CITIZENS PETITION TO FOOD AND DRUG ADMINISTRATION

Division of Dockets Management

Food and Drug Administration

Room 1061

5630 Fishers Lane

Rockville, MD 20852

ALLIANCE FOR NATURAL HEALTH USA 1011 E Jefferson St. Ste 204 Charlottesville, VA 22902 Petitioners, v. FOOD AND DRUG ADMINISTRATION Division of Dockets Management Room 1061 5360 Fishers Lane Rockville, MD 20852	Docket Number ____

ACTION REQUESTED

Pursuant to the right to petition the government clause contained in the First Amendment of the United States Constitution,[1] the Administrative Procedure Act,[2] and the Food Drug and Administration regulations,[3] Petitioners submit this petition for rulemaking under the authority of the Food and Drug Cosmetic Act 21 USC §355(e)(3) to request the U.S Commissioner of the Food and Drug Administration to undertake the following action: Issue a regulation that:

1. All 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.

STATEMENT OF GROUNDS

The Alliance for Natural Health petitions the FDA on the grounds of the Federal Food, Drug and Cosmetic Act 21 U.S.C Section 355(e)(3):

> *Withdrawal of approval; grounds; immediate suspension upon finding imminent hazard to public health*
>
> *The Secretary shall, after due notice and opportunity for hearing to the applicant, withdraw approval of an application with respect to any drug under this section if the Secretary finds…*
>
> *(3) on the basis of new information before him with respect to such drug, evaluated together with the evidence available to him when the application was approved, that there is a lack of*

[1] "Congress shall make no law ... abridging ... the right of the people ... to petition Government for a redress of grievances." U.S.Const. amend. I.
[2] 5 U.S.C. § 553 (e) (2009).
[3] 21 C.F.R. § 10.30

substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling thereof;[4]

BACKGROUND

More than 15 million Americans use prescription PPIs with an additional unknown number of people taking over-the-counter PPIs.[5] The market for PPIs is estimated to be worth $3.24 billion.[6]

PPIs reduce the production of acid in the stomach and include:

- omeprazole (Prilosec, Prilosec OTC, Zegerid)
- lansoprazole (Prevacid)
- pantoprazole (Protonix)
- rabeprazole (Aciphex)
- esomeprazole (Nexium)
- dexlansoprazole (Dexilant)

Over the past several decades, proton pump inhibitors (PPIs) have emerged as the standard of care to treat a variety of gastrointestinal disorders. Initially believed to be relatively safe, a multitude of side effects and risks are emerging.

Nutritional deficiencies, such as vitamin B12, iron, zinc, calcium, magnesium, and copper result from lower gastric acid levels; calcium malabsorption increases hip fractures; and PPIs lower the barrier to colonization and infections from invading pathogens, increasing the incidence of Clostridium difficile.[7]

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[4] 21 U.S.C § 3
[5] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5514820/
[6] https://www.bloomberg.com/press-releases/2019-06-25/proton-pump-inhibitors-ppis-market-worth-usd-3-24-billion-at-4-cagr-during-2019-2023-technavio
[7] Fohl, AL and Regal, RE. (2011). Proton pump inhibitor-associated pneumonia: Not a breath of fresh air after all? *World J Gastrointest Pharmacol Ther.* June 6: 2(3): 17-26.

Data now show that PPIs also increase the risk of both community-acquired pneumonia (CAP) and hospital-acquired pneumonia (HAP).

The causes of PPI-associated pneumonia are believed to be multifactorial, but stem from compromising the stomach's "acid mantle", which protects against pathogenic bacteria. Acid-labile pathogenic bacteria may then be aspirated.[8] PPIs, through the inhibition of extra-gastric enzymes, may also reduce the acidity of the upper aerodigestive tract, increasing colonization of the larynx, esophagus, and lungs.[9]

PPIs have also been shown to have a profound effect on cells other than those to which they are targeted. One study noted "that activation of the PPIs may occur to a certain extent in other cells, in particular within the acidic environment of lysosomes. Therefore it is possible that PPIs might also reduce the acidification of lysosomes."[10] Inhibition of lysosomes can have profound human health consequences. A study concluded "that many of the PPI adverse effects are caused by systematically compromised immunity, a result of PPI inhibition of the lysosomal enzymes."[11] It stands to reason that inhibited immunity leaves patients more open to infections, including pneumonia.

There are an estimated 4.9 million cases of pneumonia in the US per year, requiring more than 250,000 hospitalizations and resulting in 50,000 deaths.[12] The cost of treating pneumonia in the US is estimated to be $13.4 billion.[13]

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[8] Fohl, AL and Regal, RE. (2011). Proton pump inhibitor-associated pneumonia: Not a breath of fresh air after all? *World J Gastrointest Pharmacol Ther.* June 6: 2(3): 17-26. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3124633/

[9] Fohl, AL and Regal, RE. (2011). Proton pump inhibitor-associated pneumonia: Not a breath of fresh air after all? *World J Gastrointest Pharmacol Ther.* June 6: 2(3): 17-26. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3124633/

[10] Sukhovershin RA, Cooke JP. How May Proton Pump Inhibitors Impair Cardiovascular Health? *Am J Cardiovasc Drugs.* 2016 Jun; 16(3); 153-161. 111161616(https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4864131/

[11] Liu W, Baker SS, Trinidad J, Burlingame AL. Baker RD, Forte JG, Virtuoso LP, Egilmez NK, Zhu L. Inhibition of lysosomal enzyme activities by proton pump inhibitors. *J Gastroenterol.* 2013 Dec; 48(12): 1343-52.

[12] https://www.cdc.gov/dotw/pneumonia/index.html

[13] https://bmchealthservres.biomedcentral.com/articles/10.1186/s12913-018-3529-4

PPIs AND COMMUNITY-ACQUIRED PNEUMONIA

A multitude of studies have found a statistically significant increase in the incidence of community-acquired pneumonia (CAP) for those using PPI drugs. The following is a selection of studies demonstrating this increase.

In a nested case-control study, 5,551 new cases of documented pneumonia were observed from a total of 364,683 individuals. Patients were approximately four times more likely to acquire pneumonia when using PPIs compared to non-users, regardless of the appropriateness of the therapy. When adjusted for individuals currently using PPIs and those who had stopped, the relative risk of developing pneumonia was nearly 1.89 with current use, approximately two times more likely to acquire pneumonia following PPI administration.[14]

In a study of 185,533 elderly veterans conducted by Roughead et al, there was a 16% increase in hospitalization for pneumonia in the population receiving PPIs.[15]

A study by Myles et al found the risk of pneumonia increased by 55% in patients who were taking PPIs.[16] This study identified 3,709 cases of pneumonia and 22,174 controls.

Rodriguez et al found that patients had a16% increase in the incidence of pneumonia relative to matched controls in patients between the ages of 20 and 79.[17]

[14] 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;292:1955-1960. https://www.ncbi.nlm.nih.gov/pubmed/15507580
[15] Roughead EE, Ramsay EN, Pratt NL, Ryan P, Gilbert AL. Proton-pump inhibitors and the risk of antibiotic use and hospitalisation for pneumonis. *Med J Aust.* 2009; 190:114-116.
[16] 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; 18:269-275.

Johnstone et al conducted a meta-analysis including six studies evaluating almost one million patients, which showed a significant increase of pneumonia in patients taking PPIs.[18] A second meta-analysis expanded on this analysis to include 18 studies and found a 27% increase in pneumonia for PPI users.[19]

A meta-analysis of nine case-controlled and cohort studies consisting of 120,863 pneumonia cases from 1987 to 2006 conducted by Guiliano et al concluded that practitioners need to be vigilant about the adverse effects of PPIs and consider alternative therapies.[20]

Lambert, et al studied community-acquired pneumonia with outpatient proton-pump inhibitor therapy. In a systematic review of 33 studies including 226,769 cases of CAP out of 6,351,656 participants, outpatient PPI risk was associated with a 1.5-fold increased risk of CAP.[21]

The Meijvis et al study reaffirmed that the use of PPIs is associated with an increased risk of CAP in a population-based, case-control study with 430 cases with pneumonia and 1,720 matched controls.[22]

The Zirk-Sadowski et al study also found in a large cohort of older adults in primary care, PPI prescription was associated with greater risk of pneumonia.[23]

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[17] Rodriguez LA, Ruigomez A, Wallander MA, Johansson S. Acid-suppressive drugs and community-acquired pneumonia. *Epidemiology.* 2009;20:800-806.
[18] Johnstone J, Nerenberg K, Loeb M. Meta-analysis: proton pump inhibitor use and the risk of community-acquired pneumonia. *Aliment Pharmacol Ther.* 2010;31:1165-1177.
[19] 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;183:310-319.
[20] 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 May;5(3):337-44.
[21] Lambert AA, Lam J, Paik JJ, Ugarte-Gil C, Drummond MB, Crowell TA. Risk of Community-Acquired Pneumonia with Outpatient Proton-Pump Inhibitor Therapy: A Systematic Review and Meta-Analysis. *PLoS One.* 2015; 10(6):e0128004.
[22] Meijvis SCA, Cornips MCA, Voorn GP, Souverein PC, Endeman H, Blesma DH, Leufkens HGM, van de Garde EMW. Microbial evaluation of proton-pump inhibitors and the risk of pneumonia. *Eur Respir J.* 2011; 38: 1165-1172.
[23] Zirk-Sadowski J, Masoli JA, Delgado J, Hamilton W, Strain WD, Henley W, Melzer D, Ble A. Proton-pump Inhibitors and Long-Term Risk of Community=Acquired Pneumonia in Older Adults. *JAGS.* 2018; 66: 1332-1338.

Finally, it should be noted that PPIs also impact the gastrointestinal microbiota, which could be linked to reducing immunity and hence increasing pneumonia risk.[24]

PPI's AND HOSPITAL-ACQUIRED PNEUMONIA

A statistically significant increase in the incidence of hospital-acquired pneumonia (HAP) for those using PPI drugs in the hospital setting has also been shown.

Herzig et al conducted a prospective study of 63,878 admissions to a large medical center in Boston assessing the incidence of hospital-acquired pneumonia. The total incidence of HAP was 3.5%. When adjusted for co-morbidities, the odds ratio of patients with HAP who were exposed to PPIs within 48 hours of admission was 1.3, a statistically significant number.[25]

ADVERSE EVENT REPORTS FOR PPI DRUGS

FDA Adverse Event Reporting System supports the FDA's post-marketing safety surveillance program for all marketed drug and therapeutic biologic products. It contains adverse event reports (AER) FDA has received from manufacturers as required by regulation along with reports received directly from consumers and healthcare professionals.[26] The FDA began collecting AER data in 2004.

PPIs are generally treated as a single category or class of pharmacological agents during observations made of the impact of these drugs in clinical practice and scientific literature. Therefore, it

[24] 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.
[25] Herzig SJ, Howell MD, Ngo LH, Marcantonio ER. Acid-suppressive medication use and the risk for hospital-acquired pneumonia. *JAMA.* 2009;301:2120-2128.
[26] https://www.fda.gov/drugs/drug-approvals-and-databases/fda-adverse-event-reporting-system-faers

is typically recognized that an adverse reaction that is observed in relation to one PPI is likely to be found in other PPI drugs.[27]

The following AER data reflect the number of pneumonia cases, serious pneumonia cases, and deaths from pneumonia in patients taking PPIs, as reported by medical professionals, manufacturers, and consumers who believed the harm resulted from PPI drugs.

Drug alone

omeprazole (Prilosec, Prilosec OTC, Zegerid)

635 cases, 619 serious cases, 133 deaths (1989-2020)

lansoprazole (Prevacid)

432 cases, 428 serious, 180 deaths (1995-2020)

pantoprazole (Protonix)

373 cases, 372 serious, 78 deaths (2008-2020)

rabeprazole (Aciphex)

25 cases, 25 serious, 7 deaths (2004-2020)

esomeprazole (Nexium)

80 total cases, 79 serious, 14 deaths (2004-2020)

[27] https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/fda-drug-safety-communication-possible-increased-risk-fractures-hip-wrist-and-spine-use-proton-pump

dexlansoprazole (Dexilant)

50 total, 47 serious, 14 death (2010-2020)

The following AER data reflect the number of pneumonia cases, serious pneumonia cases, and deaths from pneumonia in patients taking PPIs along with other drugs, as reported by medical professionals, manufacturers, and consumers who believed the harm resulted from the drugs.

omeprazole (Prilosec, Prilosec OTC, Zegerid)---with sodium, magnesium, sodium bicarbonate

964 total, 916 serious, 190 deaths

lansoprazole (Prevacid) with amoxicillin, naproxen, metronidazole

433 total, 429 serious, 180 deaths

pantoprazole (Protonix) with magnesium, sodium, and sodium anhydrous

701 total, 697 serious, 149 deaths

rabeprazole (Aciphex) with sodium, domperidone, amoxicillin, aceclofenac (NSAID)

159 total, 158 serious, 51 deaths

esomeprazole (Nexium) with strontium, magnesium, naproxen (NSAID), sodium

136 total, 135 serious, 19 deaths

<u>PPI's AND HYPOCHLORHYDRIA</u>

One of the main reasons for taking PPIs is for gastroesophageal reflux disease (GERD), symptoms of which include heartburn and indigestion. However, these and related symptoms of GERD can often be caused by too little stomach acid (hypochlorhydria), rather than an excess.[28] In one study US researchers found that over 30% of men and women past the age of 60 suffer from *atrophic gastritis*, a condition marked by little or no acid secretion.[29] A second study found that up to 40% of postmenopausal women have no basal gastric acid secretions.[30] Long-term use of PPI's can cause hypochlorhydria, which in turn has negative effects on digestion and nutrient absorption and can lead to long-term health problems including autoimmune disorders and increased risk of infection.[31, 32]

ENVIRONMENTAL IMPACT

Petitioner claims a categorical exclusion under 21 C.F.R. §25.30.

ECONOMIC IMPACT

Pursuant to 21 C.F.R. §10.30(b), economic impact information will be submitted by the Petitioner upon the request of the Commissioner.

CERTIFICATION STATEMENT

[28] https://nutritionreview.org/2018/11/gastric-balance-heartburn-caused-excess-acid/

[29] Krasinski SD, Russell RM, Samloff IM, Jacob RA, Dallal GE, McGandy RB, Hartz SC. Fundic atrophic gastritis in an elderly population. Effect on hemoglobin and several serum nutritional indicators. J Am Geriatr Soc. 1986 Nov;34(11):800-6.

[30] Grossman MI, Kirsner JB, Gillespie IE. Basal and histalog-stimulated gastric secretion in control subjects and in patients with peptic ulcer or gastric cancer. Gastroenterology 1963;45:15-26.

[31] Kines, Kasia, MS, MA, CN, CNS, LDN and Krupczak, Tina, MS, CNS, LDN. Nutritional Interventions for Gastroesophageal Reflux, Irritable Bowel Syndrome, and Hypochlorhydria: A Case Report. Integrative Medicine: A Clinician's Journal. 2016 Aug; 15(4): 49–53.

[32] Martinsen, T.C.; Fossmark, R.; Waldum, H.L. The Phylogeny and Biological Function of Gastric Juice—Microbiological Consequences of Removing Gastric Acid. *Int. J. Mol. Sci.* 2019, *20*, 6031.

The undersigned certifies, that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner, which are unfavorable to the petition.

Respectfully submitted,

Gretchen DuBeau

Executive and Legal Director

Alliance for Natural Health USA