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December 1, 2005

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

RE: **Docket No 1976N-0052G (Formerly 76N-052G)**
**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**

To Whom It May Concern:

These comments and objections are respectfully submitted on behalf of BDI Marketing, Inc. (BDI), a division of Body Dynamics, Inc., Indianapolis, Indiana, in response to the Food and Drug Administration's proposal to amend the final monograph for over-the-counter (OTC) cough-cold combination drug products by removing the combination of an oral bronchodilator and an expectorant from the cough-cold combination drug monograph and by reclassifying the combination of an oral bronchodilator and an expectorant as not generally recognized as safe and effective for OTC use. 70 Fed. Reg. 40232 (July 13, 2005). The effect of this rulemaking would be that OTC bronchodilators, critical remedies for many asthma sufferers, will no longer be readily available to the American consumer. BDI submits that the net affect of the removal of the combination will be the removal of almost all, if not all, OTC ephedrine bronchodilators from the market.

**Docket No 1976N-0052G (Formerly 76N-052G)**
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## I.
## BACKGROUND ON BDI MARKETING

BDI is currently a member of the American Council on Regulatory Compliance ("ACRC"). The ACRC is a nonprofit organization of small to midsize businesses that engage in the manufacture, distribution and sales of over-the-counter (OTC) pharmaceuticals. BDI concurs with and adopts ACRC's comments to FDA's current proposal, which shall be submitted by ACRC prior to the extended deadline of December 9, 2005. BDI's comments contained herein are intended to be a supplementation of those comments submitted by ACRC.

BDI markets a broad range of products, including ephedrine-containing bronchodilator medications for the treatment of asthma. BDI's asthma product line includes multiple formulations of "Two-Way Action" combination products, which contain both ephedrine and guaifenesin, in various forms of packaging. BDI's ephedrine-containing products are exclusively intended for use by asthma sufferers and are sold in a variety of retail outlets including convenience stores.

BDI does not market any single active ingredient ephedrine products and is not likely to in the future. Although, as FDA admits, single active ingredient ephedrine is a safe and effective bronchodilator that should be available over-the-counter, because of issues having nothing to do with its benefits as a bronchodilator – issues dealing with diversion of precursor chemicals (i.e. ephedrine) to make methamphetamine, which have resulted in Federal and State restrictions -- it is almost impossible to sell single ingredient ephedrine OTC.

All of the company's ephedrine/guaifenesin product labeling contains the proper indications, includes all required warnings, and clearly state that the product is a bronchodilator

and expectorant intended for use in relieving the shortness of breath, tightness of chest, wheezing associated with bronchial asthma and helps loosen phlegm (mucus) and thin bronchial secretions to rid the bronchial passageways of bothersome mucus. These indications for ephedrine/ guaifenesin are all explicitly approved by the U.S. Food and Drug Administration ("FDA"). 21 C.F.R. §341 et. seq.

## II.
## ASTHMA IS A CHRONIC LUNG DISEASE

Asthma is a chronic lung disease, often striking suddenly and without warning, characterized by recurrent respiratory symptoms such as wheezing, breathlessness, chest tightness, coughing, and variable airflow obstruction that is reversible spontaneously or with treatment. During an asthma attack three things occur: bronchoconstriction, mucous production, and inflammation.

In an asthma attack, the smooth muscles of the bronchi narrow (called bronchoconstriction), and the tissues lining the airways swell from inflammation and secrete mucus into the airways. In some segments of the airway, the mucus forms clumps that nearly or completely block the airway. These clumps are called mucus plugs. The top layer of the lining of the airways can become damaged and shed cells. These actions further narrow the diameter of the airways; the narrowing requires the person to exert more effort to move air in and out of the lungs. In asthma, airway obstruction is reversible, meaning that with appropriate treatment or on their own, the muscular contractions of the airways stop, the airway obstruction ends, and the airflow into and out of the lungs returns to normal. The Merck Manual of Medical Information, Second Home Edition Online.

Although the severity of an asthma attack varies, attacks "may subside quickly or persist for hours to days. Pulmonary function abnormalities . . . may persist for weeks after an acute attack, even in asymptomatic patients." The Merck Manual at 625 (15th Edition 1987). Death is an ever-present risk in an untreated asthma attack. In 2000, there were approximately 4,500 asthma-related deaths in the United States. American Lung Association. Trends in Asthma Morbidity and Mortality. March 2003.

The number of external factors that can trigger an asthma attack is large and diverse, and include: viral infection; exercise; emotional upset; changes in barometric air pressure or temperature; inhalation of cold air or irritants such as gasoline fumes, paint, noxious odors or cigarette smoke; exposure to specific allergens, particularly airborne pollens, mold, dust or animal dander; as well as ingestion of aspirin or sulfites. Id. at 623. Thus, it is practically, if not literally, impossible for persons to completely avoid contact with all potential asthma triggers in today's society.

At one time, epinephrine and ephedrine were the only effective medications for treating asthma. Despite the development of newer medications (prescription drugs), epinephrine and ephedrine currently remain available as OTC medications.[1] OTC ephedrine is available only as an oral medication in combination with guaifenesin as gel caps, caplets, tablets, or syrup. Ephedrine is indicated for the temporary relief of the symptoms of bronchial asthma (i.e., relieving shortness of breath, tightness of chest and wheezing). 21 C.F.R. §341.76(b).

[1] Although it is important to note that the familiar metered dosage form of epinephrine products is no longer available unless a New Drug Application is approved by FDA. See 61 Fed. Reg. 25142 (May 20, 1996) and 21 C.F.R. 341.76(d)(2). Now, under the monograph, epinephrine is only permitted to be used in a hand-held rubber bulb nebulizer and is nearly absent from the marketplace since it is no longer convenient as it once was years ago.

Guaifenesin is indicated to help loosen phlegm (mucus) and thin bronchial secretions to rid the bronchial passageways of bothersome mucus, drain bronchial tubes, and make coughs more productive. 21 C.F.R. §341.78(b).

## III.
## ASTHMA IS A MAJOR PUBLIC HEALTH PROBLEM AFFECTING MILLIONS OF AMERICANS, PARTICULARY THE UNINSURED AND IMPOVERISHED

Asthma is a major public health problem in the United States. As such, it is important to keep OTC asthma medication readily available. The removal of most, if not all, OTC asthma remedies would be most difficult for the uninsured and impoverished that already suffer from asthma in a disproportionate manner than from the rest of the nation.

The disease currently affects approximately 20.3 million people, nearly 6.3 million of whom are under the age of 18 years. It accounts for an estimated 14.5 million lost workdays for adults and 14 million lost school days for children annually. The collective cost of the disease is estimated at $14.0 billion for the year 2002. American Lung Association. Trends in Asthma Morbidity and Mortality. March 2003.

The United States Government reports that in 2003, an estimated 29.8 million people had been diagnosed with asthma during their lifetime and 11.0 million people experienced an asthma attack in the previous year. Source: CDC National Center for Health Statistics Vital and Health Statistics. Compare this to the disproportionate number of minorities that have been diagnosed with asthma. In 2002, an estimated 4.8 million African Americans had been diagnosed with asthma in their lifetime and that 2 million African Americans had experienced an asthma attack in the past year. American Lung Association. Trends in Asthma Morbidity and Mortality. March

2003. In 2002, the asthma prevalence rate in African Americans was almost 38 percent higher than among whites. American Lung Association. Trends in Asthma Morbidity and Mortality. March 2003. Blacks also have higher rates of asthma mortality. In 2001, blacks were three times more likely to die from asthma than were whites.

There is a disturbing trend of increasing prevalence of asthma in the United States. Between 1980 and 1996, the prevalence of asthma in the United States increased by almost 74%. Also disturbing is amount of asthma-related health care utilization in this country. Centers for Disease Control and Prevention. Surveillance for Asthma – United States, 1980-1999. MMWR 51 (SS01); 1-13. March 29, 2002.

In 2002, asthma accounted for the following:

- 12.7 million doctor visits
- 1.2 million hospital outpatient visits
- 1.9 million emergency department visits
- 484,000 hospitalizations
- 4,261 deaths

Source: CDC National Center for Health Statistics Vital and Health Statistics.

The rates for such health care utilization have been disproportionately higher among blacks, women, and young children. Several studies point to racial differences in health services for patients with asthma. In 2001, blacks or African Americans were three times more likely to be hospitalized for asthma than whites but also five times more likely to seek care at an emergency room. National Center for Health Statistics: National Hospital Discharge Survey, 2001; National Center for Health Statistics: National Hospital Ambulatory Medical Care Survey, 2001. One reason for this is that whites make more asthma-related visits to their primary care

doctor or specialist. A 1999 Cleveland Clinic Foundation study of managed care patients hospitalized for asthma found that Caucasian patients made more asthma-related visits to their primary care doctor (70.2 percent) and specialist visits (38.8 percent) than African American patients, 47.6 percent of whom visited a primary care doctor and 27 percent of whom visited a specialist. Regular care from a primary care physician or asthma specialist can help patients keep their asthma under control and help prevent emergency room visits associated with asthma attacks. (Blixen CE, Havstad S,Tilley BC, Zoratti E.A. Comparison of asthma-related healthcare use between African-Americans and Caucasians belonging to a health maintenance organization (HMO). Journal of Asthma. 1999; 36(2): 195-204).

Nationally, approximately 41.2 million people had no health insurance in 2001. (Morgan K. and Morgan S. (Eds.). Health Care State Rankings 2003. Health Care in the 50 United States. Lawrence, KS: Morgan Quitno Press). People who are uninsured, underinsured, or impoverished are less likely to go to a doctor to be diagnosed and seek treatment, and are generally less healthy than their insured peers. It is these groups of people who presently benefit from the ready availability of OTC bronchodilators and it is these groups that will suffer when OTC bronchodilators are no longer available. They may go to a doctor to get the initial diagnosis but will be unable to continue to go to get prescriptions and to pay the exorbitant costs that the uninsured are forced to pay for both the doctor visits and the prescription medications. No doubt these people will wind up waiting in hospital emergency rooms every time they need to treat their asthma. People in the lower socioeconomic stratum also have a higher prevalence of

tobacco use, which in turn can lead to more frequent asthma exacerbations in this population due to exposure to secondhand smoke.

## IV.
## FDA'S PROPOSAL REGARDING THE COMBINATION OF A BRONCHODILATOR AND EXPECTORANT WOULD HAVE A DEVASTATING IMPACT ON MILLIONS OF AMERICANS WHO SUFFER FROM ASTHMA, PARTICULARLY THE UNINSURED AND IMPOVERISHED, AS WELL AS MOST SMALL BUSINESSES INVOLVED IN THE MANUFACTURE OR SALE OF SUCH PRODUCT(S)

Ephedrine is a drug that has a proven track record of safe and effective use in treating the symptoms of bronchial asthma. Guaifenesin is a drug that has a proven track record of safe and effective use in the clearing of bronchial passageways. Ephedrine was approved by FDA as a safe and effective OTC asthma treatment over 30 years ago. The combination of an ephedrine bronchodilator and a guaifenesin expectorant has been approved for just as long.

FDA's proposal to amend the final monograph for over-the-counter (OTC) cough-cold combination drug products by removing the combination of an oral bronchodilator and an expectorant[2] from the cough-cold combination drug monograph would have the practical effect of making OTC ephedrine practically unavailable. This is FDA's second attempt to eliminate OTC ephedrine bronchodilators from the marketplace. Its first proposal to remove ephedrine ingredients from the final monograph for OTC bronchodilator drug products in 1995 was never finalized and was withdrawn. 70 Fed. Reg. 40237 (July 13, 2005). Clearly, FDA's withdrawal of

[2] FDA's proposal also seeks to restrict the combination of ephedrine and an oral nasal decongestant. 70 Fed. Reg. 40235 BDI is not aware of any company selling this combination and does not object to FDA's proposal on this combination.

its proposed rule to remove OTC ephedrine from the marketplace was an acknowledgement that maintaining OTC ephedrine on the market is important. See 70 Fed. Reg. 40239.

FDA's withdrawal of its 1995 proposed rule cites four principle reasons why ephedrine and other bronchodilator ingredients should remain in the Final Monograph for self treatment of mild bronchial asthma. Its first reason is that "there are people with diagnosed mild bronchial asthma for whom the benefits of symptomatic treatment with OTC bronchodilators for temporary wheezing, shortness of breath, and tightness of chest outweigh the risks of use." 70 Fed. Reg. 40239. Unfortunately, should FDA's current proposal regarding combination ephedrine products be finalized, these OTC drugs will simply not be available and, as such, will not be able to benefit the millions of persons who have asthma in this country. Its second reason for withdrawing its 1995 proposal is that "additional labeling warnings and directions … provide information to promote safer use of these products." This is good and BDI does not object to labeling changes if it benefits the American consumer and permits them to continue to market the product to those in need. FDA's third reason discusses the fact that "FDA has taken regulatory action against ephedrine drug products with misleading brand names that promoted weight loss, enhancement of athletic performance, or stimulant uses." BDI supports these enforcement efforts. The last reason given by FDA why ephedrine and other bronchodilator ingredients should remain in the Final Monograph for self-treatment of mild bronchial asthma relates to the various DEA laws and regulations affecting ephedrine, which FDA says became effective after FDA published its 1995 proposal. FDA implies simply that single entity ephedrine must be sold from behind a store counter, when in fact DEA regulations make it far more

burdensome if not nearly impossible to sell the product. It is noted that many of the states currently require combination ephedrine/guaifenesin products to be sold from behind the counter as well, so any similar concern FDA may have with regard to the combination products has already been addressed.

The group which would be hit the hardest by the effects of FDA's current proposal, should it be finalized, are the uninsured and impoverished as it would be the most difficult for this population to gain access to and afford a doctor's prescription for ephedrine.

A. DEA RESTRICTIONS ON THE MARKETING OF SINGLE INGREDIENT EPHEDRINE WILL DEPRIVE ASTHMA SUFFERERS OF USEFUL AND APPROPRIATE MEDICATION

The Drug Enforcement Administration is the federal law enforcement agency charged with the responsibility for combating illicit drug manufacture and distribution, as well as the diversion of licitly produced drugs and chemicals. One such illicit drug that DEA is combating is methamphetamine. Methamphetamine is an addictive stimulant drug, chemically related to amphetamine, which strongly activates certain systems in the brain. Methamphetamine is made in illegal laboratories and has a high potential for abuse and addiction. Ephedrine is one of a handful of chemicals that can be used to manufacture methamphetamine - for this reason it is closely regulated by DEA as a precursor chemical or a "List 1 Chemical." A List 1 chemical is a chemical that, in addition to legitimate uses, is used in manufacturing a controlled substance in violation of the Controlled Substances Act.

DEA began controlling ephedrine in 1989 with the passage of the Chemical Diversion and Trafficking Act (CDTA) of 1988. The CDTA was highly effective in reducing the supply of

illicit methamphetamine. Because of the CDTA and other government controls, ephedrine and other chemicals used to manufacture methamphetamine became more difficult to divert. However, over time illegal diverters found new sources for diversion, including OTC drugs that had been exempted from the CDTA. In response, Congress passed the Domestic Chemical Diversion Control Act of 1993 (DCDCA), which required DEA registration for all manufacturers, distributors, importers and exporters of List 1 Chemicals and registration of retailers that sold single active ingredient ephedrine OTC products. It also established record keeping and reporting requirements for all transactions in single-entity ephedrine products.

Retailer registration is not free. The cost for retail registration is currently $255 ($248 annual fee plus a $7 processing fee) and the cost for annual re-registration is $116, however a recent Notice of Proposed Rulemaking by DEA proposes raising both of these fees to $1,193. 70 Fed. Reg. 69474 (November 16, 2005). For stores that may sell a few packages of OTC bronchodilators a month, the current DEA registration fees can not possibly make much business sense and sales of the product may not even cover their annual cost of goods sold. Should DEA's recent proposed increase in registration fees be finalized, it is even less likely that retailers would be able to afford to sell such products. In 1995, DEA estimated that 10,000 retailers across the country would register to be able to sell single ingredient ephedrine, however by 1999 only 47 registered. 64 Fed Reg. 67217 (December 1, 1999). Over the years the number of those retail registrants dwindled and as of November 4, 2005, only 2 retail distributors remained registered - one in North Carolina and the other in Nevada. See DEA Table of Active Chemical Registrants as Attachment A hereto.

When Congress passed the Comprehensive Methamphetamine Control Act of 1996 (MCA), which expanded regulatory control of lawfully marketed drug products containing pseudoephedrine, phenylpropanolamine and multiple active ingredient ephedrine products, it specifically exempted retailers from registration and created a reasonable sales exemption so that retailers could continue to reasonably stock the products. In particular, the MCA provided single retail transaction threshold levels for combination ephedrine and single active ingredient pseudoephedrine products, under which retail registration would not be required. In this way, the MCA ensured that certain products, which contained List 1 Chemicals, could remain OTC and available in retail stores. In enacting the MCA, particularly the threshold provisions contained therein, Congress recognized the importance of keeping OTC bronchodilators on the market. Congress also recognized that requiring retailers to register would not work because retailers will not sell OTC products if every sale of a 2-tablet packet is a DEA regulated transaction.

Now, in order for a retailer to sell single ingredient ephedrine, it must be registered with DEA. Retailers of OTC ephedrine <u>combination</u> drug products (ephedrine with guaifenesin) for personal use to consumers are exempted from the registration requirement. Sale for personal use is the sale of below-threshold quantities in a single transaction to an individual for legitimate medical use, which at the present time is 24 grams. FDA's proposal would render this registration exemption moot and all sales of OTC single ingredient ephedrine would need to be from registered retailers, which happen to not exist at this time.

Should FDA's proposal be finalized most persons in the U.S. will no longer be able to access OTC ephedrine products. FDA has provided no evidence that companies that presently market combination products will switch over and market single ingredient ephedrine products. FDA has provided no evidence that retailers who currently sell combination ephedrine products will switch over and sell single ingredient ephedrine products. The regulatory burden and cost for companies to make these switches is much too high. FDA refers to the regulatory burden stemming from registration and other DEA requirements for retailers and manufacturers as a "minor inconvenience." If this were true, why are there so few retailers currently registered [2 as of November 4, 2005 – See Attachment A] and why do very few companies, presently manufacture single ingredient ephedrine? The answer is simple, registering with DEA and complying with its regulations is an enormous burden on a company and most are not willing to take that responsibility or bear the cost. With no retailers registered, should FDA's proposal be finalized, persons in medical need of OTC asthma medication in states that permit it to be sold without a prescription may be out of luck. The fact that a few pharmacies may be able to sell OTC ephedrine without a prescription does not solve the problem. Pharmacies generally keep business-like daytime hours and are not easily accessible in all parts of the country. There are some counties in the U.S. that have but one pharmacy, if any at all.

B. STATES MANDATED PRESCRIPTION STATUS FOR SINGLE INGREDIENT EPHEDRINE WILL RESULT IN GREATLY INCREASED COSTS AND WILL DEPRIVE ASTHMA SUFFERERS OF USEFUL AND APPROPRIATE MEDICATION

The illegal manufacture and sale of methamphetamine is also a state problem. Like DEA, states have been very active in regulating the manufacture and sale of precursor chemicals

including ephedrine. In some states, the laws and regulations are even more strict than those enforced by DEA. At least 37 states have declared single ingredient ephedrine to be a controlled substance within their borders and, as such, can only be available by prescription. With few exceptions, these 37 states and many of the others also regulate OTC ephedrine combination drugs as well as both single entity and combination pseudoephedrine products in some fashion or another. While these laws and regulations may vary state to state, they all have one thing in common - they have been enacted or promulgated by elected officials or state agencies, respectively, that clearly recognize the value of keeping OTC bronchodilators and certain other OTC drug products on the market within their own state's borders. Only the state of Oregon has recently passed legislation that would make all OTC ephedrine products (combination or otherwise) and all pseudoephedrine products prescription only. Also, the state of Iowa has decided to make all ephedrine products available in pharmacies only. Recognizing the health benefits of OTC bronchodilators (and other OTC medications), states have gone to great lengths and have taken extraordinary measures to address their methamphetamine problems while keeping such OTC products available in the market.

Bronchodilator drug products have been available over the counter and used extensively for many years. The OTC availability of such products provides asthmatics ready access to this essential medication without the need for additional visits to a physician's office or to a hospital emergency room. This availability especially benefits those asthmatics whose attacks are triggered by common environmental factors (e.g., primarily by exertion, anxiety, exposure to cold, etc.) when immediate use may be essential. In addition, physician-diagnosed asthmatics

that do not have easy access to medical care will continue to benefit from OTC use. Should FDA's proposal be finalized and OTC combination ephedrine products no longer be available, state regulations making single ingredient OTC ephedrine a prescription drug would devastate asthma sufferers everywhere, particularly ones residing in or visiting states that have such regulations on the books, and particularly when they are in immediate need of an asthma treatment. Making single ingredient ephedrine available only by prescription would be particularly harsh for the millions of Americans who are uninsured, or too poor to pay the cost of a doctor's visit or the cost the prescription ephedrine drug, which is certain to be much higher than as an OTC.

C. FDA'S ACTION IS NOT A "MINOR INCONVENICE" TO ASTHMA PATIENTS

FDA had contemplated the effect that its proposal will have on the asthma population. FDA states "although this action may pose some minor inconvenience to people with asthma who currently use the combination product, they will still be able to purchase single-ingredient ephedrine products from outlets that are in compliance with DEA single ingredient ephedrine requirements." In its proposal, FDA omits the facts that few retail stores have actually registered with DEA over the years to sell single ingredient ephedrine.

The practical effect of FDA's proposal, that is requiring a doctor's prescription for an ephedrine bronchodilator, destroys the very purpose of allowing safe and effective drugs such as ephedrine to be available OTC, namely the right of Americans to a choice in making their personal medical decisions. The fact that there would be no other true over-the counter asthma medication currently approved by FDA, further aggravates the impact of this restriction of

personal freedom to make independent decisions about one's health care. It is true that some of the asthma population is currently under a doctor's care and obtaining a prescription may not be difficult, but many are not. Millions of asthma sufferers have only mild and occasional asthma symptoms, such as seasonal allergy-induced asthma (e.g. from the inhalation of pollen and animal dander). 41 Fed. Reg. 38320. For these people, an initial diagnosis by a doctor does not necessarily require follow-up visits, because the symptoms are familiar and consistent, they know they have asthma, they know what the symptoms and triggers are, and most importantly they know that they can obtain safe and effective relief by taking an ephedrine bronchodilator. The effect of the proposed rule will be to force millions of Americans to needlessly incur the expense and inconvenience of additional doctor visits, thus further aggravating the health care cost crisis in this country. Moreover, for the uninsured and impoverished seeing a doctor may not be a realistic option due to cost issues.

## V.
## THE COMBINATION OF A BRONCHODILATOR AND AN EXPECTORANT PROVIDES RATIONAL CONCURRENT THERAPY FOR A SIGNIFICANT PROPORTION OF THE TARGET POPULATION.

FDA tentatively concluded the following in its proposal: "that there is currently no role for expectorants in the pharmacological management of this chronic lung disease for a significant proportion of people with mild asthma," and "that the combination products are not rational therapy for the treatment of mild asthma because the expectorant component does not contribute to the relief of the condition for a significant portion of the population." 70 Fed. Reg. at 40234. FDA further recognizes in its proposal that there may be a "minority of cases" where an expectorant is needed, and suggests that such persons obtain an oral bronchodilator and an

expectorant separately. The problem with FDA's suggestion, as has been mentioned throughout these comments, is that obtaining a single active ingredient OTC bronchodilator is next to impossible.

FDA's regulations on OTC combination drug products provide that an OTC drug that combines two active ingredients may be generally recognized as safe and effective if all of the following conditions are met:

- Each active ingredient in the combination product is determined to be safe and effective;
- The combination of such ingredients does not decrease the safety or effectiveness of any of the individual active ingredients;
- Each active ingredient makes a contribution to the claimed effect(s) of the product;
- When used under adequate directions for use and warnings against unsafe use, the combination product provides rational concurrent therapy for a significant proportion of the target population.

21 C.F.R. § 330.10(a)(4)(iv).

FDA's decisions on OTC combination products are also governed by its guidelines issued in 1978 for such products. This guidance document provides that Category I active ingredients from different therapeutic categories (e.g. bronchodilators and expectorants) may be combined to treat different symptoms concurrently only if each ingredient is present within its established safe and effective dosage range and the combination meets the OTC combination policy in all other respects. See 43 Fed. Reg. 55466 (Nov. 28, 1978).

The combination of an ephedrine bronchodilator and a guaifenesin expectorant has been considered safe and effective by FDA for over 30 years and FDA presents no new evidence that would support its position that the combination product is no longer safe and effective for its

intended use. FDA has raised no questions and there is no doubt about the safety and effectiveness of single ingredient ephedrine for the temporary relief of shortness of breath, tightness of chest, and wheezing due to bronchial asthma, amongst other indications. In fact, concurrent with this proposal it issued a notice withdrawing its 1995 proposal to remove OTC ephedrine from the final monograph. Likewise, FDA raises no questions and there is no doubt about the safety and effectiveness of single ingredient guaifenesin for loosening phlegm (mucus) and thinning bronchial secretions to rid the bronchial passageways of bothersome mucus, amongst other indications. In addition, FDA does not put forward any evidence to suggest that that when the active ingredients are combined the safety or effectiveness of any of the individual active ingredients is decreased.

In the preamble of the final regulations establishing the procedures for the OTC drug review, FDA states that combination policy is such that each active ingredient must make a contribution to the effect claimed for it, and not that each active ingredient must contribute to all effects claimed for the product. 37 Fed. Reg. 9464 (May 11, 1972). In the matter of the combination of OTC ephedrine and OTC guaifenesin, both ingredients make such a contribution. Ephedrine temporarily relieves the symptoms of bronchial asthma (i.e., relieving shortness of breath, tightness of chest and wheezing) and guaifenesin helps loosen phlegm (mucus) and thin bronchial secretions to rid the bronchial passageways of bothersome mucus, it drains bronchial tubes, and makes coughs more productive. See 21 C.F.R. §341.76(b) and 21 C.F.R. §341.78(b), respectively. This being the case, the target population for this product is those that have bronchial asthma and mucus in the bronchial passageways. FDA admits in its proposal that this

population does in fact exist. There is no question that guaifenesin makes a contribution to its claimed effect, as does ephedrine.

The last portion of the analysis to determine whether or not a combination product is consistent with FDA policy is the determination of whether or not the combination, when used under adequate directions for use and warnings against unsafe use, provides rational concurrent therapy for a significant proportion of the target population. Given the following facts:

- Both ephedrine and guaifenesin are each considered to be safe and effective for OTC use;
- There is no evidence supporting the fact that when these ingredients are combined the safety or effectiveness of any of the individual active ingredients is decreased when used under adequate directions for use and warnings against unsafe use (as provided for in the final monograph);
- Both ingredients contribute to their claimed effects; and
- The target population is those that have bronchial asthma and mucus in the bronchial passageways;

this combination is clearly a rational concurrent therapy for a significant proportion of the target population.

## VI.
## CONCLUSION

FDA's proposal would have the practical effect of removing ephedrine bronchodilators from the OTC market, an outcome that will negatively affect the health of a significant proportion of the American population as well as this country's already overburdened health care system. FDA's proposal will also have a devastating effect on the small independent drug distributors, like BDI, who have been selling combination ephedrine/guaifenesin products for

well over a decade. Accordingly, for the reasons stated herein BDI respectfully objects to FDA's proposal to reclassify the combination of an oral bronchodilator and an expectorant as not generally recognized as safe and effective for OTC use.

Dated: December 1, 2005

Respectfully submitted,

BDI MARKETING, INC.
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By: _____

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# Active Chemical Registrants

## As of November 4, 2005

**Chemical Handler Totals: 2,843**

Business Activities

V - Retail Distributor
W - Manufacturer
X - Importer
Y - Distributor
Z - Exporter

| STATE | V | W | X | Y | Z | TOTALS |
|---|---|---|---|---|---|---|
| ALABAMA | 0 | 2 | 0 | 55 | 1 | 58 |
| ALASKA | 0 | 0 | 0 | 6 | 0 | 6 |
| ARIZONA | 0 | 4 | 0 | 22 | 0 | 26 |
| ARKANSAS | 0 | 0 | 0 | 36 | 1 | 37 |
| CALIFORNIA | 0 | 13 | 9 | 105 | 7 | 134 |
| COLORADO | 0 | 1 | 0 | 30 | 0 | 31 |
| CONNECTICUT | 0 | 1 | 5 | 30 | 1 | 37 |
| DELAWARE | 0 | 4 | 1 | 5 | 4 | 14 |
| DISTRICT OF COLUMBIA | 0 | 0 | 0 | 5 | 0 | 5 |
| FLORIDA | 0 | 10 | 9 | 102 | 12 | 133 |
| GEORGIA | 0 | 4 | 3 | 93 | 4 | 104 |
| GUAM | 0 | 0 | 0 | 4 | 0 | 4 |
| HAWAII | 0 | 0 | 0 | 16 | 0 | 16 |
| IDAHO | 0 | 1 | 1 | 17 | 1 | 20 |
| ILLINOIS | 0 | 7 | 8 | 110 | 7 | 132 |
| INDIANA | 0 | 4 | 5 | 54 | 10 | 73 |
| IOWA | 0 | 2 | 0 | 21 | 1 | 24 |
| KANSAS | 0 | 0 | 1 | 22 | 0 | 23 |
| KENTUCKY | 0 | 3 | 1 | 51 | 3 | 58 |
| LOUISIANA | 0 | 3 | 4 | 49 | 6 | 62 |
| MAINE | 0 | 0 | 0 | 8 | 0 | 8 |
| MARYLAND | 0 | 1 | 1 | 27 | 2 | 31 |
| MASSACHUSETTS | 0 | 2 | 1 | 38 | 1 | 42 |

| | | | | | | |
|---|---|---|---|---|---|---|
| MICHIGAN | 0 | 11 | 5 | 96 | 5 | 117 |
| MINNESOTA | 0 | 0 | 0 | 28 | 0 | 28 |
| MISSISSIPPI | 0 | 1 | 0 | 41 | 0 | 42 |
| MISSOURI | 0 | 6 | 4 | 47 | 3 | 60 |
| MONTANA | 0 | 0 | 0 | 8 | 0 | 8 |
| NEBRASKA | 0 | 0 | 2 | 8 | 2 | 12 |
| NEVADA | 1 | 0 | 0 | 4 | 0 | 5 |
| NEW HAMPSHIRE | 0 | 0 | 2 | 14 | 2 | 18 |
| NEW JERSEY | 0 | 35 | 66 | 95 | 37 | 233 |
| NEW MEXICO | 0 | 0 | 0 | 9 | 0 | 9 |
| NEW YORK | 0 | 22 | 15 | 119 | 8 | 164 |
| NORTH CAROLINA | 1 | 6 | 1 | 116 | 5 | 129 |
| NORTH DAKOTA | 0 | 0 | 0 | 6 | 0 | 6 |
| OHIO | 0 | 10 | 4 | 97 | 6 | 117 |
| OKLAHOMA | 0 | 2 | 0 | 24 | 4 | 30 |
| OREGON | 0 | 2 | 1 | 23 | 0 | 26 |
| PENNSYLVANIA | 0 | 8 | 14 | 99 | 10 | 131 |
| PUERTO RICO | 0 | 5 | 4 | 63 | 8 | 80 |
| RHODE ISLAND | 0 | 1 | 0 | 7 | 0 | 8 |
| SOUTH CAROLINA | 0 | 5 | 6 | 55 | 4 | 70 |
| SOUTH DAKOTA | 0 | 0 | 0 | 5 | 0 | 5 |
| TENNESSEE | 0 | 9 | 4 | 68 | 4 | 85 |
| TEXAS | 0 | 17 | 9 | 146 | 12 | 184 |
| UTAH | 0 | 2 | 0 | 15 | 2 | 19 |
| VERMONT | 0 | 0 | 0 | 5 | 0 | 5 |
| VIRGIN ISLANDS | 0 | 0 | 0 | 1 | 0 | 1 |
| VIRGINIA | 0 | 3 | 1 | 53 | 2 | 59 |
| WASHINGTON | 0 | 2 | 2 | 21 | 1 | 26 |
| WEST VIRGINIA | 0 | 1 | 2 | 14 | 1 | 18 |
| WISCONSIN | 0 | 5 | 4 | 55 | 2 | 66 |
| WYOMING | 0 | 0 | 0 | 4 | 0 | 4 |

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