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APPLICATION NUMBER:

207920Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	22 Nov 2015
From	Karen Murry Mahoney, MD, FACE Deputy Director, Division of Nonprescription Drug Products Office of Drug Evaluation IV Office of New Drugs Center for Drug Evaluation Research
Subject	Deputy Division Director Summary Review
NDA #	NDA 207920
Applicant Name	Pfizer, Inc. on behalf of AstraZeneca LP
Date of Submission	6 Feb 2015
PDUFA Goal Date	4 Dec 2015
Proprietary Name / Established (USAN) Name	Proprietary Name: Nexium 24HR Established Name: esomeprazole delayed-release tablets, 20 mg
Dosage Forms / Strength	Delayed-release tablet, 20 mg
Proposed Indication(s)	Treats frequent heartburn (occurs two or more days a week)
Action	Approval

Material Reviewed/Consulted	
OND Action Package, including:	Names of Discipline Reviewers
Biopharmaceutics Review	Tien-Mien Chen, PhD
Clinical Pharmacology Review	Dilara Jappar, PhD
Clinical Review	Elizabeth Donohoe, MD
Cross-Discipline Team Leader Review	Francis Becker, MD
Inspection (Facility)	Juandria Williams, PhD
Labeling Review	Mary Vienna, RN, MHA
Pharmacology Toxicology Review	Wafa Harrouk, PhD
Proprietary Name Review, and Labeling Review for Medication Error Prevention	Grace Jones, PharmD, BCPS
Quality (Chemistry, Manufacturing and Controls): Team Technical Lead	Swapan De, PhD
Quality: Drug Substance and Drug Product Reviews, and Environmental Assessment	Ravindra Kasliwal, PhD
Quality: Microbiology and Process Reviews	Daniel Peng, PhD
Quality: Office of Surveillance Manufacturing Process Protocol Review	Alex Viehmann, PhD
Statistical Review	Sungwoo Choi, PhD

Signatory Authority Review

1. Introduction

Pfizer, Inc., acting as agent for AstraZeneca LP, submitted a 505(b)(1) New Drug Application for Nexium® 24HR, a nonprescription (OTC) delayed-release 20 mg tablet formulation of the proton pump inhibitor (PPI) esomeprazole, for the treatment of frequent heartburn (occurring two or more times per week) in adults 18 years of age and older.

Data submitted to support this application included:

- A combined bioequivalence and food-effect study comparing this new 20 mg esomeprazole tablet to the approved OTC Nexium 24HR esomeprazole 20 mg delayed-release capsule
- Dissolution data
- Postmarketing safety data for other esomeprazole products

Overall, these data were adequate to support approval of the product.

There were a few issues that required resolution, including:

- The appropriate established name
- The question of whether food-effect labeling is needed
- An (b) (4) statement proposed by the applicant for the Principal Display Panel (PDP)
- Appropriate expression of storage conditions on the Drug Facts Label (DFL)
- Manufacturing method for demonstrating content uniformity of the product.

The above issues are specifically addressed in this signatory review. Please refer to Dr. Francis Becker's Cross-Discipline Team Leader review (Document Archiving, Reporting, and Regulatory Tracking System [DARRTS] 5 Nov 2015) for a more extensive summary of the findings of the various reviews supporting this approval action.

From this point forward, I will often refer to the proposed nonprescription Nexium® 24HR esomeprazole 20 mg delayed-release tablets as "Nexium OTC tablets," and I will usually refer to the reference approved nonprescription Nexium® 24HR OTC esomeprazole 20 mg delayed-release capsules as "Nexium OTC capsules." In general, it is not my practice to refer to drug products by proprietary names in reviews. However, because the applicant relied upon its own branded Nexium OTC capsule, and frequent reference to it is required, I found that use of the abbreviated terms Nexium OTC capsule and Nexium OTC tablet was often the least cumbersome way to express the names of these products.

2. Background

Proton pump inhibitors (PPIs) reduce gastric acid secretion by inhibition of the hydrogen/potassium adenosine triphosphate enzyme system, also referred to as the proton

pump. The proton pump is the terminal step in gastric acid production, and is responsible for secretion of H⁺ ions into the stomach. The reduction of acid in the stomach achieved by PPIs aids in prevention and healing of certain ulcers, treatment of gastroesophageal reflux disease, and relief of the symptoms of heartburn. Esomeprazole is one of several approved PPIs.

The first esomeprazole product, the prescription Nexium delayed-release capsule (NDA 21153, 20 mg and 40 mg), was approved in 2001. Its current indications are:

- Treatment of gastroesophageal reflux disease
- Reduction in the risk for occurrence of gastric ulcers during treatment with nonsteroidal anti-inflammatory drugs
- Use in triple therapy with amoxicillin and clarithromycin to eradicate *Helicobacter pylori* and reduce risk of duodenal ulcer recurrence
- Long-term treatment of Zollinger-Ellison syndrome, a pathological gastric acid hypersecretory condition

The first nonprescription esomeprazole product, the Nexium 24HR 20 mg delayed-release capsule (NDA 204655), was approved in 2014, for use for frequent heartburn. For that OTC capsule application, two replicate phase III efficacy and safety studies were done, and demonstrated efficacy versus placebo over a 14 day course of treatment. Pfizer, the holder of both NDA 204655 and the current NDA 207920, relied upon its own Nexium OTC capsule (NDA 204655) to support approval of this proposed Nexium OTC tablet (NDA 207920), via the 505(b)(1) regulatory pathway.

3. Quality (Chemistry, Manufacturing, and Controls)

Please see Dr. Swapan De's Quality Assessment Review Memo (Panorama 23 Oct 2015). Dr. De summarized all the quality reviews by the reviewers named above on the cover page. I concur with the conclusions reached by Dr. De, who stated that information regarding the drug substance, drug product, quality biopharmaceutics, microbiology, and facility were adequate to support approval. Stability testing supports a shelf life of 24 months under controlled temperature storage conditions. There are no outstanding issues.

Dr. Juandria Williams inspected the proposed manufacturing facility (Minakem Dunkerque, Dunkerque, France), and found the facility acceptable.

Three issues that arose during the Quality review concerned the appropriate established name, storage conditions, and demonstration of content uniformity.

3.1. Established Name

The established name proposed by the applicant was esomeprazole magnesium, 22.3 mg. This name was not ideal, for the following reasons:

- Use of a salt name (esomeprazole magnesium), rather than the active moiety name (esomeprazole), is not consistent with the United States Pharmacopeia (USP) naming policy for salt drug substances (USP 2013). Essentially, that policy states that, for new drug products, the salt is not to be used in the name unless the salt name provides vital

- clinical information, which would not be the case for esomeprazole. The USP salt policy also states that the strength is to be expressed as the strength of the active moiety, which in this case would be 20 mg, not 22.3 mg.
- FDA recently issued a salt-naming guidance (FDA 2015). This guidance outlines how FDA is implementing the USP salt policy. While the guidance does discuss some exceptions to the policy, none appear to apply in this case.
 - If the salt name were to be used, the correct salt name would actually be esomeprazole magnesium trihydrate.
 - The proposed tablet is imprinted with “20 mg”, as is the approved Nexium OTC capsule. This poses a risk for consumer confusion, if the PDP states the strength as 22.3 mg, and the tablet states it as 20 mg.
 - If this esomeprazole product were to be displayed on a store shelf next to a correctly named esomeprazole product with an equal strength of the active moiety, consumers could incorrectly interpret this product as being of a higher strength than the correctly named product (22.3 versus 20 mg).

Therefore, the logical established name for this product would be esomeprazole, 20 mg. However, the approved OTC capsule uses the name esomeprazole magnesium, 22.3 mg. The approved prescription (Rx) capsule uses the salt name (esomeprazole magnesium), but expresses the strengths of the Rx capsules as 20 mg (rather than 22.3 mg) and 40 mg. There is also at least one generic esomeprazole that uses the salt name.

After discussions with the clinical team; with Dr. Kasliwal, Dr. De, and Dr. Danae Christodolou of the Office of Pharmaceutical Quality; Dr. Lilian Golson of the Office of Generic Drugs; and others, I have decided that the most appropriate established name is esomeprazole, 20 mg, for the following reasons:

- It is scientifically accurate, unlike the currently used salt name.
- It is consistent with the USP salt policy, and the FDA salt-naming guidance.
- The actual salt name, esomeprazole magnesium trihydrate, does not convey vital clinical information, and is likely a cumbersome and complex term for consumers of the average reading level in the US.
- There is less likelihood of consumer confusion related to consistency of the strength expressed on the carton and container versus the strength expressed on the tablet itself.
- There is less likelihood of consumer confusion regarding relative strength (e.g. 22.3 mg versus 20 mg), if future OTC esomeprazole products in general were to use the salt name rather than the active moiety name, and consumers were to view them side-by-side on store shelves.

The applicant has agreed to express the established name as esomeprazole, 20 mg. After discussions regarding the established name of the approved Nexium OTC capsule, (b) (4)

The Office of Generic Drugs states that, upon approval of NDA 207920 by DNDP, OGC will request that the currently approved generic change its name to be in alignment also. The applicant intends to work with the Division of Gastroenterology and Inborn Errors Products

(DGIEP), which regulates prescription gastroenterological products, regarding a possible change of the established name of prescription esomeprazole products.

The final discussions surrounding this issue occurred after the quality, clinical, CDTL and other reviews were entered in DARRTS; therefore, those reviews do not reflect the final decision reached. These discussions were collaborative and collegial, with full opportunity for all views to be presented. The full review team is in agreement regarding this decision.

3.2. Storage Conditions

The applicant's proposed DFL stated [REDACTED] (b) (4).” However, Dr. De noted that real-time stability data were obtained from a 12-month study at long-term storage conditions of 25°C (77°F) and 60% relative humidity. Dr. De stated that the storage statement should be written as “Store at 20°C - 25°C (68°C -77°F). This aligns with the current approved storage statement for the reference product, nonprescription Nexium 24HR esomeprazole delayed-release capsules, 20 mg. The applicant has modified the proposed tablet DFL accordingly.

3.3. Content Uniformity

FDA requested information from the applicant regarding an aspect of its manufacturing process, specifically related to assessing intra-batch variability for content uniformity. The applicant submitted a testing protocol for its sampling plan for [REDACTED] (b) (4) uniformity, and Dr. Alex Viehmann of the Office of Surveillance in the Office of Pharmaceutical Quality found the protocol acceptable. The applicant agreed to a postmarketing commitment to provide data collected under this protocol. FDA agreed that these data could be submitted in the annual report for the product.

4. Nonclinical Pharmacology/Toxicology

Please refer to Dr. Wafa Harrouk's review (DARRTS 27 Oct 2015). No new nonclinical pharmacology/toxicology data were submitted. I concur with Dr. Harrouk's conclusion that there are no outstanding pharmacology/toxicology issues that preclude approval.

5. Clinical Pharmacology/Biopharmaceutics

Please refer to Dr. Dilara Jappar's clinical pharmacology review (DARRTS 17 Oct 2015), Dr. Peng Duan's biopharmaceutics review (Panorama 15 Oct 2015) and Dr. Sungwoo Choi's biometrics review (DARRTS 3 Aug 2015). I concur with the conclusions reached by Drs. Jappar, Duan, and Choi regarding the findings of Study B5141002, and there are no outstanding clinical pharmacology or biopharmaceutics issues that preclude approval. The bioequivalence and dissolution data submitted provide an adequate bridge between the approved Nexium OTC capsule, and the proposed Nexium OTC tablet. Below, I present the findings briefly, and also discuss Dr. Jappar's labeling recommendation regarding food effect.

5.1. Bioequivalence and Food Effect

The applicant conducted Study B5141002, a combined bioequivalence and food effect study, to bridge data from its approved Nexium OTC capsule to its proposed Nexium OTC tablet. The study was a randomized, single-dose, 6 period, cross-over, partial replicate, open-label study conducted in 46 healthy subjects to evaluate bioequivalence under both fed and fasted conditions.

Dr. Duan reviewed the bioequivalence portion of the study, and Dr. Jappar reviewed the food effect portion. Dr. Choi provided biometrics review of the overall study.

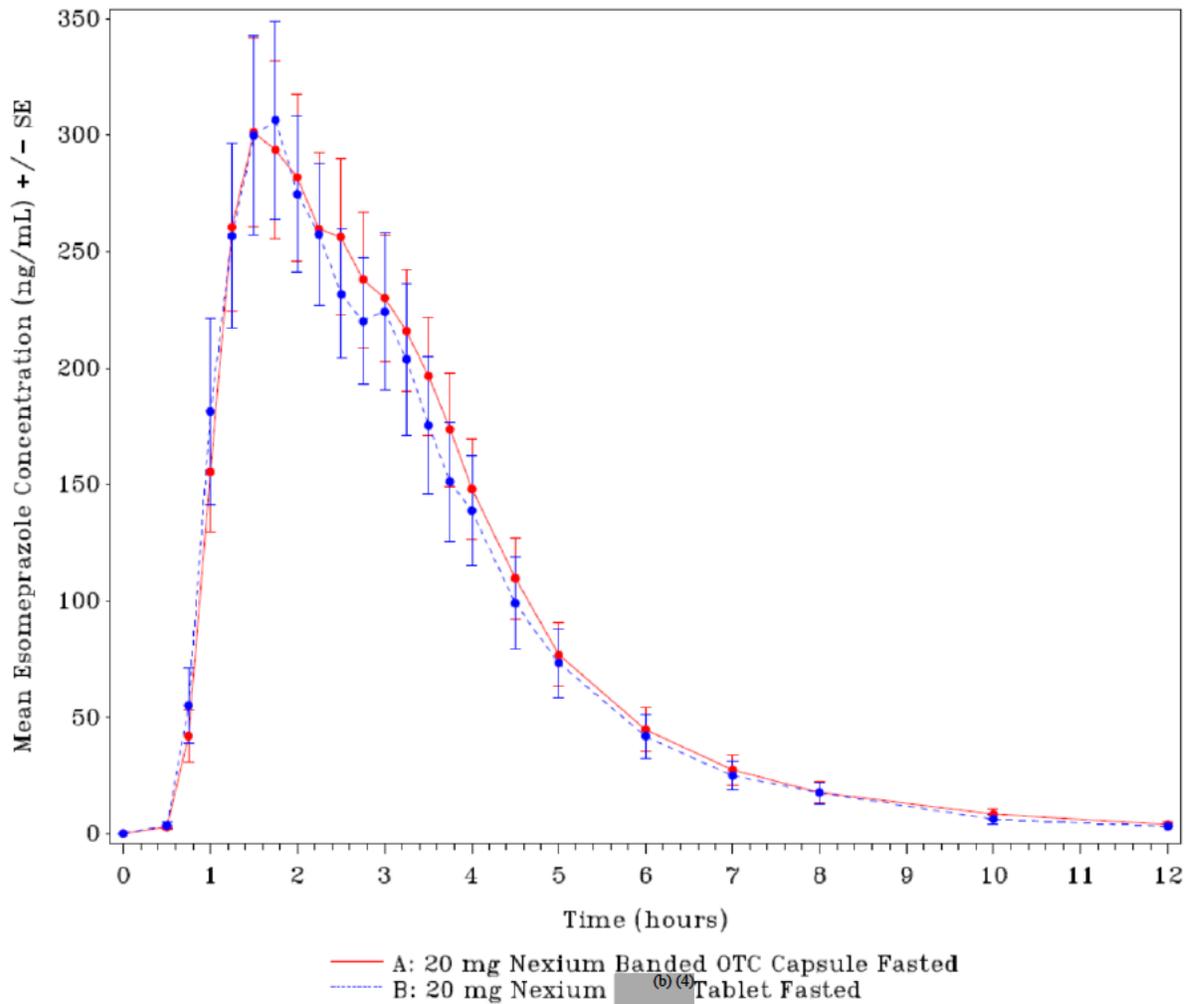
As shown in the table below, from Dr. Choi's independent statistical analysis, the proposed tablet was bioequivalent to the reference capsule under fasted conditions. Under fed conditions, the tablet and capsule met bioequivalence criteria for the parameter of area under the concentration curve (AUC), but not for the parameter of maximum plasma concentration (C_{max}). Per protocol and FDA standards, the test (tablet) and reference (capsule) formulations were considered bioequivalent if, under fasting conditions, the point estimate of the geometric mean ratio of the esomeprazole concentrations achieved by the tablet versus the capsule fell within the range of 0.80-1.25, and the upper bound of the 95% confidence interval was no greater than zero. Secondary analyses were conducted for the fed state.

Table 5.1: Bioequivalence Study Findings under Fed and Fasted Conditions (FDA Independent Biometrics Analyses), Proposed Esomeprazole 20 mg Delayed-Release Tablet versus Approved Nonprescription Nexium 24HR Esomeprazole 20 mg Delayed-Release Banded¹ Capsule						
Test Condition	Parameter	Ratio (tablet:capsule)	90% CI	95% CB	Acceptance Criteria	Bioequivalence Supported?
Fasted	AUC _{inf}	0.949	0.891, 1.011		0.80, 1.25	Yes
	C _{max}	1.022		-0.048	<0	Yes
Fed	AUC _{inf}	0.983		-0.056	<0	Yes
	C _{max}	1.270		-0.197	<0	No

Source: Biometrics Review, Dr. Sungwoo Choi, DARRTS 3 Aug 2015; pg 3, Table A, and pg 9, Table 4
¹ The Nexium OTC 20 mg capsule differs from the Nexium Rx 20 mg capsule only in the presence of a tamper-proof band on the OTC capsule.
 Abbreviations: AUC = area under the concentration curve; CB = upper bound of the 95% confidence interval; CI = confidence interval; C_{max} = maximum plasma concentration of esomeprazole; OTC = over-the-counter

Below are two figures illustrating the bioequivalence study results.

Figure 5.1: Mean (SE) Plasma Esomeprazole Concentrations (ng/mL) Over Time (h) for Proposed 20 mg Nexium 24HR Tablet and Approved Nonprescription 20 mg Nexium Banded¹ Capsule, Fasting Condition

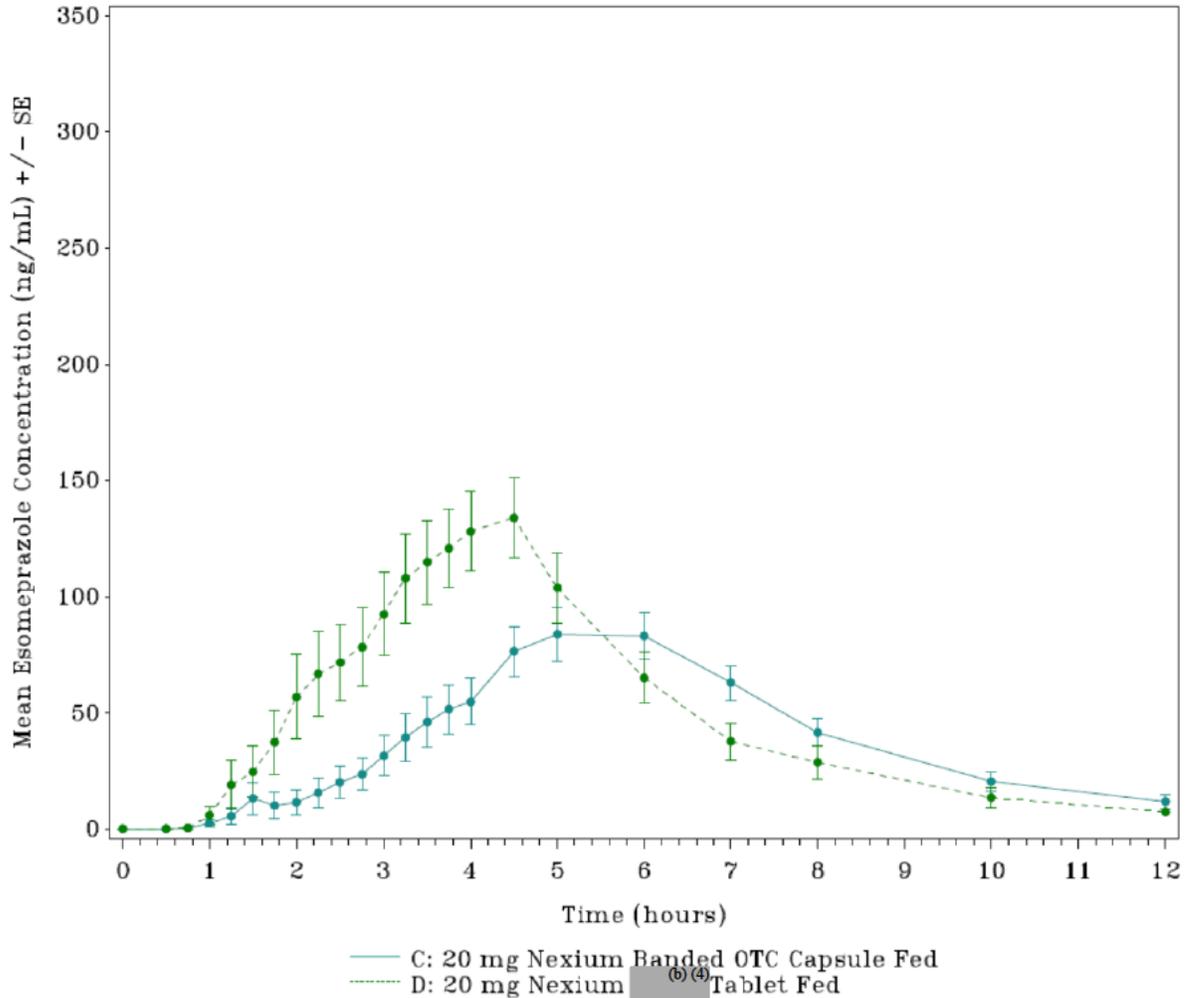


Source: NDA 207920, submission 0000, 6 Feb 2015, full study report for Protocol B5141002, pg 45, Figure 2.

¹ The Nexium OTC 20 mg capsule differs from the Nexium Rx 20 mg capsule only in the presence of a tamper-proof band on the OTC capsule.

Abbreviations: h = hours; (b)(4) delayed-release properties for the proposed tablet; OTC = over-the-counter; SE = standard error

Figure 5.2: Mean (SE) Plasma Esomeprazole Concentrations (ng/mL) Over Time (h) for Proposed 20 mg Nexium 24HR Tablet and Approved Nonprescription 20 mg Nexium Banded¹ Capsule, Fed Condition



Source: NDA 207920, submission 0000, 6 Feb 2015, full study report for Protocol B5141002, pg 46, Figure 3.

¹ The Nexium OTC 20 mg capsule differs from the Nexium Rx 20 mg capsule only in the presence of a tamper-proof band on the OTC capsule.

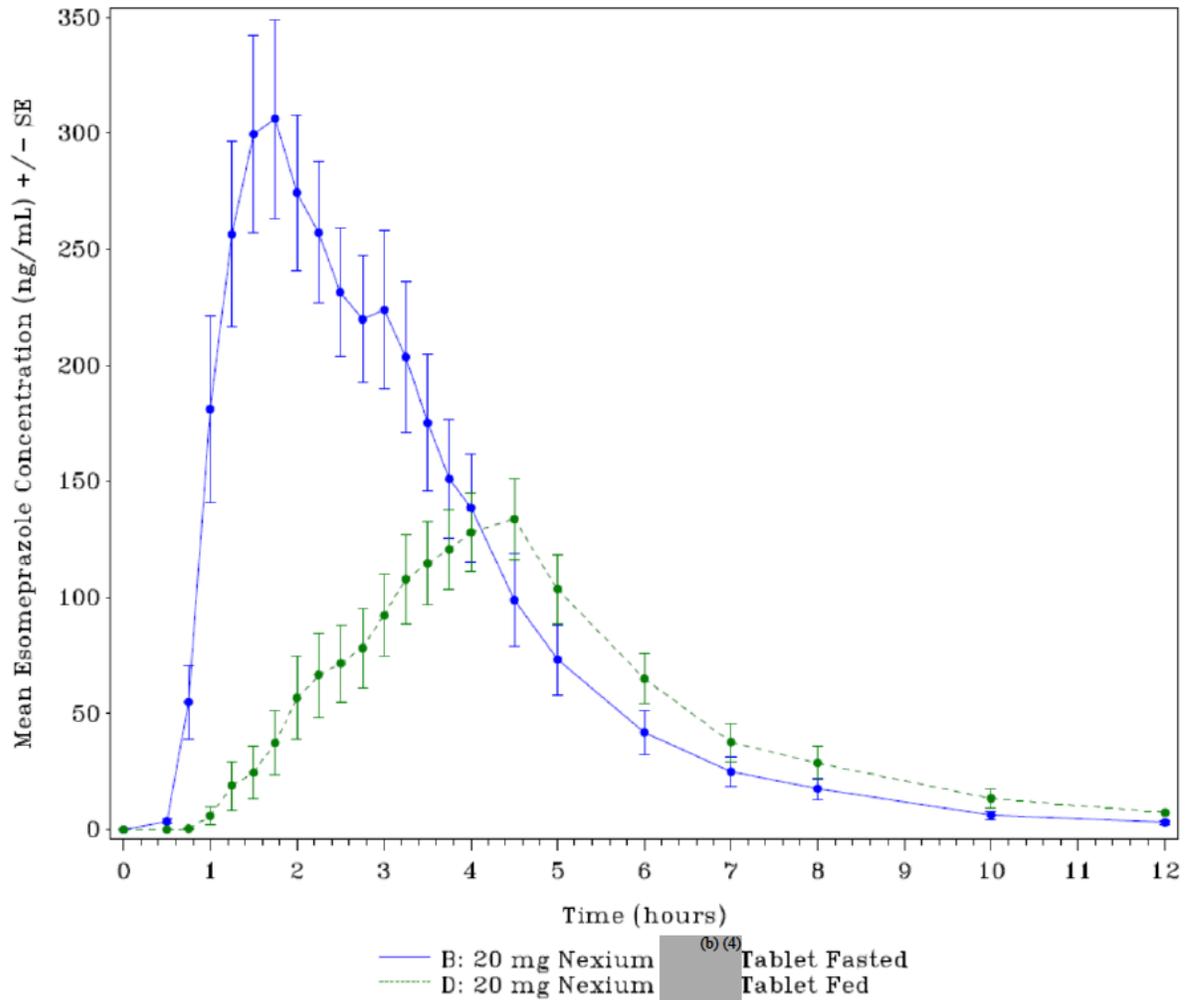
Abbreviations: h = hours; (b) (4) delayed-release properties for the proposed tablet; OTC = over-the-counter; SE = standard error

The following table illustrates the food effect results.

Table 5.2: Food Effect: Ratio of Geometric Mean for Pharmacokinetic Parameters Under Fed and Fasted Condition		
Formulation	Parameter	Ratio (Fed:Fasted)
Proposed esomeprazole 20 mg delayed-release tablet	AUC _{inf}	0.563
	C _{max}	0.317
Approved nonprescription esomeprazole 20 mg delayed-release banded¹ capsule (Nexium 24HR capsule)	AUC _{inf}	0.539
	C _{max}	0.255
Source: Biometrics Review, Dr. Sungwoo Choi (DARRTS 3 Aug 2015), pg 6, Table 2; based on applicant's table, Module 5.3.1.2, pg 10		
¹ The Nexium OTC 20 mg capsule differs from the Nexium Rx 20 mg capsule only in the presence of a tamper-proof band on the OTC capsule.		
Abbreviations: AUC = area under the concentration curve; C _{max} = maximum plasma concentration of esomeprazole		

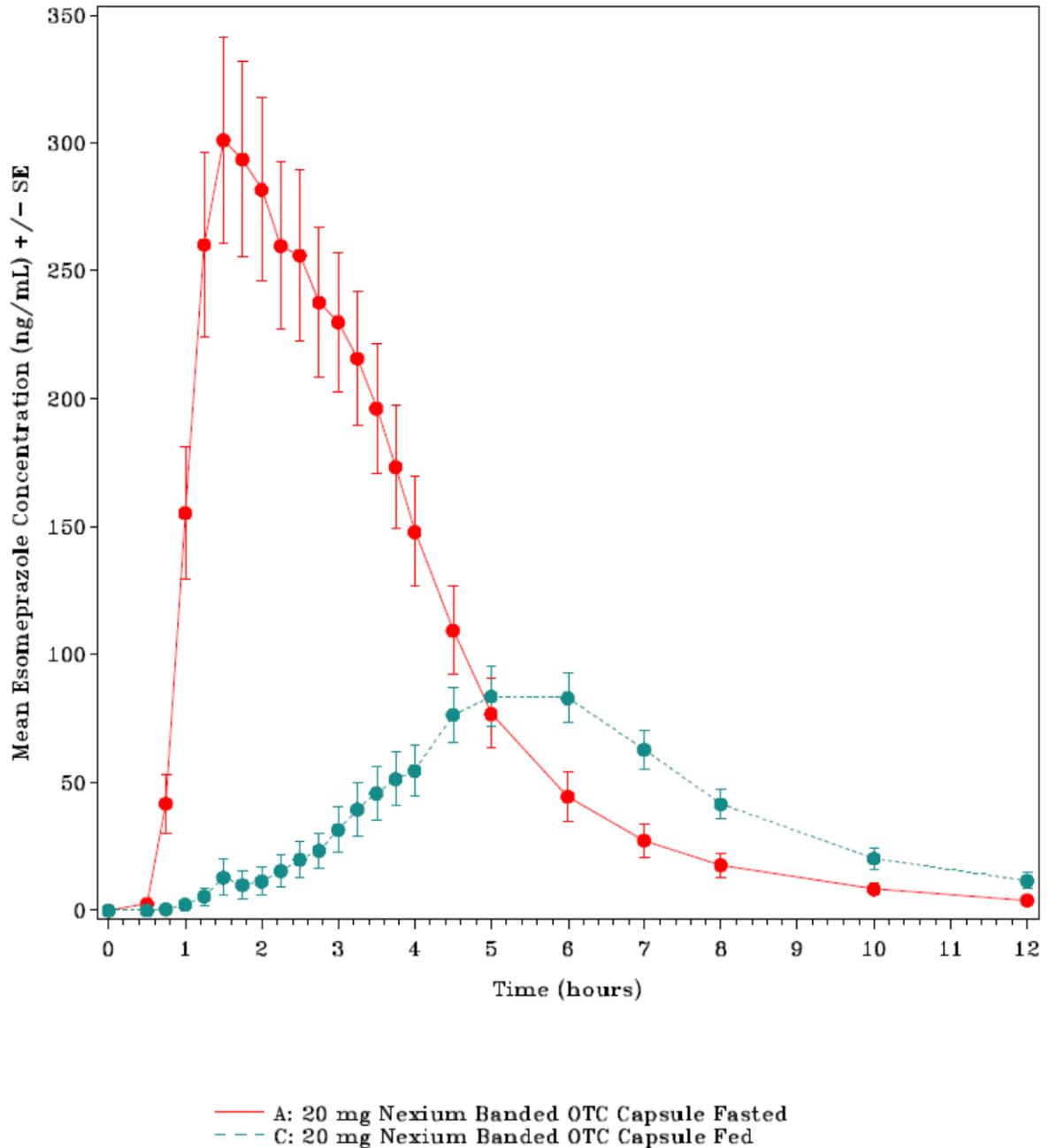
Below are two figures illustrating the food effect results.

Figure 5.3: Mean (SE) Plasma Esomeprazole Concentrations over Time (h) for Proposed Nexium 24HR Esomeprazole 20 mg Tablet in the Fed and Fasted State



Source: NDA 207920, submission 0000, 6 Feb 2015, full study report for Protocol B5141002, pg 47, Figure 4
Abbreviations: h = hours; (b) (4) delayed-release properties for the proposed tablet; OTC = ov

Figure 5.4: Mean (SE) Plasma Esomeprazole Concentrations over Time (h) for the Approved Nonprescription Nexium 24HR Esomeprazole 20 mg Banded¹ Capsule in the Fed and Fasted State



Source: NDA 207920, submission 0000, 6 Feb 2015, full study report for Protocol B5141002, pg 154, Figure 14.4.5.4
1 The Nexium OTC 20 mg capsule differs from the Nexium Rx 20 mg capsule only in the presence of a tamper-proof band on the OTC capsule.
Abbreviations: h = hours; OTC = over-the-counter; SE = standard error

Food reduced the AUC of the proposed tablet by 44%, and reduced the C_{max} by 68%. The OTC capsule, which had not had a food effect study done at the time of its approval, also showed a food effect of similar magnitude for AUC (decreased 46%). C_{max} for the approved capsule was more affected by food (decreased 75%) than was C_{max} for the proposed tablet

(decreased 68%); as mentioned above, the proposed tablet and approved capsule did not meet bioequivalence criteria on C_{max} in the fed state.

The results of the food effect study led Dr. Jappara to recommend that the DFL for the proposed tablet state that the product [REDACTED] (b) (4). She also recommended that FDA instruct the applicant to change the current DFL for the approved OTC capsule to now specify [REDACTED] (b) (4). However, several factors made this food-effect labeling question a difficult decision for the signatory.

In order to understand some of the issues involved, one needs a brief regulatory history of Nexium.

The first esomeprazole product, the prescription Nexium delayed-release capsule (NDA 21153, 20 mg and 40 mg), was approved in 2001. In food effect studies conducted with the 40 mg capsule for that application, food decreased AUC by 33-53%, and decreased C_{max} by 56-79% after single-dose administration. After multiple-dose administration, food decreased AUC by 26-50% and decreased C_{max} by 53-68%. The Full Prescribing Information for prescription Nexium capsule and suspension states that the product should be taken at least one hour before meals.

The first nonprescription esomeprazole product, Nexium 24HR esomeprazole delayed-release capsule, 20 mg (NDA 204655), was approved in 2014, for use for frequent heartburn. This approved OTC capsule product was used as the reference product for the BE and food effect study supporting the current tablet application. For that OTC capsule application, no food effect study was done because the [REDACTED] (b) (4).

[REDACTED] OTC capsule was required to have a tamper-resistant band (hence the use of the term banded capsule in several areas of this review). Two replicate phase III efficacy and safety studies were done, and demonstrated efficacy versus placebo over a 14 day course of treatment. For that study, subjects were not instructed [REDACTED] (b) (4). [REDACTED] Rather, the instruction was to take with a glass of water once a day before eating in the morning. Therefore, the Drug Facts Label (DFL) for the approved Nexium OTC capsule states "Swallow one capsule whole with a glass of water before eating in the morning". The DFL for the OTC capsule does not state that the capsule [REDACTED] (b) (4).

The fact that the applicant had demonstrated efficacy of the reference product, in an experimental design that specifically did not instruct participants [REDACTED] (b) (4) presented a regulatory question. FDA had determined that the capsule was effective as taken in the experimental design, and this new tablet has no worse food effect. In fact, the approved OTC capsule showed a greater numerical food effect than the proposed tablet for both AUC and C_{max} . The difference in C_{max} was such that the capsule and tablet are not considered bioequivalent in the fed state, with a higher C_{max} for the proposed tablet than for the reference capsule. That is, the proposed tablet showed less food effect manifested by less lowering of the C_{max} compared to the fasted state, than when the fed and fasted states were compared for the approved capsule. It is likely that the tablet will be no less effective than the

OTC capsule, and FDA made a prior regulatory decision that the OTC capsule was effective enough for approval.

Another consideration is that of the question of the correlation between pharmacokinetics (plasma level of the drug) and pharmacodynamics (e.g. effect on gastric acidity). While AUC and C_{max} may be decreased by food, that does not necessarily mean that proton pump inhibition and sustained elevation of gastric pH are better in the fasted state. Junghard et al (2002) conducted a study with esomeprazole in that they measured both PK (esomeprazole AUC and C_{max}) and pharmacodynamic effect (percentage of subjects achieving a gastric pH >4). They noted a food effect on PK of similar magnitude to that seen in the BE study in the current esomeprazole application. However, there was no difference in the percentage of subjects who attained a gastric pH >4. This was true both after a single dose, and after 5 days of administration. Some authors (Hatlebakk et al 2000) assert that proton pump inhibitors in general have better acid suppression in the fed state than in the fasted state. In a study in which the researchers used 24-hour monitoring of gastric pH, they found that subjects who took a PPI 15 minutes before breakfast had a higher percentage of time with a gastric pH ≥ 4 than did subjects who took the PPI while fasting (mean 83% versus 58% of the time, respectively, p 0.01). This study looked at omeprazole and lansoprazole, and did not report PK. In food effect studies conducted for FDA approval applications, omeprazole has had a variable food effect, depending on formulation. In FDA approval applications, lansoprazole had a food effect similar to that seen with esomeprazole. For the lansoprazole Rx NDA 20406, food decreased lansoprazole's AUC by 70% and its C_{max} by 50%. For the lansoprazole OTC NDA 21428, food decreased AUC by 52% and C_{max} by 73%. While one cannot be certain that esomeprazole would demonstrate the same findings on 24-hour gastric pH monitoring, the observation that another PPI with a large food effect actually controlled gastric pH better with food than without is of interest.

After deliberation, I have decided not to require the Drug Facts Labels for this tablet (nor for the approved Nexium OTC capsule) to include a statement that the product (b) (4) I acknowledge the scientific basis of Dr. Jappar's recommendation, but considered the totality of scientific evidence and regulatory precedent in making my decision. The summary of my reasons is:

- FDA previously found the nonprescription Nexium 24 HR esomeprazole 20 mg delayed-release capsule to be effective enough for approval.
- For that capsule, two efficacy studies were done and showed efficacy, and the instruction was simply to take before meals, without a stipulation (b) (4)
- The Directions for Use in the DFL for that capsule are consistent with the method of administration used in those successful efficacy trials, and specify only that the consumer should swallow one capsule whole with a glass of water before eating in the morning.
- That Nexium OTC capsule was the reference product to which this new tablet was compared.
- While both that Nexium OTC capsule and the new tablet showed a significant effect of food on PK, this food effect was no worse for the new tablet than for the reference

- capsule; the capsule actually showed a somewhat greater food effect than the tablet, based on C_{max} .
- There is no safety issue associated with this food effect.
 - From a regulatory standpoint, it is difficult to justify [REDACTED] (b) (4) for an approved capsule that was shown to be effective without a food effect restriction, and for a new tablet that is bioequivalent to that effective capsule.
 - Although one might hypothesize that the response rate in the Nexium OTC capsule efficacy study might have been higher had the study been done with [REDACTED] (b) (4) [REDACTED] we have no clinical data to support that hypothesis. The relationship between pharmacokinetics and pharmacodynamics for proton pump inhibitors is complex, and PK does not always correlate with PD.
 - There is some evidence that a decrease in AUC and C_{max} for esomeprazole with food is not associated with a difference in pharmacodynamic measures of gastric pH between the fed and fasted state.
 - There is some evidence from another PPI (lansoprazole), which has a similar food effect to esomeprazole, that the control of gastric pH over the 24 hour period may actually be better when lansoprazole is [REDACTED] (b) (4) [REDACTED]

The final discussions surrounding this issue occurred after the clinical pharmacology, clinical, CDTL and other reviews were entered in DARRTS; therefore, those reviews do not reflect the final decision reached. These discussions were collaborative and collegial, with full opportunity for all views to be presented. The clinical team is in agreement regarding the decision, and the clinical pharmacology team acknowledges the clinical and regulatory logic followed and stated that ultimately, this is a clinical decision.

5.2 Dissolution

The dissolution test was conducted in three commercial scale stability batches, and the dissolution profiles of all batches were similar. Dr. Duan found this acceptable. Dr. Duan requested that the applicant make a minor change in its proposed dissolution acceptance criterion in the buffer stage, and the applicant agreed.

5.3 Bioequivalence Site Inspections

FDA had recently inspected the analytical and clinical sites for the BE study, and found them acceptable. FDA determined that re-inspection was not necessary.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical-Efficacy

The applicant did not submit efficacy studies with this application, but rather relied upon FDA's previous finding of efficacy for NDA 204655, Nexium 24HR esomeprazole delayed release capsule, 20 mg. Please refer to Section 5 regarding the bioequivalence and food effect study that provided a suitable bridge between that Nexium OTC capsule and this new tablet.

8. Safety

Please refer to Dr. Elizabeth Donohoe's clinical review (DARRTS 26 Oct 2015), and to Dr. Frank Becker's CDTL review. I concur with Drs. Donohoe and Becker that the safety profile of the proposed Nexium OTC tablet supports approval.

Regarding safety, the applicant referenced all clinical trial data and postmarketing safety data that had been provided for the Nexium OTC capsule NDA; and provided updated data from AstraZeneca's safety database for prescription esomeprazole, and Pfizer's safety database for nonprescription esomeprazole. These data, along with a four-month safety update submitted during the review cycle, cover the period up to 1 Jan 2015. The applicant also provided adverse event data from the BE study conducted for this NDA.

In clinical trials of prescription esomeprazole, the most common (incidence >1%) adverse events have been:

- Headache
- Diarrhea
- Nausea
- Flatulence
- Abdominal pain
- Constipation
- Dry mouth

The applicant states that over 80,000 patients have been exposed to esomeprazole in clinical trials. It is approved in over 125 countries, and the applicant states that worldwide prescription exposure exceeds 102 million patient-years.

The Warnings and Precautions (W&P) section of the Full Prescribing Information (FPI) for Rx Nexium includes information on the following significant adverse events:

- Atrophic gastritis
- Acute interstitial nephritis
- Cyanocobalamin (vitamin B-12) deficiency
- *Clostridium-difficile*-associated diarrhea
- Osteoporosis-related fractures
- Hypomagnesemia

Most of the adverse events mentioned in the Rx FPI W&P are associated with chronic use. The OTC Nexium capsule is labeled to be used in a course of treatment not to exceed 14 days, with

no more than three courses of treatment per year. Therefore, when used as labeled, the OTC Nexium would be expected to be less likely to be associated with most of the events noted in the Rx FPI W&P.

The approved Drug Facts Label for Nexium OTC capsules includes the following safety information:

Warnings Allergy alert: Do not use if you are allergic to esomeprazole
Do not use if you have: <ul style="list-style-type: none">■ trouble or pain swallowing food, vomiting with blood, or bloody or black stools■ heartburn with lightheadedness, sweating or dizziness■ chest pain or shoulder pain with shortness of breath; sweating; pain spreading to arms, neck or shoulders; or lightheadedness■ frequent chest pain. These may be signs of a serious condition. See your doctor.
Ask a doctor before use if you have <ul style="list-style-type: none">■ had heartburn over 3 months. This may be a sign of a more serious condition.■ frequent wheezing, particularly with heartburn■ unexplained weight loss■ nausea or vomiting■ stomach pain
Ask a doctor or pharmacist before use if you are taking <ul style="list-style-type: none">■ warfarin, clopidogrel or cilostazol (blood-thinning medicines)■ prescription antifungal or anti-yeast medicines■ digoxin (heart medicine)■ diazepam (anxiety medicine)■ tacrolimus or mycophenolate mofetil (immune system medicines)■ prescription antiretrovirals (medicines for HIV infection)■ methotrexate (arthritis medicine)
Stop use and ask a doctor if <ul style="list-style-type: none">■ your heartburn continues or worsens■ you need to take this product for more than 14 days■ you need to take more than 1 course of treatment every 4 months■ you get diarrhea

The applicant states that, since launch of its nonprescription esomeprazole capsule, over 2.5 million consumer-years of exposure have occurred. The US accounts for >99% of distribution.

Dr. Donohoe did not note any new safety signals or trends.

FDA is actively monitoring three safety issues for the proton pump inhibitor class as a whole:

- A question of a link between prenatal exposure to PPIs and asthma in offspring. During the previous review of the Nexium OTC capsule, Pfizer had reported that two observational studies had noted this possible link. At that time, AstraZeneca was performing an observational cohort study (study D9612N00018) to examine this possible association, at the request of the United Kingdom's drug regulatory authority. Pfizer completed that study and submitted the final study report to FDA on 20 Oct

2015. Drs. Donohoe and Becker concur with AstraZeneca's conclusions that the cohort study did not show an association. I concur with Drs. Donohoe and Becker that, at this time, the available data do not support inclusion of information about this issue in the labeling of the proposed Nexium OTC tablet.

- A question of a link between PPI use and lupus erythematosus (cutaneous and systemic). In 2011, FDA's Division of Pharmacovigilance (DPV), in a review of postmarketing adverse event reports, noted a possible association between PPI use and cutaneous lupus erythematosus (CLE). DPV recommended that DGIEP consider class labeling changes to Rx PPIs' Full Prescribing Information. DPV also noted some cases of systemic lupus erythematosus (SLE) in the FDA Adverse Event Reporting System (FAERS). These associations appear to be very rare. A Tracked Safety Issue (TSI 1455) was created in July 2015, and adverse event monitoring continues. DGIEP and DPV continue to review this issue, and DGIEP has not yet determined what, if any, changes to Rx PPI FPLs are needed. At this time, the level of evidence does not support inclusion of information about CLE or SLE in OTC PPI labeling.
- A question of a link between PPI use and myocardial infarction. In May 2015, the Division of Epidemiology I (DEPI-I) conducted a review based on literature reports of this possible association. DEPI-I concluded that the studies had significant limitations and were not adequate to support a causal relationship. DEPI-I recommended continued surveillance of the literature, and continued pharmacovigilance. I concur with this recommendation. Of note, as shown above, the DFL for Nexium OTC capsules, in the "Do Not Use" section, warns consumers not to use the product if the consumer has cardiac symptoms. Specifically, the DFL states: "Do not use if you have 'chest pain or shoulder pain with shortness of breath; sweating; pain spreading to arms, neck or shoulders; or lightheadedness' or 'frequent chest pain'." The DFL also states that these symptoms may be signs of a serious condition, and instructs the consumer to see their doctor. These warnings are adequate at this time.

I concur with Dr. Donohoe's conclusion that the totality of the safety information submitted with this NDA does not present new or worsening safety concerns that would preclude approval. Regarding the three issues discussed above, the level of evidence for these does not warrant new labeling at this time. I concur that FDA should continue its active monitoring of these issues.

9. Advisory Committee Meeting

Not applicable.

10. Pediatrics

To date, FDA has waived a requirement for pediatric studies for OTC PPIs, because the underlying causes for heartburn in children should be evaluated by a healthcare professional, and thus PPIs are not suitable for OTC use in children. The Pediatric Review Committee recommended a full pediatric waiver for NDA 207920. I concur with the granting of this waiver.

11. Other Relevant Regulatory Issues

Dr. Donohoe conducted a review of financial disclosures by clinical investigators. No investigators had prohibited financial interests. The applicant used due diligence in obtaining thorough financial disclosure information. I concur with Dr. Donohoe's conclusion.

Please see inspection information in Sections 3 and 5.

There are no other unresolved relevant regulatory issues.

12. Labeling

Please refer to Ms. Mary Vienna's labeling reviews (DARRTS 23 Oct 2015 and 19 Nov 2015). FDA requested several changes to the applicant's proposed labeling. Among the more noteworthy were:

- The Principal Display Panel (PDP) originally contained the statement [REDACTED] (b) (4). On 16 Jul 2015, FDA sent an information request to the applicant requesting data to support the [REDACTED] (b) (4) claim. The applicant elected to remove the statement.
- The PDP contains a graphic statement of "New". This statement is acceptable, but is to be removed after six months of marketing.
- The established name was originally expressed as [REDACTED] (b) (4). FDA requested that the name be changed to "esomeprazole 20 mg", and the applicant agreed. Please see Section 3.1 above for further discussion.
- In the Drug Facts Label, the storage statement was changed from [REDACTED] (b) (4) to "Store at 20°C - 25°C (68° - 77°F)", with removal [REDACTED] (b) (4) statement. Please see Section 3.2 above for further discussion.

Please refer to the proprietary name review (DARRTS 2 Apr 2015) and labeling review (DARRTS 19 Jun 2015) by Dr. Grace Jones of the Division of Medication Error Prevention and Analysis (DMEPA). DMEPA found the proprietary name "Nexium 24HR" acceptable. Dr. Jones recommended that the Division of Nonprescription Drug Products (DNDP) ensure that the image throughout all carton and bottle sizes represents a true depiction of the actual tablet (imprint, size and color); DNDP has done so.

I concur with Ms. Vienna and Dr. Jones that the labeling is acceptable, now that the applicant has implemented FDA's requested revisions. The agreed-upon labeling is included in Ms. Vienna's 19 Nov 2015 final labeling review.

13. Decision/Action/Risk Benefit Assessment

13.1. Recommended Regulatory Action

I recommend approval.

My approval recommendation is consistent with that of the CDTL and the other discipline reviewers.

13.2. Risk Benefit Assessment

The rationale for my approval recommendation is:

- FDA previously determined that the reference drug, the Nexium OTC capsule, was effective and had an acceptable risk profile.
- The proposed Nexium OTC tablet is bioequivalent to the reference Nexium OTC capsule, and thus is likely to be equally effective when used for treatment of heartburn.
- Upon review of updated safety information, the risk profile of this tablet appears likely to be the same as that of the reference capsule.
- Because of bioequivalence and an equivalent risk profile, this tablet appears to have the same risk:benefit profile as that of the approved capsule.

13.3. Postmarketing Commitments

The applicant has agreed to submit (b) (4) uniformity data. I concur with Dr. De's recommendation that a statement similar to the following be added to the approval letter:

“Your testing protocol (sampling plan for (b) (4) uniformity) for intra-batch variability is acceptable for postapproval implementation. Collected data are to be submitted in your Annual Report, as agreed upon with the Office of Pharmaceutical Quality in our teleconferences of October 6 and 23, 2015.”

The approval letter also instructs the applicant to remove its statement “New” from the PDP after six months of marketing.

References:

FDA 2015. Guidance for industry: Naming of drug products containing salt drug substances. Accessed 21 Nov 2015 at <http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm379753.pdf>

Hatlebakk, J et al 2000. Proton pump inhibitors: better acid suppression when taken before a meal than without a meal. *Aliment Pharmacol Ther* 14:1267-72

Junghard, O et al 2002. The effect of the area under the plasma concentration vs time curve and the maximum plasma concentration of esomeprazole on intragastric pH. *Eur J Clin Pharmacol* 58:453-8

United States Pharmacopeia, 2013. Monograph naming policy for salt drug substances in drug products and compounded preparations, USP General Chapter <1121>. Accessed 21 Nov 2015 at <http://www.usp.org/usp-nf/development-process/compendial-nomenclature/monograph-naming-policy-salt-drug-substances-drug-products-and-compounded>

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/s/

KAREN M MAHONEY
11/23/2015