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# Wyeth

November 7, 2005

Food and Drug Administration  
Division of Dockets Management  
5600 Fishers Lane  
Room 1061  
Rockville, MD 20852

**RE: Docket No. 1976N-0052G  
Comments to Proposed Amendment of Tentative Final Monograph  
for Combination Drug Products**

To Whom it May Concern:

Wyeth Consumer Healthcare (WCH) hereby submits comments to the proposed amendment of the TFM for Cold, Cough, Allergy, Bronchodilator and Antiasthmatic Drug Products for OTC Use, published in the Federal Register on July 13, 2005 (70 FR 40232). WCH markets Primatene Tablets (ephedrine HCl 12.5mg/guaifenesin 200mg) which is directly affected by the proposed amendment.

WCH does not agree with the proposal to classify the combination of an oral bronchodilator and an expectorant as Category II (not generally recognized as safe and effective for OTC use).

WCH has completed a review of the published data from studies evaluating the role of mucus in **mild** asthma – a condition that consumers commonly self-treat with Primatene. As summarized in the attached document, there is extensive data indicating that goblet cell hyperplasia, increased goblet cell counts, increased levels of mucin, and excessive production of mucus regularly occur in **mild** asthmatics as well as in those with more severe forms of the disease. This body of research also demonstrates that these physiological changes closely correlate with clinically relevant symptoms of increased mucus production in the sub-population of mild asthmatics. Accordingly, WCH believes that there is a clear scientific and medical rationale, supported by extensive independent medical literature for combining an expectorant with an oral bronchodilator for use in

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consumers with mild asthma and therefore, current combinations of these two drugs should remain available to the consumer as OTC products.

Sincerely,

*Lauren Quinn for*

WYETH CONSUMER HEALTHCARE  
Sharon Heddish

## MUCUS PRODUCTION IN MILD ASTHMA

On July 13, 2005, FDA proposed an amendment to the Tentative Final Monograph “Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products for Over-the-Counter Human Use, Combination Drug Products.” The Agency raised concerns about a combination of an oral bronchodilator and an expectorant stating “this combination is not rational therapy for the treatment of mild asthma because the expectorant component does not contribute to the relief of the condition.” The Agency went on to state “asthma patients with severe asthma exacerbations and status asthmaticus may develop mucus plugging in small airways causing severe airflow limitation,” and “increased sputum production is not usually problematic in mild asthma”. Based on these concerns, the FDA has tentatively determined that OTC combination products such as Primatene® Tablets containing an expectorant and an oral bronchodilator should no longer be available.

Wyeth Consumer Healthcare (WCH) has marketed Primatene® Tablets containing theophylline and guaifenesin since 1954. In 1996, the tablets were replaced with the current combination of ephedrine hydrochloride 12.5 mg and guaifenesin 200mg. Since the introduction of Primatene® Tablets, we estimate that 3 billion doses of the tablets have been used by consumers. Following the Agency’s proposed amendment, WCH has completed a review of the published data from studies evaluating the role of mucus in **mild** asthma – a condition that consumers commonly self-treat with Primatene. As summarized below, there is extensive data indicating that goblet cell hyperplasia, increased goblet cell counts, increased levels of mucin, and excessive production of mucus regularly occur in **mild** asthmatics as well as in those with more severe forms of the disease. This body of research also demonstrates that these physiological changes closely correlate with clinically relevant symptoms of increased mucus production in the sub-population of mild asthmatics. Accordingly, WCH believes that there is a clear scientific and medical rationale, supported by extensive independent medical literature for **combining an expectorant with an oral bronchodilator for use in consumers with mild asthma** and therefore, current combinations of these two drugs should remain

available to the consumer as OTC products. The following review of the medical literature summarizes the scientific rationale for the continued OTC availability of these products.

### **Structural Remodeling in Mild Asthma**

Asthma is a chronic lung disease typically associated with airway obstruction and morphologically characterized by chronic inflammation and changes of the airway structure. Multiple factors contribute to airway remodeling in asthma including epithelial and matrix abnormalities, increased smooth muscle mass and vascularity, thickening of the airway wall, and mucus-related factors (Bai & Knight, 2005). Some structural modifications are related to disease progression and chronic airway inflammation. Other airway components, such as mucus-secreting structures, change at early stages of the disease. Mucus-related airway remodeling includes goblet cell hyperplasia (GCH), changes in goblet cell counts, and increased area of submucosal glands, all of which result in mucin hyperproduction, a major constituent of airway mucus. These factors, along with decreased mucociliary clearance, contribute to chronic airway inflammation, airway obstruction, and asthma exacerbation.

While excessive mucus production has long been considered an important cause of morbidity and mortality in asthma, early research focused predominantly on cases of severe or fatal asthma (Cluroe, 1989; Bhaskar, 1988; Jeffery, 1992). Using advanced research tools, numerous recent studies have shown that mucus-related pathology also occurs in **mild** asthma. Moreover, comparative studies in mild and severe asthmatics consistently show that mucus-related airway remodeling is independent of asthma severity.

Recognizing the clinical significance of mucus abnormalities in asthma, the National Heart, Lung, and Blood Institute (NHLBI) continuously provides a significant number of grants to research the role of mucus production in asthma. Between 1996 and 2005, NHLBI supported a total of 156 biomedical studies on mucus production using both animal and human asthma models (CRISP NIH, 2005). While many studies are still

ongoing, results of a few published NIH-grant-based studies confirm that airway remodeling specific to mucus production takes place in asthma **regardless of the disease severity**. Ordonez et al. (2001) and Fahy (2002) addressed multiple questions on mucus-related morphology in mild asthma. Twenty-five subjects including seven subjects with mild asthma (FEV1>80% predicted), six subjects with moderate asthma (FEV1<80% predicted), and twelve healthy volunteers were studied. The asthmatic subjects were treated with only a short-acting  $\beta$ -agonist. Clinical diagnosis was determined by spirometry, allergen skin testing, methacholine challenge and bronchoscopy. During bronchoscopy, up to nine biopsies were taken for morphometry, immunohistochemistry, and RNA extraction to investigate the morphological relationship between goblet cells and mucin production in mild and moderate asthmatic subjects compared to a healthy population. Stored mucin in the epithelium, secreted mucin in induced sputum, and goblet cell size and number were measured. The goblet cell number was significantly higher in subjects with mild and moderate asthma compared to controls ( $p<0.05$ ). More importantly, the amount of stored mucin in the airway epithelium was shown to be three times higher in asthmatic subjects than in healthy controls ( $p<0.005$ ). The amount of stored mucin in goblet cells in the subjects with mild asthma was numerically higher than that of the subjects with moderate asthma. Therefore, significant goblet cell hyperplasia, along with increased amounts of stored mucin, are present in subjects with mild asthma. The authors concluded that “increased amounts of mucin raise the probability of acute degranulation of goblet cells leading to mucin hypersecretion as an important component of asthma exacerbations.” This may explain the finding that 13% of subjects who die from asthma had a history suggesting only mild disease prior to their fatal attack (Robertson, 1990).

Groneberg et al. (2002) compared the molecular identity and expression of mucin genes and morphologically confirmed Ordonez’s argument on the presence of mucin hyperproduction in mild asthma. Tracheal, bronchial, and peripheral lung tissues were obtained from four patients who died from *status asthmaticus* and five patients who died from non-pulmonary conditions; bronchial biopsies were obtained from four mild asthma subjects on two separate occasions. Subjects with mild asthma were not on any treatment

except for intermittent use of short-acting bronchodilators. Morphological analysis of sections obtained from fatal *status asthmaticus* and mild asthma patients revealed goblet cell hyperplasia, increased mucus production and glandular hyperplasia. In mild asthmatics, positive extracellular mucus was found in the lumen as plugs adjacent to the epithelial lining, and in the necks of glandular secretory ducts.

Carroll (2002) investigated factors that stimulate secretion from hypertrophic goblet cells and submucosal glands. Similar to the study by Groneberg (2002), tissues were collected at necropsy from eight subjects who died from fatal asthma, eight subjects who were previously diagnosed with asthma but died from a non-respiratory cause, and a similar number of control cases who were not previously diagnosed with asthma. Asthma diagnoses were confirmed based on medical history, symptoms, previous hospitalizations, and measurements of lung function. Cases were excluded if medical records could not be obtained. The author hypothesized that if an increase in the area of submucosal glands results in an increased secretion of mucus, then stimulation of the enlarged glands may account for airway obstruction with mucus. The authors also hypothesized that inflammatory cells potentially may stimulate mucus hyper-excretion. Tissue analysis of subjects with non-fatal asthma, most of whom were mild asthmatics with no history of corticosteroid use showed an increased number of mast cells and neutrophils within the submucosal glands. The number of mast cells, neutrophils, as well as the percentage of degranulated mast cells were significantly higher in mild asthmatics compared to controls ( $p < 0.05$ ). As in the previous study, mucus was found in the small airways of mild asthmatics. Overall, the study suggested that mast cell degranulation rather than neutrophil degranulation is related to mucus secretion. Increased mast degranulation and mucus gland area both contribute to the rapid secretion of increased amounts of mucus in cases of asthma **regardless of its severity**.

Methods other than biopsy have also confirmed that mucus-related morphological changes occur in mild asthma. Lee et al. (2004) used high resolution CT scan (HRCT) to characterize structural differences seen on CT in subjects with near-fatal asthma, non-near-fatal asthma, and healthy volunteers. Of 40 asthmatic subjects, fourteen were classified as mild, ten as moderate-to-severe and sixteen as near-fatal. The study also

included sixteen normal healthy subjects as a control group. Prominent centrolobular structures were seen on HRCT scans in 36% of mild asthmatics and in 70% of moderate to severe asthmatics participating in the study. The average grade of prominence of centrolobular structures was similar in the mild and moderate-to-severe groups. The prominence of centrolobular structures was attributed, in part, to intrabronchiolar mucoid impaction. Further, bronchial wall thickening due to thickening of the basal membrane, GCH, hypertrophy of the submucosal glands, and smooth-muscle hyperplasia were also observed in subjects with mild asthma as compared to healthy volunteers (Lee et al. 2004).

In the most recent review of airway remodeling processes, Fahy (2005) re-confirmed these findings by describing relationships between qualitatively and quantitatively abnormal mucus in asthma due to GCH, mucin hyperproduction, and hypertrophy of submucosal glands, all of which are present in mild, moderate, or severe asthma. The author concludes that “mucus hyperproduction is an important cause of morbidity and mortality in patients with asthma.”

### **Functional Consequences of Structural Remodeling in Mild Asthma**

The clinical significance of mucus hypersecretion in mild asthma has been well documented (Bateman, 1983; Openshaw, 1989; Connolly, 1997; Lange, 1998; Ko, 2005). In summary, their research demonstrates that mucus hypersecretion, along with decreased mucociliary clearance, are important factors contributing to airway obstruction in mild asthma, and correlate symptomatically with inflammatory changes and hypersecretion.

Impaired tracheobronchial clearance in patients with mild stable asthma was described in 25 asthmatic subjects (none of whom were taking corticosteroids) vs. 25 healthy volunteers (Bateman, 1983). The objective, noninvasive, radio aerosol technique was used to measure whole-lung mucociliary clearance, which was found to be significantly decreased in mild asthmatics compared to a healthy control group. Mean tracheobronchial retention curves showed a significantly higher retention of deposited technetium-tagged polystyrene in the asthmatic group compared to healthy subjects

( $p < 0.01$ ), reflecting impaired clearance of mucus from the airways in the asthmatic group.

A 15-year longitudinal study investigated ventilatory function in adults with and without asthma based on the presence of mucus hypersecretion (Lange, 1998). The Copenhagen City Heart Study was a prospective epidemiological study conducted between 1976 and 1994, with a sample size of 19,698 persons  $>20$  years of age, of whom 1095 had asthma. For each subject, three measurements of lung function were obtained over a 15-year period. The study showed that in both men and women with asthma (including smokers and nonsmokers), those who self-reported chronic mucus hypersecretion had a significantly greater decline in  $FEV_1$  than those without chronic mucus hypersecretion ( $p < 0.01$ ).

A recent study by Ko et al. (2005) confirmed the observation that coexisting mucus hypersecretion accelerates the rate of lung function decline in asthmatic patients, regardless of asthma severity. In this study, asthmatic mucus hypersecretion (AMH) was defined as the clear-cut presence of increased mucus in the airways causing airway obstruction (seen at bronchoscopy), independent of asthma severity. Seven non-asthmatic subjects and 22 subjects with asthma completed a questionnaire, and underwent lung function tests and bronchoscopy. All asthmatic subjects had stable asthma as determined by their history of medication use for the prior 3 months; none of the subjects were current smokers or ex-smokers of  $>20$  pack-years. Further, subjects were classified into mild/moderate asthma (without AMH), severe asthma (without AMH), and asthma subjects with AMH. Two out of eight AMH subjects were classified as mild/moderate asthmatics based on history. The mean  $FEV_1$  was lower in AMH patients (73% of predicted, CI  $\pm 13\%$ ) compared with nonasthmatic subjects ( $95 \pm 7\%$ ) and patients with mild/moderate asthma without AMH ( $94 \pm 9\%$ ), ( $p < 0.05$ ), and was similar to that of patients with severe asthma without AMH ( $80 \pm 20\%$ ). The study also found a high proportion of subjects who had severe asthma and a history of chronic productive cough, but had no mucus plugging seen at bronchoscopy.

In conclusion, at least 13 independent studies have clearly demonstrated that mucus production was important pathophysiologic process in asthma regardless of severity.

### Expectorant Effects

Guaifenesin is the only expectorant that is currently approved in the US for over-the-counter use. It is listed in the Cough & Cold Monograph as a safe and effective drug for the following approved uses: "Helps loosen mucus and thin bronchial secretions to rid the bronchial passageways of bothersome mucus." While guaifenesin is an older drug, its exceptional safety profile and time and extent of use as an expectorant, so essential for the OTC environment, still stimulate researchers' interest. Thus, Rubin (1999) investigated the mechanism of action of several potential mucoactive agents including guaifenesin on sputum collected from 30 adults with stable chronic bronchitis. When compared to sputum that had no test agent or ARS added, all agents reduced sputum elasticity, with guaifenesin significant at  $p < 0.001$ . In addition, guaifenesin ( $p = 0.006$ ) decreased surface mechanical impedance (frictional adhesiveness) compared to untreated sputum.

### Conclusion

There is overwhelming, independent, scientific evidence that goblet cell hyperplasia, increases in goblet cell counts, mucin and mucus hyperproduction occur in asthma. These changes are present *regardless of the severity of the condition* and they contribute to airway inflammation and further airway remodeling. Pulmonary clinical experts support the assertion that mucus hypersecretion is present in asthmatic subjects regardless of the severity (please see letters included). Furthermore, there is mounting evidence that the magnitude of mucin production also contributes to the long-term decline of pulmonary function. Guaifenesin is the only OTC-approved expectorant with a proven safety profile. Since 1954, 3 billion Primatene® Tablets containing guaifenesin in combination with oral bronchodilators theophylline or ephedrine were sold to OTC consumers with mild bronchial asthma. With over 50 years on the market, Primatene®

Tablets has proven to be to be a rational combination of an expectorant and an oral bronchodilator with favorable risk-benefits ratio.

In summary, the foregoing findings do not support the Agency's viewpoint on mucus production in mild asthmatics. WCH's review of the relevant scientific and medical literature concluded that there is a convincing rationale for the combination of an expectorant and oral bronchodilator for a population with mild asthma who will benefit from the continued OTC availability of these products.

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