Gretchen DuBeau
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Alliance for Natural Health USA
1011 East Jefferson Street
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Charlottesville, VA 22902

May 12, 2023

Re: FDA-2020-P-1540

Dear Ms. DuBeau:

This letter responds to your citizen petition received by the Food and Drug Administration (FDA or Agency) on June 10, 2020 (Petition). The Petition requests that the Agency issue a regulation requiring:

> [a]ll makers of Proton Pump Inhibitor (PPI) medications for humans expand the existing warnings on their product's labeling to include warning about increased risk of pneumonia.

(Petition at 2).

You assert that data show that PPIs "increase the risk of both community-acquired pneumonia (CAP) and hospital-acquired pneumonia (HAP)" (Petition at 4).

FDA has carefully considered the information submitted in your Petition, other data available to the Agency, and relevant published literature. Based on our review of these materials, and for the reasons stated below, your Petition is denied.

I. BACKGROUND

A. PPIs

PPIs[1] are a class of drugs that treat conditions of the upper gastrointestinal (GI) tract by specifically inhibiting gastric acid secretion. PPIs are among the most commonly prescribed medications and are also some of the most utilized nonprescription drugs in the U.S. market. Prescription PPIs are approved for several indications, including:

- Short-term treatment of active duodenal ulcer

[1] The Petition requests that the warning language apply to "all makers of Proton Pump Inhibitor medications." Accordingly, we considered all approved drug products in the class, including combination products: Prilosec, Prilosec OTC, Prevacid, Protonix, Aciphex, Nexium, Dexilant, Vimovo (combination product), Talicia (combination product), Zegerid (combination product), and Yosprala (combination product).

- Short-term treatment of active benign gastric ulcer
- Treatment of symptomatic gastroesophageal reflux disease (GERD)
- Treatment of erosive esophagitis (EE) due to acid-mediated GERD
- Maintenance of healing of EE due to acid-mediated GERD
- Treatment of pathological hypersecretory conditions
- Helicobacter Pylori eradication (when used with clarithromycin and amoxicillin)
- Reduction of risk of upper GI bleeding in critically ill adult patients, and
- Prophylaxis of upper GI bleeding associated with nonsteroidal anti-inflammatory drugs (NSAIDs)

The PPIs that are available as nonprescription products (omeprazole, esomeprazole, and lansoprazole) are approved only for short-term treatment (14 days) of heartburn.

Since PPIs first entered the market in 1989, the safety of PPI use has been extensively researched. The WARNINGS AND PRECAUTIONS section of the labeling for prescription PPI products includes adverse reactions and other potential safety hazards. Ongoing, post-market review of safety data associated with PPI use, including studies, literature, and case reports, has demonstrated that PPI therapy may be associated with certain increased risks and has resulted in a number of changes to PPI labeling to reflect the new information. For example, in 2012, FDA required all PPIs to add warning language about a specific type of GI infection, *Clostridium difficile*-associated diarrhea.[2] Nonprescription PPI labeling was also updated in 2012 to include consumer-friendly language directing consumers to stop use and consult a doctor if they experience diarrhea. Several prescription PPI labels (e.g., omeprazole) have also been updated to include language describing the "effects on gastrointestinal microbial ecology" that might predispose to GI infections other than *C. difficile* infection.

In 2014, FDA responded to a petition (FDA-2011-P-0741) (the P-0741 Petition) requesting that the Agency require safety labeling changes (SLCs), including boxed warnings, for various safety risks. Infections, including CAP, were among the safety risks described in the P-0741 Petition. The P-0714 Petition requested that FDA issue medication guides and Dear Health Care Provider letters describing these risks.[3] In its response, FDA granted the P-0714 Petition in part[4] and denied it in part (P-0714 Response). With respect to the P-0714 Petition's request for warnings regarding the risk of CAP, the Agency stated, "while an association between CAP and PPI use may exist, the data showing any causal association between CAP and PPI exposure was lacking"

[2] Some of the other adverse reactions or potential safety hazards listed under the WARNINGS AND PRECAUTIONS section of the labeling for certain prescription PPI products include: (1) delayed diagnosis of gastric malignancy; (2) acute interstitial nephritis; (3) bone fractures; (4) cutaneous and systemic lupus erythematosus; (5) interaction with clopidogrel; (6) vitamin B-12 deficiency; (7) hypomagnesemia; (8) interaction with St. John's wort or rifampin; (9) interactions with diagnostic investigations for neuroendocrine tumors; (10) interactions with methotrexate; and (11) fundic gland polyps.

[3] October 31, 2014, letter from Janet Woodcock, Director, CDER to Eric Nellis, Sammy Almashat, M.D., M.P.H., Michael Carome, M.D., Sidney M. Wolfe, M.D., and Helge L. Waldum, M.D., Ph.D., Docket No. FDA-2011-P-0741 (P-7104 Response).

[4] In the P-7104 Petition response, FDA granted some of the requests.

(P-0714 Response at 10). As a result, FDA concluded that "no changes to the labeling of PPI products regarding the potential of developing pneumonia are warranted at this time" (P-0714 Response at 10).

There are currently no warnings about the risk of pneumonia in the FDA-approved labeling for any prescription PPIs under the WARNINGS AND PRECAUTIONS heading or similar warnings on nonprescription products.[5]

B. Regulatory Framework

1. *Labeling for Prescription Drugs*

Labeling for prescription drug products is generally governed by several provisions of the Federal Food, Drug, and Cosmetic Act (FD&C Act)[6] and FDA's regulations in 21 CFR part 201. Specific requirements for content and format of the prescribing information (PI) are set forth in 21 CFR 201.57.

The WARNINGS AND PRECAUTIONS section of the full prescribing information must describe clinically significant adverse reactions, other potential safety hazards, limitations in use imposed by them, and steps that should be taken if these situations occur.[7] The labeling must be revised to include a warning about a clinically significant hazard as soon as there is reasonable evidence of a causal association with a drug.[8]

FDA's guidance for industry, *Warnings and Precautions, Contraindications, and Boxed Warnings Sections of Labeling for Human Prescription Drug and Biological Products—Content and Format*[9] (October 2011) (Warnings and Precautions Guidance) describes some factors that

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[5] We note that the occurrence of pneumonia is identified in the CLINICAL TRIALS EXPERIENCE section of the labeling of two approved prescription PPI products: Prevacid [lansoprazole] and Zegerid [omeprazole plus sodium bicarbonate]. Additionally, interstitial pneumonia is listed in the POSTMARKETING EXPERIENCE section for Aciphex [rabeprazole]. Identification of pneumonia in these labeling sections does not indicate causal relationship between the drugs' use and pneumonia. See Prevacid prescribing information (revised November 2020), available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/020406s092,021428s039lbl.pdf; Zegerid prescribing information (revised November 2020), available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/021636s022,021849s016lbl.pdf; Aciphex prescribing information (revised November 2020), available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/020973s041lbl.pdf.

[6] See, e.g., sections 201(n); 502(a), (f), and (j); and 505 of the FD&C Act (21 U.S.C. 321(n); 352(a), (f), and (j); 355).

[7] 21 CFR 201.57(c)(6)(i). See also 21 CFR 201.80(e) through (f). For older drugs not described in § 201.56(b)(1), FDA regulations for specific requirements on content and format of labeling for human prescription drug and biological products are at § 201.80.

[8] Id.

[9] We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance web page at https://www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugs.

FDA may consider in assessing whether there is reasonable evidence of a causal relationship. These include:

> [T]he frequency of reporting; (2) whether the adverse event rate in the drug treatment group exceeds the rate in the placebo and active-control group in controlled trials; (3) evidence of a dose-response relationship; (4) the extent to which the adverse event is consistent with the pharmacology of the drug; (5) the temporal association between drug administration and the event; (6) the existence of dechallenge and rechallenge experience; and (7) whether the adverse event is known to be caused by related drugs.[10]

Section 505(o)(4) of the FD&C Act authorizes FDA to require holders of approved applications for prescription drug products to make certain labeling changes, based on "new safety information" or "information related to reduced effectiveness." New safety information is defined as:

> information derived from a clinical trial, an adverse event report, a postapproval study (including a study under section 505(o)(3) [of the FD&C Act]), or peer-reviewed biomedical literature; data derived from the postmarket risk identification and analysis system under section 505(k) [of the FD&C Act]; or other scientific data deemed appropriate by the [Agency] about … a serious risk or an unexpected serious risk associated with use of the drug that the [Agency] has become aware of (that may be based on a new analysis of existing information) since the drug was approved, since [a] risk evaluation and mitigation strategy (REMS) was required, or since the last assessment of the approved risk evaluation and mitigation strategy for the drug; or…the effectiveness of the approved [REMS] for the drug obtained since the last assessment of [the REMS].[11]

2. *Labeling for Nonprescription Drugs*

Labeling for nonprescription drugs is generally governed by 21 CFR 201.60, et. seq. Unlike labeling for prescription drugs, nonprescription labeling is directed at consumers. The format and content requirements for nonprescription drug labeling, also known as the "Drug Facts" label, are set forth in 21 CFR 201.66. Although there are no detailed sections in nonprescription drug labeling comparable to the "Warnings and Precautions" section that appears on prescription drug labeling, labeling for nonprescription drugs must bear adequate directions for use (section 502(f)(1) of the FD&C Act; 21 U.S.C. 351(f)(1)). If a warning on the prescription label would also apply under the conditions of nonprescription use, appropriate consumer friendly warning language appears in the nonprescription Drug Facts Label. Additionally, a drug product is misbranded if any word, statement, or other information required by or under authority of the FD&C Act to appear on the label or labeling is not "placed thereon with such conspicuousness…and in such terms as to render it likely to be read and understood by the ordinary individual under customary conditions of purchase and use" (section 502(c) of the FD&C Act).

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[10] FDA's guidance for industry *Warnings and Precautions, Contraindications, and Boxed Warnings Sections of Labeling for Human Prescription Drug and Biological Products—Content and Format*, available at https://www.fda.gov/media/71866/download.

[11] Section 505(o)(2)(c) and 505-1(b)(3) of the FD&C Act.

II. DISCUSSION

The Petition requests that FDA require PPI labeling to include a warning for "increased risk of pneumonia" (Petition at 2).[12] In support of this requested action, the Petition asserts that PPIs alter the gastric environment in a way that might predispose patients to pneumonia and discusses medical literature that includes an association between PPI use and pneumonia. As will be explained more fully below, although several observational studies report statistically significant association between PPIs and pneumonia, we did not find reasonable evidence of a causal association to warrant the labeling changes requested in the Petition.[13]

PPIs treat conditions of the upper GI tract by specifically inhibiting gastric acid secretion. Gastric acid helps protect the GI tract from infection. The Petition argues that data show that gastric acid suppression by PPIs increases the risk of infection, including pneumonia. While available literature does show that PPI use may contribute to moderate inhibition of lysosomal enzyme activities,[14] there is insufficient evidence of systematic immunosuppression by PPIs to support the argument set forth in the Petition. Our review found no convincing evidence that moderate inhibition of lysosomal enzyme activities or other changes to the gastric environment

[12] The Petitioner did not specify the content or placement of the requested warning language. Accordingly, we considered whether to include warnings under the "Warnings and Precautions" section of the labeling of prescription drugs and comparable nonprescription warning language.

[13] The Petitioner includes crude counts of reports of PPIs and pneumonia from FDA Adverse Event Reporting System (FAERS). The mere presence of adverse event reports in the FAERS database is not an indicator of the safety profile of a particular drug or biologic product. We do not agree that the FAERS reports support the Petitioner's requested action to include a warning about increased risk of pneumonia in all PPI labels for many reasons including: pneumonia's relative frequent occurrence in the underlying population; many factors other than PPI medication many influence the development of pneumonia (e.g., age, smoking status, asthma); patients with GERD, one of the indications for use, may suffer from chronic diseases (e.g., asthma), which may put them at higher risk for pneumonia; and GERD itself is associated with airway problems including pneumonia. Additionally, FAERS reports are limited because they are frequently missing information necessary for full assessment such as details about product exposure or baseline patient characteristics that are necessary to establish causality between PPIs and pneumonia.

[14] Liu W, Baker SS, Trinidad J, et al. Inhibition of lysosomal enzyme activities by proton pump inhibitors. J Gastroenterol. 2013 Dec; 48(12): 1343-52 (Showing modest inhibition of lysosomal enzyme activity, measured at a single time-point in mice, after five doses of 2.85 milligrams (mg)/kilograms (kg) dosed 12 hours apart. This dose is 8x higher when compared to the human dose of omeprazole 40 mg or 0.7 mg/kg. A direct comparison to human exposures cannot be made in the absence of omeprazole exposure data in mice, especially considering a potential increase in bioavailability due to the intraperitoneal route of administration.); Roman A. Sukhovershin and John P. Cooke. How may proton pump inhibitors impair cardiovascular health? Am J Cardiovasc Drugs. 2016 June; 16(3): 153–161. doi:10.1007/s40256-016-0160-9.

such as changes to the gastrointestinal microbiota[15] have a role in causing pneumonia.[16]

A. CAP

The Petition states that "a multitude of studies have found statistically significant increase in the incidence of community-acquired pneumonia (CAP) for those using PPI drugs" (Petition at 5). Relatedly, the P-7104 Petition asserted that PPI use has "been linked to higher risk of developing" CAP (P-7104 Petition at 9). FDA noted in its Response to the P-710 Petition that while the available studies found that there may be an association between CAP and PPI use, the "data showing any causal association" was "lacking" (P-7104 Response at 10). Here, the Petition cites six empirical[17] studies in support of its assertion that PPI use increases the risk of CAP. FDA previously reviewed four of the six studies as part of its response to the P-7104 Petition.[18] The two studies not previously reviewed that were submitted in support of the Petition include Roughead,[19] a fair quality cohort study reporting low magnitude association between PPI and

[15] Martinsen, TC. The Phylogeny and Biological Function of Gastric Juice – Microbiological Consequences of Removing Gastric Acid. *Int. J. Mol. Sci.* 2019, 20, 6031 (concluding that changes in gastric acid in the GI tract have demonstrated the strongest relationship with bacterial infection). Warnings regarding risk of *Clostridium difficile* are included in PPI labeling.

[16] Shi Y.C., Cai S.T., Tian Y.P., Zhao H.J., Zhang Y.B., Chen J., Ren R.R., Luo X., Peng L.H., Sun G., et al. Effects of Proton Pump Inhibitors on the Gastrointestinal Microbiota in Gastroesophageal Reflux Disease. *Genomics Proteomics Bioinforma*. 2019;17:52–63 (study on the effect of PPIs on the GI microbiota in GERD, conducted in China, with a study size of 40 patients total representing a healthy control, PPI users, and PPI nonusers). While Shi concluded that "PPIs have a significant effect on the abundance and structure of the gastric mucosal microbiota but only on the composition of fecal microbiota," the significance of this change and its application to the U.S. population is unclear.

[17] For purposes of this response, we consider empirical studies to be comparative studies (non-randomized or randomized) in humans. The term *observational studies* refers to comparative studies that use a case-control or cohort design in which intervention groups are allocated during the course of usual treatment decisions. The term *randomized clinical trials* (RCTs) refers to protocol-directed studies that use chance (randomization) to assign study subjects to either an investigational or comparator treatment.

[18] Laheij RJ, Sturkenboom MC, Hassing RJ, Dieleman J, Stricker BH, Jansen JB. Risk of community-acquired pneumonia and use of gastric acid-suppressive drugs. JAMA. 2004;292(16):1955-1960; Myles PR, Hubbard RB, McKeever TM, Pogson Z, Smith CJ, Gibson JE. Risk of community-acquired pneumonia and the use of statins, ACE inhibitors and gastric acid suppressants: a population-based case-control study. Pharmacoepidemiol Drug Saf. 2009;18(4):269-275; Rodriguez LA, Ruigomez A, Wallander MA, Johansson S. Acid-suppressive drugs and community-acquired pneumonia. Epidemiology. 2009;20(6):800-806; Meijvis SC, Cornips MC, Voorn GP, et al. Microbial evaluation of proton-pump inhibitors and the risk of pneumonia. Eur Respir J. 2011;38(5):1165-1172.

[19] Roughead EE, Ramsay EN, Pratt NL, Ryan P, Gilbert AL. Proton-pump inhibitors and the risk of antibiotic use and hospitalisation for pneumonia. Med J Aust. 2009;190(3):114-116. Although FDA did not directly review Roughead 2009 in its review for P-104, it was included in the two of the metanalyses that the Agency examined: Eom CS, Jeon CY, Lim JW, Cho EG, Park SM, Lee KS. Use of acid-suppressive drugs and risk of pneumonia: a systematic review and meta-analysis. CMAJ. 2011;183(3):310-319; Giuliano C, Wilhelm SM, Kale-Pradhan PB. Are proton pump inhibitors associated with the development of community-acquired pneumonia? A meta-analysis. Expert Rev Clin Pharmacol. 2012;5(3):337-344.

CAP, and Zirk-Sadowski,[20] a longitudinal study without control for mutable risk factors for CAP. Because the studies are either low quality or do not show a strong association between PPI and CAP, we find that they do not offer reasonable evidence of a causal association between PPI use and CAP.

To respond to the Petition, FDA completed a systematic literature review to update our previous assessment of the PPI-CAP literature. As part of this more recent effort, FDA identified 20 articles reporting results from observational studies not considered in response to the P-7104 Petition or cited in support of your Petition. After identifying 4 of the 20 articles as potentially containing good quality information, we determined that the statistically significant but low magnitude associations observed between PPIs and CAP could be explained by residual or uncontrolled confounding, in particular, *confounding by indication*. For example, patients with severe GERD are often prescribed PPIs and severe GERD plausibly predisposes patients to pneumonia through pulmonary aspiration of material refluxed from the stomach.

Evidence from randomized controlled trials (RCTs) does not resolve uncertainties presented by the observational studies as the RCTs had their own set of weaknesses. For example, the RCTs were typically too small to detect pneumonia signals, and some used a safety outcome that combined serious and non-serious events. Some RCTs reported similar risks of CAP between treatment with PPIs and placebo.[21] Existing RCTs reviewed by FDA do not provide meaningful evidence that PPIs cause CAP.

In addition to the studies and literature described above, we separately considered the extent to which CAP is consistent with the pharmacology of the drug in assessing whether there is reasonable evidence of a causal relationship.[22] As explained above, the evidence presented in the Petition for PPIs' pharmacological effect on lysosomes appears too speculative.[23] In the Agency's clinical judgment, after reviewing the available evidence, concerns about CAP as a potential safety hazard are too ill-defined to support requiring SLCs that warn of risks of CAP with PPI use.

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[20] Zirk-Sadowski J, Masoli JA, Delgado J, et al. Proton-pump inhibitors and long-term risk of community-acquired pneumonia in older adults. J Am Geriatr Soc. 2018;66(7):1332-1338.

[21] Estborn L, Joelson S. Occurrence of community-acquired respiratory tract infection in patients receiving esomeprazole: retrospective analysis of adverse events in 31 clinical trials. Drug Saf. 2008;31(7):627-636; Estborn L, Joelson S. Frequency and time to onset of community-acquired respiratory tract infections in patients receiving esomeprazole: a retrospective analysis of patient-level data in placebo-controlled studies. Aliment Pharmacol Ther. 2015;42(5):607-613; Moayyedi P, Eikelboom JW, Bosch J, et al. Safety of proton pump inhibitors based on a large, multi-year, randomized trial of patients receiving rivaroxaban or aspirin. Gastroenterology. 2019;157(3):682-691 e682.

[22] *Warnings and Precautions Guidance* at 3.

[23] Liu W, 2013 at 1343-1352.

B. HAP

The P-7104 Petition did not request that FDA take action with respect to risk of HAP with PPI use, and FDA's review for the P-7104 Petition did not analyze risk of HAP with PPI use. Your Petition cites one observational study that described an association between PPIs and pneumonia in hospital patients not treated in an intensive care unit (ICU).[24] However, we were unable to draw useful conclusions about the relationship of PPI treatment to HAP from this study because the cross-sectional design of this observational study precluded confident understanding of whether the PPI use occurred before onset of the pneumonia or vice versa.

Our own literature review did not yield evidence that warrants SLCs for PPI labeling regarding risk of HAP. Although there are some observational studies indicating an association between PPIs and HAP in patients with critical illness,[25] the relatively few published reports from observational studies in patients without critical illness offer evidence too inconsistent to indicate a risk necessitating labeling changes.[26]

Moreover, we find RCTs involving critically ill patients that show no increased risk of HAP-related endpoints with PPI treatment more persuasive than the inconsistent findings in the observational studies. In particular, two historic RCTs helped resolve long-standing uncertainty about the possible offsetting effects of PPIs for stress ulcer prophylaxis on clinically important GI bleeding versus serious infectious complications, including HAP.[27] Both RCTs confirmed benefit with respect to clinically important GI bleeding. One placebo-controlled RCT of

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[24] Herzig SJ, Howell MD, Ngo LH, Marcantonio ER. Acid-suppressive medication use and the risk for hospital-acquired pneumonia. JAMA. 2009;301(20):2120-2128.

[25] See e.g., Beaulieu M, Williamson D, Sirois C, Lachaine J. Do proton-pump inhibitors increase the risk for nosocomial pneumonia in a medical intensive care unit? J Crit Care. 2008;23(4):513-518 (indicating an association between nosocomial pneumonia and PPI in patients admitted to a medical ICU); Buendgens L, Bruensing J, Matthes M, et al. Administration of proton pump inhibitors in critically ill medical patients is associated with increased risk of developing *Clostridium difficile*-associated diarrhea. J Crit Care. 2014;29(4):696 e611-695 (indicating an association between PPI and pneumonia in ICU patients); MacLaren R, Reynolds PM, Allen RR. Histamine-2 receptor antagonists vs proton pump inhibitors on gastrointestinal tract hemorrhage and infectious complications in the intensive care unit. JAMA Intern Med. 2014;174(4):564-574 (indicating association between PPI and ventilator-associated pneumonia in ICU patients).

[26] See e.g., Miano TA, Reichert MG, Houle TT, MacGregor DA, Kincaid EH, Bowton DL. Nosocomial pneumonia risk and stress ulcer prophylaxis: a comparison of pantoprazole vs ranitidine in cardiothoracic surgery patients. Chest. 2009;136(2):440-447; Redelmeier DA, McAlister FA, Kandel CE, Lu H, Daneman N. Postoperative pneumonia in elderly patients receiving acid suppressants: a retrospective cohort analysis. BMJ. 2010;340:c2608; Bateman BT, Bykov K, Choudhry NK, et al. Type of stress ulcer prophylaxis and risk of nosocomial pneumonia in cardiac surgical patients: cohort study. BMJ. 2013;347:f5416.

[27] Krag M, Marker S, Perner A, et al. Pantoprazole in patients at risk for gastrointestinal bleeding in the ICU. N Engl J Med. 2018;379(23):2199-2208; PEPTIC Investigators for the Australian New Zealand Intensive Care Society Clinical Trials Group, Young PJ, Bagshaw SM, et al. Effect of stress ulcer prophylaxis with proton pump inhibitors vs histamine-2 receptor blockers on in-hospital mortality among ICU patients receiving invasive mechanical ventilation: The PEPTIC Randomized Clinical Trial. JAMA. 2020;323(7):616-626.

pantoprazole for stress ulcer prophylaxis provided no actionable[28] evidence suggesting HAP risk from PPI use.[29] Additionally, a cluster crossover RCT of treatment with PPIs versus H2 Receptor Antagonists (H2RA) reported similar treatment outcomes for HAP-related endpoints (e.g., duration of ICU stay).[30] Thus, we find that neither the available literature nor other clinical factors warrant labeling changes to warn of risk of HAP with PPI use.

III. CONCLUSION

After careful review of information related to your request, we conclude that there is not reasonable evidence of a causal association between PPIs and pneumonia (both CAP and HAP) to warrant the labeling changes requested in the Petition. For the reasons described above, the Petition is denied. FDA will continue to monitor and review available safety information related to PPIs and take any further action as appropriate.

Sincerely,

Douglas C. Throckmorton -S

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Date: 2023.05.12 10:02:12 -04'00'

Patrizia Cavazzoni, M.D.
Director
Center for Drug Evaluation and Research

[28] For the purposes of our assessment, FDA defined absence of actionable risk as a primary study result with 95% confidence interval that excludes PPI-specific increase in pneumonia risk greater that 20-30%. While the available data appears to rule out a large (>20-30%) HAP risk, it is impossible to rule out a small HAP risk.

[29] Krag 2018.

[30] PEPTIC Investigators 2020.