September 28, 2001

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Bayer

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

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

Re: PHENYLPROPANOLAMINE: PROPOSAL TO WITHDRAW APPROVAL OF NEW DRUG APPLICATIONS

Docket No. 01N-0196

COMMENTS OF BAYER CORPORATION

The federal Food and Drug Administration ("FDA") recently issued a proposal to withdraw its approval of certain new drug applications ("NDAs") and abbreviated new drug applications ("ANDAs") for products containing phenylpropanolamine ("PPA"). This notice was published in the Federal Register on August 14, 2001. 66 Fed. Reg. 42665 (2001).

All of Bayer Corporation's PPA-containing medications are immediate-release OTC medications marketed under the monograph system. Therefore, these medications, marketed as the *Alka-Seltzer Plus* line of effervescent cough/cold medications, are not subject to this notice. Nevertheless, Bayer hereby submits its comments on FDA's recent notice as an interested person. *Id.* at 42670-71.

The FDA proposal discusses both the methodology and the conclusions of the unpublished May, 2000 final report of the Hemorrhagic Stroke Project ("HSP"). It omits any reference to the published, peer-reviewed version of the results of the HSP, which differ significantly from the earlier report. However, Bayer has serious reservations about the design, results, statistical analysis, and conclusions of the HSP. At the October 19, 2000, meeting of FDA's Nonprescription Drugs Advisory Committee ("NDAC"), FDA representatives met with HSP researchers, representatives from the Consumer Healthcare Products Association ("CHPA"), and several public speakers to

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discuss the safety of PPA in OTC medications. Bayer would like to comment on the questionable methodology and conclusions of the HSP by setting forth some of the critiques of the HSP raised at that meeting.

IN GENERAL:

- In the published, peer-reviewed version of the HSP that appeared in the New England Journal of Medicine, with respect to cough/cold remedies, the study found only "a suggestion of an association" between "first use" of PPA and hemorrhagic stroke among women ages 18-49 – and no such suggestion with respect to first use among any other group of women or with respect to women generally or with respect to men in the case of cough/cold remedies.

- The low level of participation of potential HSP study subjects, especially among the controls, skewed the results as Dr. Noel S. Weiss testified (*see* p. 99 of transcript). Only 41% of potential cases are in the study, so a huge number of people did not get into the study. *See* testimony of Dr. Lewis Kuller at pp. 102-04.

- The purported association between PPA use and increased risk of hemorrhagic stroke was not balanced against the benefits of PPA. *See* testimony of Dr. Weiss at p. 100.

BIASES IN THE HSP:

- At the start of the HSP, a hypothesis had been generated despite clinical epidemiologic support for PPA safety as well as demonstrated clinical benefits. *See* testimony of Dr. R. William Soller at p. 95.

- Information bias: It is difficult to obtain valid drug exposures retrospectively, particularly with stroke patients who may have trouble recalling what medications they took. *See* testimony of Dr. Brian Strom at p. 15. Validating the timing of the use is difficult as well. *See* testimony of Dr. Charles Hennekens at p. 120.

- Selection bias: Ideally a case control study is population-based, but this was not done in the HSP. Rather, cases came from individual hospitals from different locations, not from a defined population. *See* testimony of Dr. Strom at p. 16.

- Observation bias: Cases were hospitalized with hemorrhagic stroke and 40% were aphasic which caused difficulties verifying exposure and the time of use. Controls were selected from random digit dialing. The likelihood for noncomparability between cases and controls due to selection and observation bias is substantial and also impossible to assess. *See* testimony of Dr. Hennekens at p. 120.

CHANCE IN THE HSP:

- There is no clear biological rationale to support the differences across sub-groups. For example, why an association in women and not men? It is not a consistent picture. *See* testimony of Dr. Weiss at p. 100. The inconsistent results suggest chance as an explanation. *See* testimony of Dr. Strom at p. 12.

- While this is a large study of over 700 cases and 1,400 controls, the hypothesis that PPA is associated with hemorrhagic stroke is based on just 27 exposed cases and 33 exposed controls. *See* testimony of Dr. Hennekens at p. 118.

CONFOUNDING VARIABLES MAY NOT ADEQUATELY ACCOUNTED FOR IN HSP:

- There are differences between cases and controls in terms of various confounding variables. *See* testimony of Dr. Weiss at p. 99. Cases reported a significantly higher prevalence of numerous major and independent risk factors for hemorrhagic stroke than controls. These factors include race, family history of hemorrhagic stroke, history of hypertension, cigarette smoking, alcohol use, illicit drug use including cocaine, and lower socioeconomic status. Thus, there is uncontrolled confounding. *See* testimony of Dr. Hennekens at p. 121.

Based on these concerns about the HSP and in light of the substantial amount of litigation that the HSP and FDA's reliance upon it has already fueled, Bayer submits that it would be appropriate, if and when the proposal outlined in this FDA notice becomes final, to include a disclaimer similar to the following statement from a recent final action concerning another drug ingredient, *see* 64 Fed. Reg. 10944, 10945 (March 8, 1999), removed from the market following an FDA determination regarding its safety:

> Compounding pharmacists and physicians are the intended audience for this rule...this list is not intended to be used as evidence in a product liability suit, and the addition of language designed to minimize the potential effect of the list in litigation is unnecessary to fulfill its intended purpose.
>
> * * *
>
> The agency wishes to emphasize that the inclusion of a drug product on the list does not mean that the drug product was marketed negligently, was defective, or was marketed in breach of any warranty. Even after exhaustive clinical studies, safety problems may not become apparent until a drug product has been in commercial distribution for a significant amount of time, so the fact that a drug was removed or withdrawn from the market does not mean that the drug was improperly placed in commercial distribution.

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In conclusion, Bayer Corporation's *Alka-Seltzer Plus* effervescent cough/cold medications earned a reputation for providing safe and effective relief. Despite the conclusions of the HSP and FDA's recent notice endorsing the HSP, Bayer continues to have the utmost confidence in the safety of its cough/cold medications.

Dated: September 28, 2001

Respectfully submitted,

Randy Koslo, Ph.D.
Director, Medical Affairs and Clinical Research

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