

Wyeth Consumer Healthcare
Five Giralda Farms
Madison, NJ 07940

Sharon Heddish
Vice President
Worldwide Regulatory Affairs
973-660-5753

Wyeth

November 7, 2005

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

RE: Docket No. 1995N-0205
Comments to Proposed Amendment of Final Monograph for Over
The Counter Bronchodilator Drug Products

To Whom it May Concern:

Wyeth Consumer Healthcare (WCH) hereby submits comments to the proposed amendment of the Final Monograph for OTC Bronchodilator Drug Products, published in the Federal Register on July 13, 2005 (70 FR 40237). WCH markets Primatene Tablets (ephedrine HCl 12.5mg/guaifenesin 200mg) and Primatene Mist (Epinephrine 0.22mg), which are directly affected by the proposed amendment.

WCH agrees with the Agency's conclusions that ephedrine and epinephrine should remain in the FM for self-treatment of mild bronchial asthma. We agree 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.

WCH also agrees with many of the recommended labeling changes that are presented in the proposed amendment, with one exception. The Agency is suggesting the following warning be included in Drug Facts:

When Using This Product... Increased blood pressure or heart rate can occur, which could lead to more serious problems such as heart attack, stroke, and death. Your risk may increase if you take more frequently or more than the recommended dose.



WCH objects to this proposed warning for the reason that it goes beyond that which is supported by data. We recommend the following language as being more representative of the data:

When using this product... Increased blood pressure or heart rate may occur, which could increase your risk of more serious problems, especially if you have risk factors such as a history of high blood pressure or heart disease. Your risk may increase if you take more frequently or more than the recommended dose.

The warning put forth in the ANPR fails to acknowledge that while the available data on ephedrine and epinephrine shows that both products may increase blood pressure or heart rate, (as do all sympathomimetics), the effect of that increase varies based on the individual's risk factors. Furthermore, the magnitude of the warning is not supported by the literature or adverse event data, and is unnecessarily alarming. WCH suggests that the alternative language proposed above provides consumers with more relevant information to help them decide whether to take an OTC asthma product.

Warnings should be data driven

The content of the labeling of drug products approved under section 505 of the Food Drug and Cosmetic Act, whether prescription or over the counter, must be substantiated by data. The data can be generated during clinical trials, or it can be gathered during the postmarketing use of the product, either by reports of adverse events to the company or through the literature. This principle applies to all aspects of a label, from indications to warnings and precautions. Data is so essential to the content of a label that the Agency reserves the right to deny a sponsor's request to add a warning to a label if it deems the data to be insufficient or inconclusive.

Given the standards sponsors of NDAs and ANDAs must meet in order to make a statement in a label, it is disconcerting that the Agency takes the position that "Mandating warnings in an OTC drug monograph does not require a finding that any or all of the OTC drug products covered by the monograph actually caused an adverse event..."



Proposed Warning Does Not Take Into Account Individual Risk Factors

As shown in the literature cited in the ANPR, sympathomimetics may cause modest increases in heart rate and blood pressure. However, the outcome of such increases will vary from person to person based on their underlying risk factors. WCH objects to the language of the cardiovascular warning for the reason that it implies that all consumers are at equal risk of complications resulting from increases in heart rate or blood pressure.

“FDA is aware of reported adverse drug events on the cardiovascular system associated with the use of ephedrine-containing drug products. ...The reported adverse events include elevations in blood pressure and/or heart beat, and serious adverse events include abnormal heart rhythm (arrhythmias), heart attack, and stroke. These events are consistent with the known pharmacology of sympathomimetic drugs, as reported in the literature. *The reports we have received for ephedrine-containing bronchodilator drug products were associated with use that was more frequent or in higher amounts than the labeled dose...*(emphasis added).
70 FR 40243

As noted in the passage above, reports of cardiovascular events coincident with ephedrine-containing bronchodilator drug products were associated with misuse of the product. There was no evidence presented to link the normal use of OTC bronchodilators with any of the events listed in the proposed warning.

Reports of Adverse Events Associated with Ephedra-Containing Dietary Supplements Cannot Be Correlated With OTC Bronchodilators

WCH is concerned that the labeling for OTC bronchodilator products is being painted with the same broad brush as ephedra, the dietary supplement. Ephedra and ephedrine are two different substances. Ephedra is a general term for ephedrine alkaloids used in dietary supplements marketed for weight loss and energy enhancement. The Agency’s 2004 action to prohibit dietary supplements containing ephedrine alkaloids was specific to dietary supplements. Prior to its removal from the market, ephedra was available at a variety of outlets, including



internet and mail order houses. Its relatively uncontrolled distribution and lack of adequate warnings about its stimulant effects made it prone to misuse.

In contrast, Primatene Tablets is a monograph drug containing ephedrine and guaifenesin. Since it is a drug, its labeling is regulated by FDA, and therefore carries appropriate warnings about side effects and overdose.

In the preamble to the proposed rule, FDA recognized the differences between OTC ephedrine drug products and ephedrine alkaloids that were relevant to distinguishing the risk benefit profiles of the drugs. Such differences included:

- Ephedrine in drug products meets the USP with respect to standardized identity, strength, quality and purity. Dietary supplements are not subject to the same standards, and contained varying amounts of ephedrine and other ephedrine alkaloids.
- Botanical sources of ephedrine alkaloids contain other sympathomimetics, including norephedrine, pseudoephedrine and methylephedrine, all of which are pharmacologically active.
- “FDA has received and evaluated adverse reaction reports on both drug products containing ephedrine and dietary supplements containing ephedrine alkaloids. Based on the differences in composition described in the previous paragraphs between the drug products and dietary supplements, adverse event data for dietary supplements containing ephedrine alkaloids may not be completely applicable to ephedrine drug products.”

Since it has been acknowledged that ephedrine and ephedrine alkaloids are different, each should stand on its own merits with respect to appropriate warnings. The literature cited in the proposed rule discusses the effect of ephedrine on heart rate and blood pressure, but does not discuss whether ephedrine at OTC doses is likely to cause heart attack, stroke or death.

A search of the WCH adverse event database yielded a single report of death coincident with the use of Primatene Tablets (ephedrine/guaifenesin) during the time period 1988 to present. Based on sales figures, WCH estimates the number of doses of Primatene Tablets to be 510 million from 1988 to present. This is a very low incidence of death relative to the distribution of the product.



Warning Of “Death” Is Particularly Unreasonable

Even within the realm of prescription products, warnings to consumers about the possibility of death occur in the most exceptional circumstances. A search for the word “death” among the 3005 entries in the current electronic Physician’s Desk Reference found no OTC products and 51 prescription products that warn *patients* (in Patient Leaflets) specifically about the possibility of death when taking a particular product. The products were as follows:

- Oral Contraceptives
- Protease inhibitors
- Isotretinoin
- Acitretin
- Insulin¹
- Corticosteroids
- Amphetamines
- Quinolone Antibiotics
- Lotronex (serotonin 5-HT₃ antagonist)
- NSAIDs (Prescription only)
- Opioids
- Interferon
- Nucleoside analogues

In common among all these drugs is that they are all prescription drugs, and there was a clear signal that precipitated the need for a warning. The proposed warning for OTC bronchodilators is not based on data that reaches this standard.

Conclusion

In conclusion, WCH objects to the cardiovascular warning put forth in the Proposed Rule for the OTC Bronchodilator Monograph. WCH urges the Agency to revise the proposed warning on the principle that the labeling for any drug product, be it monograph or NDA, should be guided by the available data.

¹ Insulin, while OTC, is not typical of OTC products

Page 6
Food and Drug Administration
November 7, 2005

Wyeth

Sincerely,

A handwritten signature in cursive script that reads "Sharon Heddish".

Sharon Heddish
WYETH CONSUMER HEALTHCARE