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Commissioner of Food and Drugs  
c/o Division of Dockets Management (HFA-305)  
Food and Drug Administration  
5630 Fishers Land, Room 1061  
Rockville, Maryland 20852

**Re: Phenylpropanolamine - Containing Drug Products for Over-the-Counter Human Use; Tentative Final Monographs; Notice of Proposed Rule (70 Fed Reg. 75988)**  
Docket Nos: 1976N-0052N; 1981N-0022  
RIN 0910-AF34; 0910-AF45

Dear Commissioner:

GlaxoSmithKline Consumer Healthcare LP (“GSK”) submits the following comments to the above-referenced Notice of Proposed Rule (“NPR”).

Although GSK currently has no Phenylpropanolamine (“PPA”) -containing products on the market and does not plan to market such products in the future, GSK believes that a response to the above-referenced NPR is warranted, due to the NPR’s potential to be misleading in its implications and in its conclusions. As a former manufacturer of PPA-containing cough –cold medications, GSK has significant interest in the accuracy of the record on this issue.

For almost four decades, GSK manufactured and marketed certain formulations of Contac cough–cold medication that contained PPA. We note that it also did so under the new drug application (“NDA”) process – a process that subjects the products to significantly more rigorous FDA review prior to marketing approval than the drug monograph process that is the direct subject of the NPR. The specific labeling of each product also was reviewed and approved by FDA. As recently as September 1999, the FDA approved the supplemental new drug application for GSK’s PPA-containing Contac 12 Hour Cold Capsules. In so doing, FDA “concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the submitted labeling ...” (FDA Approval letter for Contac 12 Hour Cold Capsules dated September 7, 1999).

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FDA's conclusion in its recent approval letter to GSK for Contac 12 Hour Cold Capsules is consistent with the long history of Contac as a safe and effective cough-cold medication over the decades. During the 38 years of marketing Contac, GSK and its predecessors had never received any reports of hemorrhagic stroke – the primary stated concern in FDA's NPR – when the product was used as directed in the labeling.

In fact, since the early 1990s, FDA's concern with PPA-containing products has been focused on weight control products and not cough-cold medications. FDA Medical Officer Dr. Heidi Jolson, M.D., reviewed safety data on both weight control products and cough-cold medications. Her comments of concern were with regard to weight control products, "...interpretation of [available] data suggests an association between PPA-diet pills and cerebral hemorrhage, however we are unable to measure the strength of this association with available information." (FDA memorandum dated December 26, 1991.) For these reasons, among others, Dr. Jolson concluded her memo with a recommendation that further research be directed toward PPA-containing weight control products.

More specifically, with regard to PPA-containing cough-cold medications, Dr. Raymond Lipicky, M.D., Director of FDA's Division of Cardio-Renal Drug Products stated, "previous large studies have found no statistically significant association between PPA-cough/cold products and cerebral hemorrhage." (FDA memorandum dated August 9, 1990.) Dr. Lipicky further concluded, "[i]t seems reasonably clear that 'ordinary' use of PPA cannot be considered a safety concern. If PPA could be considered a major safety concern, the Division would have acted long ago."

Therefore, FDA's concern with PPA-containing weight control products drove the initiation of the Hemorrhagic Stroke Project ("HSP" or "Yale Study"). FDA initially determined to commission the HSP to investigate the possible association between PPA-containing weight control over-the-counter (OTC) products and an increased risk of hemorrhagic stroke; and only later determined to add cough-cold medications.

With this background, it is of significant note that FDA then based its internal review of the HSP and the resulting NPR on an unpublished, non-peer reviewed version of the HSP report. As FDA itself often notes, such unpublished reports that have not been subjected to the rigor of the scientific/medical peer-review process often contain significant inaccuracies and overstated conclusions. The distinction is important enough that FDA's statute, promulgated by Congress, actually forbids the distribution of non-peer reviewed articles with information on non-labeled uses of drugs, but permits the same from peer-reviewed journals (*see* 21 U.S.C. § 360aaa-1). NIH also recently acknowledged "the process of editing and peer review as a form of quality control on the publication process." (NIH NOT-OD-04-064)

Given this, it is not surprising that the unpublished HSP report, which had not been subjected to journal-level editing and scientific peer-review, was seriously flawed in numerous respects. The magnitude of problems with the unpublished HSP report have, in fact,

resulted in significant dissent within the scientific and medical communities regarding the reliability of its conclusions. Since GSK is not interested in reintroducing PPA-containing Contac cough-cold medication to the market at this time, notwithstanding its continued belief that Contac was safe used as directed, GSK will not discuss the HSP flaws in significant detail in this response. Rather, GSK refers to a recent peer-reviewed article setting forth some of the specific inadequacies in the HSP report -- especially, the unpublished, non-peer reviewed version. (Stier BG and Hennekens CH, "Phenylpropanolamine and Hemorrhagic Stroke in the Hemorrhagic Stroke Project: A Reappraisal in the Context of Science, the Food and Drug Administration, and the Law" *Annals of Epidemiology* 16:49-52 at 51 (2006).)

When the HSP was finally completed and published in peer-review form in late 2000, these findings actually confirmed FDA's earlier conclusion based on Dr. Lipicky's review, because the use of PPA-containing cough-cold medications did not demonstrate a statistically significant increased risk of hemorrhagic stroke. Further confirmation of these results was provided when the HSP investigators later published separate findings regarding intracerebral hemorrhage and subarachnoid hemorrhage. Neither set of findings identified PPA as a risk factor. (Broderick, JP, *et al.*, "Major Risk Factors for Aneurysmal Subarachnoid Hemorrhage in the Young are Modifiable," *Stroke* 34:1375-1381 (2003); Feldmann E, *et al.*, "Major Risk Factors for Intracerebral Hemorrhage in the Young are Modifiable," *Stroke* 36:1881-1885 (2005).) In sum, the conclusions drawn in the peer-reviewed HSP study results on cough-cold medications are dramatically different from those of the unpublished report.

Today, more than a decade after the initiation of the HSP, no study has been published in the peer-reviewed literature that demonstrates an increased risk of hemorrhagic stroke associated with PPA-containing cough-cold medications in general, or with Contac in particular. This is quite significant in that one of the earmarks of scientific validity is acceptance and reproducibility of the results by others within the community.

GSK also refers to litigation-related evidence presented during a recent California Superior Court trial that was not available to the FDA or its Advisory Committee while they were reviewing the unpublished HSP report on which the NPR is based. In that case, the jury returned a defense verdict in favor of another manufacturer of PPA-containing products. Furthermore, after hearing all of the evidence regarding the HSP, the presiding judge stated on the record:

"You could almost say there was some unethical activity with that Yale Study.... I am very concerned at the integrity of those researchers.... If you have unethical, possibly dishonest research going on... I think you have the right to say something about it.... Either way, Yale gets...a big black eye on this."  
(*Lutz/O'Neill v. Novartis Consumer Health*, Hearing on Motion for JNOV and for New Trial, March 18, 2004 at 46.)

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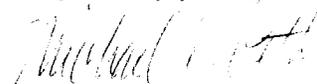
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Thus, GSK believes that FDA has placed undue reliance on the unpublished HSP study to the exclusion of the peer-reviewed published results, which are considered throughout the scientific community to be more reliable. Additionally, the NPR suggests that unidentified manufacturers reformulated products because of safety concerns raised following publication of the preliminary HSP. In fact, by 1999, because of consumer preference, most of GSK's Contac line of cough-cold medications contained pseudoephedrine as the active decongestant ingredient.

GSK believes that the totality of evidence continues to support the safety and effectiveness of PPA in cough- cold medications, including those approved through the drug monograph process. This conclusion is even more compelling, however, for products, such as Contac, which underwent multiple and product-specific full NDA reviews of drug safety and labeling. Contac, right up to the time of its reformulation, was specifically found by FDA to be "safe and effective for use" as directed on the label. For all of these reasons, GSK believes that Contac has been a safe and effective drug as labeled, and has submitted these comments to the FDA's Notice of Proposed Rule.

Respectfully yours,

  
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Ropes & Gray, LLP  
(counsel for GSK)

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