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Division of Dockets Management
Food and Drug Administration
5630 Fishers Lane
Room 1061, HFA-305
Rockville, Maryland 20852

Re: Comments on Citizen's Petition #FDA-2017-P-2733

Herein, the Consumer Healthcare Products Association (CHPA), the 136-year-old trade association representing U.S. manufacturers and distributors of over-the-counter (OTC) medicines and dietary supplements (chpa.org), provides comments on Citizen Petition # FDA-2017-P-2733¹ which requests the addition of a warning to labeling for all nonprescription (over-the-counter, OTC) drug products labeled to relieve or prevent heartburn associated with reflux disease, acid indigestion, and sour stomach noting that these products do not eliminate the risk of esophageal cancer.

Based on the paucity of evidence provided by the Petitioners' as well as the support cited below, this Petition fails to demonstrate the need for addition of a warning regarding the potential masking of esophageal cancer to the labeling for OTC drug products indicated for the treatment of heartburn. In sum, there is no credible evidence to suggest that OTC products indicated for the treatment of heartburn mask the symptoms of early esophageal cancer or delay its presentation.

Each class of OTC heartburn remedy discussed in the petition is indicated for short-term use and consumers currently are provided with instructions on the *Drug Facts* labeling to contact a healthcare professional if their symptoms do not resolve after 2 weeks of treatment. Adding an additional warning to these products would likely confuse and alarm consumers without providing any additional helpful information and lead to reduced use of products shown to be effective in treating heartburn symptoms and reducing healthcare costs.

As support for our position, we provide the following: a brief background on each of the drug product classes implicated in this Petition; discuss current labeling which clearly describes the need to stop using these products and consult a healthcare professional if symptoms worsen or persist for more than 14 days; and cite recent medical literature publications and professional Guideline documents from experts in the fields of gastroenterology and cancer incidence.

¹ Submitted by the Esophageal Cancer Action Network (dated May 1, 2017).

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A. Petition Background

The Petitioners have requested the addition of a warning to the labeling of all OTC drug products labeled to relieve or prevent heartburn associated with reflux disease, acid indigestion, and sour stomach noting that these products do not eliminate the risk of esophageal cancer. A further request is made to include information directing consumers to see their physician if they experience persistent heartburn associated with reflux disease, acid indigestion, or sour stomach due to the risk of esophageal cancer.

Evidence provided by the Petitioners' in support of their requests consists of poll results demonstrating that only 14% of ~1,000 American adults are aware that reflux disease can cause esophageal cancer. Petitioners also claim that "more than half" of subjects with Barrett's esophagus, a known risk factor for esophageal cancer, are unaware that they have the condition.

A small percentage of subjects who experience chronic GERD will develop Barrett's esophagus, a precancerous condition associated with a low probability of progression to cancer.² Barrett's esophagus is only detected in ≈1-2% of the general population, and ≈15% of patients with chronic GERD (>5 years). Of the minority population with Barrett's esophagus, the risk of progression to esophageal cancer is quite small – approximately 0.2% to 0.5% per year. There is no routine screening program for the general population beginning at age 50 for Barrett's esophagus because it is uncommon in the general population, and a very low lifetime risk for progression to cancer (far less than 1% for the general population).

This contrasts with colorectal polyps and colorectal cancer. In the United States, approximately 30 to 40 % of the population over the age of 50 has one or more adenomas, the type of polyp that can progress to colorectal cancer. According to the American Cancer Society,³ the lifetime risk of developing colorectal cancer for the general population is 4.7% for men and 4.4% for women. The Centers for Disease Control and Prevention has developed a colorectal cancer screening program beginning at age 50,⁴ as the overall risk of developing colorectal cancer is high, and colorectal cancer can be prevented by removing adenoma polyps before they progress to cancer.

While the Petitioners' note that heartburn symptoms may be the only warning for some patients with esophageal cancer, other warning symptoms (*e.g.*, hematemesis, dysphagia, weight or appetite loss or abdominal pain) may be present if cancer is the underlying condition.^{5,6} The Petitioners' fail to address the finding that subjects diagnosed with Barrett's esophagus often experience no GERD symptoms.^{7,8}

² Bhat *et al.*, 2011 Risk of Malignant Progression in Barrett's Esophagus Patients: Results From a Large Population-Based Study, *J Natl Canc Inst* 103(13):1049-1057

³ <https://www.cancer.org/cancer/colon-rectal-cancer/about/key-statistics.html>

⁴ <https://www.cdc.gov/cancer/crccp/index.htm>

⁵ Vakil *et al.*, 2006 Limited value of alarm features in the diagnosis of upper gastrointestinal malignancy: systematic review and meta-analysis, *Gastroenterol*, 131(2):390-401.

⁶ Talley *et al.*, 2005 Guidelines for the management of dyspepsia, *Am J Gastroenterol*, 100(10): 2324-2337.

⁷ Rex, DK *et al.*, Screening for Barrett's esophagus in colonoscopy patients with and without heartburn. *Gastroenterol* 2003;125(6):1670-1677.

⁸ Fan, X and Snyder, N Prevalence of Barrett's esophagus in patients with or without GERD symptoms: role of race, age, and gender. *Dig Dis Sci* 2009; 54(3):572-577.

B. Heartburn

Heartburn is a relatively common gastrointestinal symptom caused by acid regurgitation into the esophagus which is often described as indigestion or a burning sensation in the chest. The condition is experienced at least once per week by ~18-28% of adults, while ~5% suffer from it daily.^{9,10} “Episodic heartburn” occurs ≤ 1 day per week, while “frequent heartburn” occurs ≥ 2 days per week. Subjects experiencing mild or intermittent heartburn often are afforded adequate relief through lifestyle modifications or with short-term use of antacids.

Currently, there are three main OTC product categories available to prevent or relieve heartburn associated with acid indigestion or sour stomach: antacids; histamine-2 receptor antagonists (H₂RAs); and, proton pump inhibitors (PPIs).

A brief overview for each of these drug classes is provided below.

⁹ El Seag *et al.*, 2014, Update on the epidemiology of gastro-oesophageal reflux disease: a systematic review, *Gut* 63(6):871-880.

¹⁰ Sigterman *et al.*, 2013, Short-term treatment with proton pump inhibitors, H₂-receptor antagonists and prokinetics for gastro-oesophageal reflux disease-like symptoms and endoscopy negative reflux disease, *Coch Database Syst Rev*, May 31, (5):CD002095

C. OTC Drugs Indicated for the Treatment of Heartburn, Acid Indigestion, and Sour Stomach

1. Antacids

Antacid products provide relief of gastric hyperacidity by neutralizing stomach acid resulting in an increased pH of stomach contents and aid in the control of gastroesophageal reflux by increasing intraesophageal pH and decreasing pepsin activity. These products do not prevent subsequent heartburn episodes and are not recommended as primary therapy for frequent heartburn.

Table 1 provides examples of currently marketed OTC antacid products.

Table 1. Examples of Marketed OTC Antacids

Brand name	Active ingredient
Tums	calcium carbonate
Milk of Magnesia	magnesium hydroxide
Gaviscon	aluminum hydroxide, magnesium carbonate
Gelusil	aluminum hydroxide, magnesium hydroxide, simethicone
Maalox	calcium carbonate, simethicone
Mylanta	aluminum hydroxide, magnesium hydroxide, simethicone
Roloids	calcium carbonate, magnesium hydroxide
Children's Pepto Bismol	calcium carbonate

2. Histamine-2-receptor antagonists (H₂RAs)

H₂RAs are effective in the treatment of peptic ulcer disease and symptoms of GERD. These drugs inhibit the secretion of acid by inhibiting the action of histamine at H₂ receptors in gastric parietal cells. Due to the development of tolerance to their effect, these drugs are not specifically indicated for the treatment of frequent heartburn.¹¹

Table 2 provides examples of currently marketed OTC H₂RAs products.

Table 2. Examples of Marketed OTC H₂RAs

Brand name	Active ingredient
Pepcid	famotidine
Zantac	ranitidine
Tagamet	cimetidine
Axid	nizatidine

¹¹ McRorie *et al.*, 2014 Evidence-based treatment of frequent heartburn: the benefits and limitations of over-the-counter medications, *World J Gastrointest Pharm Ther*, 5(2):57-62.

3. Proton Pump Inhibitors (PPIs)

PPIs are frequently used to treat the symptoms of GERD and acid-related disorders and are considered the most effective therapy due to consistent acid suppression. There are currently four PPIs available OTC to treat frequent heartburn (*e.g.*, 2 or more days a week).

Table 3 provides examples of currently marketed OTC PPI products.

Table 3. Examples of Marketed OTC PPIs

Brand name	Active ingredient
Prilosec OTC	omeprazole
Zegerid OTC	omeprazole with sodium bicarbonate
Prevacid 24HR	lansoprazole
Nexium 24HR	esomeprazole

D. Sufficiency of Current Labeling for OTC Products

In addition to not being supported by the available evidence, the Petitioners' request to add a warning is obviated by the current labeling for these products. For each of the three separate classes of products, consumers are advised to consult a healthcare professional if symptoms persist for more than 2 weeks. Adding an additional unsubstantiated warning that these products mask symptoms of esophageal cancer provides no additional helpful information, crowds an already-extensive label, would likely only serve to alarm consumers and would result in unnecessary doctor visits.

As noted in the Petition, the current labeling for OTC products indicated to treat frequent heartburn¹² instructs consumers to:

Ask a doctor before use if you have

- had heartburn over 3 months. This may be a sign of a more serious condition.

Stop use and ask a doctor if

- your heartburn continues or worsens
- you need to take this product for more than 14 days
- had heartburn over 3 months. This may be a sign of a more serious condition.
- you need to take more than 1 course of treatment every 4 months (*for PPIs only*)

¹² Labeling for H₂RAs (indicated for the treatment of heartburn) is similar to that of PPIs, which are indicated to treat frequent heartburn (occurring two or more days a week).

Antacid products, indicated for the treatment of heartburn, acid indigestion, and sour stomach note the following:

- do not use the maximum dosage for more than 2 weeks except under the advice and supervision of a doctor
- do not take for symptoms that persist for more than 2 weeks unless advised by a doctor (*from Tums label*)

Thus, in each case consumers are advised to consult a healthcare professional if symptoms persist for more than 2 weeks. Adding an additional unsubstantiated warning that these products mask symptoms of esophageal cancer crowds an already-extensive label and would likely only serve to alarm consumers and result in unnecessary doctor visits.

E. Esophageal Cancer – Risk Factors

1. Known Risk Factors

The National Cancer Institute website on Esophageal Cancer Prevention¹³ (updated March 2017) notes that smoking and drinking may account for approximately 90% of esophageal squamous cell carcinoma cases in the U.S.¹⁴ There is an association between GERD and adenocarcinoma, particularly if symptoms are long-standing and severe.^{15,16} Known risk factors associated with esophageal adenocarcinoma (EAC) include white race, male gender, abdominal obesity, tobacco use, and chronic symptoms of GERD¹⁷ but none seem dominant.¹⁸ As stated previously however, OTC heartburn medicines are indicated for short-term use and consumers are advised to consult a healthcare professional if symptoms persist.

2. Lack of Association Between OTC Drugs Used to Prevent or Treat Heartburn with Esophageal Cancer or Barrett's Esophagus

Each of the noted classes of OTC heartburn remedies in the petition is indicated for short-term use and label directions include the warning to stop use and ask a doctor if symptoms persist. While treatment of chronic GERD with PPIs may help prevent Barrett's esophagus and esophageal cancer,¹⁹ this should be done under the guidance of a healthcare professional and would not apply to short-term (2 week) use of OTC PPIs.

¹³ https://www.cancer.gov/types/esophageal/hp/esophageal-prevention-pdq#link/171_toc (accessed June 8, 2017). Similar risk factors are identified by the [Canadian Cancer Society](#).

¹⁴ See also, Engel *et al.*, 2003, Population attributable risks of esophageal and gastric cancers, *J Natl Cancer Inst*, 95(18):1404-1413.

¹⁵ Lagergren *et al.*, 1999, Symptomatic gastroesophageal reflux as a risk factor for esophageal adenocarcinoma, *NEJM*, 340(11):825-831.

¹⁶ Cook *et al.*, 2014, Gastroesophageal reflux in relation to adenocarcinomas of the esophagus: a pooled analysis from the Barrett's and Esophageal Adenocarcinoma Consortium (BEACON), *PLoS One*, 9(7):e103508

¹⁷ Falk, 2009, Risk factors for esophageal cancer development, *Surg Oncol Clin N Am*, 18(3):469-485.

¹⁸ Kong *et al.*, 2014, Exploring the recent trend in esophageal adenocarcinoma incidence and mortality using comparative simulation modeling, *Cancer Epidemiol Biomarkers Prev*, 23(6):997-1006.

¹⁹ American Cancer Society at - <https://www.cancer.org/cancer/esophagus-cancer/causes-risks-prevention/prevention.html> (accessed July 7, 2017). Risk factors include increased age, male gender, gastroesophageal reflux disease, Barrett's esophagus, tobacco and alcohol, obesity, diet, achalasia, tylosis, Plummer-Vinson syndrome, workplace exposures, injury to the esophagus, history of other cancers, and human papilloma virus.

A recent publication²⁰ from nine international experts in gastroesophageal reflux disease reviewing the available data on the risks and benefits of OTC PPI use noted that PPIs have not been shown to mask the symptoms of early esophageal cancer or meaningfully delay its presentation. The authors further noted that “individuals adhering to label instructions for OTC PPIs are extremely unlikely to have a delay in the diagnosis of EAC [esophageal adenocarcinoma]”. The available studies they reviewed focused on whether PPI use is a risk factor for cancer or has a chemopreventive role in Barrett’s esophagus.

The rising incidence of esophageal cancer preceded the introduction of PPIs into clinical practice in 1989.²¹ There is no credible evidence demonstrating that PPIs increase the risk for esophageal cancer and indeed some studies suggest that long term PPI use may protect against cancer development in patients diagnosed with Barrett’s esophagus.²² Others have noted that the risk of masking a serious underlying disease with short-term use of an OTC PPI appears to be low.²³

F. Professional Association Recommendations Regarding Treatment of Gastroesophageal Reflux Disease (GERD)²⁴

Several professional associations have released guidelines discussing the diagnosis and treatment of GERD. Below we provide a brief overview of the recommendations each group provides. Each recommends longer term (*e.g.*, 8 weeks) treatment with a PPI (or in some cases an H2RA) with additional follow-up should patients be unresponsive to this therapy. Consumers taking an OTC antacid product whose symptoms are not alleviated by a 2-week treatment (and who may have an underlying condition such as Barrett’s esophagus) currently have access to product labeling instructing them to consult a healthcare professional if their symptoms do not resolve after this time. Thus, by following instructions on the current Drug Facts label, consumers already receive sufficient information for the safe use of the product.

1. American Society of Gastrointestinal Endoscopy (ASGE)²⁵

- We recommend that uncomplicated GERD be diagnosed on the basis of typical symptoms without the use of diagnostic testing, including esophagogastroduodenoscopy EGD.
- We recommend EGD for patients who have symptoms suggesting complicated GERD or alarm symptoms.

²⁰ Johnson *et al.*, 2017, The Safety of Appropriate Use of Over-the-Counter Proton Pump Inhibitors: An Evidence-Based Review and Delphi Consensus, *Drugs*, 77(5):547-561.

²¹ Pohl *et al.*, 2010 Esophageal Adenocarcinoma Incidence: Are We Reaching the Peak?, *Cancer Epi Bio Prev*, 19(6):1468-1470.

²² El-Sarag *et al.*, 2004, Proton pump inhibitors are associated with reduced incidence of dysplasia in Barrett's esophagus, *Am J Gastroent*, 99(10):1877-1883.; Nguyen *et al.*, 2010, Medications (NSAIDs, statins, proton pump inhibitors) and the risk of esophageal adenocarcinoma in patients with Barrett's esophagus, *Gastroenterology*, 138(7):2260-2266; Kastelein *et al.*, 2013, Proton pump inhibitors reduce the risk of neoplastic progression in patients with Barrett's esophagus, *Clin Gastroenterol Hepatol*, 11(4):382-388; Singh *et al.*, 2014, Acid-suppressive medications and risk of oesophageal adenocarcinoma in patients with Barrett's oesophagus: a systematic review and meta-analysis, *Gut*, 63:1229-1237.

²³ Boardman *et al.*, 2015, Partnership in optimizing management of reflux symptoms: a treatment algorithm for over-the-counter proton-pump inhibitors, *Curr Med Res Opin*, 31(7):1309-1318.

²⁴ We note that the products covered in this Citizen Petition (antacids, H₂RAs, and PPIs) are indicated for the treatment of heartburn associated with reflux disease, acid indigestion, and sour stomach and not GERD.

²⁵ American Society of Gastrointestinal Endoscopy, 2015 The Role of Endoscopy in the Management of GERD, *Gastrointest Endosc* 81(6):1305-1310.

- We suggest that repeat EGD be performed in patients with severe erosive esophagitis after at least an 8-week course of PPI therapy to exclude underlying BE [Barrett's Esophagus] or dysplasia.

2. American College of Gastroenterology (ACG)²⁶

- Ambulatory esophageal reflux monitoring is indicated before consideration of endoscopic or surgical therapy in patients with non-erosive disease, as part of the evaluation of patients refractory to PPI therapy, and in situations when the diagnosis of GERD is in question.
- An 8-week course of PPIs is the therapy of choice for symptom relief and healing of erosive esophagitis.
- Non-responders to PPI should be referred for evaluation.
- Maintenance PPI therapy should be administered for GERD patients who continue to have symptoms after PPI is discontinued, and in patients with complications including erosive esophagitis and Barrett's esophagus. For patients who require long-term PPI therapy, it should be administered in the lowest effective dose, including on demand or intermittent therapy.
- Histamine 2-receptor antagonist therapy can be used as a maintenance option in patients without erosive disease if patients experience heartburn relief. Bedtime H₂RA therapy can be added to daytime PPI therapy in selected patients with objective evidence of night-time reflux if needed, but may be associated with the development of tachyphylaxis after several weeks of use.

The ACG has also recently released updated Guidelines for Diagnosing and Managing Barrett's Esophagus.²⁷ They recommend to screen men with chronic symptoms (≥ 5 years) of GERD who have at least 2 additional risk factors. In patients with diagnosed Barrett's esophagus the recommendation regarding PPI use is that patients should receive once-daily therapy. Further, they state that there is now evidence of a chemopreventive effect in which PPIs decrease the risk of progression to neoplastic Barrett's esophagus and that therapy should be considered even in the absence of reflux symptoms.

3. American Gastroenterological Association (AGA)²⁸

- Patients with GERD and acid-related complications should take a PPI for short-term healing, maintenance of healing and long-term symptom control.
- Patients with uncomplicated GERD who respond to short-term PPIs should subsequently attempt to stop or reduce them.
- Patients with Barrett's esophagus and symptomatic GERD should take a long-term PPI.
- Asymptomatic patients with Barrett's esophagus should consider a long-term PPI.
- The dose of long-term PPIs should be periodically reevaluated so that the lowest effective PPI dose can be prescribed to manage the condition.

²⁶ Katz *et al.*, 2013 Guidelines for the Diagnosis and Management of Gastroesophageal Reflux Disease, *Am J Gastroenterol*, 108(3):308-328.

²⁷ Shaheen *et al.*, 2016 ACG Clinical Guideline: Diagnosis and Management of Barrett's Esophagus, *Am J Gastroenterol*, 111(1):30-50.

²⁸ Freedberg *et al.*, 2017 The Risks and Benefits of Long-term Use of Proton Pump Inhibitors: Expert Review and Best Practice Advice From the American Gastroenterological Association, *Gastroenterology* 152:706-715.

4. Clinical Guidelines Committee of the American College of Physicians (ACP)²⁹

In most patients with typical GERD symptoms, such as heartburn or regurgitation, an initial trial of empirical acid-suppressive therapy with once-daily proton-pump inhibitors (PPIs) is warranted and endoscopy is not indicated. This may be escalated to twice-daily therapy if once daily therapy is unsuccessful. If 4 to 8 weeks of twice-daily empirical PPI therapy is unsuccessful, further investigation with endoscopy is recommended.³⁰

Economic benefits

In a review performed in 2008,³¹ OTC heartburn medications (PPIs, H₂RAs, antacids) were shown to provide symptom satisfaction and cost saving benefits to consumers and the healthcare system. Ninety-four percent of consumers suffering from heartburn were satisfied with their OTC heartburn medications. Savings to the healthcare system from the availability of OTC heartburn medications to decrease office visits by consumers was estimated to be ~\$757-million annually. The annual savings to the consumer in prescription and office visits was estimated to be \$174. A review³² of economic evaluations of GERD medical management over the past decade found that PPI therapy was both more effective and less costly as empiric therapy for patients with reflux symptoms.

Conclusion

The evidence we review in this response to the Citizen Petition requesting a warning for OTC antacid product labeling regarding the potential to mask the diagnosis of more serious conditions (esophageal cancer or Barrett's esophagus) demonstrates that current product labeling provides sufficient support for the safe and effective use of these products. Addition of such a warning would not impart significant benefit to consumers. The Petitioners' have not provided sufficient evidence to warrant additional warnings and indeed it is likely that adding such a warning would only serve to confuse consumers and prevent them from using short term therapies demonstrated to be effective in the treatment of heartburn.

In regard to the use of PPIs, there is no credible evidence to suggest that use of these products increases the risk for esophageal cancer and, in fact, some studies suggest that long term PPI use may protect against cancer development in patients diagnosed with Barrett's esophagus. OTC PPIs are indicated only for short term use (2 weeks) and consumers are advised to contact a healthcare professional if their symptoms do not resolve in this time. Further, data from the National Cancer Institute's Surveillance, Epidemiology, and End Results Program³³ shows that both new cases and deaths related to esophageal cancer have either remained steady or slightly decreased since the introduction of PPIs into clinical practice in the early 1990's.

CHPA advocates for the safe use of all OTC medicines by encouraging consumers to follow directions provided on the Drug Facts panel. For patients with heartburn, OTC antacids, H₂RAs or

²⁹ Shaheen *et al.*, 2012 Upper Endoscopy for Gastroesophageal Reflux Disease: Best Practice Advice From the Clinical Guidelines Committee of the American College of Physicians, *Ann Int Med*, 157(11):808-16

³⁰ Kahrilas *et al.*, 2008 American Gastroenterological Association Institute technical review on the management of gastroesophageal reflux disease. *Gastroenterology*, 135:1392-1413

³¹ Nielsen, 2008 Benefits of over-the-counter heartburn medication to consumers and the healthcare system, *report sponsored by the Consumer Healthcare Products Association*, Mansfield, J.E. and Callahan, D.

³² Gawron *et al.*, 2014, Economic Evaluations of Gastroesophageal Reflux Disease Medical Management: A Systematic Review, *Pharmacoeconomics*, 32(8):745-758.

³³ <https://seer.cancer.gov/statfacts/html/esoph.html>

PPIs can provide effective short-term relief. If these products are taken as directed and symptoms persist, subjects are instructed to contact a healthcare professional.

We appreciate the opportunity to comment on this Petition. Please feel free to contact me should you have any questions.

Regards,

A handwritten signature in blue ink that reads "Jay Sirois". The signature is fluid and cursive, with the first name "Jay" and last name "Sirois" clearly legible.

Jay Sirois, Ph.D.
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