DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

JUL 19 2001

Thomas O. Henteleff, Esquire
Stacy L. Ehrlich, Esquire
Kleinfeld, Kaplan and Becker
1140 Nineteenth Street, N.W.
Washington, D.C. 20036-6601

Re: Docket No. 00P-1472
Comment No. CP1

Dear Mr. Henteleff and Ms. Ehrlich:

This is in response to your citizen petition, dated August 23, 2000, submitted on behalf of Braintree Laboratories, Inc., and filed in FDA's Dockets Management Branch as Comment No. CP1 under Docket No. 00P-1472. The petition requested that the agency reclassify over-the-counter (OTC) sodium phosphate bowel preparations as prescription only products and require a boxed warning on the labeling to call attention to serious safety concerns associated with use of these products. The petition also requested that the agency regulate these products as new drugs on the basis that their use for bowel preparation cannot be considered generally recognized as safe, whether marketed OTC or by prescription.

The petition recommended the following black box warning for sodium phosphate bowel preparations: "Do not exceed recommended dose. Before use, appropriate tests should be performed to rule out electrolyte, renal or cardiovascular abnormality. Serious and life-threatening adverse events have occurred with sodium phosphate in the presence of these conditions." You stated that FDA has concluded in rulemakings related to sodium phosphate products that there are serious risks associated with OTC use of these products, particularly when used as bowel preparations. You submitted journal and literature articles concerning adverse effects associated with use of sodium phosphate drug products.

The agency has reviewed the data and information in your petition and determined that they do not support your request to change the status of sodium phosphate bowel cleansers from OTC to prescription status or to regulate these products as new drugs. The data also do not support the use of a boxed warning in the products' labeling. Boxed warnings are required only for certain prescription drug products. Therefore, the petition is denied. However, as discussed below, the agency concludes that for continued OTC marketing of oral sodium phosphates drug products, the container size must be limited to

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not greater than 45 milliliters (mL) and warning statements must be broadened to inform physicians and consumers of potential adverse effects and contraindications for use.

Our review of the articles in your petition revealed that the serious adverse events secondary to ingestion of oral sodium phosphates were the result of physicians prescribing more than the 45 mL recommended dose, or prescribing the product in error to patients at medical risk. In many instances, electrolytes were inadequately monitored. Thus, the primary reason for the adverse events appears to be that physicians are not adequately informed as to how to properly use this product. We do not believe that converting this product to prescription status would be likely to solve this physician education problem. Only one patient described in the submission (who ingested a sodium phosphates enema) became ill because of unprescribed misuse of a sodium phosphate-containing product.

In your submission, one journal article by Chan, Depew, and Vanner reported a survey of Canadian colonoscopists. Their study demonstrated that physicians who routinely prescribe bowel preparations are not adequately informed as to the risks and contraindications associated with the use of oral sodium phosphates solution.

In the FEDERAL REGISTER of May 21, 1998 (63 FR 27836-27844), the agency issued a final rule limiting the container size for sodium phosphates oral solution to not greater than 90 mL (3 ounces) when used as an OTC laxative product. The final rule is codified at 21 CFR 201.307. The final rule also required warning and direction statements to inform consumers that exceeding the recommended dose of oral and rectal sodium phosphates products in a 24-hour period can be harmful. The recommended dose for sodium phosphates oral solution for adults and children 12 years of age and over for general laxative use or for use as part of a bowel cleansing regimen is 20 to 45 mL as a single daily dose. The agency also concluded that the data were not sufficient to demonstrate the safety of more than 45 mL of sodium phosphates oral solution in a 24-hour period as part of a bowel cleansing regimen (63 FR 27839-27840).

The major trade product containing sodium phosphates oral solution had previously been marketed in 45, 90, and 240 mL bottles. In the final rule, the agency limited the package size based on reports in the medical literature and other data that indicated that accidental overdosing and deaths have occurred because the 240 mL container was mistakenly used instead of the 45 mL or 90 mL container. The final rule allowed the continued marketing of the 90 mL container as a convenience for consumers to purchase and have available for future use and because physicians often recommend and prescribe the 45 mL and 90 mL container sizes for bowel cleansing prior to surgery and diagnostic procedures of the colon.

Based on your petition, the agency has reconsidered the safety information discussed in the final rule. The serious adverse events were the result of physicians prescribing more than the 45 mL recommended dose of sodium phosphates oral solution. Current data do not support removing this product from the OTC marketplace. However, we believe that removing the 90 mL container size of sodium phosphates oral solution from the OTC

market should discourage prescribing and using larger than recommended doses. We also intend to require revised labeling to inform health professionals and consumers of contraindications and potential adverse effects associated with use of sodium phosphate-containing products. Note that in the FEDERAL REGISTER of May 21, 1998 (63 FR 27886-27893), the agency published a proposed rule to include additional general and professional labeling for oral and rectal sodium phosphates drug products. In the OTC laxative final monograph, which is nearing completion, the general labeling portion will be finalized. As noted in the FEDERAL REGISTER of December 9, 1998 (63 FR 67817), the professional labeling part of the proposal was withdrawn and will be reproposed in a future issue of the FEDERAL REGISTER.

Therefore, although the agency is denying your petition, we intend to propose regulations in future FEDERAL REGISTER notices to limit the package size of sodium phosphates oral solution to not greater than 45 mL (1½ ounces) and to require revised labeling to include more information to improve safe use of these products by consumers and health professionals. Some of the articles that you provided will be discussed in the proposed regulations.

Any comment that you wish to make on the above information should be submitted in triplicate, identified with the docket and comment numbers shown at the beginning of this letter to the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Room 1061, Rockville, MD 20852.

Sincerely yours,

Dennis E. Baker
Associate Commissioner
for Regulatory Affairs

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 7.19.01

FROM: Director
Division of OTC Drug Products, HFD-560

SUBJECT: Material for Docket No. OOP-1472

TO: Dockets Management Branch, HFA-305

[X] The attached material should be placed on public display under the above referenced Docket No.

[X] This material should be cross-referenced to Comment No. CP1

Charles J. Ganley, M.D.

Attachment