nonclinical section of this NDA to the summary information provided in the original prescription Nexium 24HR Delayed-Release Capsules (**NDA 204655**). The nonclinical data presented in **NDA 204655** relied on the nonclinical overview from prescription Nexium 24HR Delayed-Release Capsules (**NDA 21153**). Dr. Harouk concluded that, based on the nonclinical evidence available and the clinical history of the prescription and OTC ingredients, there are no novel safety concerns that would prevent approvability of this NDA under the recommended conditions of use.

5. Clinical Pharmacology/Biopharmaceutics

Bioequivalence Study (B5141002)

In the current submission, the sponsor conducted a bioequivalence study (**B5141002**) comparing Nexium 24HR capsule (reference drug) to the proposed delayed-release tablet in order to bridge to the efficacy data from **NDA 204655**. This was a Phase 1, randomized, single-dose, 6-period, crossover, partial replicate, open-label study to assess the bioequivalence of esomeprazole banded OTC Capsule (the reference drug) and the esomeprazole (b) (4) tablet (the test product) in healthy subjects under fed and fasted conditions. The study was conducted in a single center in the United States.

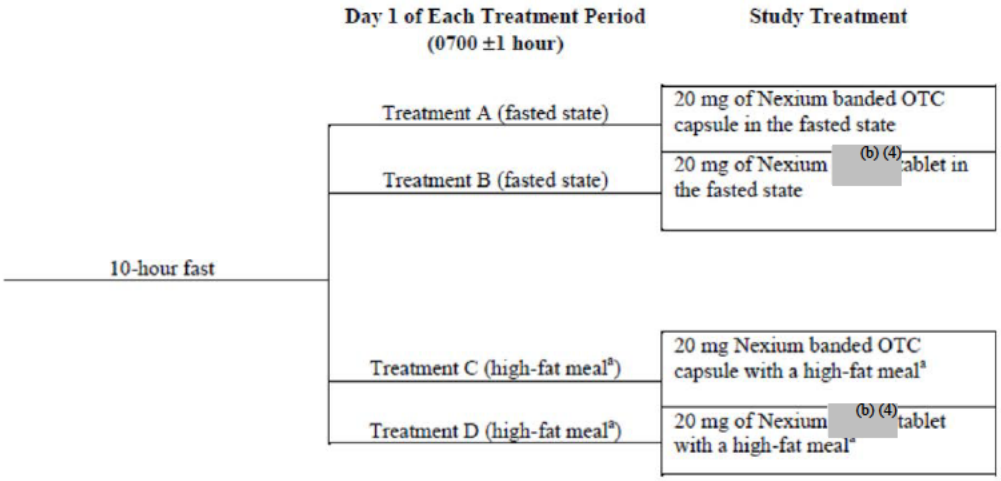
The primary objectives of the study were:

- To demonstrate bioequivalence of Nexium banded OTC capsule compared to Nexium (b) (4) tablet under fasted conditions
- To demonstrate bioequivalence of Nexium banded OTC capsule compared to Nexium (b) (4) tablet under fed conditions

Subjects were randomly assigned to receive a single dose of 1 of the following treatments (**Figure 2**) during each of the 6 treatment periods:

- Treatment A: 20 mg of Nexium banded OTC capsule in the fasted state (administered in 2 treatment periods)
- Treatment B: 20 mg of Nexium (b) (4) tablet in the fasted state
- Treatment C: 20 mg of Nexium banded OTC capsule with a high-fat meal (administered in 2 treatment periods)
- Treatment D: 20 mg of Nexium (b) (4) tablet with a high-fat meal

Figure 2: Treatments Administered During Each Treatment Period



Note: The 2 reference treatments (Treatment A and Treatment C) were administered in 2 separate treatment periods within each subject. There were 6 treatment periods during the study. The minimum washout between treatment periods was 7 days.
(b) (4) OTC = over-the-counter.
[a] Treatment C and Treatment D were administered 30 minutes after administration of a standardized high-fat meal.

(Electronically copied and reproduced from sponsor's submission: Clinical Study Report Synopsis)

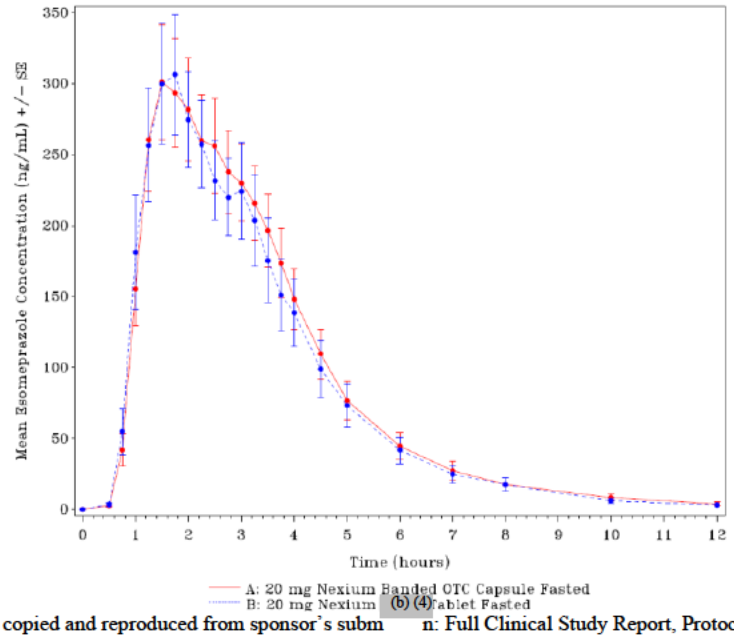
A total of 60 subjects were randomly assigned to one of six treatment sequences (10 subjects to each treatment sequence). There was a minimum 7-day washout between treatment periods. Pharmacokinetic (PK) blood samples were collected serially for 12 hours after dosing during each treatment period. The sponsor reports that since esomeprazole is considered a highly variable drug, the study was designed to enable a reference scaled average bioequivalence (RSAB) testing approach. Therefore, the two reference treatments (Treatment A and Treatment C) were administered in two separate treatment periods within each subject.

CDTL Comment: There was some discussion during the review cycle as to whether the sponsor's RSAB testing approach was acceptable. As noted in ***Section 2*** *above, at the Type B Pre-NDA Meeting on January 28, 2014 (****PIND 118964****), FDA recommended a 2-way crossover design under fasting conditions. Ultimately, however, Biometrics review (Dr. Choi) concluded that the RSAB testing approach was acceptable (see Biometrics Evaluation below).*

Forty-six completed all 6 treatment periods and 14 subjects discontinued from the study.

Under fasting conditions, the PK profile of the 20 mg Nexium (b) (4) tablet was similar to that of the 20 mg Nexium banded OTC capsule. The data demonstrated that the 20 mg delayed release tablet was bioequivalent to the 20 mg delayed-release capsule in terms of both peak esomeprazole exposure (C_{max}) and the extent of esomeprazole exposure (AUC) under fasted conditions, as illustrated in **Figure 3** below:

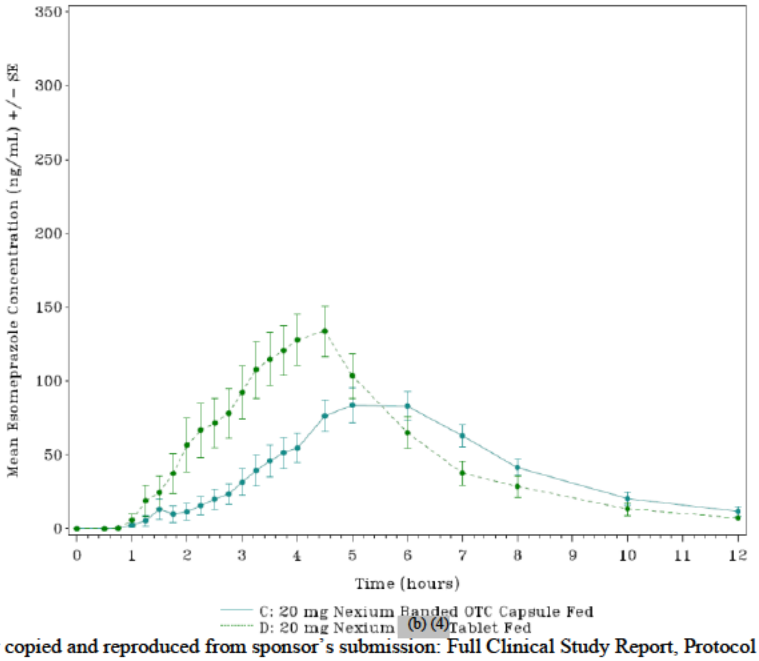
Figure 3: Mean (SE) Plasma Esomeprazole Concentrations (ng/mL) Over Time (h) – 20 mg Nexium Banded OTC Capsule (A) and 20 mg Nexium (b) (4) Tablet (B) in the Fasted State



Electronically copied and reproduced from sponsor's subm n: Full Clinical Study Report, Protocol B5141002, Figure 2, page 45

After administration with a standardized high-fat breakfast, plasma concentrations were markedly lower during the absorption phase for the 20 mg Nexium banded OTC capsule as compared to the 20 mg Nexium (b) (4) S tablet, as illustrated in **Figure 4** below:

Figure 4: Mean (SE) Plasma Esomeprazole Concentrations (ng/mL) Over Time (h) – 20 mg Nexium Banded OTC Capsule (C) and 20 mg Nexium (b) (4) Tablet (D) in the Fed State



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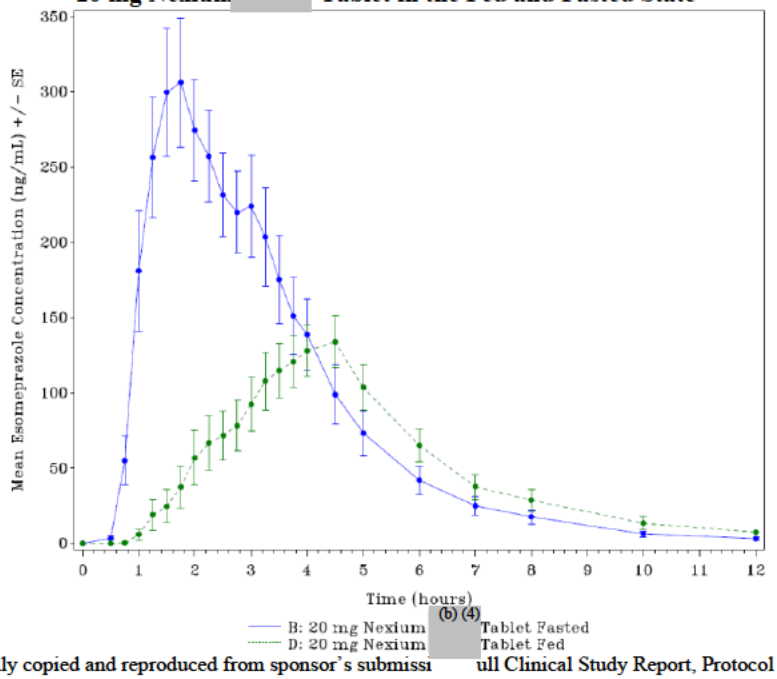
Furthermore, co-administration with a high-fat meal had a pronounced effect on the relative bioavailability of both the Nexium banded OTC capsule and the Nexium (b) (4) tablet formulations. For the Nexium banded OTC capsule, AUC_{inf} and C_{max} were reduced by approximately 46% and 75%, respectively, in the fed state as compared to the fasted state. For the Nexium (b) (4) tablet, AUC_{inf} and C_{max} were reduced by approximately 44% and 68%, respectively, in the fed state as compared to the fasted state, as shown in **Figure 5** below. In addition, co-administration with food delayed the attainment of maximal plasma concentrations by several hours for both the Nexium (b) (4) tablet and the 20 mg banded OTC capsule.

Figure 5: Mean (SE) Plasma Esomeprazole Concentrations Over Time (h) – 20 mg Nexium (b) (4) Tablet in the Fed and Fasted State



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In summary, the PK results demonstrated that under fasted conditions, both the 20 mg Nexium banded OTC capsule and the 20 mg Nexium (b) (4) tablet had numerically similar AUC_{inf}, AUC_{last}, and C_{max} values. Peak esomeprazole concentrations were observed approximately 2 hours after administration, declining thereafter with a t½ of 1.1 to 1.3 hours for both formulations. Under fed conditions, both formulations exhibited markedly reduced AUC_{inf}, AUC_{last}, and C_{max} values. Similarly, both the 20 mg Nexium banded OTC capsule and 20 mg (b) (4) tablet exhibited delayed T_{max} values as well as slightly prolonged t½ in the fed state.

Biometrics Evaluation

A statistical analysis on the sponsor's bioequivalence study was performed by Sungwoo Choi, Ph.D, Biometrics Division IV (Biometrics Consult; August 3, 2015). Dr. Choi concluded that, "In general, the sponsor's crossover design is appropriate because this design allows unbiased estimate of formulation effects under both fasted and fed conditions." Regarding the study results, Dr. Choi reached the following conclusions, as shown in **Table 3** below:

1. For the comparison between Nexium (b) (4) tablet and Nexium banded OTC capsule under the fasted condition, statistical analyses of AUC_{inf} and C_{max} supports a demonstration of bioequivalence.

2. For the comparison between Nexium (b) (4) tablet and Nexium banded OTC capsule under the fed condition, statistical analyses of AUC_{inf} supports a demonstration of bioequivalence. However, C_{max} does not establish bioequivalence.
3. Regarding the food effect, for AUC_{inf} and C_{max}, the mean values under fed condition are much smaller than the mean values under the fasted condition for both Nexium (b) (4) tablet and Nexium banded OTC capsule, consistent with the sponsor's results.

Table 3: Summary of Bioequivalence Test from FDA CMC Stats Reviewer's Independent Analysis using All Available Data. (CI = Confidence Interval; CB = Confidence Bound)

Tablet vs Capsule	Parameter	Ratio(Test/ Reference)	90% CI or 95% CB	Acceptance Criteria	Method	Support Bioequivalence?
Fasted	AUC_{inf}	0.949	(0.891,1.011)	(0.80, 1.25)	Unscaled	Yes
	C_{max}	1.022	-0.048	< 0	Scaled	Yes
Fed	AUC_{inf}	0.983	-0.056	< 0	Scaled	Yes
	C_{max}	**1.270**	-0.197	< 0	Scaled	No

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Biopharmaceutics Review

The BE study was reviewed by Dr. Peng Duan, Biopharmaceutics Reviewer in the Office of Pharmaceutical Quality (Office of New Drug Products [ONDP]). Overall, Dr. Duan concurred with the sponsor's findings and with Dr. Choi's analysis that the 20 mg (b) (4) tablet is bioequivalent to the currently marketed Nexium banded OTC capsule in terms of both C_{max} and AUCs under fasted conditions. Under fed conditions, the Nexium (b) (4) tablet met bioequivalence criteria to the Nexium banded OTC capsule for AUC; however, for C_{max}, the geometric mean of test/reference ratio was outside the bioequivalence criteria (0.80-1.25) where the C_{max} of Nexium (b) (4) tablet was 34.1% higher than that of Nexium banded OTC capsule.

Dr. Duan agreed with Dr. Choi that the sponsor's crossover design was acceptable because it allows unbiased estimate of formulation effects under fed and fasted conditions.

In addition, Dr. Duan observed that the decrease in C_{max} with food intake is slightly less in the proposed esomeprazole DR (b) (4)) tablet compared to the reference (0.317; ~68% decreased versus 0.255; ~75% decreased), as shown in **Table 4** below:

Table 4: 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

Electronically copied and reproduced from Dr. Duan's review (Table 2, page 7).

Dr. Duan concluded, "Overall, the proposed drug achieved bioequivalence with reference drug under fast condition, and it has similar food effect as the reference drug…The results of BE study B5141002 is acceptable."

Office of Clinical Pharmacology Review

A review was also completed by Dr. Dilara Jappar of the Office of Pharmacology (OCP). The focus of the OCP review was on the food effects. Dr. Jappar noted that when the first prescription Nexium (esomeprazole magnesium) delayed release capsule (20 mg and 40 mg, both administered once daily) was approved in 2001 (**NDA 21153**), food effect studies with the 40 mg dose demonstrated that food decreased AUC by 33-53% and C_{max} by 56-79% after single dose administration. Similar PK differences between fed and fasting state were noted after multiple dosing. Therefore, in the Nexium Rx label, Nexium is recommended to be taken at least one hour before meals.

In contrast, when the first OTC esomeprazole product, OTC Nexium 24HR Delayed Release 20 mg capsule was approved for treatment of frequent heartburn (**NDA 204655**) in 2014, no new clinical pharmacology studies were conducted because the manufacture and composition/formulation of the OTC product (b) (4) In support of the OTC indication, the sponsor conducted two replicate phase III efficacy and safety trials with Nexium 24HR OTC 20 mg capsule in which the patients were instructed to swallow the capsule with a glass of water once daily before eating in the morning for 14 days. Therefore, labeling for the Nexium 24HR OTC capsule states, "Swallow 1 capsule with a glass of water before eating in the morning." Dr. Jappar points out that in the Phase III trials for the Nexium 24HR OTC capsule, although the response rates for the primary endpoint (percent of heartburn-free 24 hour days during 14 days of treatment) were statistically significant in favor of the OTC capsule compared to placebo, the response rates were only ~46% for the capsule compared to ~33% for the placebo in one study and 48% for the capsule compared to ~33% for placebo in the other study. In her review, Dr. Jappar theorizes that, "As there is a clear food effect on esomeprazole exposure based on the food effect study in Nexium Rx capsule, this low response rate in these phase III studies with Nexium 24 HR OTC 20 mg capsule could be due to reduced esomeprazole exposure from the food effect if subjects took the Nexium 24 HR OTC 20 mg capsule right before eating as the study design did not specify timing of food in regard to drug administration. It is possible these response rates could have been improved by specifying the timing of food in regard to drug administration by stating 'take one capsule at least one hour before meal in the morning'".

In the current submission, as discussed above, Study **B5141002** demonstrated that, for the proposed Nexium delayed release tablet, food reduced the AUC and C_{max} of esomeprazole by ~44% and ~68%, respectively, compared to the fasted state. Dr. Jappar notes that, for the reference product, Nexium banded OTC capsule, food reduced the AUC and C_{max} of esomeprazole by ~46% and ~75%, respectively, compared to the fasted state. Thus, the magnitudes of food effect on these two Nexium products were similar to each other and also similar to that of Nexium 40 mg Rx capsule. Dr. Jappar concludes that, "Based on the result of the food effect study, we [OCP] recommend that both Nexium OTC capsule and Nexium OTC tablet products should be taken at least one hour before meal, which is consistent with Nexium Rx label."

*Comments: Based on the data submitted by the sponsor and the reviews by Drs. Choi, Duan, and Jappar, I agree with the sponsor's conclusion that the totality of the data provides the bioequivalence bridge to the approved Nexium 24HR delayed-release capsules and support the cross-referencing to the efficacy and safety data submitted in **NDA 204655** for the proposed esomeprazole delayed-release tablet formulation. It is clear, however, that there is a significant decrease in the C_{max} for both the Nexium capsule and the (b) (4) tablet in the fed condition compared to the fasted condition. This effect is slightly more significant for the capsule than for the tablet. This is not a safety concern; however, it could be an efficacy concern for both formulations. The Nexium 24HR capsules were approved based on two efficacy studies (see **Section 7** below) in the absence of pharmacokinetic data, and I agree with Dr. Jappar that the efficacy results in the pivotal studies could have been more significant compared to placebo if the capsules were administered (b) (4) before eating. Now, we have the supporting pharmacokinetic data. Furthermore, the sponsor notes in the **Summary of Biopharmaceutic Studies and Associated Analytical Methods** (page 11) that "The results of the study **[B5141002]** confirmed the well-characterized effect that food has on the bioavailability of esomeprazole with a reduction consistent in magnitude with prior esomeprazole food-effect studies," which is why the Nexium Rx label states under **Dosage and Administration**, "Nexium should be taken at least one hour before meals." Therefore, I agree with Dr. Jappar that both Nexium OTC capsule and Nexium OTC tablet products should be taken at least one hour before meal, which is consistent with directions in the Nexium Rx label.*

6. Clinical Microbiology

N.A.

7. Clinical/Statistical- Efficacy

No new clinical efficacy trials were conducted in support of this application. The sponsor references **NDA 204655** which included two pivotal, 14-day, randomized, double-blind, placebo-controlled trials in subjects with frequent heartburn, defined as heartburn occurring two or more days a week. Subjects were 18 years of age and older and could not have a diagnosis of gastroesophageal reflux disease (GERD). In both pivotal trials, the percentage of heartburn-free 24-hour days (the primary efficacy parameter) was statistically significantly higher in subjects receiving esomeprazole 20 mg daily compared to placebo. The effect size was clinically relevant in both trials and supported the Rx-to-OTC switch of esomeprazole delayed-release capsules for the treatment of frequent heartburn.

8. Safety

The safety database provided by the sponsor was adequate for review. The database included the following, which were extensively reviewed by the DNDP Medical Officer, Dr. Elizabeth Donohoe:

- Safety data obtained from the pharmacokinetic study (**B5141002**)
- Post-marketing data from:
    - AstraZeneca's safety database for prescription esomeprazole covering the period from May 1, 2013 through September 1, 2013; and
    - Pfizer's safety database for nonprescription esomeprazole covering the period from May 27, 2014 through September 1, 2014
- Reference to the ISS (for the cumulative time period through December 31, 2012) and the 4-Month Safety Update (additional data from January 1, 2013 through April 30, 2013) submitted under **NDA 204655**, which included worldwide post-marketing data from the global marketing of prescription esomeprazole
- Literature searches conducted by the sponsor for the time period from May 1, 2013 through September 1, 2014.
- A 4-Month Safety Update submitted under this NDA (**207920**) for the time period from September 2, 2014 through January 1, 2015 containing safety data from both AstraZeneca and Pfizer databases as well as updated literature search.

The sponsor states that, as of January 1, 2015, more than 80,000 subjects have been exposed to esomeprazole in clinical trials. Esomeprazole is approved in over 125 countries, and worldwide prescription exposure exceeds 102 million patient-years, a U.S. exposure of approximately 42 million patient-years. Since the launch of the nonprescription product, more than (b) (4) and tablets have been delivered to wholesalers worldwide, corresponding to an estimated exposure of over 2.5 million patient-years. The United States accounts for over 99% of the distribution of nonprescription oral esomeprazole.

No new safety signals or trends were identified in the pharmacokinetic study (**B5141002**), and no new safety concerns were identified in the postmarketing review. In general, the safety data provided in this submission is consistent with the known safety profile of esomeprazole.

Prescription labeling identifies known hypersensitivity to PPIs or to any component of the formulation as the only contraindication to Nexium use. According to prescription labeling, the most common adverse events associated with Nexium use in adults (≥18 years) are headache, diarrhea, nausea, flatulence, abdominal pain, and dry mouth.

No new studies were conducted to assess safety in subpopulations such as patients with hepatic or renal insufficiency. As Dr. Donohoe pointed out in her review, based on previous studies in subjects with hepatic impairment, Rx labeling indicates that a dose of 20 mg daily should not be exceeded in patients with severe hepatic insufficiency and dose adjustment is unnecessary in patients with lesser hepatic insufficiency. Since the kidney is responsible for

the excretion of metabolites of esomeprazole and not for elimination of the parent compound, the metabolism of esomeprazole is not expected to be changed in subjects with impaired renal function, and Rx labeling states that dose adjustment is not required in subjects with impaired renal function. Thus, the OTC dose of 20 mg is acceptable for subjects with renal or hepatic impairment.

No new studies were conducted to assess for new drug-drug interactions. The proposed DFL includes a list of drugs under "ask a doctor or pharmacist before use if you are taking" which is identical to the DFL for Nexium 24HR capsules and includes warfarin, clopidogrel or cilostazol, prescription antifungal or anti-yeast medicines, digoxin, diazepam, tacrolimus or mycophenolate mofetil, prescription antivirals, and methotrexate. This is acceptable.

8.1 Safety in Clinical Trials

No new safety signals were identified in the pharmacokinetic study (**B5141002**), the only trial conducted under this NDA. In this trial, 60 subjects were enrolled. As this was a crossover trial, the demographic characteristics were essentially the same in each arm.

There were no deaths in the trial. One subject who received Nexium (b) (4) tablet (fasted) experienced a serious adverse event (SAE) of a wrist fracture, which was clearly not related to study drug. Five subjects discontinued from the trial due to adverse events (AEs). Of those subjects, 4 discontinued treatment due to AEs judged to be not related to treatment (vessel puncture site pain, nausea/vomiting, wrist fracture/excoriation, and influenza-like illness). The fifth subject discontinued treatment due to an AE of swollen tongue which occurred immediately after receiving Nexium banded OTC capsule in Treatment Period 1, resolved in approximately 3 hours, did not require additional medication for treatment, and was assessed as a possible allergic reaction to the study drug, although this was not confirmed.

I agree with the sponsor's assessment of whether or not the AE was drug-related in these 5 subjects. Of the 4 subjects who had AEs judged not to be treatment-related, only nausea and vomiting is a known AE which may be related to Nexium. However, this subject did not experience these AEs until approximately 7 days after the last dose of study drug, so it is unlikely to be related to study medication.

Of the 60 subjects that were enrolled in the trial, 12 subjects (20%) reported 29 treatment-emergent AEs. Two subjects reported AEs of moderate severity: 1) the subject discussed above who sustained a wrist fracture after a motorcycle accident, and 2) a subject reporting moderate back pain after receiving Nexium OTC banded capsule (fed). All other AEs were reported as mild. The most commonly reported Treatment-Emergent Adverse Events (TEAEs) are listed in **Table 5** below and are consistent with the known safety profile of esomeprazole. Furthermore, the safety data from this trial do not suggest any significant differences in safety profile between the capsule and tablet or between the fed and fasted conditions.

Table 5: Incidence of Adverse Events (Study B5141002) in ≥ 2% of Subjects by Treatment, in Decreasing Frequency

Preferred Term	Total N=60 N (%)	A: 20 mg Capsule Fasted N=53 n (%)	B: 20mg Tablet Fasted N=49 n (%)	C: 20mg Capsule Fed N=55 n (%)	D: 20mg Tablet Fed N=49 n (%)
No. of Subjects	12 (20.0)	4 (7.5)	5 (10.2)	4 (7.3)	3 (6.1)
Nausea	5 (8.3)	2 (3.8)	2 (4.1)	1 (1.8)	1 (2.0)
Headache	5 (8.3)	3 (5.7)	2 (4.1)	1 (1.8)	2 (4.1)
Vomiting	2 (3.3)	0	2 (4.1)	0	1 (2.0)

Electronically copied and reproduced from Dr. Donohoe's review

8.2 Postmarketing Safety

Overall, the analysis of postmarketing data did not reveal any new or unexpected safety findings, suggesting that the safety profile of esomeprazole for over-the-counter use remains favorable.

In general, it is difficult to determine causality or incidence from spontaneously reported postmarketing cases. The spotty quality of the case reports, under-reporting due to the voluntary nature of reporting, lack of a control group, use of concomitant medication, and various biases and confounders make determination of causality difficult.

The postmarketing safety review included analysis of data in two different safety databases:

1. AstraZeneca's global safety database (Sapphire) for prescription esomeprazole covering the period from May 1, 2013 through September 1, 2014
2. Pfizer's safety database (PSD) for non-prescription esomeprazole covering the period from May 27, 2014 through September 1, 2014.

In addition, the sponsor submitted a 4 Month Safety Update covering the period from September 2, 2014 through January 1, 2015 with data from both the AstraZeneca and Pfizer databases.

Dr. Donohoe provides a detailed description of postmarketing data from all databases in her review.

AstraZeneca Global Safety Database (Sapphire)

There were 4898 case reports received and entered into the Sapphire database from May 1, 2013 through September 1, 2014 involving 14,496 AE terms. U.S. reports comprised 1611 cases and 7320 AEs. The reporting did not include intravenous or OTC use with the exception of the pregnancy search.

The pattern of reported AE terms was similar for both the cases received globally and those received from the U.S. with regard to case characteristics, with the exception of reporting source. In the U.S. the majority of cases (1396 [~87%]) originated from consumers whereas only 211 (~13%) were from medically confirmed sources. In contrast, among global cases, reporting was comparable among medically confirmed sources and consumers (53.5% and 46.4%, respectively).

Globally, there were 60 fatal cases (1.2%). In five of the fatal cases, the event of "Fall" was reported; however, the cause of death was not attributed to the fall. The mean age for these patients was 77 years (age was not reported in 1 case). In 4 of the cases, concomitant medical conditions were noted including cardiomyopathy, cardiac failure, chronic obstructive pulmonary disease and arrhythmias, although causal relationship could not be established. In one of the cases, the information was too limited to make a causal assessment.

Focusing on the U.S. cases, there were 17 fatal outcomes (with 73 associated AEs) and 3442 serious AEs (involving 430 cases). The average age for all cases was 60 years and for fatal cases was 65 years. Analyses by gender, race, and age did not reveal any unusual subgroup patterns. The most frequently reported AEs for fatal cases in the U.S. is listed in **Table 6** below.

Table 6: Most Frequently Reported Adverse Events with Prescription Esomeprazole by Preferred Term (PT) for Fatal Cases: US (Count ≥ 2)

AE Preferred Term	Count	Percentage
Death	5	6.8
Osteoporosis	3	4.1
Toxicity to various agents	3	4.1
Bone disorder	2	2.7
Chronic obstructive pulmonary disease	2	2.7
Completed suicide	2	2.7
Diarrhoea	2	2.7
Multiple fractures	2	2.7
Rheumatoid arthritis	2	2.7
Total	73	100

Electronically copied and reproduced from sponsor's submission: Interim Update of Safety, Table 11, page 25.

For serious non-fatal reports for prescription esomeprazole in the U.S., the most common reported AEs (≥1.9%) were intentional drug misuse (3%), GERD (2.4%), off-label use (2.1%), osteoporosis (2.0%), and fall (1.9%). In general, the cases of intentional drug misuse were not primarily related to safety/adverse reaction of esomeprazole, but often reflected situations where patients were not able to receive their medication as intended and/or were out of medication and as a result might experience symptoms of the underlying disease for which they were being treated. Other examples related to misuse included taking medication intended for others (e.g., spouse or neighbor) , taking an extra dose due to worsening symptoms, or decreasing the daily dose to make the supply of medication last longer. Thus, the Preferred Terms of intentional drug misuse or drug dose omission were not considered serious per se, but were categorized as serious because at least one other adverse event judged as serious was reported together with the term drug dose omission/intentional drug misuse.

Most of the commonly reported AE terms were either considered to reflect the underlying disease or represented terms which are included in product labeling. In the U.S., the most frequently reported AEs (>2%) with prescription esomeprazole by Preferred Term (PT) were intentional drug misuse (5.1%), gastrooesophageal reflux disease (4.1%), off label use (3.3%), drug dose omission (2.9%), and dyspepsia (2.9%). Information regarding dose was available in 29.5% of U.S. cases. There were no relevant differences in AE patterns between dose groups (defined as 20 mg. 40 mg, and other/unknown).

Pfizer's Safety Database

Overall, there were a total of 668 cases involving 1871 AE terms with the use of non-prescription esomeprazole. All of the cases except one were reported in the U.S. One consumer received esomeprazole in the U.S. but the AE occurred while the consumer was in Canada. There were 70 (10.5%) serious cases and no fatalities. However, case outcome was unknown for the majority (~80%) of cases.

Analysis and evaluation of these cases was complicated by the fact that consumers frequently reported a non-specific period of use. In addition, for most of the cases reporting dose, individuals receiving non-prescription esomeprazole had previous experience with omeprazole and/or prescription esomeprazole. Thus, upon review, it was difficult to assess how many patients were new users of the non-prescription esomeprazole.

As in the AstraZeneca Global Safety Database, most of the commonly reported (≥ 2%) AE terms were either considered to reflect the underlying disease or represented terms which are listed for esomeprazole in the product labeling. The most frequently reported AEs in this database are listed in **Table 7** below.

Table 7: Most Frequently Reported Adverse Events with Non-Prescription Esomeprazole by PT (≥ 2%)

Preferred Term	Count	Percentage
Intentional drug misuse	329	49.3
Drug ineffective	164	24.6
Drug ineffective for unapproved indication	55	8.2
Gastrooesophageal reflux disease	48	7.2
Dyspepsia	45	6.7
Malaise	44	6.6
Nausea	43	6.4
Drug dose omission	42	6.3
Abdominal pain upper	39	5.8
Diarrhoea	34	5.1
Off label use	34	5.1
Poor quality drug administered	32	4.8
Abdominal discomfort	27	4.0
Feeling abnormal	26	3.9
Dizziness	23	3.4
Overdose	23	3.4
Chest pain	19	2.8
Vomiting	18	2.7
Dyspnoea	15	2.2
Drug effect incomplete	14	2.1
Headache	14	2.1
Product physical issue	14	2.1
Total	1871	100

Electronically copied and reproduced from sponsor's submission: Interim Update of Safety, Table 21, page 40

Similar to the findings in the AstraZeneca Global Safety Database, the most commonly reported term, "Intentional drug misuse," was not primarily related to safety/adverse reaction of esomeprazole, but often reflects situations where patients intentionally and inappropriately used non-prescription esomeprazole not in accordance with the authorized dose, route of administration, and/or indication(s) or not within the legal status of its supply. The majority of "Drug ineffective" cases were from consumers who had previous experience with prescription PPIs. However, the duration of use was not provided in the majority of these cases and, as described in OTC product labeling, the time to obtain a full treatment effect is 1-4 days. "Drug dose omission" mostly involved patients who ran out of esomeprazole, and "off label use" refers to situations where a physician prescribed non-prescription esomeprazole for medical purposes outside the conditions of label/instructions.

Other frequently reported events such as diarrhoea, nausea, malaise, and abdominal pain are included in the product labeling or described terms related to the conditions for which individuals seek out non-prescription treatment. In summary, the reports are consistent with the known safety profile of esomeprazole.

8.3 Special Safety Topics

Abuse Potential

No potential for abuse or misuse has been identified from the postmarketing data. As discusses in **Section 8.2** above, the most commonly reported term "Intentional drug misuse" was not primarily related to safety/adverse reaction of esomeprazole. No signals for abuse have been identified in previous clinical trials and in previous reviews of DAWN data. Esomeprazole is not known to produce neuropsychiatric effects.

Overdose

Exceeding recommended doses has not been clearly associated with a significant safety issue. In the AstraZeneca database, there were 43 cases (0.9% of total dataset of cases) reporting 75 events in association with overdose. Twenty-nine of these 43 cases contained no safety-related adverse event (other than the overdose term) in connection with the reported overdose. The majority of the remaining cases were non-serious (10 cases; 23%). There was one death: a 76-year-old male with a history of hypertension, diabetes, hypercholesterolemia and atrial fibrillation who suffered an ischemic stroke. Information is limited and it is unclear if an overdose actually occurred. Thus, causality is considered unlikely.

Nexium prescription labeling states, "The symptoms described in connection with deliberate Nexium overdose (limited experience of doses in excess of 240 mg/day) are transient. Single doses of 80 mg of esomeprazole were uneventful." Thus, there appears to be a wide safety margin for overdose with the OTC 20 mg dose.

Pregnancy and Lactation

In support of this supplemental NDA, the sponsor did not conduct any new non-clinical or clinical studies that provide data effects of omeprazole on pregnancy or lactation. Prescription Nexium is classified as Pregnancy Category C. The prescription labeling notes that there are no adequate and well-controlled studies with Nexium in pregnant women. However, changes in bone morphology were observed in offspring of rats dosed through most of pregnancy and lactation at doses greater than or equal to approximately 34 times an oral human dose of 40 mg. Therefore, prescription labeling states that "Nexium should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus."

The excretion of esomeprazole in milk has not been measured. However, Nexium prescription labeling states that esomeprazole is likely present in human milk and that "Caution should be exercised when Nexium is administered to a nursing woman."

During the review cycle for Nexium 24 HR Delayed Release Capsules (**NDA 204655**; approved March 30, 2014), the sponsor reported two observational studies linking prenatal exposure to PPIs to increased risk of asthma. At that time, at the request of United Kingdom's Regulatory Authority, AstraZeneca was performing an observational study investigating the possible association between pregnancy exposures and childhood asthma. In the current

submission, the sponsor reports that a cohort study (**D9612N00018**) using The Health Improvement Network (THIN) database in the UK between 1995 and 2010 conducted by AstraZeneca concluded that the previously suggested modest association between prescription of any acid-suppressive drug during pregnancy and asthma in the offspring may be explained by underlying environmental or genetic factors in the families. The sponsor has determined that there is no association between prenatal exposure to PPIs and asthma in childhood (b) (4) (b) (4) The current NDA submission contains a summary of the study report; however, the full study report was not submitted. Therefore, a request was made to the sponsor on October 6, 2015 to submit the full study report. The sponsor complied with this request on October 16, 2015. I have reviewed the full study report, and I concur with the study findings and with the sponsor's conclusions.

Pfizer reviewed its post-marketing safety database for non-prescription esomeprazole since launch (May 27, 2014) through September 1, 2014 using terms related to pregnancy and lactation and identified four cases. Two cases involved pregnancy. In one case, the patient was not sure whether she was taking esomeprazole or omeprazole at the time of her pregnancy. The other case described exposure during pregnancy for an 8-month pregnant woman with 80 mg of non-prescription esomeprazole. In both cases, the outcome of the pregnancy was unknown. In two other cases, "Lactation disorder" was reported and both cases described spontaneous lactation with an unknown outcome.

In summary, no clinically significant increased risk for severe complications and/or malformations has been confirmed when PPIs, including esomeprazole, are used during pregnancy. In addition, only limited data are available on the use of esomeprazole during nursing. Esomeprazole's safety for pregnant and nursing women has been monitored closely in the postmarketing experience and in the peer reviewed medical literature. However, esomeprazole is not intended for use in pregnant or nursing women. The proposed OTC labeling Nexium 24HR tablets states, "If pregnant or breast-feeding, ask a health professional before use." This language is identical to the OTC labeling language for Nexium 24HR capsules, is consistent with other PPIs, and is also consistent with other OTC drugs that are Pregnancy Category B or C in prescription labeling.

Possible Association of PPIs with Lupus

In 2011, based on postmarketing reports, the Division of Pharmacovigilance (DPV) conducted a review and found an association between PPI use and cutaneous lupus erythematosus (CLE). Subsequently, DPV recommended to the Division of Gastroenterology and Inborn Errors Products (DGIEP) that class labeling changes to include (b) (4) be considered. It was also noted that a cursory search of the FAERS database found cases of systemic lupus erythematosus (SLE) associated with PPI use. As a result, a Tracked Safety Issue (TSI 1455) was created related to SLE and PPIs in July, 2015. Currently, Nexium prescription labeling does not include any information about potential association with CLE or SLE. From the standpoint of OTC use, it appears that the association is rare is still under review by DGIEP and DPV. Therefore, I recommend no changes to the proposed DFL regarding this issue until the TSI investigation is complete and DGIEP has determined what, if any, changes to prescription PPI labeling are necessary.

Possible Association of PPIs and Myocardial Infarction

In May 2015, the Division of Epidemiology-I (DEPI-I) conducted a review based on reports in the literature of possible association of PPIs with myocardial infarction (MI). However, DEPI-I concluded that the studies have significant limitations as a result of which the studies failed to support a causal association between PPIS and major adverse cardiovascular events. DEPI-I recommended continued surveillance of the medical literature and routine pharmacovigilance for adverse cardiovascular outcomes with PPI use. I agree with DEPI-I recommendations. Currently, there is no conclusive data to suggest an association between PPI use and cardiovascular events. In her Clinical Review for Nexium 24HR capsules (**NDA 204655**; February 19, 2014), Dr. Jane Filie provided plausible explanations for any such association. First, patients with underlying cardiovascular disease who concomitantly have GERD or dyspepsia may be taking PPIs. Second, patients may mistakenly attribute epigastric discomfort to gastrointestinal cause when the symptoms are actually of cardiac etiology. I agree with Dr. Filie. Furthermore, the proposed DFL for Nexium 24HR tablets contains warnings to not use the product if you have potential cardiac symptoms (chest pain or shoulder pain with shortness of breath; sweating; pain spreading to arms, neck or shoulders; or heartburn with **lightheadedness, sweating or dizziness**. Therefore, there is no need for changes to the DFL regarding this issue.

9. Advisory Committee Meeting

N.A.

10. Pediatrics

The sponsor is requesting a full waiver for all pediatric populations. An initial Pediatric Study Plan (iPSP) was submitted by AstraZeneca on October 24, 2013 under **PIND 118964.** FDA correspondence dated January 22, 2014 provided edits to the iPSP to which AstraZeneca agreed. The pediatric plan was presented to FDA Pediatric Review Committee (PeRC) on February 5, 2014. The PeRC concurred with the agreed upon iPSP. The PeRC had previously agreed to a full pediatric waiver for OTC Nexium 24HR Capsules (January 22, 2014) "because the product would be ineffective or unsafe for pediatric patients."

I concur with the request for a waiver of pediatric studies. FDA has waived pediatric studies for the other PPIs because, as stated by Dr. Leonard-Segal in her Summary Review of OTC lansoprazole (**NDA 22327**; May 11, 2009), "it would not be safe to use this medication OTC in the pediatric population since the underlying causes for heartburn in children should be evaluated by a healthcare professional."

The proposed labeling states under ***Directions***, "adults 18 years of age and older" and "children under 18 years of age: ask a doctor before use. Heartburn in children may sometimes be caused by a serious condition." This is consistent with prior OTC PPI labels and is acceptable to me.

11. Other Relevant Regulatory Issues

As noted by Dr. Donohoe in her **NDA 207920 Clinical Investigator Financial Disclosure Review**, the sponsor provided certification for 13 of the 13 investigators in the Bioequivalence Study. There were no disclosable financial interests reported. In her **Clinical Review**, Dr. Donohoe concludes that there were no financial disclosures that would cast doubt on the findings of the studies, and I agree.

12. Labeling

The Division of Medication Error Prevention and Analysis (DMEPA) reviewed the proposed proprietary name, Nexium®24HR. The primary reviewer, Grace P. Jones, Pharm D, concluded that it was conditionally acceptable, and I agree

The proposed Drug Facts label (DFL) is nearly identical to the most recently approved DFL for the reference drug, Nexium 24HR Capsules, except for "***Inactive Ingredients***" (b) (4) The DFLs for both Nexium products are very similar to the DFLs for Prilosec OTC (**NDA 21229**) and Prevacid 24HR (**NDA 22327**). "***Uses***," "***Directions***," and "***Warnings***" sections are essentially identical between the Nexium 24HR Capsule DFL and the proposed Nexium 24HR Tablet DFL.

A detailed labeling review was conducted by Mary Vienna, RN, MHA, of DNRD. Important comments and recommendations from her review are as follows:

- The statement (b) (4) appears on the proposed Principal Display Panel (PDP). See **Appendix I** for sponsor's proposed PDP. An Information Request (IR) was sent to the sponsor on July 16, 2015, requesting data to support the (b) (4) claim. The sponsor responded on July 31, 2015 with a representative 14-count carton label that removed the claim. DNRD recommends that the sponsor be reminded to submit all labeling with the (b) (4) statement removed.
- The PDP has a blue oval in the upper left corner with the statement "New" in white letters. DNRD recommends reminding the sponsor to delete the "New" graphic after six months of marketing.
- The DFL for the 2-ct carton contains a peel-back label that consists of 5 panels. As the approved 2-ct label for the Nexium capsule contains the entire DFL on the carton itself, it is not clear why a peel-back label for this product is necessary. The peel-back label can be removed from the carton and is less optimal than DFL printed on the carton itself. Additionally (b) (4) DFL information such as (b) (4) appear on the peel-back label, and the (b) (4) appear on the top flap of the carton itself. DNRD recommends that the 2-ct carton reflect the format of the 2-ct carton for Nexium capsule.

- Based on the review and recommendations of the Office of Clinical Pharmacology regarding the food effects study (see **Section 5** above), DNRD recommends changing the direction statement from "swallow 1 tablet with a glass of water before eating in the morning" to "swallow 1 tablet with a glass of water ***at least 1 hour*** before eating in the morning" (bold italics added by this reviewer to emphasize recommended change).
- Under "***Other Information***," the proposed DFL states, (b) (4) (b) (4), and DNRD defers to OPQ for resolution of this issue (see **Section 3**).
- In addition, under "***Other Information***," the statement, (b) (4) is not present in the DFL for Nexium 24HR Capsules. DNRD recommends requesting that the sponsor provide a rationale for this change or remove this statement.
- On the PDP, below the "Nexium" section of the proprietary name and to the left of the "24HR" section of the proprietary name appears the statement "Esomeprazole (b) (4) Delayed-release Tablets (b) (4) mg/Acid Reducer" that is identical in size and prominence to the approved label for the capsule product (**NDA 204655**). DNRD defers to OPQ and to ongoing internal discussions regarding the correct established name and dose to be stated on the PDP.

*CDTL Comments: I agree with the proposed changes to the PDP and the DFL. The sponsor has submitted no data in support of the (b) (4) claim. Removal of the "New" graphic after 6 months of marketing is standard. It is not clear why a peal-back label is needed for the 2-ct carton but not for the others. As discussed in **Section 5**, the directions to take the tablet at least 1 hour before eating is important to ensure adequate efficacy and consequently better results for consumers. I agree with the recommendations regarding "**Other Information**": the storage conditions to be included on the label are recommended by the Quality Assessment Team, and the sponsor has provided no data to date to justify the claim, (b) (4) which is not present in the DFL for Nexium 24HR Capsules. As I have previously stated, the proprietary name for the PDP which is scientifically accurate and which is the least confusing to consumers is "Esomeprazole 20 mg." The exact wording and graphics for the proprietary name are still under discussion at this time.*

The agreed upon language to take at least one hour before a meal and regarding the proprietary name should also be applied to the Nexium 24HR capsule PDP and DFL to ensure consistency.

13. Recommendations/Risk Benefit Assessment

13.1 Recommended Regulatory Action

I recommend an approval action. My recommendation is in agreement with the Clinical Reviewer, Dr. Donohoe and with the other relevant Divisions as discussed above.

My recommendation is contingent on agreement with the sponsor on the content of the DFL and PDP. Important issues to be addressed include:

- Agreement on the established name to be on the PDP. I recommend "esomeprazole 20 mg." See **Section 3.**
- Agreement to change DFL ***Directions*** to state that the tablet should be taken at least one hour before eating. See **Section 5**.
- Under ***Other Information*** in the DFL, change labeling to address storage conditions per CMC recommendations: "Store at 20°C - 25°C (68°F - 77°F)." See **Section 3**.
- Agreement on the additional labeling recommendations (see **Section 12**).

For my labeling recommendations for the PDP, see **Appendix II**.

13.2 Risk Benefit Assessment

The risk/benefit profile of Nexium 24HR tablet is identical to previously approved Nexium 24HR capsules and is comparable to the risk/benefit profiles of other approved OTC PPIs (omeprazole and lansoprazole). Thus, the risk/benefit profile for esomeprazole remains favorable for OTC use. As noted by Dr. Donohoe, consumers have been safely self-treating heartburn with OTC PPIs since 2003.

The benefit of Nexium 24HR capsules in the treatment of heartburn was clearly demonstrated in two pivotal trials conducted under **NDA 204655**. In the current submission, the sponsor has provided adequate pharmacokinetic data to bridge to the efficacy data from **NDA 204655**. In addition, safety review of the BE study (**B5141002**) and postmarketing data did not identify any new safety signals. Common adverse reactions associated with esomeprazole use include headache, abdominal pain, diarrhea, flatulence, nausea/vomiting and constipation. In general, AEs are mild and transient in nature and are either already identified in Nexium labeling or are related to the underlying disease.

As Dr. Donohoe notes in her review, dose adjustment with the OTC product is not necessary in subjects with underlying diseases such as hepatic and renal insufficiency. Known drug reactions of concern are adequately addressed in the proposed DFL and are identical to Nexium 24HR capsule DFL. Furthermore, Warnings in the DFL will alert consumers regarding the use of esomeprazole with known risk factors (hypersensitivity to PPIs, pregnancy, and drug interactions).

13.3 Recommendation for Postmarketing Risk Evaluation and Management Strategies

None.

13.4 Recommendations for Other Postmarketing Requirements and Commitments

As described in Dr. De's review, the sponsor agreed to a post-approval commitment that the testing protocol (sampling plan for (b) (4) uniformity) would be implemented on commercial batches to perform additional testing of content uniformity on bulk tablets for a specified number of batches. It was agreed that the (b) (4) uniformity data generated from the post-approval testing would be provided in the first Annual Report.

13.5 Recommended Comments to the Sponsor

The following comment may be conveyed in the NDA action letter:

OPQ Comments:

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 10/6/2015 and 10/20/2015.

Labeling Comments:

- *Submit all labeling with the (b) (4) statement removed.*
- *After 6 months of marketing, delete the "New" graphic from the PDP.*

Additional comments may be forthcoming based on labeling negotiations.

4 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

FRANCIS E BECKER
11/05/2015