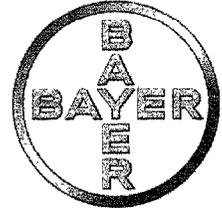


Bayer HealthCare  
Consumer Care Division

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November 2, 2005

Division of Dockets Management  
5630 Fishers Lane Rm. 1061  
Rockville, MD 20852

Bayer HealthCare LLC  
Consumer Care Division  
36 Columbia Road  
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Morristown, NJ 07962-1910

Re: **Docket No 1976N-0052G**  
**RIN 0910-AF33**  
**Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug**  
**Products for Over-the-Counter Human Use; Proposed Amendment**  
**of the Tentative Final Monograph for Combination Drug Products**

Dear Sir or Madam:

Introduction:

The Food and Drug Administration (FDA) recently issued two notices in the Federal Register Vol. 70, No. 133, July 13, 2005, proposing to amend the Tentative Final Monograph for OTC Cough, Cold, Allergy, Bronchodilator, and Asthmatic Drug Products.

One notice<sup>1</sup> proposed retaining over-the-counter (OTC) availability for oral ephedrine salts as Category I bronchodilator (generally recognized as safe and effective) single-ingredient products. The agency addressed specific safety concerns with labeling changes. It was concluded that such products have a favorable benefit/risk ratio, are safe and effective for OTC use, and provide a meaningful therapeutic option for patients with mild asthma.

In the other notice<sup>2</sup> the agency proposed reclassification of the combination of an oral bronchodilator and an expectorant from Category I to Category II (not generally recognized as safe and/or effective). The agency concluded that these combination products are not a rational therapy for the treatment of mild asthma.

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Position:

Bayer HealthCare believes that oral bronchodilator/expectorant combinations are safe and effective for OTC use. The clinical data presented herein support the safety and efficacy of oral bronchodilator/expectorant combinations in the symptomatic relief of bronchial asthma, as well as the superiority of the combination when compared to single-ingredient bronchodilator products. Based upon these data, combination products would appear to have a more favorable benefit/risk ratio than single-ingredient bronchodilators and therefore should continue to be classified as Category I.

Comments:

**The major issues cited for the reclassification of oral bronchodilator/expectorant combination products from Category I to Category II were<sup>2</sup>:**

- (a) The efficacy of expectorants in the pharmacological management of asthma;
- (b) The exclusion of expectorants from current asthma management guidelines;
- (c) Safety concerns with the use of guaifenesin in the therapy of mild asthma.

These issues are discussed below in order:

a) Efficacy of Expectorants in the Management of Mild Asthma

***Mechanism of Action***

Guaifenesin (glyceryl guaiacolate) is approved by FDA for OTC use both alone (21CFR314.18 and 341.78) and in combination (21CFR 341.40 h, j, n, o, p, q) and is indicated to "help loosen phlegm (mucus) and thin bronchial secretions to rid the bronchial passageways of bothersome mucus and/or drain bronchial tubes and make coughs more productive". FDA states that the effectiveness of guaifenesin in the symptomatic relief of sputum removal in asthmatics has not been demonstrated, and that the usual recommended dose is of doubtful value for asthma<sup>2</sup>.

Guaifenesin is thought to act by irritating the gastric mucosa and subsequently stimulating respiratory tract secretions. This increase in fluid increases the volume and decreases the viscosity of bronchial secretions. This activity should not differ in an asthmatic patient compared to a patient with a common cold. According to Clarke<sup>3</sup>, certain mucolytic agents including guaifenesin were found to provide statistically significant enhancement of tracheobronchial secretion clearance in asthmatic patients (statistical comparison was not provided).

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***Clinical Trials***

Combinations of bronchodilators with guaifenesin were approved by FDA and marketed for many years. Also, in the trials presented below, combinations of bronchodilators with guaifenesin have been shown to be more effective than bronchodilators alone in the treatment of asthma. These findings support the fact that the expectorant portion of the combination makes a contribution to the overall efficacy of the product.

Brechter<sup>4</sup> conducted a double blind, crossover study comparing an oral combination of 2.5 mg terbutaline and 100 mg guaifenesin with 2.5 mg terbutaline alone, over a 14-day treatment period, in 23 outpatients with bronchial asthma. Product was dosed at 2 tablets (200 mg guaifenesin) three times a day. Patients rated subjective symptoms (difficulty of breathing, volume of sputum, ease of clearing sputum and consistency of sputum) on categorical scales and also recorded the number of times an aerosol rescue medication (isoprenaline) was needed for acute attacks. A statistically significant improvement was seen with the use of the combination product compared to the single-ingredient product in the symptom score for sputum consistency ( $p < 0.01$ ) and for ease of clearing sputum ( $p < 0.05$ ). The difference in the scores for difficulty of breathing between treatments did not reach statistical significance. The volume of sputum produced was similar between the two treatments. The mean number of times that the inhaled rescue medication was used was significantly lower for the combination therapy compared to the single-ingredient therapy (2.01 vs. 2.42,  $p < 0.01$ ). The adverse events reported (tremor, palpitations) were mild in nature and seen for both treatments.

Radha et. al.<sup>5</sup> compared a 2-week treatment with a combination of ephedrine, aminophylline and phenobarbitone to the combination plus guaifenesin in a crossover trial in 75 patients with asthma (11) or chronic bronchitis (64). The product dosage was not provided. An overall composite symptom score for the frequency severity and duration of cough and dyspnea and the quantity, character and consistency of sputum was calculated. Pulmonary function test parameters including vital capacity (VC), forced expiratory volume in 1 second ( $FEV_1$ ), maximum ventilatory volume (MVV) and  $FEV_1$  as a percent of vital capacity ( $FEV_{1\%}$ ) were evaluated. In patients treated with the guaifenesin combination, a statistically significant difference was seen in composite symptom score improvement from baseline as compared to the expectorant-free product in the asthma patients (4.73 vs. 2.70,  $0.01 < p < 0.05$ ) and in the chronic bronchitis patients (4.01 vs. 2.81,  $p < 0.01$ ). While both treatments significantly improved pulmonary function from baseline in the bronchitis population, the difference in pulmonary function improvement between the two treatments was not statistically significant. Improvement in pulmonary function did not reach statistical significance in the asthma subset of the study population. The authors concluded: "When the obstruction is reversible, as in the case of asthma, guaifenesin seems to have a potentiating action on (the) bronchodilator by facilitating the removal of viscus mucus pellets." Adverse event data were not reported in this trial.

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Sethi et. al.<sup>6</sup> studied 40 bronchial asthma patients in a 1-month crossover trial. Patients were treated with an oral combination of 24 mg ephedrine; 130 mg theophylline and 7 mg phenobarbitone with and without 10 mg guaifenesin. Product was dosed at 1 tablet three times a day. The authors stated that the combination with guaifenesin was "definitely superior" to the combination without guaifenesin in therapeutic efficacy (statistical comparisons were not provided). Also, according to the authors, both treatments provided symptomatic improvement. Adverse events were reported in 6% of the subjects, and were reported equally in both treatment groups. The adverse events cited included palpitations, restlessness, insomnia and epigastric distress.

Townley and Bronstein<sup>7</sup> performed a double-blind crossover clinical evaluation in patients with chronic bronchitis, asthma or emphysema (patient distribution not provided). Twenty-seven patients completed both of the 28-day treatments, 200 mg choline theophyllinate and 200 mg choline theophyllinate combined with 100 mg guaifenesin. Product was dosed at 1 tablet 4 times a day. The patients rated several symptoms (severity of cough, frequency and severity of wheezing, amount and ease of expectoration), and pulmonary function tests were performed. All symptoms generally improved with both therapies. For two parameters, there was statistically significant improvement from baseline seen with the combination treatment, while improvement on the single ingredient therapy did not reach statistical significance. These parameters were: improvement in wheezing frequency for patients with an initial frequency of at least once daily ( $p < 0.02$ ) and ease of expectoration for patients with an initial rating of difficult ( $p < 0.02$ ). Also, small, nonsignificant improvements in pulmonary function were seen with both treatments. The authors point out that responses to study treatments were based on comparisons to their baseline medications rather than to placebo, which could have resulted in a greater degree of improvement.

Of the 37 patients who were enrolled in this trial, 5 discontinued due to adverse reactions to the study treatments. Three of these patients experienced nausea and vomiting with the study medication, one patient did not tolerate oral asthmatic therapy, and one patient experienced palpitation, nervousness, excitability and tachycardia. This last patient had a prior history of Grave's disease and experienced a similar episode one-week following study medication discontinuance, while on another oral asthma medication. A relatively high incidence of adverse events was reported in patients who completed the trial, with 66% and 75% of patients reporting side effects for the combination and single-ingredient therapies, respectively. However, the incidence of adverse events was not higher than that seen in these patients on pre-study therapy. Generally, the adverse events reported were mild and were similar in both treatment groups. The most frequently reported events were symptoms of upper gastrointestinal discomfort (nausea, epigastric pain), irritability (or excitability), and palpitations. Most patients complaining of adverse events prior to the study were using theophylline medications, and the authors hypothesize that the theophylline moiety was the cause of most of the adverse events reported during the trial since it was common to both treatments. Clinical laboratory evaluations for safety were unchanged after exposure to the study medications.

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Puls<sup>8</sup> conducted a double-blind, crossover trial in 17 patients with chronic pulmonary disease, the majority of patients having chronic bronchitis. The trial compared the effectiveness of 200 mg oxtriphylline alone to a combination of 200 mg oxtriphylline with 100 mg guaifenesin over a 4-week period. Product was dosed at 1 tablet three times a day. The efficacy parameters evaluated were severity of cough, frequency and severity of wheezing, amount and ease of expectoration, physical chest examination, VC and timed VC. According to the author, both treatments appeared to be effective in reducing the symptoms of the disease (data not reported). While VC and timed VC values were higher for both treatments compared to baseline, only the mean improvement in VC in patients on combination therapy was statistically significant ( $+0.29L \pm 0.14$ ,  $p < 0.05$ ). Timed VC was improved by both treatments and while the author states that the combination therapy provided superior improvement, the differences from baseline for this parameter did not reach statistical significance for either treatment. For most of the patients, pulmonary function test results after each study treatment were compared to the test results at baseline, representing their status while on their usual medications rather than a placebo. Three patients were discontinued from the trial due to nausea, mental confusion or heartburn (the study treatment associated with each of these events was not specified).

**b) Exclusion of Expectorants from Current Asthma Management Guidelines**

FDA has stated that the current therapeutic treatment guidelines for the management of asthma do not include expectorant therapy<sup>2</sup>. However, the National Institute of Health's Guidelines for the Diagnosis and Management of Asthma<sup>9</sup>, identifies mucus plug formation as being one of the contributing factors to airflow limitation. Since guaifenesin has been shown, in clinical studies and in practice, to clear bronchial secretions and facilitate expectoration, it would seem to be a logical therapeutic option. Moreover, the clinical trial data presented above support the efficacy of guaifenesin in the overall management of asthma.

Combinations of oral theophylline derivative bronchodilators with guaifenesin, were available by Rx and were a mainstay of therapy for asthmatic patients for many years. The use of these combinations declined due to the narrow therapeutic index and resultant systemic toxicity associated with theophylline and its derivatives, not due concerns about the safety or efficacy of guaifenesin, nor the rationale for the combination. Also, the safety of oral bronchodilators contributed to the shift from oral to inhaled agents in the management of asthma.

**c) Safety of Guaifenesin in the Therapy of Mild Asthma**

Guaifenesin has a wide margin of safety; adverse effects are infrequent and include minor GI events (nausea, vomiting, diarrhea, stomach pain dizziness, headache, skin rash and urticaria<sup>10</sup>). FDA has approved the OTC use of guaifenesin under the Cough, Cold, Allergy, Bronchodilator, and Asthmatic Drug Products Monograph (21CFR314.18), and more recently, has approved the drug as an OTC expectorant in an extended release dosage form (Mucinex<sup>®</sup>, NDA 21-282).

Safety concerns about the use of guaifenesin in the treatment of asthma were cited by the FDA<sup>2</sup>: *"Moreover, in asthma, the drying of secretions along with the narrowing of the airways could potentially result in inspissated (thickened or dried) material and mucus plugs. This could then further increase airway obstruction and lead to further breathing difficulties."*

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Pharmacologically, it does not seem plausible that the use of guaifenesin could lead to drying of secretions, since it acts to dilute them. The FDA supports this rationale in that they have approved the use of the ingredient to thin bronchial secretions, rid the bronchial passageways of bothersome mucus and drain bronchial tubes<sup>2</sup>.

In the clinical trials above, while patient numbers were small, there were no apparent differences in adverse event reporting between treatments with and without guaifenesin. Generally, authors associated the reported adverse events with the bronchodilator drug rather than the expectorant. Based on these findings, the contribution of guaifenesin to the overall toxicity of an oral bronchodilator/expectorant combination should be minimal.

**Other Considerations:**

The clinical studies cited above provide evidence to support the combination of an oral bronchodilator and an expectorant in the treatment of asthma. In addition, using an expectorant and a bronchodilator simultaneously may facilitate the removal of sputum by the expectorant because it is acting in a dilated airway.

Asthma is a condition with a spectrum of symptomologies, which can benefit from a multi-pharmacological approach. OTC combination products are available for other conditions, such as the common cold. These combination products offer the patient convenience and lessen the expense of purchasing several single-ingredient products. For more than forty years, consumers have safely used Bronkaid®, a combination of ephedrine sulfate and guaifenesin. Consumers who benefit from combination therapy rely on the convenience of these products, leading to enhanced compliance and improved disease management, providing a benefit to public health.

**Conclusion:**

The combination of an OTC expectorant with an OTC bronchodilator meaningfully increases the therapeutic benefit and does not significantly increase risk as compared to a single ingredient bronchodilator. Therefore, the benefit/risk ratio for the OTC combination exceeds that for the OTC bronchodilator as a single ingredient.

FDA has recognized that there is a population of mild asthmatic patients that can benefit from the use of OTC bronchodilators<sup>1</sup>. Combination with an expectorant is a logical and rational therapeutic approach. These combination products should continue to be classified as Category I.

Bayer Healthcare appreciates the opportunity to submit comments in response to this proposed amendment. We believe that our input into this proposal is very important and should be considered as the agency reviews the comments they receive. If you have any questions regarding the content of this submission, please contact the undersigned at 973-408-8181.

Sincerely,



Linda F. Bowen  
Associate Director, Regulatory Affairs  
Bayer HealthCare LLC, Consumer Care Division

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**References:**

1. Federal Register (7/13/2005) 70(133), 40237-49.
2. Federal Register (7/13/2005) 70(133), 40232-37.
3. Clarke SW. Management of Mucus Hypersecretion. Eur. J. Resp. Dis. (1987) 71, Suppl. 153, 136-144.
4. Brechter C. Clinical Trial with Terbutaline and Guajacol. Scand. J. Resp. Dis. (1973) 54, 78-82.
5. Radha TG, et.al. The Effect of the Combination of Phenobarbitone, Ephedrine, Aminophylline and Glyceril Guaiacolate on Asthma and Chronic Bronchitis. Indian J. Chest Dis. (1973) 15, 323-30.
6. Sethi J, et. al. Tedral-E in Bronchial Asthma. Aspects of Allergy and Applied Immunology. (1971) V, 188-192.
7. Townley RG, Bronstein SB. A Double Blind Clinical Evaluation of Glyceril Guaiacolate. Ann. Allergy (1963) 21, 683-691.
8. Puls RJ. Clinical Study with Oxtriphylline-Glyceril Guaiacolate Tablets in Chronic Pulmonary Disease: A Double-blind Crossover Study. Current Therapeutic Research (1964) 6, 353-356.
9. Guidelines for the Diagnosis and Management of Asthma. National Institutes of Health Publication No. 97-4051 (1997).
10. USP DI® Drug Information for the Health Care Professional, 25th Ed., Guaifenesin monograph (2005).