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Ralph Nader, Founder

June 16, 1993

Dr. Carl C. Peck
Director, Center for Drug Evaluation
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Peck:

We write in response to the April 9, 1993 meeting of the Nonprescription Drugs Advisory Committee which considered portions of our January 7, 1993 petition to ban and/or relabel five antidiarrheal drugs. At that meeting, the Advisory Committee concluded that the studies offered in favor of kaolin in the treatment of diarrhea were sufficient to merit a finding of efficacy. In so doing, it cited unpublished studies 295, 302, and 303. We believe that this finding is unsupportable for at least four reasons:

1. *Important additional information, including published studies, was ignored by Committee members in reaching their decision.*

Advisory Committee members presented findings from four kaolin/pectin trials and were apparently given additional information for review, which was not presented. Excluded from presentation were two placebo-controlled, randomized trials of kaolin versus placebo, the very question that was before the Committee. Even using the "cosmetic" endpoints relied upon by the Committee in making its finding of efficacy (endpoints which we reject), both of these studies show no difference between kaolin and controls. The only time these two studies were even mentioned during the entire hearing was in our presentation. Copies of the transparencies used in our presentation are enclosed. We cannot understand why published articles with unfavorable findings are ignored, while unpublished data is used to assert findings of efficacy.

2. *Study 302 was excluded from the hearing.*

In Dr. Gilbertson's March 11, 1993 letter to Upjohn Vice President, Dr. George Ishler, he lists only studies 295 and 303 as "pivotal information" in the evaluation of kaolin. Thus, study

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302 was not to form part of the Committee's deliberations. Although the Committee was apparently provided information, perhaps only in summary form, on 302 prior to the meeting, for members of the public there was access only to the very cursory presentation of the findings by the Medical Officer, Dr. Gallo-Torres. Even from that presentation, however, it was clear that significant differences in interpretation of the study findings exist between the manufacturer and the FDA.

3. *Study 302 fails to support kaolin's efficacy.*

Since the hearing we have had the opportunity to review study 302. It is a randomized, double-blinded, placebo-controlled trial comparing the efficacy of kaolin/pectin, kaolin, pectin and placebo in 232 adults with acute diarrhea. As the hearing focused on the efficacy of kaolin alone, we consider only results for that compound and not the other treatment arms of the study.

The results reveal a statistically significant increased number of formed stools in the kaolin group compared to placebo. Interestingly, kaolin/pectin did not show any improvement over placebo on this measure on day 1. The more notable finding is not the minor differences between placebo and kaolin (0.37 v. 0.17 formed stools on day 1), but the major decrease in watery stools between baseline and day 1 consistency in all four treatment arms. At baseline, subjects were experiencing about 4.6 watery stools per day, compared with day 1 results of 0.98 for kaolin and 1.30 for placebo, a statistically nonsignificant difference. In other words, the most remarkable finding was the degree to which diarrhea spontaneously improved, not the minor cosmetic benefit conferred by kaolin. There were no differences between kaolin and placebo with respect to number of patients continuing to have or recovering from diarrhea, mean number of stools, or time from drug administration to change in bowel movement consistency.

With respect to "stool variables," the study provides evidence that the mean total stool dry weight went up and the mean total stool percent water went down for kaolin, although other indices were unaffected by the therapy (mean total stool net weight, mean total stool volume, mean total stool water weight, mean total stool bulk density, and fecal excretion rate). However, about one-quarter of subjects failed to provide a stool sample at each point in the study period, and when they did may not have provided all their stools. The investigators state the stools were a "representative sampling of stools passed," but provide no justification for this assertion. Consequently, the study is unable to properly assess fluid balance, the true outcome of interest for any antidiarrheal drug.

In summary, Study 302 demonstrates only extremely minor changes in stool consistency and fails to assess fluid balance in a meaningful fashion. We therefore believe that it cannot be used to support a finding of kaolin's antidiarrheal efficacy.

4. *Study 295 contributes nothing to the evaluation of kaolin as a single ingredient.*

As study 295 was a randomized trial of the kaolin/pectin combination versus placebo, it cannot be used in a finding of efficacy for kaolin alone.

For these four reasons, we believe that you should reject the findings of the Advisory Committee with respect to kaolin. It should be noted that the Committee properly rejected the evidence of efficacy of attapulgite, which has replaced kaolin/pectin in most of the biggest-selling OTC antidiarrheal products.

In summary, we agree with the 1990 World Health Organization's assessment of these drugs: *"kaolin and pectin cannot be recommended for the treatment of diarrhea, and there is thus no rationale for the production and sale of products that contain these agents."*

For the Food and Drug Administration, in the face of a clear lack of evidence of efficacy of either kaolin or attapulgite, to permit continued sale of either by allowing them to be classified as Class I ingredients -- safe and effective -- makes a further mockery of the beleaguered OTC drug review process.

We look forward to a prompt response to these concerns.

Sincerely,

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Health Research Group

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cc: David Kessler, M.D.
Commissioner
Food and Drug Administration

Summary

A. Attapulgite

- There are three placebo-controlled trials of attapulgite
- Of these only one assessed fluid balance, and in that trial attapulgite was found to be ineffective in preventing fluid loss

B. Kaolin/pectin

- There are six placebo-controlled trials of kaolin/pectin or its ingredients
- Of these only three assessed fluid balance, and in all three kaolin/pectin or its ingredients were found to be ineffective in preventing fluid loss

C. Conclusion

- Due to lack of evidence of efficacy in preventing fluid loss, both attapulgite and kaolin/pectin and its ingredients should be immediately removed from the market

Author: Watkinson, J Trop Peds, 1982

Design: Randomized, ? blinded

Comparison: Kaolin v. placebo

Subjects: 97 subjects, aged 3 - 18 months, with acute diarrhea

Findings: No difference between groups with respect to:

a. duration of diarrhea
b. stool water content
c. mean number of stools per day
d. maximum number of stools per day
e. change in body weight

Author: Nalin and Cash, J Pakistani Med Assoc, 1970

Design: Randomized, ? blinded

Comparison: Kaolin v. placebo

Subjects: 49 adult cholera subjects

Findings: No difference between kaolin and control with respect to:

a. total stool volume
b. duration of diarrhea
c. time to first negative rectal swab