CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207920Orig1s000

OTHER REVIEW(S)

Labeling Review for Nexium®24HR Delayed-Release Tablets *Draft Labeling*

SUBMISSION DATES:	November 17, 2015
NDA/SUBMISSION TYPE:	207920
ACTIVE INGREDIENTS:	Esomeprazole 20 mg
DOSAGE FORM	Delayed-release tablet
SPONSOR:	Pfizer, Inc. Christine Chirdo Director, U.S. Regulatory Strategy Category Lead 973-660-5602
REVIEWER:	Mary R. Vienna, RN, MHA, DNDP, ODE IV
TEAM LEADER:	Steven Adah, Ph.D., DNDP, ODE IV
ASSOCIATE DIRECTOR for LABELING	Ruth E. Scroggs, PharmD, DNDP, ODE IV
REGULATORY PROJECT MANAGER	Jung Lee, PharmD, Project Manager, DNDP, ODE IV

I. BACKGROUND

AstraZeneca LP (AstraZeneca) and its agent, Pfizer, Inc, submitted on February 6, 2015, and as amended July 31, and November 17, 2015, an original new drug application (NDA) 207920, under Section 505(b)(2) of the Federal Food Drug and Cosmetic Act (FD&C Act). The sponsor proposes to market a delayed-release tablet form of the proton pump inhibitor (PPI) esomeprazole 20 mg as an over-the-counter (OTC) product for the treatment of frequent heartburn (occurring 2 or more times per week) in adults 18 years of age and older.

The October 23, 2015 labeling review discusses the February 6 and July 31, 2015, labeling submissions, and includes labeling recommendations that were communicated to the sponsor on November 3, 2015. This review, the second of two, amends our October 23, 2015 labeling

review. This is a review of the labeling submitted November 17, 2015 compared to the labeling reviewed on October 23, 2015.

Submitted Labeling	Representative of Following SKUs	Submission date/replaces
2-count immediate container (bottle)	N/A	November 17, 2015, replaces February 6, 2015
2-count sample carton	N/A	November 17, 2015, replaces February 6, 2015
14-count immediate container (bottle)	N/A	November 17, 2015, replaces February 6, 2015
14-count carton	N/A	November 17, 2015, replaces July 31, 2015
28-count carton	N/A	November 17, 2015, replaces February 6, 2015
42-count carton	N/A	November 17, 2015, replaces February 6, 2015
42-count "Club" carton with backer card	N/A	November 17, 2015, replaces February 6, 2015

II. REVIEWER'S COMMENTS

A. 2-, 14-, 28-, 42-count and 42-count "Club" cartons

i. Outer Carton Label Outside Drug Facts

Principal Display Panel

a. Below the "Nexium" section of the proprietary name and to the left of the "24HR" section of the proprietary name appears the statement "esomeprazole delayed-release tablets 20 mg/Acid Reducer" as requested in November 3, 2015 labeling comments.

Comment: The change is an accurate statement of the established name and dose as per the Cross-Discipline Team Leader review dated November 5, 2015, and is acceptable.

b. The statement [redacted] (b) (4) is removed from all labeling as agreed in the July 31, 2015, amendment by the sponsor.

Comment: This is acceptable.

ii. Outer Carton Drug Facts Label

a. ***Directions***
The ***Directions*** section on the revised labeling is identical to the approved Drug Facts label (DFL) for the Nexium capsule. During labeling negotiations, the FDA agreed that this section should be the same as the reference listed drug. For details, refer to the Director's Summary.

Comment: This is acceptable.

b. ***Other Information***
The storage statement on the third bullet is revised to read "Store at 20°C - 25°C (68° - 77°F) as recommended in the CMC review. The (b) (4) bullet regarding (b) (4) is removed.

Comment: These changes reflect the labeling recommendations of CMC and are acceptable.

c. ***Questions or comments?***
The "call toll-free **1-866-226-1600**" statement is revised to read "call toll-free: weekdays 9AM to 5PM EST at **1-866-226-1600**" in response to our November 3, 2015 labeling recommendation.

Comment: This is acceptable.

d. **Other Sections/Issues**
For all carton sizes, the DFL specifications comply with 21CFR 201.66(d).

Comment: This is acceptable.

During labeling negotiations, the sponsor explained that the approved 2-ct capsule carton format cannot be used for the 2-ct tablet carton as the carton size is smaller for the tablet product. As agreed to in the November 8, 2015 email, (b) (4) (b) (4) on the carton is eliminated and the "KEEP CARTON FOR COMPLETE WARNINGS AND IMPORTANT INFORMATION" boxed statement and the DFL begins on the carton itself, up to the Pregnancy/breastfeeding warning. The remainder of the DFL and "Tips for Managing Heartburn" is on the peel-back label. The peel-back section of the label still consists of 5 panels:

- Panel #1 is the top panel, which contains the "Keep out of reach of children" warning and "Directions". The top panel has a "LIFT HERE" instruction on the lower right corner and a directional arrow that complies with 21CFR 201.66(d).
- Panel #2 and #3 appear when the peel-back label is lifted according to the directions. These panels contain the remainder of the DFL content.

- Panel #4 and #5 appear when the second peel-back label is lifted, and panel #5 is fixed to the carton. Panel #4 contains the "Tips for Managing Heartburn" information, and panel #5 contains the Nexium 24HR logo.

Comment: This is acceptable.

iii. Immediate Container (2- and 14-count bottle) Label

- The statement of identity on the top face of the "peel-back" type label now reads "esomeprazole delayed-release tablets 20 mg". See Section II.A.i.a. for details.
- The DFL on the remaining two panels conform to the changes described in Section II.A.ii.b and c.

Comment: These changes are all acceptable.

III. RECOMMENDATIONS

Issue an **APPROVAL** letter to the sponsor for the submitted Nexium 24HR delayed release tablet labeling and request final printed labeling. The final printed labeling (FPL) must be identical to the labeling submitted on November 17, 2015, as follows: 2-count immediate container (bottle), 2-count sample carton, 14-count immediate container (bottle), 14-, 28- and 42-count carton labels and 42-count "Club" carton with backer card label.

Please remind the sponsor to delete the "New" graphic after six months of marketing.

IV. SUBMITTED LABELING

The labels on the remaining pages of this labeling review were submitted and were evaluated in this labeling review:

8 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/

MARY R VIENNA
11/19/2015

RUTH E SCROGGS
11/19/2015

Labeling Review for Nexium®24HR Delayed-Release Tablets *Draft Labeling*

SUBMISSION DATES:	February 6, 2015 July 31, 2015
NDA/SUBMISSION TYPE:	207920
ACTIVE INGREDIENTS:	Esomeprazole 20 mg
DOSAGE FORM	Delayed-release tablet
SPONSOR:	Pfizer, Inc. Christine Chirdo Director, U.S. Regulatory Strategy Category Lead 973-660-5602
REVIEWER:	Mary R. Vienna, RN, MHA, DNRD, ODE IV
TEAM LEADER:	Steven Adah, Ph.D., DNRD, ODE IV
ASSOCIATE DIRECTOR for LABELING	Ruth E. Scroggs, PharmD, DNRD, ODE IV
REGULATORY PROJECT MANAGER	Jeff Buchanan, Project Manager, DNCE, ODE IV

I. BACKGROUND

AstraZeneca LP (AstraZeneca) and its agent, Pfizer, Inc, submitted on February 6, 2015, and as amended July 31, 2015, an original new drug application (NDA) 207920, under Section 505(b)(2) of the Federal Food Drug and Cosmetic Act (FD&C Act). The sponsor proposes to market a delayed-release tablet form of the proton pump inhibitor (PPI) esomeprazole magnesium 22.3 mg as an over-the-counter (OTC) product for the treatment of frequent heartburn (occurring 2 or more times per week) in adults 18 years of age and older. The delayed-release capsule form of esomeprazole magnesium 22.3 mg is currently approved as an OTC product in NDA 204655 (Nexium® 24HR), and is the reference listed drug (RLD) for this application.

AstraZeneca requested Agency approval of the proposed OTC proprietary trade name Nexium®24HR. The Division of Medication Error Prevention and Analysis (DMEPA) reviewed the proposed proprietary name and concluded that it was conditionally acceptable in their April 14, 2015 communication to the sponsor.

An information request (IR) was sent to the sponsor on March 25, 2015, requesting an exact-size model of the proposed 2-count sample carton with a peel-back Drug Facts label. The sponsor shipped a sample carton directly to the project manager on March 31, 2015, but did not officially respond to the IR with a submission to the application until July 31, 2015. An IR was sent to the sponsor on July 16, 2015, requesting 3 tablets of the to-be-marketed tablet and data to support the labeling claim (b) (4) The sponsor responded to the IR on July 31, 2015, with a shipment of the requested tablets and a revised label for the 14-ct carton that removes the (b) (4) statement from the label.

The submitted labeling is compared to the most recently approved labeling of the RLD for this application, Nexium 24HR capsules (NDA 204655, S-002).

Submitted Labeling	Representative of Following SKUs	Submission date/replaces
2-count immediate container (bottle)	N/A	February 6, 2015
2-count sample carton	N/A	February 6, 2015
14-count immediate container (bottle)	N/A	February 6, 2015
14-count carton	N/A	February 6, 2015 Revised July 31, 2015
28-count carton	N/A	February 6, 2015
42-count carton	N/A	February 6, 2015
42-count “club” carton with backer card	N/A	February 6, 2015

II. REVIEWER'S COMMENTS

A. 2-, 14-, 28- and 42-count cartons

i. Outer Carton Label Outside Drug Facts

Principal Display Panel

a. The principal display panel’s (PDP’s) upper left corner has a blue oval, with the statement “New” in white font.

Comment: This is acceptable. Please remind the sponsor to delete the "New" graphic after six months of marketing.

b. Across the top center portion of the PDP is the statement "Treats Frequent Heartburn".
Comment: This statement is a true statement of the "Uses" section of the Drug Facts label and is acceptable.

c. The proposed proprietary name "Nexium® 24HR" is located on the purple oval graphic at the center of the PDP.
Comment: From an IDS perspective, the proposed proprietary name is acceptable. The proprietary name itself is conditionally acceptable (see DMEPA's letter of April 14, 2015).

d. The PDP has a yellow background with purple edging in the lower left corners. In the PDP's center is a large graphic of a solid purple oval shape with a gold double band outline. This graphic is identical to the approved graphic for the Nexium 24HR capsule.
Comment: This is identical to the RLD label and is acceptable.

e. 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).
Comment: The prominence of the established name is identical to the RLD label and is acceptable. The correct established name and dose itself will be determined by CMC review and labeling discussions.

f. For the 14-, 28-, and 42-count cartons, the statement "May take 1 to 4 days for full effect" appears below the purple oval graphic. For the 2-count sample carton, this statement appears on the lower left portion of the PDP, and the statement "SAMPLE – NOT FOR SALE" appears above it.
Comment: These statements are identical to the statements on the approved labeling for the capsule product and are acceptable.

g. For the 14-, 28- and 42-count cartons, the word "TABLETS" and the image of the tablet appears below the statement "May take 1 to 4 days for full effect." For the 2-ct sample carton, only the tablet graphic appears to the right of this statement. The June 14, 2015, label review from the DMEPA recommended that the agency ensure that the tablet image "represents a true depiction of the actual tablet, reflecting the true tablet imprint, size and color." In response to our July 16, 2015, communication requesting 3 tablets of the to-be-marketed tablet, the sponsor submitted a 14-ct bottle of the tablets on July 31, 2015. This was compared to the image on the 2-ct model carton and other labeling.
Comment: The proposed tablet image represents a true depiction of the actual tablet in regards to tablet imprint, size and color, and is therefore acceptable.

However the tablet is imprinted with 20mg as the dose, which reflects the active ingredient dosage, but not the (b) (4) reflected on the PDP. The correct established name and dose itself will be determined by CMC review and labeling discussions.

h. The declaration of net quantity of contents appears inside the dark purple edging of the lower left section of the PDP.
Comment: This is acceptable.

i. For the 2-count sample carton, the statement "First two doses of a 14-day course of treatment" appears below the declaration of net quantity. The font size of the statement appears to be identical to the approved 2-ct sample carton for the capsule product.
Comment: This is acceptable.

j. For the 14-count carton label, the statement "One 14-day course of treatment" appears underneath the declaration of net quantity. For the 28-count carton label, the statement "Two 14-day courses of treatment" appears underneath the declaration of net quantity. For the 42-count carton label, the statement "Three 14-day courses of treatment" appears underneath the declaration of net quantity.
Comment: This is acceptable.

k. The top flaps of the 14-, 28- and 42-count cartons display the proposed proprietary name "Nexium 24HR and the statement "Clinically Proven to **Treat Frequent Heartburn**" divided by two vertical graphic bars in the center. The top flap of the 2-count carton label (b) (4)
Comment: This is acceptable.

l. The statement (b) (4) appears in (b) (4) font on the upper right hand corner of the 2-count carton PDP and top flap, and on the upper right hand corner of the top flap of the 14-, 28- and 42-count cartons. An information request 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.
Comment: The revision to delete the statement is acceptable. The sponsor must submit this revision for all labels.

m. Tamper-evident feature statement:
The right side panel's bottom margin displays the tamper-evident feature statement "Do Not Use if seal under bottle cap imprinted with "SEALED for YOUR PROTECTION" is broken or missing" in dark purple, bolded print for the 14-, 28, and 42-count cartons. The statement appears in a similar font size and color on the left side panel of the 2-count sample carton.
Comment: This is acceptable.

n. The right side panels of the 14-, 28- and 42-count cartons display a graphic of the 14-count immediate container (bottle), with a statement of the net number of bottles above the bottle graphic. An image of a tablet appears below the bottle, with the statement "ACTUAL SIZE" to the left of the tablet graphic.
Comment: This is identical to the approved capsule labeling and is acceptable.

o. Left side panel

- "Tips for Managing Heartburn" appears on the upper portion of the left side panel for the 14-, 28- and 42-ct cartons. The same information appears on the top flap of the 2-ct sample carton.
Comment: This is acceptable.

- The left side-panel for the 2-, 14-, 28- and 42-count cartons displays the manufacturing information:
Marketed by:
Pfizer, Madison, NJ 07940 USA
©2015 Pfizer Inc.
Comment: This is acceptable.

- Below the manufacturing information is the country of origin statement:
"Made in France"
Comment: This is acceptable in accordance with 19 CFR 102, Rules of Origin. The content of the statement will rely on the findings of the CMC review.

- Below the country of origin statement appears the statements:
"For most recent product information, visit www.Nexium24HR.com" and "Nexium is a registered trademark of AstraZeneca AB and is used under license."
Comment: This is acceptable.

p. Carton back :
- The boxed statement "KEEP CARTON FOR COMPLETE WARNINGS AND IMPORTANT INFORMATION" is in bolded font above the Drug Facts label on all cartons.
Comment: This is acceptable.

ii. Outer Carton Drug Facts Label

The Drug Facts Label (DFL) on each label has identical content regardless of count size. The different sections include the following:

a. ***Active ingredient (in each capsule)***: "Esomeprazole 20 mg (each delayed release tablet corresponds to 22.3mg esomeprazole magnesium trihydrate)."

Comment: This is identical to the Nexium capsule DFL (RLD) and is acceptable.

b. ***Purpose***: "Acid reducer"
Comment: This is acceptable as required under 21 CFR 201.66(d)(1).

c. ***Uses***:
- treats frequent heartburn (occurs **2 or more** days a week)
- not intended for immediate relief of heartburn; this drug may take 1 to 4 days for full effect

Comment: This is identical to the Nexium capsule DFL and is acceptable.

d. ***Warnings***

1. Other warnings:
"**Allergy alert:** Do not use if you are allergic to esomeprazole"
Comment: This warning complies with 21CFR 201.66(c)(5)(ii)(B) and is acceptable.

2. "**Do not use**"
- (b) (4) trouble or pain swallowing food, vomiting with blood, or bloody or black stools. (b) (4)
- (b) (4)
- 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.
Comment: This warning is identical to the most recently approved warning for the Nexium capsule and is acceptable.

3. "**Ask a doctor before use if you have**"
- 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

Comment: This warning is identical to the most recently approved warning for the Nexium capsule and is acceptable.

4. "**Ask a doctor or pharmacist before use if you are** taking":
- warfarin, clopidogrel or cilostazole (blood-thinning medicines)
- prescription antifungal or anti-yeast medicines

- digoxin (heart medicine)
- diazepam (anxiety medicine)
- tacrolimus or mycophenolate mofetil (immune system medicine)
- prescription antiretrovirals (medicines for HIV infection)
- methotrexate (arthritis medicine)

Comment: This warning is identical to the most recently approved warning for the Nexium capsule and is acceptable.

5. "**Stop use and ask a doctor if**" :
   - 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

   Comment: This warning is identical to the most recently approved warning for the Nexium capsule and is acceptable.

6. Pregnancy/breastfeeding :
   "**If pregnant or breast-feeding,** ask a health professional before use."
   Comment: This statement complies with 21CFR 201.63(a) and 201.66(c)(5)(ix), and is therefore acceptable.

7. Keep out of reach of children:
   "**Keep out of reach of children.** In case of overdose, get medical help or contact a Poison Control Center right away."
   Comment: This statement complies with 21CFR 330.1(g) and 201.66(c)(5)(x), and is therefore acceptable.

e. ***Directions***

1. The first three bullets state:
   - adults 18 years of age and older
   - this product is to be used once a day (every 24 hours), every day for 14 days
   - (b) (4) may take 1 to 4 days for full effect, (b) (4)

   Comment: This statement is identical to the most recently approved *Directions* section for the Nexium capsule and is acceptable.

2. Under the heading "**14-Day Course of Treatment**", the following bullets state:
   - swallow 1 tablet with a glass of water before eating in the morning
   - take every day for 14 days
   - do not take more than 1 tablet a day
   - swallow whole. Do not crush or chew tablets.
   - do not use for more than 14 days unless directed by your doctor

   Under the heading "**Repeated 14-Day Courses (if needed)**, the following bullets state:

- you may repeat a 14-day course every 4 months
- **do not take for more than 14 days or more often than every 4 months unless directed by a doctor**

Comment: As per the Clin/Pharm review of October 17, 2015, the fasting-fed study supports the additional qualification that the tablet should be taken one hour before a meal. Recommend changing the direction statement to read "swallow 1 tablet with a glass of water at least one hour before eating in the morning".

3. The last bullet in the Directions section states by proposing: "children under 18 years of age: ask a doctor before use. Heartburn in children may sometimes be caused by a serious condition".
   Comment: This statement is identical to the Nexium capsule label and is acceptable.

f. ***Other Information***

- read the directions and warnings before use
- keep the carton. It contains important information.
- (b) (4)
-

Comment: The first two bullets are identical to the approved DFL for the Nexium capsule and are acceptable. (b) (4) (b) (4) **Defer to CMC review regarding the acceptability of the proposed storage statement. The** (b) (4) **statement is an addition to the approved Nexium capsule DFL with no specific rationale provided in the annotated labeling. Request that the sponsor provide a rationale for the deviation from the RLD label or remove the statement.**

g. ***Inactive ingredients***

The inactive ingredients are listed in alphabetical order in compliance with 21 CFR 201.66(c)(8).
Comment: This is acceptable. Refer to CMC review regarding acceptability of inactive ingredients.

h. ***Questions or comments?***

Call toll-free 1-866-226-1600
Comment: Recommend that the time that the toll-free number is in operation be included under this Drug Facts subheading.

i. **Other Sections/Issues**

- For all carton sizes, the Drug Facts label specifications comply with 21CFR 201.66(d).

Comment: This is acceptable.

The DFL for the 2-ct carton introduces a peel-back label that consists of five panels:

- Panel #1 is the top panel, which contains the [redacted] The top panel has a "LIFT HERE" instruction on the lower right corner and a directional arrow that complies with 21CFR 201.66(d). [redacted] statement appears above the Drug Facts title.
- Panel #2 and #3 appear when the peel-back label is lifted according to the directions. These panels contain the [redacted]
- Panel #4 and #5 appear when the second peel-back label is lifted, and panel #5 is fixed to the carton. These panels contain [redacted] of the DFL.
- The [redacted] of the DFL appear on the top flap of the 2-ct carton itself.

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, the [redacted] DFL information such as [redacted] appear on the peel-back label, and the [redacted] appear on the top flap of the carton itself.

Comment: Recommend that the 2-ct carton reflect the format of the approved 2-ct carton for the Nexium capsule.

B. 42-count "Club" carton with backer card

This component is a card printed on both sides. The front card contains the principal display panel (PDP) information and has a clear window, through which the PDP of the three 14-count bottles will appear. The back of this card contains the Drug Facts and other back pane information.

i. Outer Carton Label Outside Drug Facts

Principal Display Panel

a. The PDP's upper left corner has a blue oval, with the statement "New" in white letters.

Comment: This is acceptable. Please remind the sponsor to delete the "New" graphic after six months of marketing.

b. Across the top center portion of the PDP is the statement "Treats Frequent Heartburn"
Comment: This is acceptable.

c. The proposed proprietary name "Nexium® 24HR" is located on the large capsule graphic at the center of the PDP.
Comment: From an IDS perspective, the proposed proprietary name is acceptable. The proprietary name itself is conditionally acceptable (see DMEPA letter of April 15, 2015).

d. PDP has yellow background with purple edging on upper right and lower left corner. In the center of the PDP is a large graphic of a solid purple oval shape with a gold double band outline.
Comment: This is acceptable.

e. Below the "Nexium" and to the left of the "24HR" section of the proprietary name appears the statement "Esomeprazole (b) (4) Delayed-release (b) (4) (b) (4) mg/Acid Reducer" that is identical in size and prominence to the approved label for the capsule product (NDA 204655).
Comment: See Section II.A.i.e.

f. Under the capsule graphic appears the statement "May take 1 to 4 days for full effect".
Comment: This is acceptable.

g. The statement (b) (4) appears in (b) (4) font on the upper right corner of the PDP. An information request 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.
Comment: See Section II.A.i.l.

h. The graphic image of a purple tablet appears on the upper right portion of the PDP, above the "Treats Frequent Heartburn" statement.
Comment: This is acceptable. See Section II.A.i.g.

i. The statement "3 Pack" appears in purple font on the left side of the PDP, above the cut-out for the bottle display.
Comment: This statement is truthful and acceptable.

j. The declaration of net quantity of contents appears inside the dark purple edging of the lower right section of the PDP.
Comment: This is acceptable.

k. The statement "Three 14-day courses of treatment" appears underneath the declaration of net quantity.
Comment: This is acceptable. See Section II.A.i.j.

l. Card back:

- The back card label displays the tamper-evident feature statement "Do Not Use if seal under bottle cap imprinted with "SEALED for YOUR PROTECTION" is broken or missing" on the top of the backer card. The appearance of this statement is identical to the approved 42-ct "club" carton for NDA 204655.
Comment: This is acceptable.

- The Nexium graphic identical to the one described in Section II.B.i.c-e appears beneath the tamper-evident feature statement, with "Tips for Managing Heartburn" placed to the left of the graphic.
Comment: This is acceptable.

- The statement "KEEP CARD FOR COMPLETE WARNINGS AND IMPORTANT INFORMATION" is in bold letters against a white background immediately above the Drug Facts label.
Comment: This is acceptable.

The manufacturing information appears below the Drug Facts label:

- Marketed by:
Pfizer, Madison, NJ 07940 USA
©2015 Pfizer Inc.
Comment: This is acceptable.

- Below the manufacturing information is the country of origin statement: "Made in France"
Comment: This is acceptable in accordance with 19 CFR 102, Rules of Origin. The content of the statement will rely on the findings of the CMC review.

- Below the country of origin statement appears the statements:
"For most recent product information, visit www.Nexium24HR.com" and "Nexium is a registered trademark of AstraZeneca AB and is used under license."
Comment: This is acceptable.

ii. Outer Carton Drug Facts Label

See Section II.A.ii.

iii. Immediate Container (2- and 14-count bottle) Label

The "peel-back" type label for both bottles is divided into three panels, identified by the firm as:

a. Top (face) – This is the panel visible to the consumer before the Top panel is peeled back and displays non-Drug Facts information
b. Top (back) – This is the backside of the top panel and displays part of the Drug Facts label content. It is hinged to connect directly to the "Base" panel so that the text continues onto the Base panel.
c. Base – This panel continues the Drug Facts content and is affixed directly to the bottle.

a. **Top (face) panel**

- The statement "Treats Frequent Heartburn" appears at the top of the front side of the panel.
  Comment: This statement is a true statement of the "Uses" section of the Drug Facts label and is acceptable.

- The top panel center has a yellow background with purple edging on upper right and lower left corner. In the center of the top panel is the proposed proprietary name and large graphic described in Section II.A.i.c and d.
  Comment: This is acceptable.

- The statement of identity "Esomeprazole (b) (4) Delayed-release Tablets (b) (4) mg/Acid Reducer appears on the capsule graphic.
  Comment: See Section II.A.i.e.

- Under the capsule graphic appears the statement "May take 1 to 4 days for full effect."
- Below this statement is the declaration of net quantity of contents, which reads: "2 TABLETS" or "14 TABLETS" for each respective immediate container count.
- For the 14-ct immediate container, the statement "One 14-day course of treatment" appears at the bottom margin of the top panel's front side. The statement "SAMPLE – NOT FOR SALE" appears on the 2-ct immediate container.
- In the upper right corner is the boxed statement "KEEP CARTON FOR COMPLETE WARNINGS AND IMPORTANT INFORMATION".
- In the lower right corner is the direction to "LIFT HERE For More Information" followed by an arrow.
- The tamper-evident feature statement "Do Not Use if seal under bottle imprinted with "*SEALED for YOUR PROTECTION*" is broken or missing.
- The manufacturer's address information, country of origin and website for product information appears below the tamper-evident feature statement.
  Comment: These are all acceptable.

b. **Top (back) panel**

The unformatted Drug Facts label content found under the Active ingredient, Purpose, Uses headings, and the Warnings through to drug-drug interactions subheading is found on the Top-back panel (i.e., backside of the top panel). A directional arrow leads the reader to the adjacent base panel.

Comment: See Section II.A.ii.

c. **Base panel**

The base panel continues the unformatted Drug Facts label content from the Top (back) panel with the remainder of the Warnings drug-drug interactions subheading, "Stop use and ask a doctor if, pregnancy breast-feeding and Keep out of reach of children warnings. It includes Directions and Other Information (storage statement), "Keep the carton…" and Questions and comments. The inactive ingredients are not listed on the immediate container labels and are not required to be as they are listed on the cartons.

Comment: See Section II.A.ii.

III. RECOMMENDATIONS

Please communicate the following to the sponsor:

A. The following revisions are to be made by the sponsor:

i. Non Drug Facts Labeling

a. Revise the established name and dose in accordance with the CMC review and labeling discussions, where it appears on the carton and immediate container labels.
b. Configure the 2-ct carton to include the full Drug Facts Label on the carton similar to the configuration approved for NDA 204655.

ii. Drug Facts Label

a. ***Directions*** section, "14-Day Course of Treatment," first bullet: revise the statement "swallow 1 tablet with a glass of water before eating in the morning" to "swallow 1 tablet with a glass of water at least one hour before eating in the morning" to reflect the clin/pharm review findings.
b. ***Other Information*** section, third bullet: revise the storage statement to reflect the recommendations of the CMC review.
c. ***Other Information*** section, fourth bullet, "[bullet] (b) (4) provide a rationale for the deviation from the Nexium capsule label or remove the statement.

B. We also recommend that the sponsor make the following revisions:

i. Drug Facts label:

a. ***Questions or comments*** section: include the time that the toll-free number is in operation.

In addition to the changes listed under III. Recommendations, remind the sponsor to submit all labeling with the (b) (4) statement removed to reflect the July 31, 2015 amendment to the application.

IV. SUBMITTED LABELING

The labels on the remaining pages of this labeling review were submitted and were evaluated in this labeling review:

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

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/s/

MARY R VIENNA
10/23/2015

RUTH E SCROGGS
10/23/2015

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	June 19, 2015
Requesting Office or Division:	Division of Nonprescription Drug Products (DNDP)
Application Type and Number:	NDA 207920
Product Name and Strength:	Nexium 24HR (Esomeprazole Magnesium) Delayed-Release Tablets, 22.3 mg
Product Type:	Single Ingredient Product
Rx or OTC:	OTC
Applicant/Sponsor Name:	Pfizer Inc. (On behalf of AstraZeneca)
Submission Date:	February 6, 2105
OSE RCM #:	2015-430
DMEPA Primary Reviewer:	Grace P. Jones, PharmD, BCPS
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD

1 REASON FOR REVIEW

As a part of NDA 207920 submission, this labels and labeling review evaluates the proposed container labels and carton labeling for Nexium 24HR (esomeprazole magnesium) Delayed-Release Tablets, 22.3 mg, for areas of vulnerability that could lead to medication errors.

Esomeprazole magnesium 22.3 mg capsules, under NDA 204655, has been marketed since March 28, 2014 as an over-the-counter (OTC) product under the name Nexium 24HR, for the management of frequent heartburn that occurs two or more days a week. AztraZeneca is seeking approval for the proposed esomeprazole magnesium 22.3 mg tablets. Upon approval, Pfizer will market and distribute the proposed product. The product difference between the proposed NDA 207920 and approved NDA 204655 is the dosage form (tablets vs. capsules). Otherwise, both products share the same product characteristics (active ingredients, indication of use, strength, route of administration, dose and frequency, etc.), and the change in dosage form does not affect the proposed NDA 207920 product's use in the usual clinical setting.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C – N/A
ISMP Newsletters	D
FDA Adverse Event Reporting System (FAERS)*	E
Other	F – N/A
Labels and Labeling	G

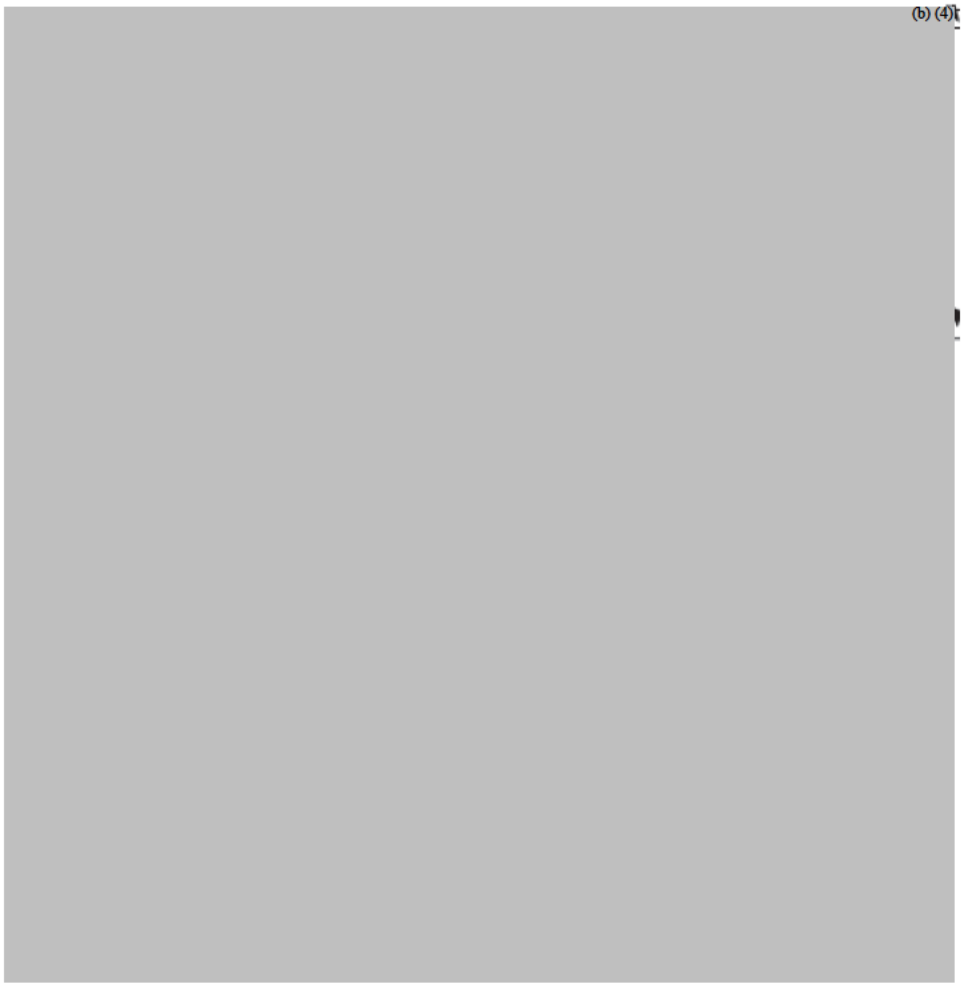
N/A=not applicable for this review
*We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

The proposed container labels and carton labeling for Nexium 24HR tablets follows the same format and color scheme as the currently marketed Nexium 24HR capsules (NDA 204655). Differences between the proposed container labels and carton labeling for Nexium 24HR tablets (See Appendix G) and the capsules (Figure 1) include the new tablet dosage form and

the different color of bottle image on the carton labeling (bottle color is purple for the proposed Nexium 24HR tablets vs. white for the marketed Nexium 24HR capsules).

Figure 1. Nexium 24HR (capsules) from Drugs@FDA accessed 6/9/2015.



Our searches of FAERS and ISMP did not identify medication error cases relevant to this review. Our review of the proposed container labels appear acceptable from a medication error perspective; however, the image of the tablet in the carton labeling could be improved to reflect the actual representation of the true imprint, size, and color of the tablet.

4 CONCLUSION & RECOMMENDATIONS

We determined that the proposed Nexium 24HR tablets carton labeling could be improved to increase prominence and readability of important information to promote the safe use of the product.

4.1 RECOMMENDATIONS FOR PFIZER (ON BEHALF OF ASTRAZENECA)

We recommend the following be implemented prior to approval of this NDA:

A. Carton Labeling
    a. Ensure that the image of the tablet throughout all carton bottle sizes represents a true depiction of the actual tablet, reflecting the true tablet imprint, size and color.

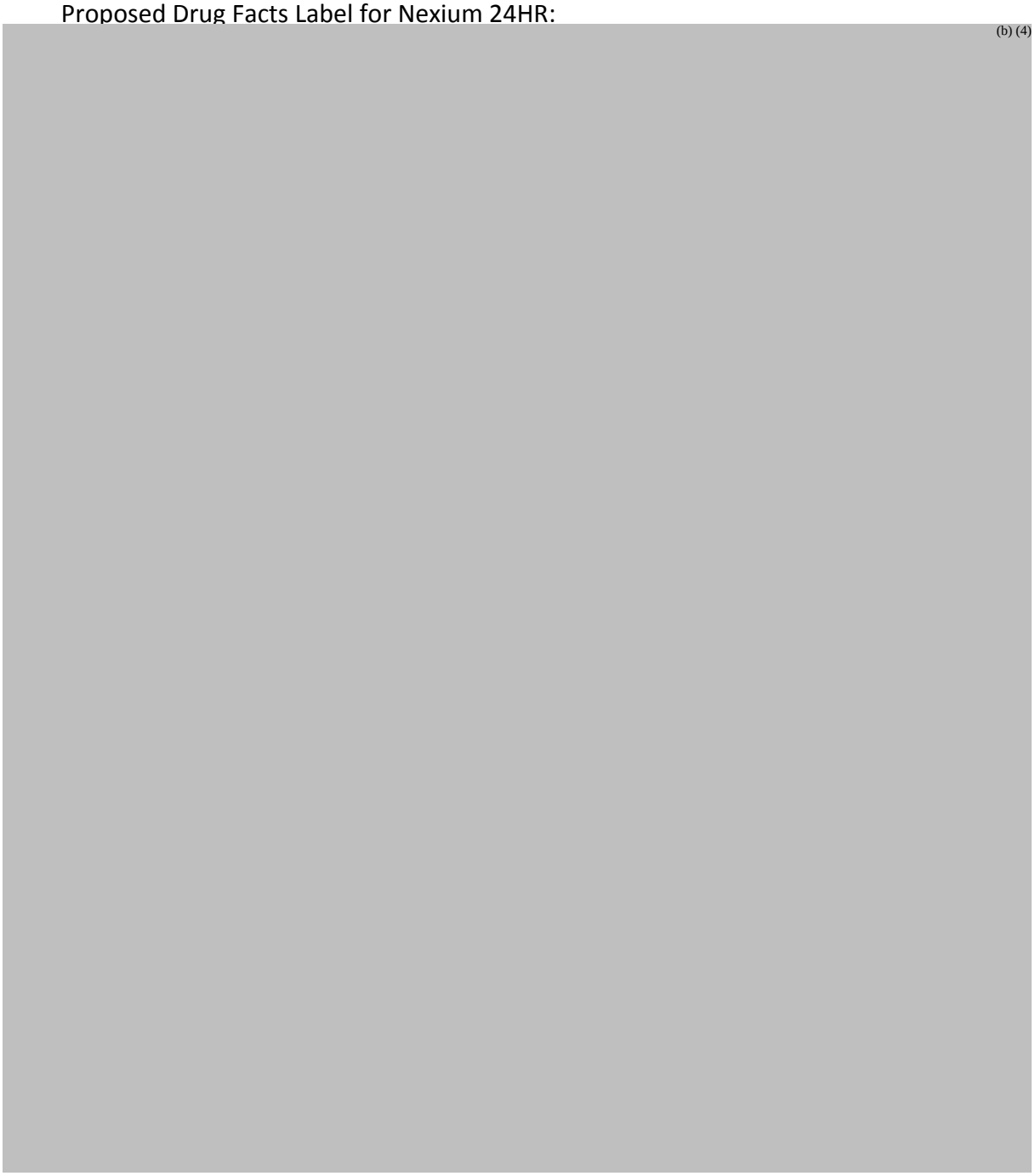
APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Nexium 24HR that Pfizer submitted on February 6, 2105.

Proposed Drug Facts Label for Nexium 24HR:

(b) (4)



- How supplied: bottles containing 2 tablets (sample) and 14 tablets. Outer carton contains 1, 2, or 3 bottles for a total of 14, 28, or 42 capsules.

- Container and Closure System: bottle contains a seal under the bottle cap that is imprinted with “Sealed for Your Protection”

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On June 8, 2015, we searched the L:drive and AIMS using the terms, Nexium 24HR to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified one previous review[1], and we confirmed that our previous recommendations were implemented or considered.

[1] Tu, C. Label and Labeling Review for Nexium 24HR NDA 204655. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2014 JAN 07. RCM No.: 2013-1563.

APPENDIX D. ISMP NEWSLETTERS

D.1 Methods

On May 29, 2015, we searched the Institute for Safe Medication Practices (ISMP) newsletters using the criteria below, and then individually reviewed each newsletter. We limited our analysis to newsletters that described medication errors or actions possibly associated with the label and labeling.

ISMP Newsletters Search Strategy	
ISMP Newletter(s)	Acute Care Newsletter Community Newsletter Nursing Newsletter
Search Strategy and Terms	Match Exact Word or Phrase: "Nexium 24HR"

D.2 Results

Our search of the ISMP newsletter did not yield any results.

APPENDIX E. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

E.1 Methods

We searched the FDA Adverse Event Reporting System (FAERS) on May 21, 2015 using the criteria in Table 3, and then individually reviewed each case. We limited our analysis to cases that described errors possibly associated with the label and labeling. We used the NCC MERP Taxonomy of Medication Errors to code the type and factors contributing to the errors when sufficient information was provided by the reporter[2]

Table 3: FAERS Search Strategy	
Date Range	**January 1, 2014 to May 1, 2015**
Product	**Nexium 24HR** [product name]
Event (MedDRA Terms)	**DMEPA Official FBIS Search Terms Event List:** Medication Errors [HLGT] Product Packaging Issues [HLT] Product Label Issues [HLT] Product Adhesion Issue [PT] Product Compounding Quality Issue [PT] Product Formulation Issue [PT] Inadequate Aseptic Technique in Use of Product [PT]

E.2 Results

Our search identified 89 cases, but after further evaluation, we did not identify any medication error cases that were relevant to this review and any that could be addressed by labels and labeling revisions.

E.3 Description of FAERS

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's postmarket safety surveillance program for drug and therapeutic biologic products. The informatic structure of the FAERS database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. FDA's Office of Surveillance and Epidemiology codes adverse events and medication errors to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Product names are coded using the FAERS Product Dictionary. More information about FAERS can be found at: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm.

[2] The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Taxonomy of Medication Errors. Website http://www.nccmerp.org/pdf/taxo2001-07-31.pdf.

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/s/

GRACE JONES
06/19/2015

CHI-MING TU
06/19/2015

M E M O R A N D U M

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

DATE: May 26, 2015

TO: Division of Nonprescription Clinical Evaluation (DNCE)

FROM: Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Recommendation to accept data without an on-site inspection**

RE: NDA 207920

The Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS) recommends accepting data without an on-site inspection. The rationale for this decision is noted below.

OSIS recently inspected the sites listed below. The inspectional outcome from the inspections was classified as No Action Indicated (NAI).

Requested Sites Inspection

Facility Type	Facility Name	Facility Address
Analytical	(b) (4)	(b) (4)
Clinical	Bio-Kinetic Clinical Applications	1816 W. Mt. Vernon Springfield, MO 65802

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/s/

SHILA S NKAH
05/26/2015

OSI Consult Request for Biopharmaceutical Inspections	
Date	3/26/2015
Subject	Request for Biopharmaceutical Inspections (BE)
Addressed to	William H. Taylor, PhD Director, Division of BE and GLP Compliance Office of Scientific Investigations william.taylor1@fda.hhs.gov
Consulting Office/Division	Division of Biopharmaceutics/Office of New Drug Product
Project Manager	Andrew J Shiber
Application Type	PEPFAR? ☐ Yes ☒ No
	☒ NDA ☐ BLA ☐ ANDA
Application Number	NDA 207920
Drug Product	Esomeprazole magnesium
Sponsor Name	AstraZeneca
Sponsor Address	Bio-Kinetic Clinical Applications 1816 W. Mt. Vernon Springfield MO, 65802 UNITED STATES
US Agent (if applicable)	
US Agent Address	
Electronic Submission	☒ Yes ☐ No
PDUFA/BsUFA Due Date	12/4/2015
Action Goal Date	08/01/2015
OSI Review Requested By	Vincent(Peng) Duan, Ph.D.

Inspection Request Detail (All fields should be fill out completely)				
Study #1				
Study Number	**B5141002**			
Study Title	**A Phase I, Randomized, Single-Dose, 6-Period, Crossover, Partial Replicate, Open-Label Study to Assess the Bioequivalence of Esomeprazole Banded OTC Capsule and (b) (4) Tablet in Healthy Volunteers Under Fed and Fasted Conditions**			
Study Type	☒ In vivo BE	☐ In vitro BE	☐ Permeability	☐ Others (specify)
☒ Inspection Request - Clinical Site		☒ Inspection Request - Analytical Site		
Facility #1 Name: **Bio-Kinetic Clinical Applications** Address: **1816 W. Mt. Vernon Springfield, MO 65802 US** (Tel) (Fax)		Facility #1 Name: (b) (4) Address: (b) (4) (Tel) (Fax)		

Clinical Investigator: **Dr. Thomas J. Legg** (email)	Principal Analytical Investigator: (email)
Facility #2 Name: Address: (Tel) (Fax)	Facility #2 Name: (if applicable) Address: (Tel) (Fax)
Clinical Investigator: (email)	Principal Analytical Investigator: (email)
Check one: ☐ Routine inspection ☐ For cause	Check one: ☐ Routine inspection ☐ For cause
(please include specific review concerns or items to be addressed during the inspection in the appendix below)	
☐ Study Report: (location, eg., 5.3.1.2)	☐ Validation Report: (eg., 5.3.1.2) ☒ Bioanalytical Report: (eg., 5.3.1.4) **Quantitation of Omeprazole in Human Plasma via HPLC with MS/MS Detection (Protocol No. B5141002)**

Note: International inspection requests or requests for five or more inspections require sign-off by the OND Division Director and forwarding through the Director, OSI.

I. Appendix

Specific Items To be Addressed During the Inspection
1. Evaluate whether the study was conducted as per approved protocol (*i.e., the study subject recruitment followed the specified inclusion/exclusion criteria and dropouts followed the protocol's criteria and were properly documented*). 2. Evaluate whether protocol deviations were properly documented and justified. 3. Evaluate whether the blood/plasma samples were taken, stored, transported, and analyzed as per approved SOPs and the analytical and PK data analysis results were properly documented. 4. Evaluate whether the data excluded from the bioequivalence data analysis is justified.

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/s/

ANDREW J SHIBER
04/27/2015

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data]

<table>
<tr><th colspan="3">Application Information</th></tr>
<tr><td>NDA # 207920</td><td>NDA Supplement #: S- N/A</td><td>Efficacy Supplement Category:
☐ New Indication (SE1)
☐ New Dosing Regimen (SE2)
☐ New Route Of Administration (SE3)
☐ Comparative Efficacy Claim (SE4)
☐ New Patient Population (SE5)
☐ Rx To OTC Switch (SE6)
☐ Accelerated Approval Confirmatory Study (SE7)
☐ Animal Rule Confirmatory Study (SE7)
☐ Labeling Change With Clinical Data (SE8)
☐ Manufacturing Change With Clinical Data (SE9)
☐ Pediatric</td></tr>
<tr><td colspan="3">Proprietary Name: Nexium 24HR
Established/Proper Name: esomeprazole magnesium
Dosage Form: delayed-release tablets
Strengths: 22.3 mg</td></tr>
<tr><td colspan="3">Applicant: Pfizer, Inc.
Agent for Applicant (if applicable):</td></tr>
<tr><td colspan="3">Date of Application: 02/06/15
Date of Receipt: 02/06/15
Date clock started after UN:</td></tr>
<tr><td colspan="2">PDUFA/BsUFA Goal Date: 12/06/15</td><td>Action Goal Date (if different): 12/04/15</td></tr>
<tr><td colspan="2">Filing Date: 04/07/15</td><td>Date of Filing Meeting: 03/25/15</td></tr>
<tr><td colspan="3">Chemical Classification (original NDAs only) :
☐ Type 1- New Molecular Entity (NME); NME and New Combination
☐ Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination
☒ Type 3- New Dosage Form; New Dosage Form and New Combination
☐ Type 4- New Combination
☐ Type 5- New Formulation or New Manufacturer
☐ Type 7- Drug Already Marketed without Approved NDA
☐ Type 8- Partial Rx to OTC Switch</td></tr>
<tr><td colspan="3">Proposed indication(s)/Proposed change(s): Treatment of frequent heartburn</td></tr>
<tr><td colspan="2">Type of Original NDA:
AND (if applicable)
Type of NDA Supplement:

If 505(b)(2): Draft the “505(b)(2) Assessment” review found at:
http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499.</td><td>☒ 505(b)(1)
☐ 505(b)(2)
☐ 505(b)(1)
☐ 505(b)(2)</td></tr>
</table>

Type of BLA ***If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team***	☐ 351(a) ☐ 351(k)
Review Classification: ***The application will be a priority review if:*** • ***A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH)*** • ***The product is a Qualified Infectious Disease Product (QIDP)*** • ***A Tropical Disease Priority Review Voucher was submitted*** • ***A Pediatric Rare Disease Priority Review Voucher was submitted***	☒ Standard ☐ Priority ☐ Pediatric WR ☐ QIDP ☐ Tropical Disease Priority Review Voucher ☐ Pediatric Rare Disease Priority Review Voucher
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system (syringe, patch, etc.) ☐ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Separate products requiring cross-labeling ☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)

☐ Fast Track Designation ☐ Breakthrough Therapy Designation ***(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)*** ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies (FDCA Section 505B) ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
Collaborative Review Division (*if OTC product*): DGIEP (Reviewer is MOTL Rob Fiorentino)	
List referenced IND Number(s): NDA 204655, PIND 118964, NDA 021153, IND 053733, IND 111185	

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA/BsUFA and Action Goal dates correct in tracking system? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	☒	☐		
Are the established/proper and applicant names correct in tracking system? ***If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name***	☒	☐		

to the supporting IND(s) if not already entered into tracking system.				
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? ***Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:*** ***http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm*** ***If no, ask the document room staff to make the appropriate entries.***	☒	☐	☐	Standard review
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***	☐	☒		
If yes, explain in comment column.				
If affected by AIP, has OC/OMPQ been notified of the submission? **If yes,** date notified:	☐	☐		
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?	☒	☐		

User Fee Status ***If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.***	Payment for this application *(check daily email from UserFeeAR@fda.hhs.gov):* ☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.	Payment of other user fees: ☒ Not in arrears ☐ In arrears
User Fee Bundling Policy ***Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:*** ***http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf***	Has the user fee bundling policy been appropriately applied? ***If no, or you are not sure, consult the User Fee Staff.*** ☒ Yes ☐ No

505(b)(2) (NDAs/NDA Efficacy Supplements only)	**YES**	**NO**	**NA**	**Comment**
Is the application a 505(b)(2) NDA? *(Check the 356h form,*	☐	☒		

cover letter, and annotated labeling). **If yes**, answer the bulleted questions below:				
• Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	☐	☐		
• Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? **[see 21 CFR 314.54(b)(1)].**	☐	☐		
• Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug **[see 21 CFR 314.54(b)(2)]?** ***If you answered yes to any of the above bulleted questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs for advice.***	☐	☐		
• Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm*** **If yes**, please list below:	☐	☐		

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug Designations and Approvals list at:*** ***http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm***	☐	☒		
If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness **[see 21 CFR 316.3(b)(13)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy***	☐	☐	☒	
NDAs/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? **If yes**, # years requested: ***Note:*** *An applicant can receive exclusivity without requesting it;*	☐	☒	☐	

therefore, requesting exclusivity is not required.				
NDAs only: Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?	☐	☒	☐	
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact the Orange Book Staff (CDER-Orange Book Staff).***	☐	☐	☐	
BLAs only: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? ***If yes, notify Marlene Schultz-DePalo, OBP Biosimilars RPM*** ***Note**: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	☐	☐	☒	

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☒ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance?[1] **If not,** explain (e.g., waiver granted).	☒	☐	☐	
Index: Does the submission contain an accurate comprehensive index?	☒	☐		
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including:	☒	☐		

[1] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) **If no**, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #	☐	☐	☒	

Forms and Certifications				
Electronic *forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise,* ***paper*** *forms and certifications with hand-written signatures must be included.* ***Forms*** *include: user fee cover sheet (3397/3792), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	☒	☐		
Are all establishments and their registration numbers listed on the form/attached to the form?	☒	☐	☐	
Patent Information (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	☒	☐	☐	
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? ***Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*	☒	☐		
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."***	☒	☐		

If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant				
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature? ***Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].*** ***Note:*** *Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*	☒	☐	☐	
Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***	☐	☐	☒	
Controlled Substance/Product with Abuse Potential	**YES**	**NO**	**NA**	**Comment**
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* <u>For non-NMEs</u>: *Date of consult sent to Controlled Substance Staff*:	☐	☐	☒	
Pediatrics	**YES**	**NO**	**NA**	**Comment**
<u>PREA</u> Does the application trigger PREA? ***If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting[2]*** ***Note****: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), new indications, new dosage*	☒	☐		Full waiver was granted

[2] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027829 htm

forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.				
If the application triggers PREA, is there an agreed Initial Pediatric Study Plan (iPSP)? ***If no, may be an RTF issue - contact DPMH for advice.***	☒	☐	☐	
If required by the agreed iPSP, are the pediatric studies outlined in the agreed iPSP completed and included in the application? ***If no, may be an RTF issue - contact DPMH for advice.***	☐	☐	☒	Full waiver requested & granted
BPCA: Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***[3]	☐	☒		
Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***	☒	☐	☐	Proprietary name conditionally accepted on 4/14/15
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the CDER OSI RMP mailbox***	☐	☒	☐	
Prescription Labeling	☒ **Not applicable**			
Check all types of labeling submitted.	☐ Package Insert (PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☐ Medication Guide (MedGuide) ☐ Carton labels ☐ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request applicant to submit SPL before the filing date.***	☐	☐		

[3] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027837.htm

Is the PI submitted in PLR format?[4]	☐	☐		
If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.***	☐	☐	☐	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	☐	☐	☐	
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)	☐	☐	☐	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	☐	☐	☐	
OTC Labeling	☐ **Not Applicable**			
Check all types of labeling submitted.	☒ Outer carton label ☒ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☒ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***	☒	☐		
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***	☒	☐	☐	
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***	☒	☐	☐	
All labeling/packaging sent to OSE/DMEPA?	☒	☐	☐	
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:***	☒	☐	☐	OPQ has consulted Biometrics for assistance with the SAS
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**

[4] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576 htm

End-of Phase 2 meeting(s)? **Date(s):** ***If yes, distribute minutes before filing meeting***	☐	☒		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** 01/28/2014 ***If yes, distribute minutes before filing meeting***	☒	☐		
Any Special Protocol Assessments (SPAs)? **Date(s):** ***If yes, distribute letter and/or relevant minutes before filing meeting***	☐	☒		

ATTACHMENT

MEMO OF FILING MEETING

DATE: 03/25/15

BACKGROUND: see DARRTS record

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Jeffrey Buchanan	Y
	CPMS/TL:	Dan Brum	Y
Cross-Discipline Team Leader (CDTL)	Francis Becker		Y
Division Director/Deputy	Theresa Michele Karen Mahoney		Y N
Office Director/Deputy	Charles Ganley		N
Clinical	Reviewer:	Elizabeth Donohoe	Y
	TL:	Francis Becker	Y
Social Scientist Review (*for OTC products*)	Reviewer:		
	TL:		
OTC Labeling Review (*for OTC products*)	Reviewer:	Mary R. Vienna	Y
	TL:	Steven Adah/Betsy Scroggs	Y
Clinical Microbiology (*for antimicrobial products*)	Reviewer:		
	TL:		
Clinical Pharmacology	Reviewer:	Dilara Jappar	N
	TL:	Sue Chih Lee	Y
Biostatistics	Reviewer:		
	TL:	Yi Tsong	N

Nonclinical (Pharmacology/Toxicology)	Reviewer:	Wafa Harrouk	Y
	TL:	Paul Brown	N
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) *(for protein/peptide products only)*	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:		
	TL:	Swapan De	Y
Biopharmaceutics	Reviewer	Peng Duan	Y
	TL:	Tien Mien Chen	Y
Quality Microbiology	Reviewer:		
	TL:		
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name, carton/container labels))	Reviewer:	Grace Jones	Y
	TL:	Chi Ming Tu	N
OSE/DRISK (REMS)	Reviewer:		
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers/disciplines	Reviewer:		
	TL:	Robert Fiorentino (DGIEP)	Y
Other attendees	Peter Diak/Jenna Lyndly (OSE/DPV)		

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues: o Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? o Did the applicant provide a scientific "bridge" demonstrating the relationship between the proposed product and the referenced product(s)/published literature? Describe the scientific bridge (e.g., BA/BE studies):	☒ Not Applicable ☐ YES ☐ NO ☐ YES ☐ NO
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments **List comments**:	☐ Not Applicable ☒ No comments
CLINICAL **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	☒ YES ☐ NO

• Advisory Committee Meeting needed? **Comments**: ***If no, for an NME NDA or original BLA, include the reason. For example:*** o ***this drug/biologic is not the first in its class*** o ***the clinical study design was acceptable*** o ***the application did not raise significant safety or efficacy issues*** o ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	☐ YES Date if known: ☒ NO ☐ To be determined Reason:
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CONTROLLED SUBSTANCE STAFF • Abuse Liability/Potential **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL MICROBIOLOGY **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☒ YES ☐ NO
BIOSTATISTICS	☐ Not Applicable ☐ FILE ☐ REFUSE TO FILE

Comments:	☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter

IMMUNOGENICITY (protein/peptide products only) **Comments**:	☐ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
New Molecular Entity (NDAs only) • Is the product an NME?	 ☐ YES ☒ NO
<u>Environmental Assessment</u> • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments**:	 ☒ YES ☐ NO ☐ YES ☐ NO ☐ YES ☐ NO
<u>Quality Microbiology</u> • Was the Microbiology Team consulted for validation of sterilization? **Comments**:	☐ Not Applicable ☐ YES ☐ NO

Facility Inspection • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? **Comments**:	☐ Not Applicable ☒ YES ☐ NO ☒ YES ☐ NO
Facility/Microbiology Review (BLAs only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CMC Labeling Review **Comments**:	☐ Review issues for 74-day letter
APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs) • Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days?	☒ N/A ☐ YES ☐ NO ☐ YES ☐ NO
• What late submission components, if any, arrived after 30 days?	
• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?	☐ YES ☐ NO

• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?	☐ YES ☐ NO
• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?	☐ YES ☐ NO

REGULATORY PROJECT MANAGEMENT

Signatory Authority: Theresa Michele, MD, Director, DNDP

Date of Mid-Cycle Meeting (for NME NDAs/BLAs in "the Program" PDUFA V):

21st Century Review Milestones (see attached) (listing review milestones in this document is optional):

Comments:

REGULATORY CONCLUSIONS/DEFICIENCIES

☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. Review Issues: ☐ No review issues have been identified for the 74-day letter. ☒ Review issues have been identified for the 74-day letter. Review Classification: ☒ Standard Review ☐ Priority Review

ACTIONS ITEMS

☒	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, orphan drug).
☐	If RTF, notify everyone who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	351(k) BLA/supplement: If filed, send filing notification letter on day 60
☐	If priority review:

	• notify sponsor in writing by day 60 (see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
☒	Send review issues/no review issues by day 74
☐	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☐	Update the PDUFA V DARRTS page (for applications in the Program)
☐	Other

Annual review of template by OND ADRAs completed: September 2014

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

/s/

JEFFREY A BUCHANAN
04/16/2015

Filing Review for
Nexium 24HR Tablets

SUBMISSION DATES:	February 6, 2015
NDA/SUBMISSION TYPE:	NDA 207920
ACTIVE INGREDIENTS:	Esomeprazole magnesium, 22.3mg mg
DOSAGE FORMS:	Delayed release tablets
SPONSOR:	AstraZeneca Pfizer, Inc. - Agent Christine Chirdo Director, U.S. Regulatory Strategy Category Lead
REVIEWER:	Mary R. Vienna, R.N., M.H.A.
TEAM LEADER:	Steven Adah, Ph.D.

Submitted Labeling	Representative of Following SKUs
2-count immediate container (bottle)	N/A
14-count immediate container (bottle)	N/A
2-count sample carton	N/A
14-count carton	N/A
28-count carton	N/A
42-count carton	N/A
42-count Club Pack carton	N/A

Issues	Yes/No	Comments
Is the supplement correctly assigned as a PA, CBE0, CBE30?	N/A	This is a new NDA
Are the outer container and immediate container labels, and consumer information leaflet and other labeling included for all submitted SKUs?	Yes	Tips for Heartburn on carton in lieu of Consumer Information Leaflet

Issues	Yes/No	Comments
If representative labeling is submitted, does the submitted labeling represent only SKUs of different count sizes (same flavor and dosage form)?	N/A	
Is distributor labeling included?	No	
Does the submission include the annotated specifications for the Drug Facts label?	Yes	
Is Drug Facts title and Active ingredient/Purpose section of Drug Facts label visible at time of purchase?	Yes	
Do any of the labels include "prescription strength" or similar statements?	No	
Do any of the labels include "#1 doctor recommended" or similar endorsement statements?	No	
Do any labels include text in a language other than English?	No	
Is a new trade name being proposed? If multiple trade names, is the primary or preferred trade name identified?	Yes	
Does a medical officer need to review any clinical issues?	Yes	New NDA
If SLR, should ONDQA also review?	N/A	

Information Request:
Information request is necessary. Request that the sponsor submit an exact-size model of the proposed 2-count sample carton with peel-back Drug Facts label for review.

Reviewer's Comment:
From a labeling perspective, this NDA is fileable.

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

/s/

MARY R VIENNA
03/25/2015

STEVEN A ADAH
03/25/2015