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September 13, 2001

VIA FACSIMILE AND REGULAR MAIL

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: ***Phenylpropanolamine; Proposal to Withdraw Approval of New Drug Applications; Opportunity for a Hearing, Docket No. 01N-0196***

To the Dockets Management Branch:

Schering-Plough Healthcare Products ("Schering-Plough"), through its undersigned counsel, submits these comments in response to the above notice ("Notice") published at 66 Fed. Reg. 42665 to 42671 (Aug. 14, 2001). That Notice proposes the withdrawal of various new drug applications and abbreviated new drug applications for certain drug products, prescription and over-the-counter, containing phenylpropanolamine ("PPA"), including Demazin Extended-Release Tablet, NDA 18-556. In or about 1996, Schering-Plough discontinued the marketing of Demazin Extended-Release Tablet and, as a result of that action, does not request a hearing. Nonetheless, Schering-Plough

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believes certain comments are appropriate and, in particular, requests that the FDA include in any final determination an express disclaimer of the relevance of the FDA's actions in product liability suits involving PPA.

As an initial matter, because the FDA has based its actions on the results of the Yale Hemorrhagic Stroke Project ("HSP"), Schering-Plough notes that prior to the HSP, there was no scientifically reliable evidence of an association between PPA in either cough-cold remedies or diet products and hemorrhagic stroke. Indeed, in 1996, the FDA expressly determined that it was unnecessary and inappropriate to withdraw PPA-containing OTC products pending completion of the HSP because there was no existing evidence that PPA "represents a substantial public health risk." 61 Fed. Reg. at 5913. Likewise, the HSP investigators themselves noted that the one epidemiologic study done prior to the HSP "found no association" between PPA and hemorrhagic stroke. (Kernan et al. "Phenylpropanolamine and the Risk of Hemorrhagic Stroke," 343 New Eng. J. Med. 1826, 1831 (Dec. 21, 2000) (citing Jick et al., Phenylpropanolamine and cerebral hemorrhage, Lancet 1984; 1:1017)), and that prior case reports suggesting an association failed to satisfy "the usual criterial for valid scientific inference."

In addition, the HSP has certain limitations and, more significantly, provides no meaningful information with respect to cough-cold products containing PPA and hemorrhagic stroke:

- The investigators acknowledge that the HSP "did not establish a causal connection between PPA and hemorrhagic stroke." [See Response to "Comments on the Hemorrhagic Stroke Project" by CHPA Phenylpropanolamine Working Group at 2 (Sept. 19, 2000).]

- As reported in the published, peer-reviewed version of the HSP that appeared in the New England Journal of Medicine, with respect to cold/cough remedies such as Demazin Extended Release Tablet, the study found only "a suggestion of an association" among women ages of 18 to 49 between "first use" of PPA and hemorrhagic stroke – and no such suggestion with respect to first use among any other group of women or with respect to women generally in the case of cold/cough remedies.
- The HSP investigators have also admitted that the odds ratio for the "suggestion of an association" found among women 18 to 49 years old "did not reach conventional criteria for statistical significance." Letter to Editor, from W.J. Kernan, M.D., et al., New England Journal of Medicine (April 5, 2001). Given this acknowledgment, it appears that the contrary assertion in the Notice that this odds ratio "reached statistical significance" is in error. 66 Fed. Reg. at 42668.
- Among men, the HSP results did not show any increased risk of hemorrhagic stroke in association with the use of PPA-containing cold/cough remedies.

For the reasons stated above, although Schering-Plough is not requesting a hearing, we believe that the various limitations and weaknesses of the HSP study raise serious questions as to the validity of its limited conclusions – weaknesses that were in part noted by a panel of experts in the immediate wake of the study's release. See CHPA Phenylpropanolamine Working Group's Comments on the Hemorrhagic Stroke Project (May 24, 2000). In addition, besides those weaknesses, the HSP investigators themselves have admitted that the HSP study found no

statistically significant association between cough-cold products containing PPA and hemorrhagic stroke.

Therefore, Schering-Plough submits that it would be entirely appropriate for the FDA to include a disclaimer that its actions will not be improperly or unfairly used in products liability litigation involving cough-cold products that formerly contained PPA. In particular, Schering-Plough believes that language similar to that used by the FDA in a recent final action listing – 64 Fed. Reg. 10944, 10945 (March 8, 1999) – would be appropriate.

Respectfully submitted,

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MESSAGE: Submission of Schering-Plough Healthcare Products in response to Phenylpropanolamine; Proposal to Withdraw Approval of New Drug Applications; Opportunity for a Hearing, Docket No. 01N-0196

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