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October 8, 1997

2149 '97 OCT -9 10:02

VIA FEDERAL EXPRESS

Dockets Management Branch
(HFA-305)
Food and Drug Administration
12420 Parklawn Drive, Room 1-23
Rockville, Maryland 20857

Re: Laxative Drug Products for Over-the-Counter Human Use
Docket 78N-036L

Dear Sir/Madam:

We represent C. B. Fleet Company, Inc., of Lynchburg, Virginia (Fleet). Fleet manufactures and distributes FLEET® Ready-to-Use Enema (Sodium Phosphates Enema) and FLEET® Enema for Children, and FLEET® PHOSPHO-SODA® (Sodium Phosphates Oral Solution), laxative, purgative products which are subject to the rulemaking in Docket 78N-036L.

These products are currently labeled in compliance with the Tentative Final Monograph on Laxative Drug Products for Over-the-Counter Human Use, published at 50 Fed. Reg. 2124, et seq., on January 15, 1985. These products are available as general purpose laxatives for OTC use, and their labeling complies with the TFM as to the required warnings, directions for use and other labeling information for laxative use.

These products are, however, also indicated for use and used as purgatives for preparation of the bowel prior to colonoscopy, surgery and radiology procedures. The TFM does provide in proposed 21 C.F.R. § 334.80, 50 Fed. Reg. 2157-8, for professional labeling of these products for these purposes. See proposed 21 C.F.R. § 334.80(a)(2) and (b)(2), Id.

Since the publication of the TFM, Fleet has brought to the attention of the Agency changes in the Professional Use warnings it uses with regard to these products. (See my letter dated August 26, 1987 to Dr. William Gilbertson of the Office of OTC Drugs, a copy of which is attached as Exhibit A.) The purpose of this letter is to notify you that Fleet has made some changes in the Professional Use labeling for these products, that will appear in the 1998 Physician's Desk Reference®. The changes that have been made are in the information on PROFESSIONAL USE WARNINGS, OVERDOSAGE and, for FLEET® PHOSPHO-

78N-036L

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Arent Fox

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SODA®, DOSAGE AND ADMINISTRATION. For ease of reference, I am enclosing a marked up copy of the current labeling information plus a copy of the new labeling information. (See Exhibit B.)

Please note that Fleet does place professional use information on these products, and such information has helped to reduce side effects and adverse reactions caused by misuse of these products. (See my letter of February 23, 1994, a copy of which is attached as Exhibit C.)

Fleet understands that the comment period for this rulemaking is not currently open and that the Final Monograph for Laxative Drug Products for OTC Human Use is close to publication. Nevertheless, as the innovator and brand name for these products, Fleet believed it important to bring these changes to the attention of the Agency so that the Agency is aware of them and can take whatever action it deems appropriate.

Should the Agency have any questions about these changes, please contact the undersigned.

Sincerely,



Peter S. Reichertz

Enclosures

Filed in triplicate

cc: Debra Bowen, M.D.,
Director of OTC Drug Products
Ms. Sarah S. Post

Arent, Fox, Kintner, Plotkin & Kahn

Washington Square 1050 Connecticut Avenue, N.W.
Washington, D.C. 20036-5339

Peter S. Reichertz
(202) 857-6378

August 26, 1987

William D. Gilbertson, Pharm. D.
Director, Division of OTC Drug Evaluation
(HFN-210)
Office of Drug Standards
Center for Drugs and Biologics
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Dear Dr. Gilbertson:

We represent C. B. Fleet Company, Inc. (Fleet) of Lynchburg, Virginia with regard to the regulation of its products under the Federal Food, Drug and Cosmetic Act. As you know, Fleet manufactures and distributes the Fleet® Ready-to-Use Enema, containing sodium phosphate and sodium biphosphate. Fleet also markets a smaller size unit with these ingredients for use in children.

Sodium phosphate/sodium biphosphate enemas have been proposed for monograph status under the Tentative Final Monograph on OTC Laxative Drug Products. In addition, the professional labeling indication ["For use as part of a bowel cleansing regimen in preparing the patient for surgery or for preparing the colon for x-ray endoscopic examination", proposed 21 C.F.R. § 334.80(a)(2), 50 Fed. Reg. 2157 (January 15, 1987)] has been proposed for monograph status.

FDA has proposed that the following warning be used when a sodium phosphate and/or sodium biphosphate enema is used for these purposes:

Do not use in patients with megacolon,
as hypernatremic dehydration may
occur. Use with caution in patients
with impaired renal function.

Proposed 21 C.F.R.
§ 334.80(b)(2)

Arent, Fox, Kintner, Plotkin & Kahn

William D. Gilbertson, Pharm. D.
August 26, 1987
Page Two

This language is similar to the proposal first published as Proposed 21 C.F.R. § 334.80(a)(1), 40 Fed. Reg. 12942 (March 21, 1975), except that the words "as hyperphosphatemia or hypocalcemia may occur" have been deleted.

Fleet has no problem with the need for these warnings. The purpose of this letter is to inform you of certain additions Fleet has made to its professional labeling for this product. Since Fleet is a leader in this segment of the industry, we believe it is important for FDA to know of Fleet's actions in this area.

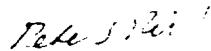
Exhibit A is the language to be used in the Physician's Desk Reference under Professional Use Warnings. It will also appear on any other professional labeling distributed by the Company.

Exhibit B is a summarized version of this warning which will appear on the carton of these products.

Exhibit C contains additions to the dosage and directions for use which will appear on the container as well as all other labeling, including the Physician's Desk Reference. Please note that Fleet no longer recommends any sodium phosphate/sodium biphosphate enema for use in children less than 2 years of age.

Should you have any questions about these changes, please contact the undersigned.

Sincerely,



Peter S. Reichertz

Enclosure

EXHIBIT A

PROFESSIONAL USE WARNING

Do not use in patients with congenital megacolon, imperforate anus or congestive heart failure as hypernatremic dehydration may occur. Use with caution in patients with impaired renal function, heart disease, or pre-existing electrolyte disturbances (such as dehydration or those secondary to the use of diuretics) or in patients on calcium channel blockers, diuretics or other medications which may affect electrolyte levels -- or where colostomy exists, as hypocalcemia, hyperphosphatemia, hypernatremia and acidosis may occur. Calcium and phosphorous levels should be carefully monitored. Since FLEET® Ready-To-Use Enema contains sodium phosphate and sodium biphosphate, there is a risk of acute elevation of sodium concentration in the serum and consequent dehydration, particularly in children with megacolon or any other condition where there is retention of enema solution. Additional fluids by mouth are recommended where appropriate (Fonkalsrud, E. and Keen, J.: "Hypernatremic Dehydration Hypertonic Enemas in Congenital Megacolon," JAMA 199:584-586, 1967. Zumoff, B. and Hellman, L.: "Rectal Absorption of Sodium from Hypertonic Sodium Phosphate Solutions," data on file, C. B. Fleet Company, Inc. Gilman, A., Goodman, L., Gilman, A., eds., The Pharmacological Basis of Therapeutics, Sixth Edition, 1980, p. 1005.) In addition, elevated levels of serum phosphates and decreased levels of serum calcium have been reported in patients with renal disease (and with prolonged use). (McConnell, T. H., "Fatal Hypocalcemia from Phosphate Absorption from Laxative Preparation," JAMA, 216:147-148, 1971.) If any of these complications occur following administration of Fleet® Ready-To-Use Enema or if the enema solution is retained, immediate corrective action should be taken to restore electrolyte balance with appropriate fluid replacements and continued monitoring of calcium and phosphorous levels.

EXHIBIT B

PROFESSIONAL USE WARNINGS:

Consult professional labeling for complete directions for use. Do not use in patients with congenital megacolon, imperforate anus or congestive heart failure as hypernatremic dehydration may occur. Use with caution in patients with impaired renal function, heart disease, or pre-existing electrolyte disturbances (such as dehydration or those secondary to the use of diuretics) or in patients on calcium channel blockers, diuretics or other medications which may affect electrolyte levels -- or where colostomy exists, as hypocalcemia, hyperphosphatemia, hypernatremia and acidosis may occur.

EXHIBIT C

DOSAGE:

DO NOT ADMINISTER TO CHILDREN UNDER 2 YEARS OF AGE. IF AFTER THE ENEMA SOLUTION IS ADMINISTERED THERE IS NO RETURN OF LIQUID, CONTACT A PHYSICIAN IMMEDIATELY AS DEHYDRATION COULD OCCUR.

DIRECTIONS FOR USE:

Discontinue Use if Resistance encountered. Forcing the Enema can result in injury.

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sists over a period of 2 weeks, consult a physician before using a laxative. Rectal bleeding or failure to have a bowel movement may indicate a serious condition. Discontinue use and consult a physician. Laxative products should not be used longer than 1 week unless directed by a physician. ~~Each teaspoonful (5 mL) contains 550 mg (9.4 mEq) equivalent sodium. DO NOT USE THIS PRODUCT IF YOU ARE ON A SODIUM RESTRICTED DIET OR IF YOU HAVE KIDNEY DISEASE UNLESS DIRECTED BY A DOCTOR. SERIOUS SIDE EFFECTS FROM OVERDOSAGE MAY OCCUR.~~ Keep this and all drugs out of the reach of children. In case of accidental overdose or ingestion, seek professional assistance or contact a Poison Control Center immediately. As with any drug, if you are pregnant or nursing a baby, seek the advice of a health professional before using this product.

OVERDOSAGE

Overdosage with Fleet® Phospho-soda may cause hypocalcemia, hyperphosphatemia, hypernatremia, hypernatremic dehydration and acidosis.

X Hypocalcemia, hyperphosphatemia, hypernatremia and acidosis

Calcium, Phosphate, Chloride and Sodium levels should be carefully monitored. Immediate corrective action should be taken to restore electrolyte balance with appropriate fluid replacements.

2. Hypernatremic Dehydration

Calcium, Phosphate, Chloride and Sodium levels should be carefully monitored. Prompt parenteral administration of fluids with lower concentrations of Sodium and Chloride than extracellular fluid (40-50 mEq/liter) and moderate concentration of Potassium (20-30 mEq/liter) administered at a rate of 3,000 to 4,000 cc/sq. m of body surface during the first 12 to 24 hours dependent on the severity of dehydration and the clinical response (Ponkalerud, E. and Keen, L. "Hypernatremic Dehydration from Hypertonic Enemas in Congenital Megacolon." JAMA 190:584-586, 1967). See article for more details.

or retention of

Potassium

DOSAGE AND ADMINISTRATION

For purgative or laxative, best taken on an empty stomach. Most effective when taken upon rising, at least 30 minutes before a meal, or at bedtime for overnight action. Dilute recommended dosage with one-half glass (4 fl. oz.) cool water. Drink, then follow with one glass (8 fl. oz.) cool water. DOSAGE: SINCE FLEET® PHOSPHO-SODA IS AVAILABLE IN TWO SIZES, PRESCRIBE BY VOLUMES; DO NOT PRESCRIBE BY THE BOTTLE. DO NOT EXCEED RECOMMENDED DOSAGE AS SERIOUS SIDE EFFECTS MAY OCCUR.

SINGLE DAILY DOSAGE: DO NOT EXCEED.

LAXATIVE: Adults and children 12 years and over:
4 teaspoonfuls (20 mL).

Children 10 to under 12 years: 2 teaspoonfuls (10 mL).

Children 5 to under 10 years: 1 teaspoonful (5 mL).

PURGATIVE: Adults only: 3 tablespoonfuls (45 mL).

DO NOT GIVE TO CHILDREN UNDER 5 YEARS.

For colonoscopy, especially useful when taken as follows:

1 1/2 fl. oz. (added to 4 fl. oz. water) 7 PM evening before.

Add

PROFESSIONAL DOSAGE AND ADMINISTRATION

Colonoscopy and Barium Enema Prep: On the day before the procedure, drink only clear liquids that are not colored red or purple for breakfast, lunch, and dinner. At 7 p.m., add 45 ml, 1 1/2 fl. oz. (3 tablespoonfuls) Fleet® Phospho-Soda to one-half glass (4 fl. oz.) of cold clear liquid and drink. Follow with one full glass (8 fl. oz.) of approved clear liquid. Drink at least three (3) more 8 fl. oz. portions of "clear liquids" before retiring. The day of the procedure at 6 a.m. or 3 hours before you leave for procedure, add 45 ml, 1 1/2 fl. oz. (3 tablespoonfuls) Fleet® Phospho-Soda to one-half glass (4 fl. oz.) of cool water and drink. Follow with one full glass (8 fl. oz.) of approved clear liquid.

Do not increase the dosage of this prep. If laxative action is inadequate, consider adding a non-saline laxative.

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~~exam (followed by three (3) 8 fl. oz. portions of clear liquids
before retiring) and 1 1/2 fl. oz. (added to 4 fl. oz. water)
morning (6 AM) of exam. It is recommended that the prep be
completed at least 2 hours in advance of appointment. Tim-
ing of dosage regimen can be adjusted by the physician.
Each teaspoonful (5 mL) contains: Active Ingredients: Mon-
obasic Sodium Phosphate 2.4 g and Dibasic Sodium Phos-
phate 0.9 g. Each teaspoonful (5 mL) contains 330 mg (24.1
milliequivalents) sodium.~~

HOW SUPPLIED

Regular or Flavored, in bottles of 1 1/2, and 3 fl. oz. Fleet®
Phospho®-soda should not be confused with Fleet® Enema,
a sodium phosphates disposable ready-to-use enema. Fleet®
Enema, Adult and Child size, ARE NOT INTENDED FOR
ORAL CONSUMPTION, in any dosage size.

~~IS THIS PRODUCT OTC?~~

~~Yes.~~

(Keep this)

LITERATURE AVAILABLE

Professional literature mailed on request.

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FLEET® PHOSPHO®-SODA OTC
A BUFFERED ORAL SALINE LAXATIVE

COMPOSITION

Each 5 mL of regular or flavored Phospho®-Soda contains 2.4 g. Monobasic Sodium Phosphate and 0.9 g. Dibasic Sodium Phosphate in a stable, buffered aqueous solution.

INDICATIONS

As a laxative, for the relief of occasional constipation. As a purgative, for use as part of a bowel cleansing regimen in preparing the patient for surgery or for preparing the colon for x-ray or endoscopic examination.

ACTION AND USES

Versatile in action as a gentle laxative or purgative, according to dosage. This product produces a bowel movement in 1/2 to 6 hours, depending on dosage. Especially useful as a bowel prep for colonoscopy, surgery, and radiology procedures. See DOSAGE AND ADMINISTRATION. Patient instruction pads available upon request.

CONTRAINDICATIONS

DO NOT USE THIS PRODUCT IF YOU HAVE KIDNEY DISEASE OR ARE ON A SODIUM RESTRICTED DIET UNLESS DIRECTED BY A PHYSICIAN. EACH TEASPOONFUL (5 ML) CONTAINS 556 MG (24.17 MILLIEQUIVALENTS) SODIUM.

PROFESSIONAL USE WARNINGS

Do not use in patients with congenital megacolon, bowel obstruction, ascites or congestive heart failure.
Use with caution in patients with impaired renal function, pre-existing electrolyte imbalances or with debilitated patients.

Since Phospho-Soda contains sodium phosphates, there is a risk of elevated serum levels of sodium and phosphate and decreased levels of calcium and potassium and consequent hypocalcemia, hyperphosphatemia, hypernatremia, and acidosis may occur. Additional fluids by mouth are recommended with all bowel cleansing dosages.

PRECAUTIONS

DO NOT EXCEED RECOMMENDED DOSE UNLESS DIRECTED BY A PHYSICIAN, AS SERIOUS SIDE EFFECTS MAY OCCUR. IF THERE IS NO BOWEL MOVEMENT AFTER MAXIMUM DOSAGE, CONTACT A PHYSICIAN AS DEHYDRATION COULD OCCUR.
SINCE FLEET® PHOSPHO®-SODA IS AVAILABLE IN TWO SIZES, PRESCRIBE BY VOLUMES. DO NOT PRESCRIBE "BY THE BOTTLE" AS SERIOUS SIDE EFFECTS FROM OVERDOSAGE MAY OCCUR.

GENERAL LAXATIVE WARNINGS

Do not use a laxative product when nausea, vomiting, or abdominal pain is present unless directed by a physician. If you have noticed a sudden change in bowel habits that persists over a period of 2 weeks, consult a physician before using a laxative. Rectal bleeding or failure to have a bowel movement may indicate a serious condition. Discontinue

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use and consult a physician. Laxative products should not be used longer than 1 week unless directed by a physician. Keep this and all drugs out of the reach of children. In case of accidental overdose or ingestion, seek professional assistance or contact a Poison Control Center immediately. As with any drug, if you are pregnant or nursing a baby, seek the advice of a health professional before using this product.

OVERDOSAGE

Overdosage or retention of Fleet® Phospho®-soda may cause hypocalcemia, hyperphosphatemia, hypernatremia, hypernatremic dehydration and acidosis.

Hypocalcemia, hyperphosphatemia, hypernatremia and acidosis

Calcium, Phosphate, Potassium and Sodium levels should be carefully monitored. Immediate corrective action should be taken to restore electrolyte balance with appropriate fluid replacements. Prompt parenteral administration of fluids with lower concentrations of Sodium and Chloride than extracellular fluid (40-50 mEq./liter) and moderate concentration of Potassium (20-30 mEq./liter) administered at a rate of 3,000 to 4,000 cc/sq. m of body surface during the first 12 to 24 hours dependent on the severity of dehydration and the clinical response.

DOSAGE AND ADMINISTRATION

For purgative or laxative, best taken on an empty stomach. Most effective when taken upon rising, at least 30 minutes before a meal, or at bedtime for overnight action. Dilute recommended dosage with one-half glass (4 fl. oz.) cool water. Drink, then follow with one glass (8 fl. oz.) cool water.

DOSAGE: SINCE FLEET® PHOSPHO®-SODA IS AVAILABLE IN TWO SIZES, PRESCRIBE BY VOLUMES; DO NOT PRESCRIBE BY THE BOTTLE. DO NOT EXCEED RECOMMENDED DOSAGE AS SERIOUS SIDE EFFECTS MAY OCCUR.

SINGLE DAILY DOSAGE: DO NOT EXCEED.

LAXATIVE: Adults and children 12 years and over: 4 teaspoonfuls (20 mL).

Children 10 to under 12 years: 2 teaspoonfuls (10 mL).

Children 5 to under 10 years: 1 teaspoonful (5 mL).

PURGATIVE: Adults only: 3 tablespoonfuls (45 mL).

DO NOT GIVE TO CHILDREN UNDER 5 YEARS.

PROFESSIONAL DOSAGE AND ADMINISTRATION

Colonoscopy and Barium Enema Prep: On the day before the procedure, drink only clear liquids that are not colored red or purple for breakfast, lunch, and dinner. At 7 p.m., add 45 ml, 1½ fl. oz. (3 tablespoonfuls) Fleet® Phospho-Soda to one-half glass (4 fl. oz.) of cold clear liquid and drink. Follow with one full glass (8 fl. oz.) of approved clear liquid. Drink at least three (3) more 8 fl. oz. portions of "clear liquids" before retiring. The day of the procedure at 6 a.m. or 3 hours before you leave for procedure, add 45 ml, 1½ fl. oz. (3 tablespoonfuls) Fleet® Phospho-Soda to one-half glass (4 fl. oz.) of cool water and drink. Follow with one full glass (8 fl. oz.) of approved clear liquid.

Do not increase the dosage of this prep. If laxative action is inadequate, consider adding a non-saline laxative.

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HOW SUPPLIED

Regular or Flavored, in bottles of 1½, and 3 fl. oz. Fleet® Phospho-soda should not be confused with Fleet® Enema, a sodium phosphates disposable ready-to-use enema. Fleet® Enema, Adult and Child size, ARE NOT INTENDED FOR ORAL CONSUMPTION, in any dosage size.

IS THIS PRODUCT OTC?

Yes.

LITERATURE AVAILABLE

Professional literature mailed on request.

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FLEET® ENEMA, A SALINE LAXATIVE OTC
FLEET® ENEMA FOR CHILDREN, A SALINE LAXATIVE

COMPOSITION

FLEET® ENEMA: Each 118 mL (delivered dose) contains 19 g. monobasic sodium phosphate and 7 g. dibasic sodium phosphate. The FLEET® Enema unit, with a 2-inch, pre-lubricated Comfortip®, contains 4 1/2 fl. oz. of enema solution in a hand-size plastic squeeze bottle. **FLEET® ENEMA FOR CHILDREN:** Each 59 mL (Delivered Dose) contains 9.5 g. monobasic sodium phosphate and 3.5 g. dibasic sodium phosphate. The FLEET® Enema for children unit, with a 2-inch, pre-lubricated Comfortip® contains 2 1/2 fl. oz. (66.5 mL) of enema solution in a hand-size plastic squeeze bottle. Designed for quick, convenient administration by nurse or patient according to instructions. Disposable after single use.

ACTION AND USES

FLEET® Enema is useful as a laxative in the relief of occasional constipation, and as part of a bowel cleansing regimen in preparing the patient for surgery or for preparing the colon for x-ray and endoscopic examination. Used as directed, FLEET® Enema provides thorough yet safe cleansing action and induces complete emptying of the left colon usually within 2 to 5 minutes without pain or spasm. Also used for general postoperative care and to help relieve fecal or barium impaction.

GENERAL LAXATIVE WARNINGS

Do not use laxative products when nausea, vomiting, or abdominal pain is present. If you notice a sudden change in bowel habits that persists over a period of 2 weeks, consult a physician. Rectal bleeding or failure to have a bowel movement after use of a laxative may indicate a serious condition. Discontinue use and consult a physician. Laxative products should not be used longer than 1 week unless directed by a physician. As with any drug, if you are pregnant or nursing a baby, seek the advice of a health professional before using this product. Keep this and all drugs out of the reach of children. In case of accidental ingestion or overdose, seek professional assistance or contact a Poison Control Center immediately.

PROFESSIONAL USE WARNINGS

Do not use in patients with congenital megacolon, imperforate anus or congestive heart failure as hypernatremic dehydration may occur. Use with caution in patients with impaired renal function, heart disease, or pre-existing electrolyte disturbances (such as dehydration or those secondary to the use of diuretics) or in patients on diuretics, osmotic laxatives, diuretics or other medications which may affect electrolyte levels — or where colostomy exists, as hypocalcemia, hyperphosphatemia, hypernatremia and acidosis may occur. Calcium and phosphorus levels should be carefully monitored. Since FLEET® Ready-To-Use Enema contains dibasic sodium phosphate and monobasic sodium phosphate, there is a risk of acute elevation of sodium concentration in the serum and consequent dehydration, par-

Do not use in patients with congenital megacolon, bowel obstruction, imperforate anus or congestive heart failure.

Use with caution in patients with impaired renal function, pre-existing electrolyte disturbances or patients on diuretics or other medications which may affect electrolyte levels — or where colostomy exists.

Since Fleet®Enema contains sodium phosphates, there is a risk of elevated serum levels of sodium phosphate and decreased levels of calcium and potassium and consequent hypocalcemia, hyperphosphatemia, hypernatremia, and acidosis may occur. This is of particular concern in children megacolon or any other condition where there is retention of enema solution.

Additional fluids by mouth are recommended with all bowel cleansing dosages



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~~particularly in children with megacolon or any other condition where there is retention of an enema solution. Additional fluids by mouth are recommended where appropriate.~~
~~Boekalsrud, E. and Kees, J. "Hypernatremic Dehydration Hypertonic Enemas in Congenital Megacolon." JAMA 199;584-586, 1967. Zimrod, B. and Benham, L. "Rectal Absorption of Sodium from Hypertonic Sodium Phosphate Solutions." data on file, C. B. Fleet Company, Inc., Gilman, Goodman, and Gilman, A. eds. The Pharmacological Basis of Therapeutics, Sixth Edition, 1980, p. 1095. In addition, elevated levels of serum phosphates and decreased levels of serum calcium have been reported in patients with renal disease (and with prolonged use). (McCannell, R. H. "Fatal Hypocalcemia from Phosphate Absorption from Lavative Preparation." JAMA 216:147-148, 1973.) SINCE FLEET® BRAND ENEMAS ARE AVAILABLE IN ADULT AND CHILDREN'S SIZES, PRESCRIBE CAREFULLY.~~

PRECAUTIONS

DO NOT ADMINISTER 4 1/2 oz. ADULT SIZE TO CHILDREN UNDER 12 YEARS OF AGE. DO NOT ADMINISTER 2 1/2 oz CHILDREN'S SIZE TO CHILDREN UNDER 2 YEARS OF AGE. IF AFTER THE ENEMA SOLUTION IS ADMINISTERED THERE IS NO RETURN OF LIQUID, CONTACT A PHYSICIAN IMMEDIATELY AS DEHYDRATION COULD OCCUR.

OVERDOSAGE

Overdosage with Fleet® Enema may cause hypocalcemia, hyperphosphatemia, hypernatremia, hypernatremic dehydration and acidosis. or retention of

~~X Hypocalcemia, hyperphosphatemia, hypernatremia and acidosis~~

~~Calcium, Phosphate, Chloride and Sodium levels should be carefully monitored. Immediate corrective action should be taken to restore electrolyte balance with appropriate fluid replacements.~~ Potassium

~~X Hypertonic Dehydration~~

~~Calcium, Phosphate, Chloride and Sodium levels should be carefully monitored. Prompt parenteral administration of fluids with lower concentrations of Sodium and Chloride than extracellular fluid (40-50 mEq/liter) and moderate concentration of Potassium (20-30 mEq/liter) administered at a rate of 3,000 to 4,000 cc/sq. m of body surface during the first 12 to 24 hours dependent on the severity of dehydration and the clinical response.~~

~~Boekalsrud, E. and Kees, J. "Hypernatremic Dehydration from Hypertonic Enemas in Congenital Megacolon." JAMA 199:584-586, 1967. See article for more details.~~

ADMINISTRATION AND DOSAGE

REMOVE PROTECTIVE SHIELD FROM TIP BEFORE ADMINISTERING.

Preferred position: Lying on left side with left knee slightly bent and the right leg drawn up, or knee-chest position. Dosage: Adults, 4 fl. oz. in a single daily dose. Child, 2 fl. oz. in a single daily dose. Rubber diaphragm at base of tube prevents accidental leakage and assures controlled flow of the enema solution. May be used at room temperature. Adult, each 118 mL (delivered dose) contains 4.4 g. (191 mEq) sodium. Child, each 59 mL (delivered dose) con-

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tains 2.2 g (95.5 mEq) sodium.

PROFESSIONAL DOSAGE AND ADMINISTRATION

Fleet® Ready-To-Use 4 1/2 oz. Adult Size Enema should not be used in children under 12 years of age. In those cases where complications are reported, infants and young children are often involved. Fleet® Ready-To-Use Enema for Children should be used with caution in children of any age. Careful consideration of the use of enemas in general in children is recommended. The adult size enema should not be used in children under 12 years of age. For children 2 to 12 years of age, use Fleet® Ready-To-Use Enema for Children, which contains a dosage of one-half the adult size enema. For children less than 2 years of age, Fleet® Glycerin Suppositories for Children should be used.

Proper and safe use of Fleet® Ready-To-Use Enema also requires that the product be administered according to the Directions for Use. Health care professionals should remember, when administering the product, to gently insert the enema into the rectum with the tip pointing toward the navel. Insertion may be made easier by having the patient bear down as they would in having a bowel movement. Care during insertion is necessary due to lack of sensory innervation of the rectum and due to possibility of bowel perforation. Once inserted, squeeze the bottle until nearly all the liquid is expelled. If resistance is encountered on insertion of the nozzle or in administering the solution, the procedure should be discontinued. Forcing the enema can result in perforation and/or abrasion of the rectum.

If an enema containing phosphate or sodium is not advised, use FLEET Bisacodyl Enema. Please see complete prescribing instructions for Fleet Bisacodyl Enema.

HOW SUPPLIED

FLEET® Enema is supplied in a 4 1/2 fl. oz. (133 mL) ready-to-use squeeze bottle. Children's size, 2 1/4 fl. oz. (66.5 mL). **IMPORTANT: Fleet® Enema, Adult and Child size, ARE NOT INTENDED FOR ORAL CONSUMPTION, in any dosage size.**

IS THIS PRODUCT OTC?

Yes.

~~OTC~~

LITERATURE AVAILABLE

Professional literature mailed on request.



1050 Connecticut Avenue, NW
Washington, DC 20036-5339

February 23, 1994

Peter S. Reichertz
Tel: 202/857-6378
Fax: 202/857-6395

VIA FEDERAL EXPRESS

Mr. Richard Chastonay
Director
Division of Drug Labeling Compliance
Office of Compliance
Center for Drug Evaluation and Research
Food & Drug Administration
7520 Standish Place, Room 166
Rockville, MD 20855

**Re: FLEET® Ready-to-Use Enema and
Other FLEET® Brand Laxative Products**

Dear Mr. Chastonay:

As you recall, we represent C.B. Fleet Co., Inc. (Fleet) of Lynchburg, Virginia. This letter follows up on my letter of December 17, 1993, in which Fleet committed to do certain things in response to the Agency's concerns about Professional Use Warnings which Fleet placed on Fleet® brand laxative products in 1987.

Fleet has looked into the matters discussed in our meeting of December 16, 1993. They believe, based on the overwhelming evidence found in their review, that the current labeling -- with Professional Use Warnings -- is appropriate, has saved lives and reduced misuse of the product and is necessary for protection of the public health. **Fleet does not believe the Professional Use Warnings should be removed from these products.** They believe it would be an abdication of their responsibility as an ethical manufacturer to remove these warnings. Furthermore, it could expose them to product liability litigation.

Arent Fox

Mr. Richard Chastonay

February 23, 1994

Page 2

Addressing the various issues raised in our meeting, please be advised as follows.

In item number 1 of my letter of December 17, 1993, I indicated that Fleet agreed to add the words "as directed by your physician" after any "bowel cleansing" or similar claims. Attached as Exhibit A hereto are the proposed revisions to the "Indications" sections of the various laxative drug products affected by this change. We will gladly discuss this proposed wording with you at your convenience.

With regard to items number 2 and 4 of the letter, we agreed that we would review the literature and the reports of adverse reactions received by Fleet before and after the Professional Use Warnings were added in August of 1987 to see what effect, if any, they have had. We agreed to review the need for placing these warnings on the containers and to propose alternatives to their use.

Based on a review of the literature and reports of adverse reactions, we believe that the addition of these warnings has had the intended effect -- it has saved lives and reduced the incidence of serious adverse effects. As indicated in my letter of December 17, 1993 (and my letter of August 26, 1987 to Dr. Gilbertson of the OTC Drug Review Staff), Fleet added the Professional Use Warnings to the labels for these products to alert physicians, nurses, and other healthcare personnel using the product in professional situations to misuse of the products. Fleet put these warnings on the product containers, since it believed these warnings were not being observed and that healthcare personnel do not always refer to professional labeling sources such as the Physicians' Desk

Arent Fox

Mr. Richard Chastonay
February 23, 1994
Page 3

Reference. Since the labeling was changed in 1987 to add these warnings, reports of misuse of the products -- and, in particular, reports as to misuse of Fleet® Ready-to-Use Enema -- have declined. Please note the following.

With regard to adverse reactions reported directly to Fleet on Sodium Phosphates enemas, please see Exhibit B. A review of Exhibit B shows an extremely low reporting of any adverse reactions, less than one per million units sold, both before and after the professional use warning. Looking only at adverse reactions, which may, even remotely, be in the Professional Use Warnings, the numbers drop from .06 to .04 reactions per million units sold after the Professional Use Warnings were added. Of course, it should be noted that there has been a greatly increased emphasis on reporting of adverse reactions since 1987 (i.e., the MEDWATCH Program) and, hence, this drop is more significant than it seems.

With regard to adverse reactions reported in the published literature, there are similar dramatic findings. Attached as Exhibit C is a chart listing adverse reactions reported in the published literature to Sodium Phosphates enemas, since 1967. Out of 23 adverse reactions reported in the literature concerning sodium phosphates enemas, 16 of the patients had contraindications described in the current Fleet® Ready-to-Use Enema Professional Use Warnings.

Since late 1987, when the Professional Use Warnings were added to the Fleet® Ready-to-Use Enema carton, there have been no reports in the literature of Fleet® Ready-to-Use Enemas used in situations contraindicated in the Professional Use Warnings. Of the five adverse reactions reported in the

Arent Fox

Mr. Richard Chastonay
February 23, 1994
Page 4

literature since 1988, four were for sodium phosphates enemas with no Professional Use Warnings: Travad, Fletcher's Phosphate Enema, and Fleet Enema - Israel (a C.B. Fleet Licensee). The fifth one was an extreme overdose of a five-month old baby. See Exhibit D for the bibliography of these references.

In short, Fleet believes the Professional Use Warnings are doing their job and have significantly reduced adverse reactions and may have even saved lives and that they should not, in Fleet's opinion, be removed from the containers of the products. Fleet believes after review of this analysis you will agree that the proper action is to leave the Professional Use Warnings on the carton labeling.

Lastly, as to item number 3 in my letter of December 17, 1993, you asked us to provide you with an estimate of how long it would take to change the labeling of the affected products, once a decision is made to change the labeling (even if only to add "as directed by your physician"). The following is an estimated timetable:

<u>Product</u>	<u>Time</u>
Fleet® Ready-to-Use Enema	3 months
Fleet® Ready-to-Use Enema for Children	3 months
Fleet® Phospho-Soda®	
Flavored 1½ oz.	7 months
Flavored 3 oz.	6 months
Unflavored 1½ oz.	5 months
Unflavored 3 oz.	5 months
Fleet® Castor Oil Emulsion	
1½ oz.	1 year
3 oz.	10 months
Fleet® Bisacodyl Enema	5 months
Fleet® Ready-to-Use Mineral Oil Enema	3 months

Arent Fox

Mr. Richard Chastonay
February 23, 1994
Page 5

Please note the last three products do not contain the Professional Use Warnings; they need only add the "as directed by your physician" language to the "Indications" section.

I believe this addresses the requests raised in our meeting of December 16, 1993. We will gladly meet further with you and your staff to review and resolve these matters. If you require any additional information, please give me a call.

Sincerely,



Peter S. Reichertz

Attachments

cc (all with attachments):

Mr. Brian Duffy, C.B. Fleet Company, Inc.
Ms. Sarah Post, C.B. Fleet Company, Inc. (Via Facsimile
and First Class Mail)

Mr. Robert Heller, FDA, Room 168
Ms. Mary Richardson, FDA, Room 166
Mr. Jonathan Lane, FDA, Room 168

PSR/lrk

EXHIBIT A

ADDITION OF "AS DIRECTED BY A PHYSICIAN"
TO INDICATIONS ON CARTON LABELING

FLEET ENEMA - ADULT

For relief of occasional constipation. For bowel cleansing, as directed by a physician, prior to rectal examinations. This product generally produces a bowel movement in 2 to 5 minutes.

FLEET ENEMA FOR CHILDREN

For relief of occasional constipation. For bowel cleansing, as directed by a physician, prior to rectal examinations. This product generally produces a bowel movement in 2 to 5 minutes.

FLEET MINERAL OIL ENEMA

For the relief of fecal impaction. For the relief of constipation without straining or irritating the mucosa of the bowel. For cleansing the bowel and removal of residue, as directed by a physician, after barium enema administration.

FLEET CASTOR OIL EMULSION

As a laxative, for relief of occasional constipation. As a purgative, for use as part of a bowel cleansing regimen, as directed by a physician, in preparing the patient for surgery or for preparing the colon for x-ray or endoscopic examination.

Generally produces a bowel movement in 6 to 12 hours.

FLEET PHOSPHO-SODA - FLAVORED AND UNFLAVORED

As a laxative, for relief of occasional constipation. As a purgative, for use as part of a bowel cleansing regimen, as directed by a physician, in preparing the patient for surgery or for preparing the colon for x-ray or endoscopic examination.

Generally produces a bowel movement in 30 minutes to 6 hours. When taken as directed, laxative action is gentle, virtually free from the likelihood of gastrointestinal discomfort or irritation and is safe for the age groups indicated.

EXHIBIT B

ANALYSIS OF ADVERSE REACTIONS FOR FLEET ENEMA
1981 - 1993

	<u>Number of Adverse Reactions</u>	
	<u>Before Professional Use Warnings (1981-1987)</u>	<u>After Professional Use Warnings (1987-1993)</u>
<u>Adverse Reactions Which Could Be Remotely Associated With Professional Use Warning Concerns</u>		
Nauseated, felt hot and sweating with or without increased heart beat	5	1
Painful stomach with or without vomiting	3	3
Hypotensive and shocky	1	0
Hypocalcemia in 1½ year old	1	0
Vasovagal response	<u>0</u>	<u>2</u>
Total	10	6
Units Sold	178 million	163 million
Adverse Reactions per Million Units Sold	0.06/per million units sold	0.04/per million units sold
<u>Others Not Related To Professional Use Warning</u>		
Rectal or anal burning/injury	5	19
Irritated bowel	1	2
Severe Diarrhea	0	2
Allergic Reaction	3	2
Chemical Peritonitis	0	1
Others	<u>2</u>	<u>1</u>
Total	11	27
Grand Total	21	33
Adverse Reactions per Million Units Sold	0.12/per million units sold	0.20/per million units sold

EXHIBIT C

SODIUM PHOSPHATE ENEMA
ADVERSE REACTIONS REPORTED IN THE LITERATURE
(EXCLUDING BOWEL OR RECTAL INJURIES)

<u>Publication Year</u>	<u>Author</u>	<u>Patient Age</u>	<u>Predisposing Factor</u>	<u>Outcome</u>
1967	Fonkalsrud ¹	4 years	Hirschsprung's Disease	Full recovery
1968	Young ²	21 years	Hirschsprung's Disease	Full recovery
1968	Moseley ³	21 months	Hirschsprung's Disease	--
		3 years*	Hirschsprung's Disease	--
		8 months*	Unknown	--
		7 months	Hirschsprung's Disease	--
1974	Oxnard ⁴	5 years	Renal Insufficiency	Full recovery
1974	Chesney ⁵	12 years	Renal Insufficiency	Full recovery
1975	Honig ⁶	5 months	Imperforated Anus	Full recovery
1977	Sotos ⁷	3 years	Thoraco-Lumbar Meningomylocele	Full recovery
1977	Loughnan ^{8*}	9 months	Colonic ileus	Brain damage
1977	Davis ⁹	4 months	Dehydration	Full recovery
		3 years	Dehydration	Full recovery
1979	Forman ¹⁰	3 years	Sub-Acute Neuropathic Gaucher Disease	Full recovery
1983	Reedy ¹¹	17 months	Hirschsprung's Disease	Cardiac arrest and recovery
1985	Biberstein ¹²	81 years	Renal Insufficiency	Full recovery
1985	Haskell ¹³	58 years	Renal insufficiency	Full recovery
1985	Rohack ¹⁴	77 years	Hypertonic Anal Sphincter - 6 x dose; no return	Recovery
1987	Martin ¹⁵	11 months	Imperforated Anus	Fatal
1988**	Spinrad ¹⁶	91 years	Renal Insufficiency and Hypotonic Colon	Fatal
1989	Wason ¹⁷	5 months	Overdose	Full recovery
1992**	Korzets ¹⁸	77 years	Paralytic ileus and Renal insufficiency	Full recovery
1993***	Hunter ¹⁹	4 years	Appendicostomy - overdose	Full recovery

* Travad Enema (no professional use warnings)

** Fleet Enema licensee in Israel (no professional use warnings)

*** Fletcher's Phosphate Enema (no professional use warnings)

EXHIBIT D

REFERENCES

- 1) Fonkalsrud, E.W. and Keen, J., "Hypernatremic Dehydration From Hypertonic Enemas in Congenital Megacolon." JAMA, Vol. 199, No. 8, pp. 152-154, February 20, 1967.
- 2) Young, J.F. and Brooke, B.N., "Enema Shock in Hirschsprung's Disease." Dis Colon Rectum, Vol. 11, pp. 391-395, 1968
- 3) Moseley, P.K. and Segar, W.E., "Fluid and Serum Electrolyte Disturbances as a Complication of Enemas in Hirschsprung's Disease." Amer J Dis Child, Vol. 115, pp. 714-718, June 1968.
- 4) Oxnard, S.C., O'Bell, J., and Grupe, W.E., "Severe Tetany in an Azotemic Child Related to a Sodium Phosphate Enema." Pediatrics, Vol. 127, pp. 105-106, 1974.
- 5) Chesney, R.W. and Haughton, P.B., "Tetany Following Phosphate Enemas in Chronic Renal Disease." Amer J Dis Child, Vol. 127, pp. 584-586, April 1974.
- 6) Honig, P.J. and Holtzapple, P.G., "Hypocalcemic Tetany Following Hypertonic Phosphate Enemas." Clinical Pediatrics, Vol. 14, No. 7, pp. 678-679, July 1975.
- 7) Sotos, J.F., Cutler, E.A., Finkel, M.A., et al., "Hypocalcemic Coma Following Two Pediatric Phosphate Enemas." Pediatrics, Vol. 60, No. 3, pp. 305-307, September 1977.
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REFERENCES

-2-

- 14) Rohack, J.J., Mehta, B.R., and Subramanyam, K., "Hyperphosphatemia and Hypocalcemic Coma Associated with Phosphate Enema." *Southern Medical Journal*, Vol. 78, No. 10, October 1985.
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- 16) Spinrad, S., Grosskopf, Y., Blum, I., et al., "Treating Constipation with Phosphate Enema: An Unnecessary Risk." *Israel J Med Sci*, Vol. 25, pp. 237-238, 1989.
- 17) Wason, S., Tiller, T., and Cunha, C., "Severe Hyperphosphatemia, Hypocalcemia, Acidosis, and Shock in a 5-Month Old Child Following the Administration of an Adult Fleet Enema." *Annals of Emergency Medicine*, Vol. 18, pp. 696-700, June 1989.
- 18) Korzets, A., Dicker, D., Chaimoff, C., et al., "Life-Threatening Hyperphosphatemia and Hypocalcemic Tetany Following the Use of Fleet Enemas." *J American Geriatrics Society*, Vol. 40, No. 6, pp. 620-621, June 1992.
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1050 Connecticut Avenue, NW
Washington, DC 20036-5339

October 29, 1997

2273 '97 NOV -5 A11 :13

Peter S. Reichertz
Tel: 202/857-6378
Fax: 202/857-6395
reicherp@arentfox.com
<http://www.arentfox.com>

Debra Bowen, M.D.
Director (HFD-560)
Division of OTC Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
9200 Corporate Boulevard
Rockville, Maryland 20850

Re: FLEET® Prep Kits
76N-036L/CP0008

Dear Dr. Bowen:

We represent C. B. Fleet Company, Inc., of Lynchburg, Virginia (Fleet). As counsel to Fleet, we recently received a letter dated August 22, 1997, from Ronald G. Chesemore, Associate Commissioner for Regulatory Affairs, about three citizen petitions Fleet had filed with regard to proposed amendments to the Tentative Final Monograph on OTC Laxative Drug Products (TFM). A copy of that letter is attached as Exhibit A.

As you may recall, Fleet had also filed a citizen petition on November 13, 1987, to request that the Agency amend the TFM to include certain bowel cleansing systems as part of the final monograph on OTC Laxative Drug Products. (That petition was assigned the docket number 76N-036L/CP0008.) Fleet did receive a response to that citizen petition on October 26, 1989 (a copy of which is attached as Exhibit B). In that letter, Dr. Gilbertson indicated that the Division of OTC Drug Evaluation would recommend that Fleet® Prep Kits Nos. 1 and 3 be included in the final monograph on OTC Laxative Drug Products. We are not certain whether Mr. Chesemore's letter of August 22, 1997, was intended to be a full response to all of the citizen petitions filed on behalf of Fleet to amend the TFM, but Fleet wanted to make sure that this recommendation had not been overlooked.

An additional item should be noted with regard to the October 26, 1989, letter. In the letter, Dr. Gilbertson indicated that the Agency would not recommend the inclusion of Fleet® Prep Kit No. 2, as it contained a Castile Soap large volume enema as a final cleansing step, after administration of 7.56 g sodium phosphate and 20.2 g sodium biphosphate in oral solution, followed by 20 mg of bisacodyl orally administered 3 hours after the sodium phosphate/sodium biphosphate oral solution. This kit was the same as

78N-036L

LET 171

Arent Fox

Debra Bowen, M.D.

October 29, 1997

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Fleet® Prep Kits Nos. 1 and 3 found acceptable, except the final cleansing step is a large volume enema in lieu of a bisacodyl suppository (Fleet® Prep Kit No. 1) or a bisacodyl enema (Fleet® Prep Kit No. 3). The Agency indicated it would not include Fleet® Prep Kit No. 2, since adverse reactions to soap enemas had been reported in the literature.

Please be advised that Fleet has changed Fleet® Prep Kit No. 2 to delete the Castile Soap. In lieu of the Castile Soap enema, a large volume tap water enema – using Fleet's BAGENEMA® product, which is a listed medical device – is included as the final cleansing step. Fleet® Prep Kit No. 2 thus includes two monograph drug products (sodium phosphate/biphosphate oral solution and bisacodyl tablets) and an enema kit marketed in compliance with medical device regulations for sequential administration. As such, we believe it is an acceptable prep kit for bowel cleansing, and the Agency's concerns having been addressed, believe it should be included in the final monograph on OTC Laxative Drug Products as well.

We look forward to confirmation that these three bowel cleansing system products will be included in the final monograph on OTC Laxative Drug Products. Should there be any questions, please contact the undersigned.

Sincerely,



Peter S. Reichertz

Enclosures

cc (w/enc.): Mr. Ronald G. Chesemore
Associate Commissioner for Regulatory Affairs (HFC-1)
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

cc (w/four copies): Dockets Management Branch (HFA-305)
Food and Drug Administration
12420 Parklawn Drive, Room 1-23
Rockville, Maryland 20857

cc (w/enc.): Ms. Sarah S. Post, C. B. Fleet Company, Inc.

ATTACHMENT A



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

AUG 22 1997

Peter S. Reichertz, Esquire
Arent, Fox, Kintner, Plotkin & Kahn
1050 Connecticut Avenue, NW
Washington, DC 20036-5339

Re: Docket No. 78N-036L
Comment No. CP10.
Docket No. 78N-036L
Comment No. CP14.
Docket No. 78N-036L
Comment No. CP16.

Dear Mr. Reichertz:

This letter concerns your above referenced citizen petitions submitted on behalf of C. B. Fleet Company, Inc., requesting amendment of the tentative final monograph (TFM) on over-the-counter (OTC) laxative drug products. The TFM was published in the Federal Register on January 15, 1985 (50 FR 2124).

For the reasons given below, the agency considers action on the petitions as completed.

78N-036L\CP10

The petition, dated April 22, 1991, requests that the TFM be amended to list the response times for the different forms of rectally administered stimulant laxatives so as to include a different response time (5-20 minutes) for enemas.

On July 23, 1991, Dr. Gilbertson issued a letter to you indicating that your request is reasonable and that based on your earlier petition 78N-036L\CP7, we plan to address the issue of response time for a stimulant laxative enema in the final monograph for OTC laxative drug products (copy enclosed).

Therefore, this petition (CP10) is moot. We are adding the petition to the public record for this rulemaking.

REC'D SEP 02 1997

Peter S. Reichertz, Esquire
Arent, Fox, Kintner, Plotkin & Kahn
Page 2

78N-036L\CP14

The petition, dated March 23, 1993, requests that the TFM be amended to include two 45 mL doses of dibasic sodium phosphate/monobasic sodium phosphate solution (sodium phosphates oral solution, U.S.P.) in sequential administration 10 to 12 hours apart as a bowel cleansing system.

On March 1, 1996, Debra Bowen, M.D., Director, Division of OTC Drug Products, issued a letter to you concluding that the data submitted with the petition support the effectiveness, but not the safety, of two 45-mL doses of sodium phosphates oral solution given 10 to 12 hours apart, for OTC use as a bowel cleansing system (copy enclosed).

Accordingly, this petition is denied.

78N-036L\CP16

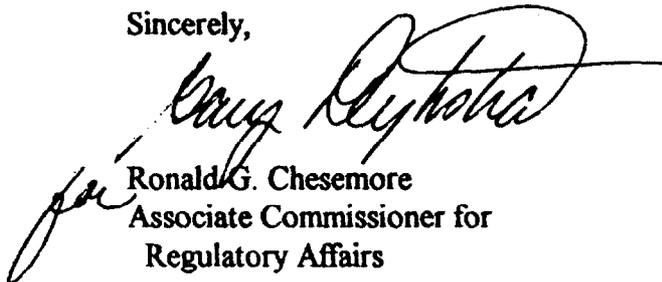
The petition, dated November 8, 1993, requests that the TFM be amended to include the following statement for an enema dosage form of glycerin: "This product generally produces a bowel movement in 2 to 15 minutes."

On July 24, 1995, Debra Bowen, M.D., Director, Division of OTC Drug Products, issued a letter to you concluding that the data submitted with the petition were inadequate to support your requested amendment of the TFM (copy enclosed).

Accordingly, this petition is denied.

If you have any questions regarding any of the petitions, please refer to the docket and comment numbers above, and submit all inquiries, in triplicate, to the Dockets Management Branch (HFA-305), Food and Drug Administration, 12420 Parklawn Drive, Room 1-23, Rockville, MD 20857.

Sincerely,



Ronald G. Chesemore
Associate Commissioner for
Regulatory Affairs

Peter S. Reichertz, Esquire
Arent, Fox, Kintner, Plotkin & Kahn
Page 3

Attachments:

July 23, 1991, letter from
William E. Gilbertson, Pharm. D.
To Peter S. Reichertz, Esq.

July 24, 1995, letter from
William E. Gilbertson, Pharm. D.
To Peter S. Reichertz, Esq.

March 1, 1996, letter from
Debra Bowen, M.D.
to Peter S. Reichertz, Esq.

Peter S. Reichertz, Esquire
Arent Fox Kinter Plotkin & Kahn
50 Connecticut Avenue, N.W.
Washington, D.C. 20036-5339

Re: Docket No. 78N-036L
Comment No. CP10

91 JUL 26 AM 11:14
Dockets Management Branch

Dear Mr. Reichertz:

July 23/1991
This is in response to your citizen petition dated April 22, 1991, submitted on behalf of C. B. Fleet Co., Inc., and filed in FDA's Dockets Management Branch as CP10 under Docket No. 78N-036L. The petition requests amendment of the tentative final monograph for over-the-counter (OTC) laxative drug products to list separately the response times for the different forms of rectally administered stimulant laxatives (i.e., suppositories and enemas) so as to include a different response time (5 to 20 minutes) for enemas.

In your petition, you state that the tentative final monograph on OTC laxative drug products presently does not distinguish the response times for the different forms of rectally administered stimulant laxatives. You mention that the response time for rectal dosage forms is listed in proposed § 334.60(b)(2) as 1/4 to 1 hour, based only on a review of suppositories. You add that a response time for an enema dosage form of stimulant laxatives is needed because the agency plans to add this dosage form to the monograph as discussed in my October 26, 1989 letter (coded LET40 under the same docket) to you responding to a citizen petition (coded CP7) filed by Fleet.

You state in the petition that enemas, because of the introduction of a liquid, work faster than suppositories, which must melt. In addition, enemas introduce a greater volume of liquid which also has an osmotic volume laxative effect. You cite two unpublished studies (a 1978 study by Salen and Keating, "A Comparative Study of Four Laxative Products", and a study by B. B. Swerdlow, "An Evaluation of a Bisacodyl Small Volume Enema") as supporting evidence that the mean response time for the bisacodyl enema is from 5 to 20 minutes, not 15 minutes to 1 hour. Accordingly, you requested amendment of the tentative final monograph for OTC laxative drug products to include a response time of 5 to 20 minutes for stimulant laxative enemas and that this information be included in the final monograph on OTC laxative drug products when published.

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LET49

As noted in my letter of October 26, 1989, I informed you that we have determined that a 10-milligram (mg) dose of bisacodyl, administered in a 37.5 milliliter (ml) aqueous suspension rectal enema formulation, is safe and effective for use by adults and children 12 years of age and over. Based on the study by Salen and Keating, comparing two dosages of a bisacodyl enema with a bisacodyl suppository and a bisacodyl microenema, the agency determined that only the criterion "time to response" provides information suggesting that the bisacodyl products can be differentiated from one another. Based on the 59-percent patient response rate within 15 minutes for the bisacodyl enema and the 32-percent patient response rate within 15 minutes for the bisacodyl suppository control group, the agency found that the study, although qualitative and not optimally designed, provided substantial evidence that the enema containing 10 mg bisacodyl in a 37.5 ml aqueous suspension is at least as effective as the 10 mg bisacodyl suppository.

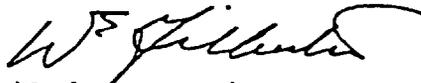
The study by Swerdlow showed a 90-percent response rate with a mean time of 10 minutes to first response after the administration of the bisacodyl enema. The agency determined that, although this study was uncontrolled, its favorable results are of value primarily as support for the results of the Salen and Keating study.

Based on these studies, the response time that you suggest appear to be reasonable. Based on the earlier petition (CP7) that we reviewed and information already included in the administrative record for the rulemaking for OTC laxative drug products, the agency already plans to address the issue of response time for a stimulant laxative enema in the final monograph for OTC laxative drug products. Therefore, we do not plan to propose such a response time in an amendment to the tentative final monograph. Your petition will remain part of the public record for this rulemaking and, as you have requested, the issue of response time will be addressed in the final monograph.

Any comment you may wish to make on the above information or any additional information that you may wish to provide 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, Room 1-23, 12420 Parklawn Drive, Rockville, MD 20857.

We hope this information will be helpful.

Sincerely yours,



William E. Gilbertson, Pharm. D.
Director
Division of OTC Drug Evaluation
Office of Drug Standards
Center for Drug Evaluation and Research



MAR 1 1996

Food and Drug Administration
Rockville MD 20857

Peter S. Reichertz, Esquire
Arent, Fox, Kintner, Plotkin & Kahn
1050 Connecticut Avenue, NW
Washington, DC 20036-5339

Re: Docket No. 78N-036L
Comments No. CP14, SUP8,
AMD10, LET71, and SUP11

Dear Mr. Reichertz:

This letter concerns your citizen petition submitted on behalf of C. B. Fleet Company, Inc., dated March 23, 1993, and additional data and information submitted on December 22, 1993, June 13, 1994, and January 18, 1995. The submissions are identified as CP14, SUP8, AMD10, LET71, and SUP11, respectively, filed under Docket No. 78N-036L in the Dockets Management Branch. You requested that the tentative final monograph for OTC laxative drug products (published in the FEDERAL REGISTER of January 15, 1985, 50 FR 2124) be amended to include two 45 milliliter (mL) doses of dibasic sodium phosphate/monobasic sodium phosphate solution (sodium phosphates oral solution, U.S.P.) in sequential administration 10 to 12 hours apart as a bowel cleansing system.

Your March 23, 1993 citizen petition contained a published clinical study by Vanner et al. (Ref. 1), an unpublished report by Del Piano et al. (Ref. 2), six abstracts (Refs. 3 through 8), and a section of a textbook (Ref. 9). Your December 22, 1993 letter contained the following: (a) your response to comments submitted by Braintree Laboratories; (b) a study by Kolts et al. (Ref. 10), which was previously provided as an abstract (Ref. 3), (c) your comments that "Fleet has not yet received any reports of serious side effects from the use of the regimen described in the citizen petition;" and (d) brief information on a recently completed clinical study (Ref. 11) of two sequential doses of sodium phosphates oral solution as a colonic preparation in 450 subjects. The study had not yet been completed and the institution where the study was done had requested that it not be distributed at that time. Your June 13, 1994 letter contained

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the unpublished report of the study (Ref. 11) mentioned in your December 22, 1993 letter, five abstracts (Refs. 12 through 16), and material presented at a postgraduate course given in May 1994 (Ref. 17). Your January 18, 1995 letter contained a new study by Huynh et al. (Ref. 18).

We have reviewed your submissions and other data pertaining to sodium phosphates and determined that the data are insufficient to demonstrate the safety of two 45-mL doses of sodium phosphates oral solution in sequential administration 10 to 12 hours apart. Therefore, based on the existing information, two 45-mL doses of sodium phosphates oral solution in sequential administration 10 to 12 hours apart as a bowel cleansing system will not be included in the final monograph for OTC laxative drug products at this time.

We have the following specific comments regarding the data submitted in support of your petition: You did not categorize the submitted studies into pivotal and supportive clinical studies. Your submissions included three published, controlled clinical studies (Refs. 1, 10, and 18) on sodium phosphates oral solution administered as a bowel cleansing system. Thus, we reviewed these three studies as the pivotal studies to determine the safety and effectiveness of two 45-mL doses of sodium phosphates oral solution in sequential administration 10 to 12 hours apart as a bowel cleansing system.

In the first study, Vanner et al. (Ref. 1) compared a standard polyethylene glycol (PEG) based gastrointestinal solution to a sodium phosphates oral solution prior to colonoscopy. In this parallel, single-blinded, randomized study, 54 subjects received two 45-mL doses of the sodium phosphates oral solution 11 hours apart, and 48 subjects received 4 liters (L) of the PEG solution. The subjects had blood tests on admission and the morning of the procedure. The authors concluded that the sodium phosphates oral solution was safe and effective because serial measurements of blood tests, postural pulse, and blood pressure changes did not reveal any clinically significant changes in intravascular volume. One "syncopal episode" occurred in the sodium phosphates group. The authors mentioned that the subject's vital signs did not appear to indicate that hypovolemia was the cause. The authors reported that hyperphosphatemia occurred with sodium phosphates, but serum phosphate values returned to normal within

24 hours, and no concomitant decrease in calcium was seen. They added that histological assessment of the rectal mucosa for possible preparation-induced changes revealed no difference between the two drugs.

We note that numerous induced electrolyte abnormalities occurred in this study. The data showed statistically significant decreases in potassium and increases in hematocrit, sodium, chloride, osmolarity, and phosphate. Extreme serum phosphate levels reached 11.6 milligrams (mg)/deciliter (dL) in the sodium phosphates group and 4.7 mg/dL in the PEG group; normal values are 2.5 to 4.1 mg/dL. In hyperphosphatemia, excessive complexing of calcium with phosphate may contribute to a decrease in plasma ionized calcium, which results in hypocalcemia. Calcium levels were not reported for the entire sodium phosphates group nor was the risk of hypokalemia mentioned. The postural changes in pulse, systolic blood pressure, and the one "syncopal episode" were reasonably related to decreased intravascular volume in subjects in the sodium phosphates group.

Because elevated phosphate levels are known to occur with sodium phosphates use, 15 subjects were randomly selected to have serum phosphate and calcium levels measured at 4:00 p.m. on the day of colonoscopy and at 8:00 a.m. the following day. Seven of the 15 subjects received the sodium phosphates regimen. Vanner et al. reported that 2 hours after the second dose, the mean serum phosphorus was 7.2 mg/dL (nearly twice the prestudy value of 3.7 mg/dL), while the total calcium values continued to decline for at least 24 hours after the dose was taken.

We believe that the Vanner et al. study showed that postural increases in pulse, decreases in systolic blood pressure, and serum electrolyte and plasma volume shifts were greater in the sodium phosphates group than in the PEG group. The incidence of postural elevation in heart rate, indicating significant reduction in intravascular volume, was also three times higher in the sodium phosphates group than in the PEG group. Because of the small sample size, the fact that none of the study subjects died or had serious side effects that required hospitalization cannot be interpreted to mean that two 45-mL doses of sodium phosphates oral solution are safe to take without a physician's supervision.

In the second study, Kolts et al. (Ref. 10) conducted a single-center, single-blind, parallel, controlled clinical study to evaluate the safety and efficacy of sodium phosphates oral solution as a bowel cleansing system for colonic preparation. The investigators sought to replicate the results published by Vanner et al. (Ref. 1) on the safety and efficacy of sodium phosphates. The investigators also attempted to evaluate the safety and efficacy of a 95 percent castor oil product as a colonic preparation for colonoscopy.

One hundred and thirteen subjects were randomized to a standard PEG solution, sodium phosphates oral solution, or the castor oil product. At 6:00 p.m. the evening prior to the colonoscopy, 38 subjects received 4 L of the PEG solution (240 mL every 10 minutes), 34 subjects received 45 mL of sodium phosphates oral solution in 45 mL of water, and 41 subjects received 60 mL of castor oil. Subjects receiving the sodium phosphates or castor oil were instructed to drink at least 90 to 360 mL of water 1 hour after receiving the solutions. All subjects received nothing by mouth after midnight. Subjects in the sodium phosphates group received 45 mL of the solution in 45 mL of water at 6:00 a.m. on the day of the procedure.

The investigators reported that both sodium phosphates and PEG were significantly better for bowel cleansing than castor oil, and that both sodium phosphates and castor oil were significantly easier to completely ingest than PEG. The investigators reported that sodium phosphates oral solution was better in achieving an excellent (38 percent) or good (41 percent) cleansing score compared with PEG (32 percent and 29 percent) or with castor oil (20 percent and 12 percent).

Although no clinical manifestations of hypocalcemia were reported, the independent evaluation of serum phosphate and calcium concentration in 5 subjects who took sodium phosphates showed a significantly greater mean serum phosphate concentration over mean baseline value 2 hours after the second sodium phosphates dose. There was a significant mean serum phosphate concentration increase of 3.5 ± 1.6 mg/dL, important because hyperphosphatemia can cause hypocalcemia and increased neuromuscular excitability. Reportedly, the mean serum calcium concentration also decreased in the 5 subjects evaluated

(individual subject data were not presented in the publication). The mean phosphate and calcium concentrations normalized after 10 hours, and the mean serum phosphate concentration returned to baseline after 24 hours. Neither muscular spasms nor clinically overt tetany was reported.

In the third study, Huynh et al. (Ref. 18) assessed the safety profile of sodium phosphates oral solution to determine whether clinically significant hypocalcemia and hypovolemia would be near the threshold for causing serious side effects. Fifty subjects (27 outpatients and 23 inpatients) were each given a 45-mL dose of sodium phosphates oral solution at 10 hours and again at 15 hours (two doses 5 hours apart) before colonoscopy. Subjects with renal failure, active heart disease, ileus, and gross ascites were excluded. All subjects were on a liquid diet for 24 hours prior to the colonoscopy and were encouraged to drink fluids liberally during the colonic lavage phase. The investigators stated that intravenous fluid replacement was used for some inpatients in this study, but the number of inpatients on intravenous fluid replacement was not specified. The investigators reported that sodium phosphates oral solution is safe for colonic cleansing in most subjects, even when using a 5-hour regimen. However, they also stated that because some subjects developed asymptomatic intravascular volume contraction and borderline hypocalcemia, sodium phosphates oral solution may have a lower therapeutic index than other bowel cleansing drugs.

You indicated that C. B. Fleet believes that this study provides the necessary evidence to demonstrate that two 45-mL doses of sodium phosphates oral solution are safe for use 12 hours apart. We believe that the study did not provide sufficient evidence to support your petition. The publication lacked data for individual subjects such as baseline medical conditions, concomitant diseases and medications, laboratory and vital sign data, fluid intake, ages and genders, and adverse drug reaction profiles.

We also believe that this study did not provide sufficient evidence that two 45-mL doses of sodium phosphates oral solution given 5 hours apart are safe. The investigators reported that intravascular volume depletion was clinically significant in 40 percent of the inpatients and 7 percent of the outpatients, respectively. The investigators indicated that the hypocalcemia

observed in some of the subjects was minor and probably reflected increased sensitivity of ionized calcium measurements used in this study because no subject complained of paresthesia or numbness. The investigators stated that some experts in calcium metabolism suggest that minor perturbations in ionized calcium levels below the established normal range, such as described in this study, should not cause symptoms that would be harmful to the patient. However, we note that the article states that such patients may develop asymptomatic intravascular volume contraction and borderline hypocalcemia. The authors also mentioned that sodium phosphates has a lower therapeutic index than other agents and that, in some circumstances, alternate colonic cleansing agents should be used. In addition, hypokalemia can occur with sodium phosphates use, but the investigators failed to monitor potassium levels in this study. Further, most inpatients were on intravenous fluid replacement, which is not routinely administered as part of a colonoscopy procedure. Finally, subjects in the study should have been primarily outpatients if the product is to be promoted for outpatient use. Thus, we do not find this study adequate to support your petition or the safety of a 5-hour bowel cleansing regimen.

We believe that the three studies (Refs. 1, 10, and 18) provide evidence of the effectiveness of two sequential doses of sodium phosphates for bowel cleansing for colonoscopy in adult subjects. However, the studies did not demonstrate the safety of two 45-mL doses of sodium phosphates oral solution in sequential administration 10 to 12 hours apart as a bowel cleansing system. Along with vital signs and clinical evaluations, monitoring of ionized calcium, phosphorus, potassium, and sodium levels in all subjects should be obtained at baseline, at specific intervals throughout the study, and until all values have returned to baseline after the second sodium phosphates dose is given in order to provide a complete safety profile of this dosage regimen.

The following two unpublished studies were submitted in support of your petition. The first study by Del Piano et al. (Ref. 2) compared three different methods in colonoscopy preparation in a randomized study in 150 subjects (ages 33 to 84 years of age, average age 58 years), using 50 subjects per group. The first group was randomized to a 3-day preparation of a liquid diet, a

cathartic, and an enema; the second group was randomized to 4 L of PEG solution; and the third group was randomized to four doses (20 mL each) of a sodium phosphates oral solution containing 48 grams (g) of monobasic sodium phosphate and 18 g of dibasic sodium phosphate per dL. The total 80 mL dose of the sodium phosphates oral solution used by Del Piano et al. is equivalent to 38.4 g of monobasic sodium phosphate and 14.4 g of dibasic sodium phosphate. This total 80 mL dose is about 12 percent less than the total sodium phosphates 90 mL dose tested by Vanner et al. and Kolts et al.

The day before the exam, subjects in one group ingested PEG solution (time not given). The subjects in another group were given a two dose regimen (40 mL each) of sodium phosphates at 4:00 p.m. and 8:00 p.m., 4 hours apart. Both doses were followed by 1 to 2 L of oral fluids. Serum electrolytes, including sodium, potassium, calcium, and phosphorus, were obtained before and after the endoscopy. The investigators reported that the sodium phosphates and the 3-day preparation were significantly more effective ($p < 0.01$) than PEG in reducing the volume of fluid flowing out during the endoscopy. However, the sodium phosphates group experienced increased mean serum phosphorus and decreased mean serum calcium concentrations. No muscular spasms, tetany, or adverse clinical reactions were reported. This study does not support the times of administration and doses of sodium phosphates requested by your petition. In addition, the investigators did not demonstrate the safety of the sequential doses of sodium phosphates compared to alternative therapies.

In a randomized, endoscopist-blinded, unpublished study by Cohen et al. (Ref. 11), 422 subjects received either standard PEG colonic lavage (138 subjects), a newer sulfate-free 4 L PEG solution (PEG-SF) (141 subjects), or a sequential two-dose regimen of 45-mL sodium phosphates oral solution as a bowel cleansing preparation (143 subjects). The sodium phosphates was administered at 4:00 p.m. and 6:00 a.m. (14 hours apart). Before and after study participation, all subjects were weighed and serum electrolytes as well as phosphate, magnesium, calcium, and osmolarity were measured.

Although statistically significant differences were noted in all parameters measured (except blood urea nitrogen), the investigators stated that none of the changes was clinically

significant. However, in our view, this study does not adequately demonstrate the safety of two 45-mL doses of sodium phosphates oral solution in sequential administration 10 to 12 hours apart as a bowel cleansing system. The subjects in the sodium phosphates group lost more weight and experienced more electrolyte and osmolarity changes than those in the PEG groups. Ionized calcium levels and normal serum electrolyte ranges used to determine the biochemical changes were not given. Values presented in tables of the study were inconsistently reported, sometimes as means and sometimes as medians. Statistical "p" values for certain comparisons were presented differently in the text versus the tables. In addition, the time interval between doses in this study was longer than the time specified in the petition.

The Cohen et al. study may provide electrolyte and clinical data on the safety of the two doses of 45-mL of sodium phosphates oral solution given 14 hours apart. However, individual subject data are needed to completely evaluate: (a) any relationship to demographics (age), prior medical history or concomitant illness, electrolyte shifts, and adverse event reports; (b) any relationship of timing between doses taken and adverse events; (c) recovery timeline from any experienced adverse event; and (d) any relationship between effectiveness and compliance with the regimen. In addition, normal ranges for the laboratory values listed in table 3 of the study need to be provided with some explanation of serum calcium levels in relationship to albumin and other factors that may affect ionized calcium (or measured ionized calcium levels).

You also submitted eleven abstracts (Refs. 3 through 8, and 11 through 16) in support of your petition. However, these abstracts did not adequately document the safety of the sequential dose bowel cleansing system mentioned in the petition.

Lyles et al. (Ref. 3) was an abstract of the Kolts et al. study (see the above discussion for reference 10).

Haroon and Iber (Ref. 4) conducted a randomized clinical trial to determine the oral tolerance, safety, and effectiveness of sodium phosphates oral solution for bowel cleansing prior to colonoscopy. Thirty-six adult subjects (18 subjects per group) between 65 to 92 years of age (mean age was 73 years) were

randomly assigned to be treated with sodium phosphates oral solution or PEG. One group took two 45-mL doses of sodium phosphates oral solution diluted with 90 mL of water 11 hours apart. The other group took 4 L of PEG on the evening of admission. The efficacy endpoints, safety monitoring, and formulations used were similar to those described in the Vanner et al. and Kolts et al. studies. The report indicated that the "degree of colonoscopic cleansing" was significantly greater in the sodium phosphates group in comparison to the PEG group (excellent = 71 percent versus 53 percent, respectively). The sodium phosphates regimen was reported to be easier to complete, and was associated with less nausea, vomiting, abdominal discomfort, and diarrhea.

Sodium phosphates was reported to produce more depletion of water and electrolytes with a decrease in potassium and a significant increase in serum phosphorus, sodium, chloride, and osmolarity. Calcium concentration was not provided. The report states that approximately 90 percent of the electrolyte changes remained within the normal laboratory ranges, and values returned to baseline within 24 to 48 hours. Therefore, the investigators concluded that sodium phosphates is a safe and well-tolerated oral colonic preparation for older individuals, and that it produces better colonic cleansing than PEG.

Reanalyzed by chi-square and Fisher's Exact Test, there is no significant difference in bowel cleansing between the two treatment groups. However, the information provided in the abstract indicated that at least two subjects in the sodium phosphates group had a significant abnormal increase in serum phosphorus, sodium, chloride, and osmolarity. This safety information is critical because renal clearance is diminished in older subjects and the elderly may be at risk for hyperphosphatemia, hypocalcemia, convulsions, and tetany with sodium phosphates use.

Clarkston et al. (Ref. 14) compared PEG to a sodium phosphates oral regimen for bowel cleansing prior to colonoscopy. In this randomized trial, 26 subjects took 4 L of the PEG solution and 25 subjects took two 45-mL doses of sodium phosphates oral solution 11 hours apart. The subjects had a chemistry panel and ionized calcium done prior to taking the drug and on the morning of the colonoscopy. The results indicated that the sodium phosphates

oral solution caused a decrease in ionized serum calcium and serum potassium, with concomitant increases in phosphate. The investigators stated that the sodium phosphates oral regimen resulted in statistically significant changes in serum sodium, potassium, phosphorus, and calcium ($p < 0.01$). The investigators concluded that the risk of symptoms of hypocalcemia must be considered due to the abnormal low levels of ionized calcium that frequently occur with this regimen.

Our review of this abstract shows that the majority of the subjects experienced hyperphosphatemia with this sodium phosphates regimen. The large reductions in ionized serum calcium and serum potassium were of particular concern. Therefore, we do not believe this abstract can be used to document the safety of two 45-mL doses of sodium phosphates oral solution given 11 hours apart as a bowel cleansing regimen.

Stone et al. (Ref. 15) randomized 45 subjects to either 4 L of PEG solution (25 subjects) or two 45 mL dosages of sodium phosphates oral solution (30 subjects) before elective outpatient colonoscopy. The authors reported that hypoxia and cardiac arrhythmias were not significantly different in the two groups. This abstract is inadequate because the time sequence for the PEG and sodium phosphates was not given. However, we note that hypotension occurred more often with sodium phosphates (14/30 subjects) than PEG (5/25 subjects), and that more subjects receiving sodium phosphates required intravenous fluid boluses to maintain hemodynamic stability during colonoscopy.

Thomson et al. (Ref. 16) randomized 116 subjects to receive PEG (55 subjects) or sodium phosphates (61 subjects) before colonoscopy. The subjects reported that sodium phosphates was slightly more tolerable than PEG, although the difference was not statistically significant. The colonoscopists found no difference in the quality of the bowel preparation. However, we note that the sodium phosphates subjects developed hyperphosphatemia (value not given) and a lower mean serum potassium of 3.8 millimoles (mmol)/L than the PEG group (4.2 mmol/L).

Individual subject data for analysis from the two abstracts (Refs. 15 and 16) may allow a better evaluation of safety issues related to the requested sequential dosing regimen. We suggest

that the company obtain data from the individual investigators.

We have reviewed the other abstracts and do not consider them sufficient for the following reasons. Several authors did not provide the time sequence and amount of sodium phosphates oral solution given: Golub et al. (Ref. 5), Raymond et al. (Ref. 7), and Rossetti et al. (Ref. 8). Afridi et al. (Ref. 12) gave bisacodyl and sodium phosphates oral solution in combination. The time between sequential dosages differed from the petition and electrolyte data were not provided in the abstracts by Bawani et al. (Ref. 6) and Henderson et al. (Ref. 13).

The material from a postgraduate course given in May 1994 (Ref. 17) contains no new clinical data. However, the author concluded that sodium phosphates oral solution should not be used in patients with renal insufficiency, congestive heart failure, or cirrhosis with ascites because it may have deleterious effects. The chapter from a textbook titled "Colon and Rectal Surgery" (Ref. 9) did not contain any new clinical data that could be evaluated to support your petition.

We conclude that the data provided support the effectiveness of two 45-mL doses of sodium phosphates oral solution given 10 to 12 hours apart for bowel cleansing. However, we are concerned that this dosage regimen may not be safe for OTC use because of the electrolyte and vascular volume changes that occur. It is possible that this dosage regimen could be included under professional labeling only (i.e., labeling that is provided to health professionals, but not to the general public); however, adequate safety data, as described above, must be submitted. Therefore, we have determined that the data submitted in the citizen petition are insufficient to support the safety of two 45-mL doses of sodium phosphates oral solution in sequential administration 10 to 12 hours apart as a bowel cleansing system. This bowel cleansing system will not be included in the final monograph for OTC laxative drug products.

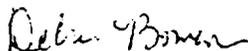
We intend to recommend to the Commissioner that the agency respond to your comments in the above manner in the final monograph for OTC laxative drug products, which will be published in a future issue of the FEDERAL REGISTER. Following publication, you may file a citizen petition to amend the final monograph or file a new drug application. Should the company

wish to perform the clinical studies needed for this bowel cleansing system, we would be glad to review any proposed protocols. They may be submitted prior to publication of the final monograph.

Any comment you may wish to make on the above information should be submitted in three copies, identified with the docket number shown at the beginning of this letter, to the Dockets Management Branch (HFD-305), Food and Drug Administration, Room 1-23, 12420 Parklawn Drive, Rockville, MD 20857. This letter should not be considered a formal ruling on your petition. That occurs when you are sent a response by the Associate Commissioner for Regulatory Affairs.

We hope this information will be helpful.

Sincerely yours,



Debra Bowen, M.D.

Director

Division of OTC Drug Evaluation

Office of Drug Evaluation V

Center for Drug Evaluation and Research

REFERENCES

(1) Vanner, S. J. et al., "A Randomized Prospective Trial Comparing Oral Sodium Phosphate with Standard Polyethylene Glycol-Based Lavage Solution (GoLytely) in the Preparation of Patients for Colonoscopy," The American Journal of Gastroenterology, 85:422-427, 1990.

(2) Del Piano, M. et al., "Comparison Between Three Methods in Preparation for Colonoscopy (unpublished report)," The Greater Charity Hospital, Novara, Italy.

(3) Lyles, W. E. et al., "A Randomized, Prospective, Physician-Blinded Study Examining the Effectiveness and Patient Acceptance of Three Colonoscopy Preparations (Abstract)," American Gastroenterological Association, A-529:2111, 1992.

(4) Haroon, N., and F. L. Iber, "A Randomized Clinical Trial Comparing Oral Sodium Phosphate with Standard Polyethylene Preparation of Patients for Colonoscopy (Abstract)," American Gastroenterological Association, A-529:2112, 1992.

(5) Golub, R. W. et al., "Colonoscopic Bowel Preparations-Which One? A Blinded Prospective, Randomized Trial (Abstract)," presented at the 91st Annual Convention of American Society of Colon and Rectal Surgeons, June 7-12, 1992.

(6) Bawani, M. et al., "A Single Blinded, Prospectively Randomized Comparison of Oral Phospho-Soda with Polyethylene Glycol Based Solution as a Colonic Lavage for Colonoscopy (Abstract)," The American Journal of Gastroenterology, 86:9, 1991

(7) Raymond, P. L. et al., "Colonoscopy Preparation, Tolerance, and Efficacy: Polyethylene Glycol Lavage Versus Phospho-Soda Laxative or Avatar 2100 PEE

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(8) Rossetti, C. et al., "Comparision of Two Methods of Preoperative Colonic Cleansing. Results of a Randomized Clinical Trial (Abstract)," presented at the Second World Week of Professional Updating in Surgery and in Surgical and Oncological Disciplines of the University of Milan, July 15-21, 1990.

(9) Corman, M. L., Colon and Rectal Surgery, 3rd ed., J. B. Lippincott Co., Philadelphia, pp. 32-35, 1993.

(10) Kolts, B. E. et al., "A Comparison of the Effectiveness and Patient Tolerance of Oral Sodium Phosphate, Castor Oil, and Standard Electrolyte Lavage for Colonoscopy or Sigmoidoscopy Preparation," The American Journal Gastroenterology, 88:1218-1223, 1993.

(11) Cohen, S. M. et al., "Prospective, Randomized, Endoscopic-Blinded Trial Comparing Precolonoscopy Bowel Cleansing Methods (unpublished report)," presented at the meeting of The American Society of Colon and Rectal Surgeons, Orlando, Florida, May 8 to 13, 1994.

(12) Afridi, S. et al., "Prospective, Randomized Trial Comparing a New Sodium Phosphate-Bisacodyl Regimen with PEG-Lavage for Colonoscopy Preparation (Abstract)," Gastrointestinal Endoscopy, 40:15, 1994.

(13) Henderson, J. M. et al., "Single Day Oral Sodium Phosphate Laxative Preparation for Colonoscopy vs. Intestinal Lavage: Efficacy and Patient Tolerance (Abstract)," Gastrointestinal Endoscopy, 40:22, 1994.

(14) Clarkston, W. K. et al., "A Single Blind Comparison of Serum Electrolytes, Serum Phosphorus, Serum Calcium, and Ventricular Arrhythmias in Outpatients Receiving Nulytely Versus Fleet Phospho-soda Preparation for

Colonoscopy: Preliminary Results (Abstract),
"Gastrointestinal Endoscopy, 20:92, 1994.

(15) Stone, D. et al., "Fluid Requirements and Hypotension During Colonoscopy: A Comparison of the Effects of Oral Polyethylene Glycol (PEG) versus Oral Phospho-Soda Saline (PSS) Prep (Abstract)" Gastrointestinal Endoscopy, 40:35, 1994.

(16) Thomson, A. et al., "Bowel Preparation for Colonoscopy: A Randomized Prospective Trial Comparing Sodium Phosphate and Polyethylene Glycol (Abstract)," Department of Gastroenterology Heidelberg Repatriation Hospital Melbourne, correspondence to Dr. B. Crotty.

(17) Keefe, E. B., "Colonoscopy Preps- What's Best," presented by the American Society for Gastrointestinal Endoscopy Postgraduate Course, New Orleans, May 19-20, 1994.

(18) Huynh, T., S. Vanner, and W. Paterson, "Safety Profile of 5-Hour Oral Sodium Phosphate Regimen for Colonoscopy Cleansing: Lack of Clinically Significant Hypocalcemia or Hypovolemia," The American Journal Gastroenterology, 90:104-107, 1995.



Laxative

July 24, 1995

Peter S. Reichertz, Esquire
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1050 Connecticut Avenue, N. W.
Washington, D. C. 20036-5339

Re: Docket No. 78N-036L
Comments No. CP16 and C151

Dear Mr. Reichertz:

This letter is in response to your citizen petition dated November 8, 1993, submitted on behalf of the C. B. Fleet Company and a subsequent submission concerning the petition dated March 17, 1994, submitted by Sarah S. Post, Vice President of Administration, C. B. Fleet Company. These submissions were filed under Docket No. 78N-036L in FDA's Dockets Management Branch as Comments No. CP16 and C151, respectively. The petition requested amendment of the tentative final monograph for OTC laxative drug products to include the following statement for an enema dosage form of glycerin: "This product generally produces a bowel movement in 2 to 15 minutes." The March 17, 1994 submission was made in response to my January 26, 1994 letter requesting additional information concerning the clinical studies presented in the petition.

Your petition was submitted in response to the notice of proposed rulemaking published in the FEDERAL REGISTER on January 15, 1985, in which the agency proposed time frames within which different types of laxatives are expected to produce bowel movement (50 FR 2124 at 2129). The agency included a time frame of ¼ to 1 hour for glycerin and other hyperosmotic laxatives (50 FR 2124 at 2154). Your petition contained data from two clinical studies as supporting evidence that the mean response time for a glycerin enema is from 2 to 15 minutes, not 15 minutes to 1 hour. The petition stated that the tentative final monograph did not distinguish response times for different dosage forms of hyperosmotic laxatives and that the proposed ¼ to 1 hour response time is not accurate for a glycerin rectal enema.

The Office of OTC Drug Evaluation has reviewed your submissions and finds the data inadequate to support the response time of 2 to 15 minutes for a glycerin enema. We have the following comments:

1. In-House Rectal Glycerin Study

This parallel crossover study compared effectiveness and subject acceptance of a regular strength glycerin suppository (2 grams (g) glycerin), a maximum strength glycerin suppository (3 g glycerin), and a glycerin microenema (5.5 g glycerin in 5.5

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mL). Ten female subjects, age 28 to 60, were selected from a group of C. B. Fleet Company employees with a 1-month or longer history of constipation. Each subject was given one dose of each of the three products with instructions to take one of the products when constipated, followed by the other two products taken at least 2 days apart. The order of usage of the three products was randomized prior to initiation of the study, and products were numbered 1, 2, and 3. Thus, $\frac{1}{3}$ of the subjects started with the regular strength suppository, $\frac{1}{3}$ with the maximum strength suppository, and $\frac{1}{3}$ with the microenema. Subjects were provided with stop watches to report onset times of bowel movements and recorded results on data sheets. Subjects were asked to compare the three products on a separate report form and return the report form to the laboratory when completed. All non-exempt employees received 3 hours of pay as compensation at the conclusion of the study. Average onset time reported was 23.4 minutes for the regular suppository, 14.6 minutes for the maximum strength suppository, and 4.8 minutes for the microenema.

2. Glycerin Microenema - Glycerin Suppository Use Test

The second study enrolled 5 male and 36 female subjects, age 23 to 76 years, with a minimum 2 to 3 month history of constipation. Effectiveness and product acceptance were evaluated in a parallel crossover study comparing a regular strength glycerin suppository (2 g glycerin) with a glycerin microenema (5.5 g glycerin in 5.5 mL). Each subject received one suppository and one glycerin enema, one labeled "A" and the other labeled "B". Half of the subjects used the suppository first and the other half used the enema first. Subjects were instructed to use the product marked "A" as soon as they were constipated and record the results on a data sheet. Subjects were instructed to wait at least 3 days before using product "B" for the next episode of constipation. Again, subjects recorded the results on a data sheet. Subjects also completed a daily diary. No other laxative use was allowed during the study. As in the first study, subjects were given a stop watch to record the time between the use of the laxative and the bowel movement. Average onset time was reported as 16.4 minutes for the suppository and 9.4 minutes for the microenema.

We have the following comments regarding these studies:

1. Parallel studies would be preferred over these crossover studies. Both studies were non-blinded.
2. The sample sizes in both studies are small, with no estimate of what an adequate sample size should be to adequately detect differences in onset times between the suppository and the enema. The Fleet study enrolled only female subjects and both studies excluded subjects under the age of 18. The submission did not clarify the age range of consumers for whom the product is intended; however, a currently marketed product containing 7.6 mL of liquid glycerin in a single-use disposable applicator is

labeled for use by children 6 years of age and older and by adults. An additional product containing 4 mL of glycerin in a single daily dose is marketed for children 2 to 6 years of age.

3. There is no description of how the volunteers were solicited. Both studies allowed unstructured, investigator-directed selection of subjects. If the investigator selected the subjects based on "reliability", was there investigator bias in the selection?

4. No instructions were given regarding the use of other laxative products during the course of the Fleet study.

5. "Time to onset" measurements may not have been consistent between the two studies. In the first study, subjects were instructed to use the stop watch to report onset times, "the time that expires between the use of the laxative and the actual bowel movement." In the second study, subjects were instructed to start the stop watch after the laxative was inserted and to stop the stop watch with the first bowel movement. In both studies there was room for variability in when to stop the watch, and in the first study there was no specification of when to start the watch.

6. Glycerin is believed to act by inducing laxation with primarily an "irritative" effect on the bowel mucosa. On this basis alone, one would predict a greater effect along with more side effects for the higher glycerin concentration in the enema preparation (which contained 5.5 g) compared to the suppositories (which contained only 2 or 3 g). The active control should contain the same concentration of drug as the test product.

7. It is unclear why time to onset for the glycerin enema was almost twice as long in the second study compared to the first study, while the time to onset for the glycerin regular strength suppository was only 70 percent of that in the first study, emphasizing a lack of robust outcomes in these studies.

8. Statistical differences were tested for only using one-sided or two-sided t-tests. There was no accounting for period effects in the crossover trials or carryover interactions secondary to the order in which the different products were used. There was no indication of adjustments made where multiple comparisons were carried out. Accounting should be made for the effects of the crossover design.

Although there is evidence suggesting a shorter onset time for the enema dosage form, the studies submitted were not designed or statistically analyzed to provide confidence in results for time to onset of comparative glycerin laxative products. The data did not clearly demonstrate that the onset time for production of a bowel movement is in a range of 2 to 15 minutes. One person (ten percent) in the first study had an onset time of 15 minutes for the enema product, while 10 subjects (24 percent) in the second study had an onset time of 15 minutes or longer, or found the product ineffective. Although

the reported results in the second study were that 80.5 percent of the subjects had an onset time of 15 minutes or less, 19.5 percent of the subjects had an onset time of more than 15 minutes. These times ranged from 18 to 45 minutes. The agency finds that the procedures used were inadequate to verify the times to onset of laxation reported. Further, the results obtained do not support the request (2 to 15 minutes) for all users of the rectal enema dosage form.

A well designed, adequately randomized, double-blind clinical study should be conducted to provide a head-to-head comparison of the enema dosage versus the suppository, without possible crossover confounding effects. See comment 6 above regarding drug concentration. We would be happy to review and comment on any protocols developed for time to onset studies for glycerin enemas prior to initiation of a clinical study.

The Office of OTC Drug Evaluation intends to recommend to the Associate Commissioner for Regulatory Affairs that the agency respond to your petition in the above manner and in the final monograph for OTC laxative drug products, which will be published in a future issue of the Federal Register. Following that publication, you may submit a petition to amend the final monograph.

Any comment you wish to make on the above information should be submitted in three copies, 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, Room 1-23, 12420 Parklawn Drive, Rockville, Maryland 20857.

We hope this information will be helpful.

Sincerely yours,



William E. Gilbertson, Pharm. D.
Director
Monograph Review Staff
Office of OTC Drug Evaluation
Center for Drug Evaluation and Research

ATTACHMENT B



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Peter S. Reichertz, Esq.
Arent, Fox, Kintner, Plotkin & Kahn
1050 Connecticut Avenue, NW
Washington, DC 20036-5339

OCT 26 1989

Re: Docket No. 78N-036L
Comments No. CP0008
and SUP005

Dear Mr. Reichertz:

This letter concerns your citizen petition (Coded CP0008) submitted on behalf of the C. B. Fleet Company, Inc., dated November 12, 1987, and filed under Docket No. 78N-036L in the Dockets Management Branch on November 13, 1987. The petition requested that the tentative final monograph for OTC laxative drug products (published in the FEDERAL REGISTER of January 15, 1985; 50 FR 2124) be amended to include 6 additional bowel cleansing systems.

In my letter of May 16, 1988, I informed you that we were in the process of evaluating your petition and that additional data were needed for us to complete our evaluation. On August 16, 1988 you provided the additional data requested in my letter. This submission was coded SUP005 by the agency.

We have completed our review and determined that two of the proposed bowel cleansing systems are safe and effective for use by adults and children 12 years of age and over. The other four proposed bowel cleansing systems require additional data to demonstrate their safety and effectiveness.

We have the following specific comments regarding each of the six bowel cleansing systems and the data submitted in support of them:

Kit Number 1: A kit containing the following 3 laxative drug products for sequential administration: 7.56 grams (g) of sodium phosphate and 20.2 g of sodium biphosphate in oral solution, 20 milligrams (mg) of bisacodyl administered orally at least 3 hours after administration of the sodium phosphate/sodium biphosphate oral solution, 10 mg of bisacodyl administered by suppository at least 9 hours after the administration of the oral bisacodyl and at least 1 hour before the scheduled x-ray or examination.

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Kit number 1 substitutes 7.56 g of sodium phosphate and 20.2 g of sodium biphosphate for 25 g of magnesium citrate in the bowel cleansing system listed in § 334.32(a) of the OTC laxative tentative final monograph (50 FR 2153). It also slightly alters the current dosing regimens of oral and rectal bisacodyl from 15-20 mg bisacodyl orally 2 hours after magnesium citrate to 20 mg bisacodyl at least 3 hours after sodium phosphate/sodium biphosphate, and from 10 mg bisacodyl suppository 9 hours after oral bisacodyl and at least 2 hours before the x-ray to at least 9 hours after the oral bisacodyl and at least 1 hour before the x-ray. The proposed bowel cleansing system containing these dosages and regimen has been marketed for over 15 years.

Both magnesium citrate and sodium phosphate/sodium biphosphate are listed in the OTC laxative tentative final monograph as single ingredient Category I saline laxatives, and the dosages in the bowel cleansing systems would be the maximum single daily dose permitted for each. In addition, in § 334.80 professional labeling claims have been proposed for both magnesium citrate and sodium phosphate/sodium biphosphate for use as part of a bowel cleansing regimen in preparing the patient for surgery, x-ray, and endoscopy (50 FR 2157). The data provided included a summary report of a clinical evaluation of kit no. 1 compared to Evac-Q-Kit, a bowel cleansing system listed in § 334.32(b) of the OTC laxative tentative final monograph (50 FR 2153) and consisting of magnesium citrate, phenolphthalein, and a carbon dioxide-releasing suppository.

In this single blind randomized study of 108 patients being prepared for barium enema, 57 patients received kit number 1 and 51 patients received Evac-Q-Kit. Thirty-one percent of the patients treated with kit number 1 showed moderate to extensive gas retention after treatment compared with 53 percent of the patients treated with Evac-Q-Kit. Seventy five percent of the patients treated with kit number 1 showed good to excellent mucosal detail on examination compared to 54 percent of the patients treated with Evac-Q-Kit. Overall evaluation (satisfactory/unsatisfactory) of the colon preparation showed no significant difference between the two bowel cleansing systems. There were no significant differences in side effects produced by the two kits.

Although this study does not provide a comparison between kit number 1 and the most similar bowel cleansing system (magnesium citrate followed by bisacodyl), it does compare another Category I bowel cleansing system (magnesium citrate, phenolphthalein, and carbon dioxide-releasing suppositories, (§ 334.32(b), 50 FR 2156) with one in which sodium

phosphate/sodium biphosphate is substituted for magnesium citrate. The results of this study, together with other data already considered by the agency in the laxative tentative final monograph (50 FR 2137), support the contention that sodium phosphate and sodium biphosphate can be interchanged for magnesium citrate safely and effectively in a Category I bowel cleansing system. This interchangeability would apply to either of the bowel cleansing systems specified in proposed § 334.32 in the OTC laxative tentative final monograph (50 FR 2153). The safety and effectiveness of the dose and dose regimen proposed for kit number 1 are supported by previous agency findings in the tentative final monograph and by the data provided. Appropriate additions to § 334.32 will be included in the final monograph.

Kit Number 3: A kit containing the following 3 laxative drug products for sequential administration: 7.56 g of sodium phosphate and 20.2 g of sodium biphosphate in oral solution, 20 mg of bisacodyl administered orally at least 3 hours after administration of the sodium phosphate/sodium biphosphate oral solution, 10 mg of bisacodyl administered by enema 9 hours after the administration of the oral bisacodyl and at least 1 hour before the scheduled x-ray or examination.

This kit is identical to kit number 1 except for the substitution of a 10 mg bisacodyl enema for the 10 mg bisacodyl suppository. As discussed in my other letter to you of this date, we concur that the submitted data support the substitution of the 10 mg bisacodyl enema formulation for the Category I 10 mg bisacodyl suppository.

We therefore concur that a Category I bowel cleansing system substituting a 10 mg bisacodyl enema for a 10 mg bisacodyl suppository is acceptable. Appropriate additions to § 334.32 will be included in the final monograph.

Kit Number 2: A kit containing the following 3 laxative drug products for sequential administration: 7.56 g of sodium phosphate and 20.2 g of sodium biphosphate in oral solution, 20 mg of bisacodyl administered orally at least 3 hours after administration of the sodium phosphate/sodium biphosphate oral solution, and administration of a large volume liquid castile soap enema at least 9 hours after administration of the oral bisacodyl and at least 2 hours before the scheduled x-ray or examination.

Bowel cleansing kit number 2 is the same as bowel cleansing kits 1 and 3 except for the substitution of a soap enema in place of the bisacodyl suppository or bisacodyl enema. As noted in your submission of August 16, 1988 (SUP005), no

clinical studies of the liquid castile soap enema have been performed, although some textbooks of the 1940s and 1950s do refer to soap water enemas. No data on soap water enemas have been submitted to the OTC drug review and such products are not discussed in the OTC laxative tentative final monograph (50 FR 2124). In view of the literature reports noted in your own submission that soap enemas have caused adverse reactions and are irritating, as well as the lack of clinical data on their safety and effectiveness, there is no adequate basis to recommend approval of kit number 2 or any bowel cleansing kit containing a soap enema. Should the company wish to pursue approval of kits containing a soap enema, well-controlled clinical trials comparing a bowel cleansing kit with a soap enema to that with a bisacodyl enema or suppository will be necessary.

Kit Number 4: A kit containing the following 3 laxative drug products for sequential administration: 60 milliliters (mL) of castor oil emulsion in oral solution, 20 mg bisacodyl administered orally at least 3 hours after administration of the castor oil emulsion in oral solution, 10 mg of bisacodyl administered by suppository at least 9 hours after the administration of the oral bisacodyl and at least 1 hour before the scheduled x-ray or examination.

Proposed bowel cleansing kit number 4 is the same as kit number 1 but substitutes castor oil for sodium phosphate and sodium biphosphate. Castor oil is in Category I in the OTC laxative tentative final monograph both as a stimulant laxative and for use alone in preparing the colon for endoscopic examination. There is no discussion in the laxative tentative final monograph regarding the use of castor oil with other laxatives as part of a bowel cleansing regimen. The proposed combination in kit number 4 would combine two stimulant laxatives rather than a saline laxative and a stimulant laxative. Such a substitution must be supported by adequate clinical data. The argument that because each ingredient proposed for kit number 4 is separately approved for bowel cleansing in the OTC laxative tentative final monograph, the combination must be safe and effective as a bowel cleansing system is not in keeping with the agency's guidelines on OTC combination drug products. The discussion of FDA's combination policy in comment 88 in the laxative tentative final monograph clearly states that "data are necessary to establish the safety and effectiveness of other specific combinations or to demonstrate that the specific ingredients in a pharmacological class are chemically and pharmacologically interchangeable." (See 50 FR 2146.)

The study by Strates and Hofmann (Pharmatherapeutica, 5:57-61, 1987) was a single-blind randomized study of 195 patients being prepared for barium enema, in which one group of patients received 2 ounces (oz) of castor oil followed by tap water enemas, while the other group received magnesium citrate, phenolphthalein, and a bisacodyl suppository. This study did not demonstrate any significant differences between the two bowel cleansing systems, although some significant differences were noted in patient preference for the magnesium citrate-containing kit. The authors of this study also noted that a previous study by Irwin et al. (Gastroenterology, 67: 47-50, 1974) found that a bowel preparation kit containing magnesium citrate, phenolphthalein, and a carbon dioxide-releasing suppository gave significantly superior results in preparing patients for barium enema than did 2 oz of castor oil followed by cleansing enemas. Neither of the aforementioned studies provide the support needed to establish the safety and effectiveness of a bowel cleansing kit containing castor oil followed by a cleansing tap water enema, nor do these data support the safety and effectiveness of a kit containing castor oil followed by oral bisacodyl and a soap water enema (kit number 5), or castor oil followed by oral and then rectal bisacodyl (kit number 6).

It is not possible to predict whether the castor oil-containing kits would produce results equivalent to, better than, or worse than the magnesium citrate bowel cleansing systems currently proposed as Category I in the laxative tentative final monograph. Such a kit would contain only stimulant laxatives, and the repetitive administration of such active agents may not be needed and may cause an increase in adverse reactions. Data from well-controlled clinical studies comparing castor oil to magnesium citrate would be necessary for further evaluation of these proposed kits, and for the castor oil kit containing soap enema, a separate evaluation, as noted above for proposed kit number 2, would be necessary.

Kit number 5: A kit containing the following 3 laxative drug products for sequential administration: 60 mL of castor oil emulsion in oral solution, 20 mg bisacodyl administered orally at least 3 hours after administration of the castor oil emulsion in oral solution, and administration of a large volume liquid castile soap enema (2/3 fluid oz of liquid castile soap) at least 9 hours after the administration of the oral bisacodyl and at least 2 hours before the scheduled x-ray or examination.

The deficiencies discussed for proposed kits number 2 and number 4 above apply equally to this proposed bowel cleansing system.

Kit number 6: A kit containing the following 3 laxative drug products for sequential administration: 60 mL of castor oil emulsion in oral solution, 20 mg of bisacodyl administered orally at least 3 hours after administration of the castor oil emulsion in oral solution, 10 mg of bisacodyl administered by enema at least 9 hours after the administration of the oral bisacodyl and at least 1 hour before the scheduled x-ray or examination.

The deficiencies mentioned in the discussion of proposed kit number 4 above apply equally to this proposed kit.

The Division of OTC Drug Evaluation is therefore proposing that the following bowel cleansing systems (identified as kit numbers 1 and 3 above) be included as Category I for adults and children 12 years of age and over in the final monograph for OTC laxative drug products:

A kit containing the following 3 laxative drug products for sequential administration: sodium phosphate/sodium biphosphate marketed as an oral solution identified in § 334.16(d) and bisacodyl identified in § 334.18(b) in both an oral dosage form and a suppository dosage form. (Kit number 1)

A kit containing the following 3 laxative drug products for sequential administration: sodium phosphate/sodium biphosphate marketed as an oral solution identified in § 334.16(d) and bisacodyl identified in § 334.18(b) in both an oral and an enema dosage form. (Kit number 3)

Please note that the dosage schedules for these kits will be included in § 334.66(d) in the final monograph and an appropriate cross-reference will be included in the above kit descriptions when included in § 334.32 of the final monograph.

The submitted data are insufficient to support the inclusion of your other proposed bowel cleansing kits (identified as kit numbers 2, 4, 5, and 6 above) as Category I at this time. Therefore, we are not proposing that any of those bowel cleansing systems be included in the OTC laxative final monograph.

The Division of OTC Drug Evaluation intends to recommend to the Commissioner that the agency respond to your comment in the above manner in the final monograph for OTC laxative drug products, which will be published in a future issue of the FEDERAL REGISTER. Following that publication, you may file a citizen petition to amend the final monograph or file a new drug application for any of the kits not included in the monograph. Should the company wish to perform the clinical studies needed for any of these other kits, the agency would be glad to review proposed protocols.

Peter S. Reichertz, Esq.

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Any comment you may wish to make on the above information should be submitted in three copies, identified with the docket number shown at the beginning of this letter, to the Dockets Management Branch (HFA-305), Food and Drug Administration, Room 4-62, 5600 Fishers Lane, Rockville, MD 20857.

We hope this information will be helpful.

Sincerely yours,

A handwritten signature in black ink, appearing to read "W. E. Gilbertson", written in a cursive style.

William E. Gilbertson, Pharm. D.
Director
Division of OTC Drug Evaluation
Office of Drug Standards
Center for Drug Evaluation and Research



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Peter S. Reichertz
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June 10, 1998

VIA FEDERAL EXPRESS

1595 '98 JUN 12 P3:09

Debra Bowen, M.D.
Director (HFD-560)
Division of OTC Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
Woodmont Office Complex I
1401 Rockville Pike
Rockville, Maryland 20852

Re: Docket No. 78N-036L; RIN 0910-AA01
Package Size Limitations for Sodium Phosphates Oral Solution
and Warning and Directions Statements for Oral and Rectal
Sodium Phosphates for Over-the-Counter Human Laxative Use

Dear Dr. Bowen:

We represent C. B. Fleet Company, Incorporated, of Lynchburg, Virginia (Fleet).
As you are aware, Fleet is the manufacturer and distributor of FLEET® Phospho-Soda®
Oral Saline Laxative, FLEET® Ready-to-Use Enema and FLEET® Enema for Children.
All of these products are subject to the above-referenced final rule, which was published in
the *Federal Register* of May 21, 1998 at 63 *Fed. Reg.* 27836, *et seq.*

As you know, that rule had two principal features. The first dealt with package size
limitations for Sodium Phosphates Oral Solution. As indicated in the preamble to the rule,

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Fleet voluntarily initiated a market withdrawal of packages of FLEET® Phospho-Soda containing more than 90 mL in 1993, and no longer markets Sodium Phosphates Oral Solution products containing more than 90 mL. Fleet does not object to, or contest, that part of this final rule.

The other part of the final rule required a new warning and new directions for use for both oral and rectal sodium phosphates for laxative use. Fleet does have serious concerns about the substantial changes made between the final rule, which was just published, and the proposed rule, which was published at 59 *Fed. Reg.* 15139 on March 31, 1994. In the proposed rule, FDA had proposed the following warning:

Do not exceed recommended dose unless recommended by a doctor. Serious side effects may occur from excess dosage.

See proposed 21 C.F.R. § 334.58(c)(2)(iv), 59 *Fed. Reg.* 15139.

In response to that proposal, Fleet submitted comments on May 18, 1994, indicating that it would comply with the proposal as worded for Sodium Phosphates Oral Solution,^{1/} but that it did not agree with the need for such a warning on rectally administered sodium phosphates enemas. The Agency cited no evidence in the proposed rule as to the need for such a warning on rectally administered products, but only stated in a conclusory fashion

^{1/} Please note Fleet indicated it could comply with a final rule in 120 days. However, as it did not believe a warning should apply to the enema, it gave no estimate of when it could comply. That time period is much too short to change the labeling for its enema products.

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that an electrolyte imbalance “could occur if an excess dose of either the oral solution or the rectal enema dosage form were used.” 59 *Fed. Reg.* 15141. Fleet did not object to the proposed warning on the oral solution, as a similar statement was already in use in product labeling at the time the proposed rule was published.

The Agency, in the final rule published on May 21, 1998, not only kept the requirement for this warning for the enema dosage form, but substantively changed the content of the warning, and added a new requirement for directions for use for both the oral and rectal dosage forms. Under the final rule as published, the following warnings and directions are required:

(2) Warnings. The following sentences shall appear in boldface type as the first statement under the heading “Warnings.”

(i) Oral dosage forms. “Taking more than the recommended dose in 24 hours can be harmful.”

(ii) Rectal enema dosage forms. “Using more than one enema in 24 hours can be harmful.”

(3) Directions—(i) The labeling of all orally or rectally administered OTC drug products containing sodium phosphates shall contain the following directions in boldface type immediately preceding the dosage information: “Do not” (“take” or “use”) “more unless directed by a doctor. See Warnings.”

(ii) For products containing dibasic sodium phosphate/monobasic sodium phosphate identified in § 334.16(d) marketed as a solution. Adults and children 12 years of age and over: Oral dosage is dibasic sodium phosphate 3.42 to 7.56 grams (g) and monobasic sodium phosphate 9.1 to 20.2 g (20 to 45 mL dibasic sodium phosphate/monobasic sodium phosphate oral solution) as a single daily dose. “Do not take more than 45 mL (9 teaspoonfuls or 3 tablespoonfuls)

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in a 24 hour period.” Children 10 and 11 years of age: Oral dosage is dibasic sodium phosphate 1.71 to 3.78 g and monobasic sodium phosphate 4.5 to 10.1 g (10 to 20 mL dibasic sodium phosphate/monobasic sodium phosphate oral solution) as a single daily dose. “Do not take more than 20 mL (4 teaspoonfuls) in a 24-hour period.” Children 5 to 9 years of age: Oral dosage is dibasic sodium phosphate 0.86 to 1.89 g and monobasic sodium phosphate 2.2 to 5.05 g (5 to 10 mL dibasic sodium phosphate/monobasic sodium phosphate oral solution) as a single daily dose. “Do not take more than 10 mL (2 teaspoonfuls) in a 24-hour period.” Children under 5 years of age: ask a doctor.

See 21 C.F.R. § 201.307(b), 63 Fed. Reg. 27843-4.

As is obvious from a reading of this rule, the Agency has substantively changed the warning from a warning which only addresses the side effects which could occur from overdosage, to a rule that now not only addresses side effects, but also limits the amount of these products that can be taken in a 24 hour period. Indeed, in discussing the significant changes from the proposed rule, the Agency noted it was “adding a *new* warning” and “*new* directions” for both oral and rectal dosage forms as to the 24 hour limitations.

(Emphasis supplied.) *63 Fed. Reg. 27841-2.*

Fleet objects to the contents of this new warning and these new directions for use. Fleet does not believe they are justified and, furthermore, believes that the rule as published substantively changed the content of the proposed rule. The Agency should have issued a revised proposed rule setting forth these issues, and given Fleet, and other

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affected parties, the opportunity to comment on the revised rule, as required by the Administrative Procedure Act (APA) and case law.

Under the APA, an Agency must give the public adequate notice of the content of a final rule and the opportunity to submit comments thereon. 5 U.S.C. § 553(c). An administrative agency such as the FDA cannot substantively change the content of a proposed rule without giving the public opportunity to comment thereon, unless the final rule is a logical outgrowth thereof. It is the duty of any agency to convey to the public in the proposed rule what the content of the final rule will be. *Shell Oil Co. v. EPA*, 950 F.2d 741, 751 (D.C. Cir 1991). Where an agency gives no hint in the proposed rule of the content of the final rule as published, the rule is invalid and must be republished for comment. *See, e.g., Kooritzky v. Reich*, 17 F.3d 1509 (D.C. Cir. 1994); *American Med. Ass'n v. Reno*, 57 F.3d 1129 (D.C. Cir. 1995); *Chocolate Mfrs. Ass'n of the U.S. v. Block*, 755 F.2d 1098 (4th Cir. 1985); and *American Paper Institute v. EPA*, 660 F.2d 954 (4th Cir. 1981).

Fleet believes that the final rule published on May 21, 1998, is invalid as to the new warnings and directions for use, as it was "new," as conceded by FDA, not based on information in the administrative record, and was not a logical outgrowth of the proposed rule. A limitation on frequency of use (the final rule) differs significantly and substantially from a warning notice (the proposed rule) as to the effects of an overdose.

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Fleet is particularly concerned that the new warnings and directions requirements are to apply to all Fleet® enema products. As indicated above, Fleet specifically noted in its comments on the proposed rule that there was no information in the administrative record supporting any such warning for sodium phosphates enemas. The Agency has now not only required a warning, but also limited its frequency of use to every 24 hours. The Agency, in Comment 5, 63 *Fed. Reg.* 27840-1, states its position and cites a number of reports to support its position. None of the supporting studies were cited in the proposed rule. Fleet has had no opportunity to comment upon the content of the final rule as published, nor upon the evidence in the administrative record to support the proposal as it relates to enemas – as it was not included until publication of the final rule.

As has been shown, the Agency, in publishing a final rule requiring new warnings and directions for use, violated the APA. Fleet would prefer not to engage the Agency in a legal contest over the content of the final rule, but, at the same time, it does not agree with the final rule, particularly as to the enema products. While Fleet does not agree with the provisions of the rule as to either dosage form, it has begun the process of changing labeling for FLEET® Phospho-Soda®.

As to the enema products, Fleet believes that a meeting with appropriate Agency officials is appropriate – at the earliest opportunity – to discuss its concerns about the content of the final rule and to determine if some understanding can be reached which would eliminate the need for a legal challenge to the final rule by Fleet. At that meeting,

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representatives of Fleet (Ms. Sarah S. Post, Vice President of Administration and Dr. Thomas Wood, Manager of Research and Development) would be present, as would I and Fleet's outside consultant on the safety issue – Dr. Thomas Garvey. We would like to schedule the meeting for anytime between June 18 and June 26.

* * * *

Please call me to arrange for such a meeting.

Sincerely,



Peter S. Reichertz

cc: Dockets Management Branch (HFA-305)
Food and Drug Administration
12420 Parklawn Drive, Room 1-23
Rockville, Maryland 20857
(in triplicate)
Ms. Cheryl Turner (FDA, HFD-560)

Ms. Sarah S. Post
Dr. Thomas Wood
Dr. Thomas Garvey

Arent Fox
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August 19, 1998

Dockets Management Branch
(HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20857

Re: Laxative Drug Products for Over-the-Counter Human Use;
Proposed Amendment to the Tentative Final Monograph
Docket 78N-036L

Dear Sir/Madam:

We represent C. B. Fleet Company, Incorporated, of Lynchburg, Virginia (Fleet).

We are submitting the following comments on behalf of Fleet, in response to the Notice of Proposed Rulemaking (NPR) published by the Food and Drug Administration ("FDA") on May 21, 1998, to amend the Tentative Final Monograph (TFM) on Laxative Drug Products for Over-the-Counter Human Use. 63 Fed. Reg. 27886. The proposed rule would amend the TFM to include additional general and professional labeling for oral and rectal dibasic sodium phosphate/monobasic sodium phosphate (sodium phosphates) drug products. FDA has proposed new warnings and directions for these products and a new time-to-effect statement for rectal products "based on new data submitted after publication

78N-036L
Arent Fox Kintner Plotkin & Kahn, PLLC
Washington, DC New York, NY Budapest, Hungary Jeddah, Saudi Arabia

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Arent Fox

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of the tentative final monograph for OTC laxative drug products.” *Id.*

I. INTRODUCTION

In the Federal Register of March 21, 1975, FDA published an advance notice of proposed rulemaking to establish a monograph for OTC laxative, antidiarrheal, emetic and antiemetic drug products. 40 Fed. Reg. 12902. In 1985, the Agency published a proposed rule on OTC laxative drug products in the form of a TFM. 50 Fed. Reg. 2124 (January 15, 1985). Included in the TFM are oral and rectal dosage forms of products containing dibasic sodium phosphate and/or monobasic sodium phosphate for laxative purposes and for professional use as a bowel cleanser. The proposed rule refers to these products as “sodium phosphates enemas.”^{1/}

On May 21, 1998, FDA proposed to amend the TFM to add additional general and professional labeling for OTC oral and rectal sodium phosphates laxative products. 63 Fed. Reg. 27887. The proposal specified that comments are due by August 19, 1998.

^{1/} Consistent with FDA’s usage, we have denominated a laxative enema containing dibasic sodium phosphate and monobasic sodium phosphate as a “sodium phosphates enema” throughout these comments. FDA explained that the Agency used that term because it is the official name for a solution of dibasic sodium phosphate and monobasic sodium phosphate in the U.S. Pharmacopeia 23/National Formulary 18, 1995. Fleet believes, however, that the phrase is awkward and ungrammatical and will not generally be used by consumers. Fleet is therefore applying to the U.S. Pharmacopeia to change the official product name to “sodium phosphate enema”.

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On the same day that the proposed rule was published, FDA also published a final rule imposing package size limitations and certain warnings and directions for use for oral and rectal sodium phosphates for OTC laxative use. 63 Fed. Reg. 27836. The industry had serious concerns about the content (and procedural validity) of the final rule, which were expressed to the Agency during a feedback meeting on July 15, 1998 with the Nonprescription Drug Manufacturers Association (NDMA) and members of industry. At that meeting, the industry suggested new language for the warnings and directions for use; the new language would have alleviated the industry's concerns while adequately accomplishing the Agency's objective of warning the public about risks possibly associated with over-use of sodium phosphates enemas. The industry committed to placing the reworded warning and directions for use on all product labels by December 31, 1998. Agency representatives attending the feedback meeting appeared satisfied with the suggested language and requested that NDMA put the suggestions formally in front of the Agency by submitting a Petition for Reconsideration and a Petition for Stay of Action. On July 22, 1998, the NDMA task group including the sodium phosphates manufacturers did so. The sodium phosphates enema manufacturers worked closely with NDMA in preparing the petitions.

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In light of its imminent effective date, the final rule required immediate action from the industry. Because of the necessity for NDMA and industry members to focus their efforts on articulating to FDA the industry's objections to the final rule, NDMA requested an extension of time to comment on the proposed rule. FDA has not formally responded to that extension request but has orally indicated that the Agency is not inclined to grant the extension. By letter dated August 5, 1998, however, FDA informed counsel for Fleet that "the Agency plans to issue a notice to repropose the professional labeling for sodium phosphates enemas." Letter to Peter S. Reichertz from Debra Bowen, M.D., Director of the Division of OTC Drug Evaluation, Center for Drug Evaluation and Research, United States Food and Drug Administration, at page 2. The letter gave no indication as to which specific aspects of the rule would be re-proposed.

In light of the Agency's denial of Fleet's request for an extension of time to comment and of the Agency's plan to re-propose the professional labeling provisions for sodium phosphates enemas, the company is not focusing its immediate efforts on the professional labeling provisions. Fleet does have substantial concerns about the content of those provisions, however, and the company intends to submit comments on those provisions subsequently.

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With respect to the "general" OTC labeling requirements included in the May 21, 1998 NPR, Fleet has the following comments.

II. Sodium Phosphates Enemas

A. Indications

The proposed rule includes a requirement that the label for sodium phosphates enemas give a time-to-effect of one to five minutes. Specifically, proposed 21 C.F.R. § 334.58(b)(2) requires that the label of rectal dosage forms state, "This product generally produces bowel movement in 1 to 5 minutes." Fleet believes that consumers who retain a sodium phosphates enema for only one minute may find the enema ineffective. Fleet believes that there is insufficient support for a one minute time-to-effect in the literature or in clinical practice.

The labeling of Fleet enema products currently indicates that the product should produce bowel movement in two to five minutes. This time-to-effect is supported by a number of studies, both published and unpublished; copies of these studies are appended hereto at Tab A. Although time-to-effect was not the primary endpoint being measured in several of the studies and none of these studies was of sufficient size by itself to serve as the basis for a labeling claim, the accumulated data do provide a picture of average response times. Fleet has tabulated the results of these studies (Tab B); there was only one

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participant in any of the studies who could clearly be identified as having had a response time of less than two minutes. Based upon this information, Fleet does not believe that one minute is normally a sufficient amount of time for a sodium phosphates enema to take effect. Further, because reducing the stated time-to-effect may result in insufficient evacuation, the proposed labeling may encourage product misuse.^{2/} Fleet therefore urges that the time-to-effect statement be revised to read, "This product generally produces bowel movement in 2 to 5 minutes."

B. Warnings

1. Dehydration

The proposed rule would require that the labeling of sodium phosphates enemas state, "Do not use if you have kidney disease, heart problems, or are dehydrated, or for more than three days, without asking a doctor." Proposed 21 C.F.R. § 334.58(c)(2).

For several reasons, Fleet recommends that the reference to being "dehydrated" be deleted from this provision. First, Fleet believes that the reference to "dehydration" is meaningless for most consumers, who are not generally familiar with the symptoms of dehydration.

^{2/} Use of a sodium phosphates enema for less than two minutes may also affect the safety and effectiveness of medical procedures that require an empty bowel.

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Second, "dehydration" is not a contraindication for use of a sodium phosphates enema, and nothing in the literature supports the designation of "dehydration" as a contraindication. Rather, "dehydration" is an adverse outcome associated with misuse or overuse of the product. If anything, dehydration would be an outcome to be warned against. However, FDA has not cited any literature that actually supports a conclusion that the product presents a risk of dehydration when used according to the labeled directions.

FDA does cite two references in support of an association between sodium phosphates enemas and dehydration. The first is a discussion in *Goodman & Gilman's Pharmacologic Basis of Therapeutics* (the current standard pharmacology reference) on sodium phosphates laxatives, but the discussion concerning the risks of dehydration deals with *oral* sodium phosphates products. Gilman A. et al. 1992. *The Pharmacological Basis of Therapeutics*, 8th edition. Pergamon Press, New York:1005. Because the different route of administration affects the absorption of the product, potential adverse outcomes associated with the rectally-administered product cannot be extrapolated from experience with the oral products. The second reference is a case report involving a four-year-old child with congenital megacolon. Fonkalsrud EW. 1967. Hypernatremic Dehydration from Hypertonic Enemas in Congenital Megacolon. *Journal of the American Medical Association* 199(8):584. Because the case involved use of a sodium phosphates product

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where the patient's condition clearly contraindicated use of such a product, this reference is also inapposite.

Not only are the references cited by FDA not supportive of the proposed warning language, Fleet is unaware of *any* studies or reports that link the proper use of a sodium phosphates enema to a risk of dehydration. In fact, published data relevant to fluid and electrolyte shifts associated with label-directed use of sodium phosphates enemas indicate that absorption of sodium and loss of water and potassium are clinically inconsequential. Zumoff B and Hellman L. Absorption of Sodium from Hypertonic Sodium Phosphate Enema Solutions. *Dis. Colon and Rectum* 1978; 21(6):440-3; Flentie EH and Baptist VH. Enema Studies. *West J. Surg. Obstet. Gynec.* 1957; 65:302-5; Flentie EH and Cherkin A. Electrolyte Effects of the Sodium Phosphate Enema. *Dis. Colon and Rectum* 1958; 1:295-9. Because the warning is unsupported by scientific evidence or clinical use, Fleet urges that the warning relating to dehydration be deleted. Moreover, Fleet suggests the following wording for the warning: "Ask a doctor before using this product if you have kidney disease or have a heart problem." Fleet believes that this warning would provide the necessary information in a less confusing and more accurate manner than the warning proposed by FDA.

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2. *Three-Day Limitation*

The proposed rule also includes a warning to refrain from using rectal sodium phosphate enemas for more than three days. Two of the citations relied upon by FDA involve use of the oral solution, however, and are therefore not directly relevant to a discussion of the appropriate period of use for rectal dosage forms. The other citations are cases involving patients with contra-indicating conditions or involving clear overdosing. Moreover, none of the references cited by FDA examine the question of length of use. Although the references do discuss dehydration and electrolyte imbalance, they do not demonstrate, or even suggest, that using an enema for more than three days will cause such problems. In short, these citations simply do not support a three-day limitation for sodium phosphates enemas when properly used. Furthermore, Fleet has searched the literature and is unable to discover any studies or cases that would provide support for such a limitation. In fact, the only study in the literature cited in the proposed rule that addresses the issue of the consequences of consecutive daily dosing with sodium phosphates enemas, albeit indirectly, indicates that seven days of such dosing in healthy male subjects is not associated with clinically detectable adverse manifestations of electrolyte or fluid imbalance. Bodi T and Grey GH, Clinical Evaluations of Small-Volume Enemas. Penn. Med. J.; 68(6):35-8.

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The labeling for all other laxative products permits use for seven days, and there is no scientific or clinical reason for the labeling of sodium phosphates enemas to be more restrictive. The risk of harmful effects associated with sodium phosphates enemas is extremely small^{3/} and, when used according to the labeling, sodium phosphates enemas can safely be used on a daily basis for periods of time even exceeding seven days. Fleet therefore believes that, for sodium phosphates enemas, the warning should be modified to remove the three-day limitation. As laxatives, sodium phosphates enemas would then be subject to the same general warning requirement that is applicable to all other laxative products, instructing consumers to restrict use that is not medically supervised to seven days.^{4/}

^{3/} As discussed by NDMA in its July 22, 1998 Petition for Stay of Action and Petition for Reconsideration of portions of FDA's Final Rule on Package Size Limitation for Sodium Phosphates Oral Solution and Warning and Direction Statements for Oral and Rectal Sodium Phosphates for Over-the-Counter Laxative Use, 63 Fed. Reg. 27836 (May 21, 1998), serious non-nozzle-related adverse events associated with sodium phosphates enemas are extremely rare. (The industry has committed to submitting a full report on the safety of these enemas to FDA by October 1, 1998.)

^{4/} As oral sodium phosphates solutions are primarily used for bowel cleansing prior to certain medical procedures, Fleet does not object to putting a three-day limit in the labeling for the oral solution.

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3. *Other Suggested Changes*

Fleet believes that the proposed statement "Do not use more unless directed by a doctor" is not as clear as it might be. Fleet recommends substituting the phrase, "Use only a single daily dose unless directed by a doctor."

Fleet also believes that the warnings should include a warning to stop using the product if the consumer has rectal bleeding, and a warning to consult a doctor before using the product if the consumer has kidney or heart disease. Such statements currently appear in FDA's proposed directions for use (see discussion below), but Fleet believes that they should be repeated under "warnings."

4. *Revised Warnings*

In sum, Fleet urges that § 334.58(c)(2) be revised to read

(2) *For products containing dibasic sodium phosphate or monobasic sodium phosphate identified in §334.16(d), (e), or (f) — (i) Do not use if (these four words in bold print) "you have kidney disease or heart problems."*

(ii) *Oral dosage forms.* Do not use for more than 3 days, or give to children under 5 years of age, without asking a doctor.

(iii) *Rectal dosage forms.* Do not give to children under 2 years of age. Stop using this product if you have no bowel movement after the enema is given or have rectal

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bleeding. Ask a doctor before using this product if you have kidney disease or have a heart problem.”

C. Directions for Use

The proposed rule would require that the label of a rectal enema state that “If no urge is felt after 5 minutes of using, try to empty bowel. Call a doctor promptly if no liquid comes out of the rectum after 30 minutes because dehydration could occur.” Proposed § 334.58(d)(5)(ii)(B). This proposed warning is, according to FDA’s explanation in the preamble to the proposal, related to the fact that “effectiveness is not increased when a sodium phosphates enema is retained for more than five minutes. Fleet closely examined the literature that FDA cited as the basis for this contention and found no support for it. In fact, the studies on enema retention time in Tabs A and B support the two to five minute average response time and additionally show that anywhere from 17% to 70% of the subjects retained the enema for more than five minutes. These data suggest that ten minutes is a better limit and more likely to encompass the current practices of the vast majority of users. Fleet agrees that forcing an evacuation of the enema solution if no urge to move the bowels may be appropriate, but the company suggests that a ten minute waiting period would better reflect current clinical practice. A shorter interval may be confusing to

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the consumer and perhaps risk an ineffective bowel cleansing (which could be a serious consequence when the enema is used before a medical examination).

The literature, however, does not support the inference that retention of a single sodium phosphates enema for more than 30 minutes is dangerous and should, as a matter of course, prompt a call to a physician. In fact, the oral solution is normally retained by the body for several hours without causing dehydration or other ill effects. Further, published clinical data show that following rectal administration of sodium phosphates products, phosphate absorption, though detectable and, possibly, correlated with expulsion-time, is far slower than following oral administration of sodium phosphates. Schuchman GD and Barcia PJ. Phosphate Absorption from Fleet Enemas in Adults. *Curr. Surg.* 1989; 46:120-22; Grosskopf I, Graff E, et al., Hyperphosphataemia and Hypocalcaemia Induced by Hypertonic Phosphate Enema -- An Experimental Study and Review of the Literature. *Human and Experiment. Toxicol.* 1991;10:351-55; Cohan CF, Kadakia SC and Kadakia AS. Serum Electrolyte, Mineral and Blood pH Changes After Phosphate Enema, Water Enema and Electrolyte Lavage Solution Enema for Flexible Sigmoidoscopy. *Gastrointest. Endoscop.* 1992; 38(5)575-78; Wiberg JJ, Turner GG et al. Effect of Phosphates or Magnesium Cathartics on Serum Calcium. *Arch Intern. Med.* 1978;138:1114-16; Vanner SJ, MacDonald PH et al. A Randomized Prospective Trial Comparing Oral Sodium

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Phosphate with Standard Polyethylene Glycol-Based Lavage Solution (Golytely®) in the Preparation of Patients for Colonoscopy. *Am. J. Gastroenterol.* 1990; 85(4):422-27; Kolts BE, Lyles WE, et al. A Comparison of the Effectiveness and Patient Tolerance of Oral Sodium Phosphate, Castor Oil and Standard Electrolyte Lavage for Colonoscopy for Sigmoidoscopy Preparation. *Am. J. Gastroenterol.* 1993; 88(8):1218-23. Fleet therefore urges that the proposed regulation be revised to read simply, "If no urge to empty the bowel is felt ten minutes after use, try to empty bowel." Fleet does, however, continue to recommend the warning that is currently in place on its enema labeling to "Stop using this product and consult a doctor if you have no bowel movement after the enema is given. These symptoms may indicate a serious medical condition."

The proposed rule would also require that the directions for use for rectal enemas instruct the user to "stop using if the tip is hard to insert" and state that "forcing the tip into the rectum can cause injury (especially if you have hemorrhoids). If enema tip causes rectal bleeding or pain, get immediate medical care." Proposed 21 C.F.R.

§ 334.58(d)(5)(ii)(C). Fleet concurs with the need to direct consumers not to use force when inserting an enema. Although rectal dosage forms of saline laxatives are safe when used properly, injuries can result from forcing the enema tip into the rectum where there is resistance. In fact, the majority of "adverse events" associated with Fleet enemas are

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nozzle injuries, rather than reactions to the drug product itself. For that reason, Fleet's current labeling advises that the consumer should stop using the product and seek a physician's advice if he or she has rectal bleeding.

Fleet believes, that the reference to "pain" in the proposed statement requires a modifier. Use of an enema may, by its nature, cause discomfort that some users may interpret as "pain," causing them unnecessary anxiety. Transient or minor discomfort is not, however, a cause for concern. Fleet therefore recommends that the statement be revised to read, "Stop using if the tip is hard to insert. Forcing the tip into the rectum can cause injury (especially if you have hemorrhoids). If enema tip causes rectal bleeding or severe or persistent pain, get immediate medical care. Such bleeding or pain may indicate a serious condition."

III. ORAL SODIUM PHOSPHATES

FDA's proposal would require the labeling for oral sodium phosphates products to state, "Do not use if you have a kidney disease, heart problem or are dehydrated or for more than 3 days without asking a doctor. Do not give to children 5 years of age and under without asking a doctor." Proposed 21 C.F.R. § 334.58(c)(2).

As discussed above, dehydration is not a contraindicating condition for sodium phosphates laxative products and, in any case, the term "dehydration" may be meaningless

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for many consumers. Moreover, the literature does not support an association between proper use of oral sodium phosphates products and dehydration. Fleet therefore believes that the reference to being dehydrated should be deleted.

Fleet also recommends changing the wording of the direction statement somewhat, to be clearer and less grammatically awkward. Specifically, Fleet suggests that the statement read "ask a doctor before using this product if you have kidney disease, have heart disease, have already used the product for three days, or are giving the product to a child 5 years of age or under."

IV. CONCLUSION

In conclusion, several of the Agency's new directions and warnings for labeling of sodium phosphates enemas, *i.e.* limitation of consecutive single daily use to three rather than seven days, the direction that a physician be called if no enema return is seen within 30 minutes of administration, and the conclusion that sodium phosphates enemas "can cause electrolyte imbalances within 24 hours after the initial dose is taken" even in the absence of renal failure or active heart disease, seem, on review of the literature that was cited by FDA as support, to be without discernible basis, based on reports of adverse events occurring in children, in adults with diagnosed contraindicating conditions or in association

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with overdosing, or based on extrapolation of results in studies of administration of oral sodium phosphates.

For the reasons set forth above, Fleet believes that the proposed rule should be revised as to the indications, warnings and directions for use. We are attaching hereto, at Tab C, a table comparing Fleet's current labeling, FDA's proposed labeling, and the labeling recommended by Fleet, as discussed herein.^{2/}

Fleet requests that the Final Rule, when published, be amended accordingly.

We thank you for your consideration of these comments.

Sincerely,

Peter S Reichertz by [Signature]
Peter S. Reichertz
Counsel to C. B. Fleet Company, Incorporated

(in triplicate)

Enclosure

^{2/} The recommended labeling uses a "bullet-point" format, to conform to FDA's proposed Drug Facts Format. 62 Fed. Reg. 9024 (February 27, 1997).



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Peter S. Reichertz
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reicherp@arentfox.com

October 9, 1998

VIA FEDERAL EXPRESS

Dockets Management Branch
(HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20857

Re: Laxative Drug Products for OTC Human Use
Docket 78N-036L

Dear Sir/Madam:

This letter responds to the letter dated September 16, 1998, from Mark vB. Cleveland, Ph.D., Vice President, New Product Development, Braintree Laboratories, Inc. In that letter, Dr. Cleveland complained about a "Dear Doctor" letter sent by our client, C. B. Fleet Company, Incorporated, Lynchburg, Virginia, to physicians about use of FLEET® PHOSPHO-SODA® oral sodium phosphate solution.

All Dr. Cleveland states is that the "letter contradicts the intent" of the May 21, 1998 Federal Register notice on Package Size Limitation for Sodium Phosphates Oral Solution and Warning and Direction Statements for Oral and Rectal Sodium Phosphates for Over-the-Counter Laxative Use, 63 Fed. Reg. 27836 ("the May 1998 Final Rule"). He does not, however, give one specific example of how the "Dear Doctor" letter referred to contradicts the May 1998 Final Rule. The purpose of that letter was to inform physicians that FLEET® PHOSPHO-SODA® could still be used as a bowel cleansing preparation. It was necessary for C. B. Fleet to issue this letter, since representatives of Braintree were representing that FLEET® PHOSPHO-SODA® could no longer be used for bowel cleansing and that physicians could face legal liability for using it. The May 1998 Final Rule did not prohibit the use of oral sodium phosphates for bowel cleansing; in fact it only dealt with consumer labeling of the product. Fleet's letter was necessitated because Braintree representatives were making false and misleading statements; C. B. Fleet issued the "Dear Doctor" letter to clarify what was being misrepresented to professionals by

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Washington, DC New York, NY Budapest, Hungary Jeddah, Saudi Arabia

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Braintree.^{1/} Braintree is in no position to complain about Fleet's accurate description of the May 1998 Final Rule, having misrepresented it to the medical profession.

Furthermore, there is absolutely nothing inaccurate about the "Dear Doctor" letter. It accurately reflects the content of the May 1998 Final Rule, a rule that C. B. Fleet long ago complied with by changing the package sizes of its FLEET® PHOSPHO-SODA® product and by relabeling it prior to the deadline of the May 1998 Final Rule. (A copy of the revised labeling is attached.) Furthermore, the letter does not advocate any specific bowel regimen; it merely states that doctors can use what they deem appropriate (and provides warnings as to when it should not be used). As stated in the letter, the consumer package warning is "Do not take more unless directed by a doctor" (emphasis added). See 21 C.F.R. § 201.307(b)(3)(i), 63 Fed. Reg. 27843 (May 21, 1998). Professional labeling for the products is addressed in a proposed rule, also published May 21, 1998. See proposed 21 C.F.R. § 334.80(b)(2), 63 Fed. Reg. 27893.

C. B. Fleet stands by the safety of FLEET® PHOSPHO-SODA®, for use as both a general purpose laxative and bowel cleanser. It is generally recognized as safe and effective by the medical community for these purposes. C. B. Fleet is continuing to do research to support its safety and effectiveness, as it has been and will continue to be discussed with the Agency.

In short, there is nothing false or misleading about the "Dear Doctor" letter complained about by Dr. Cleveland, or contrary to the intent of the May 1998 Final Rule. It is an accurate, carefully worded description of that rule, which was only necessitated by Braintree's false and misleading representations that FLEET® PHOSPHO-SODA® could no longer be used as a bowel cleanser and that legal liability could result to physicians who used it. C. B. Fleet stands by the content of the "Dear Doctor" letter. If any action is appropriate, it would be action by the Agency to prevent Braintree from making further false and misleading statements about the regulatory status of oral sodium phosphate solution products such as FLEET® PHOSPHO-SODA®.

^{1/} By letter dated July 27, 1998, C. B. Fleet wrote to Harry P. Keegan, President of Braintree Laboratories, Inc., about the activities. See attached.

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Thank you for your consideration of this comment.

Sincerely,



Peter S. Reichertz

Counsel to C. B. Fleet Company, Incorporated

Enclosure

Filed in Triplicate

cc (w/enc.): Ms. Cheryl Turner, Food and Drug Administration
Mr. Douglas Bellaire
Ms. Sarah S. Post

WARNINGS:

TAKING MORE THAN THE RECOMMENDED DOSE IN 24 HOURS CAN BE HARMFUL.

Ask a doctor before using this product if you:

- Are on a sodium restricted diet
- Have a kidney disease
- Are pregnant or nursing a baby

Ask a doctor before using any laxative if you:

- Have nausea, vomiting, or abdominal pain
- Have a sudden change in bowel habits lasting more than 2 weeks
- Have already used a laxative for more than 1 week

Stop using this product and consult a doctor if you:

- Have rectal bleeding
- Have no bowel movement after use as dehydration may occur

These symptoms may indicate a serious condition.

Keep out of reach of children.

In case of overdose or accidental ingestion, get medical help right away.

MOUTH OF BOTTLE SEALED FOR YOUR SAFETY. IF FOIL IMPRINTED "SEALED FOR YOUR PROTECTION" IS BROKEN OR MISSING, DO NOT USE.

Fleet

PHOSPHO-SODA®



procedures
of relief of
occasional
constipation

1.5 Fl Oz (45 mL)



WARNINGS:
TAKING MORE THAN
THE RECOMMENDED
DOSE IN 24 HOURS
CAN BE HARMFUL.

Ask a doctor before
using this product if you:

- Are on a sodium restricted diet
- Have a kidney disease
- Are pregnant or nursing a baby

Ask a doctor before
using any laxative if you:

- Have nausea, vomiting,
or abdominal pain
- Have a sudden change
in bowel habits lasting
more than 2 weeks
- Have already used a laxative
for more than 1 week

Stop using this product and
consult a doctor if you:

- Have rectal bleeding
- Have no bowel movement
after use as dehydration
may occur

These symptoms may indicate
a serious condition.

Keep out of reach of children.
In case of overdose or
accidental ingestion, get
medical help right away.

**MOUTH OF BOTTLE SEALED
FOR YOUR SAFETY. IF FOIL
IMPRINTED "SEALED FOR YOUR
PROTECTION" IS BROKEN OR
MISSING, DO NOT USE.**

Fleet

PHOSPHO-SODA.

Cleansing prior
to medical
procedures
or relief of
occasional
constipation



1.5 Fl Oz (45 mL)



WARNINGS:

TAKING MORE THAN THE RECOMMENDED DOSE IN 24 HOURS CAN BE HARMFUL.

Ask a doctor before using this product if you:

- Are on a sodium restricted diet
- Have a kidney disease
- Are pregnant or nursing a baby

Ask a doctor before using any laxative if you:

- Have nausea, vomiting, or abdominal pain
- Have a sudden change in bowel habits lasting more than 2 weeks
- Have already used a laxative for more than 1 week

Stop using this product and consult a doctor if you:

- Have rectal bleeding
- Have no bowel movement after use as dehydration may occur

These symptoms may indicate a serious condition.

Keep out of reach of children. In case of overdose or accidental ingestion, get medical help right away.

MOUTH OF BOTTLE SEALED FOR YOUR SAFETY. IF FOIL IMPRINTED "SEALED for YOUR PROTECTION" IS BROKEN OR MISSING, DO NOT USE.

Fleet

PHOSPHO-SODA



For medical procedures or relief of occasional constipation

Multi-Dose Container

3 Fl Oz (90 mL)



10



WARNINGS:
**TAKING MORE THAN
THE RECOMMENDED
DOSE IN 24 HOURS
CAN BE HARMFUL.**

**Ask a doctor before
using this product if you:**

- Are on a sodium restricted diet
- Have a kidney disease
- Are pregnant or nursing a baby

**Ask a doctor before
using any laxative if you:**

- Have nausea, vomiting, or abdominal pain
- Have a sudden change in bowel habits lasting more than 2 weeks
- Have already used a laxative for more than 1 week

**Stop using this product
and consult a doctor
if you:**

- Have rectal bleeding
- Have no bowel movement after use as dehydration may occur

These symptoms may indicate a serious condition.
Keep out of reach of children. In case of overdose or accidental ingestion, get medical help right away.

MOUTH OF BOTTLE SEALED FOR YOUR SAFETY. IF FOIL IMPRINTED "SEALED for YOUR PROTECTION" IS BROKEN OR MISSING, DO NOT USE.

Fleet

PHOSPHO-SODA®



For bowel
cleansing prior
to medical
procedures
or relief of
occasional
constipation

Multi-Dose Container

3 Fl Oz (90 mL)





C. B. FLEET COMPANY, INC.

July 27, 1998

**VIA FACSIMILE &
CERTIFIED MAIL/
RETURN RECEIPT REQUESTED**

**Mr. Harry P. Keegan
President
Braintree Laboratories, Inc.
P. O. Box 850929
Braintree, MA 02185-0929**

Dear Mr. Keegan:

It has come to our attention from concerned health professionals that your sales personnel appear to be making false and misleading statements about our product, Fleet® Phospho-Soda®, specifically its acceptance by FDA and legal liability for using the product. We are seriously concerned that the medical community may be misled by statements such as these by what we trust are overzealous Braintree employees.

If you are unaware of these activities, you may want to conduct your own investigation and take steps to stop any such false and misleading statements about our product.

If the practice does not stop, we will be forced to seek legal recourse.

Please let me know the results of your investigation and your intentions in writing within ten (10) days of your receipt of this letter.

Sincerely,

A handwritten signature in black ink, appearing to read "Sarah S. Post".

**Sarah S. Post
Vice President of Administration**

SSP:dhp

pc: Peter S. Reichertz, Esq.

 **Arent Fox**
Attorneys at Law

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BY FEDERAL EXPRESS

November 24, 1998

Dockets Management Branch
(HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20857

Re: Laxative Drug Products for Over-the-Counter Human Use;
Final Rule on Package Size Limitations and Warning and
Directions Statements and
Proposed Amendment to the Tentative Final Monograph
Docket 78N-036L

Dear Sir/Madam:

We represent C. B. Fleet Company, Incorporated, of Lynchburg, Virginia ("Fleet"), on whose behalf we are submitting the enclosed report entitled, "Integrated Safety Summary for Hypertonic Sodium Phosphate Enemas," prepared by Thomas Q. Garvey III, M.D. of Garvey Associates, Inc. We are submitting this report in response to a request from the Food and Drug Administration (FDA) during a feedback meeting on July 15, 1998 with the Nonprescription Drug Manufacturers Association (NDMA) and members of

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Washington, DC New York, NY Budapest, Hungary Jeddah, Saudi Arabia

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industry (including Fleet), during which the industry expressed concerns about the content of FDA's Final Rule on "Package Size Limitations for Sodium Phosphates Oral Solution and Warning and Directions Statements for Oral and Rectal Sodium Phosphates for Over-the-Counter Human Laxative Use" ("Final Rule"). That Rule was published on May 21, 1998 in the *Federal Register* at 63 Fed. Reg. 27836.

We are also submitting this report as a comment to the docket on FDA's proposal, published in the *Federal Register* on May 21, 1998, 63 Fed. Reg. 27887, to amend the proposed rule on OTC laxative drug products.^{1/} The proposed amendment would add additional general and professional labeling for OTC oral and rectal sodium phosphates laxative products.

As described below, Dr. Garvey's report demonstrates clearly that there is no evidence whatsoever to support FDA's conclusion that the use of two sodium phosphates enemas within a twenty-four hour period, in preparation for flexible sigmoidoscopy, may be harmful. The report also demonstrates that there is no evidence to support the Agency's conclusion that using a single enema for more than three days is associated with adverse events. Finally, there is no evidence to support the conclusion the labeling of sodium

^{1/} The Proposed Rule was originally published in the form of a Tentative Final Monograph (TFM) on January 15, 1985. 50 Fed. Reg. 2124.

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phosphates enemas should instruct users to contact a physician if a enema is retained for more than 30 minutes. Because these conclusions are without scientific support, their codification as regulations would be legally unsupported.

I. BACKGROUND

In the Federal Register of March 21, 1975, FDA published an Advance Notice of Proposed Rulemaking to establish a monograph for OTC laxative, antidiarrheal, emetic and antiemetic drug products. 40 Fed. Reg. 12902. In 1985, the Agency published a Proposed Rule on OTC laxative drug products in the form of a TFM. 50 Fed. Reg. 2124 (January 15, 1985). Included in the TFM are oral and rectal dosage forms of products containing dibasic sodium phosphate and/or monobasic sodium phosphate for laxative purposes and for professional use as a bowel cleanser. The Proposed Rule refers to these products as "sodium phosphates enemas."

On May 21, 1998, FDA published a Final Rule imposing package size limitations and certain warnings and directions for use for oral and rectal sodium phosphates for OTC laxative use. 63 Fed. Reg. 27836. The industry had serious concerns about the content (and procedural validity) of the Final Rule, which were expressed to the Agency during a feedback meeting on July 15, 1998, between FDA and NDMA and other members of industry. At that meeting, the industry suggested new language for the warnings and

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directions for use; the industry believed that the new language would have alleviated the industry's concerns while adequately accomplishing the Agency's objective of warning the public about risks possibly associated with over-use of sodium phosphates enemas. The industry committed to placing the re-worded warning and directions for use on all product labels by December 31, 1998. Agency representatives attending the feedback meeting appeared satisfied with the suggested language and requested that NDMA put the suggestions formally in front of the Agency by submitting a Petition for Reconsideration and a Petition for Stay of Action.

On July 22, 1998, the NDMA task group including the manufacturers of sodium phosphates enemas did submit such petitions. The petitions requested an indefinite stay of those portions of the Final Rule that (1) require a warning on the labels of all enemas containing sodium phosphates reading, "Using more than one enema in 24 hours can be harmful" and (2) require that the directions for use on the labels of such enema products contain a statement reading, "Do not" ("take" or "use") "more unless directed by a doctor."

The petitions also requested that the Commissioner of Food and Drugs reconsider those portions of the rule, and revise them to take into account the product's professional labeling. Specifically, it was requested that the warning be revised to read, "Do not use more than one enema in a 24-hour period unless directed by a doctor", and that the

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instructions for use be revised to read, "Only use recommended dose unless directed by a doctor. See Warnings."

On the same day that FDA published the Final Rule, described above, the Agency also proposed to amend the TFM to add additional general and professional labeling for OTC oral and rectal sodium phosphates laxative products. 63 Fed. Reg. 27887 (hereinafter the "1998 Proposed Rule"). On August 19, 1998, Fleet submitted comments on the 1998 Proposed Rule. Among other things, those comments urged that the proposed labeling for sodium phosphates enemas be revised to remove a proposed three-day limitation on use. As laxatives, sodium phosphates enemas would then be subject to the same general warning requirement that is applicable to all other laxative products, instructing consumers to restrict use that is not medically supervised to seven days. In those comments, Fleet indicated that it would subsequently submit to FDA a report analyzing existing safety information on sodium phosphates enemas. This report is intended to fulfill that commitment.

II. THE SAFETY REPORT

The studies and data summarized in the enclosed report establish that, when a sodium phosphates enema is used according to the labeled dosages and in conformity with labeled contraindications, use of more than one sodium phosphates enema during a twenty-

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four hour period daily or use of a sodium phosphates enema for seven consecutive days is safe.

Section 3 of the report addresses animal studies of hypertonic sodium phosphates enemas. The studies described show that rectal administration of very large volumes of hypertonic sodium phosphate solution followed by forced retention (i.e. conditions resulting in massive sodium phosphate loading of the systemic circulation) can cause severe toxicity, characterized by very high serum phosphate concentrations associated with reciprocal hypocalcemia, hypernatremia, metabolic acidosis, and in some cases, hypokalemia. Electrolyte and metabolic derangements sufficient to cause clinical problems are associated with doses that would be equivalent to tremendous overdosing in humans.

Section 4 of the report addresses studies in humans. Not all of the studies in humans have included systematic monitoring of blood electrolytes and metabolic indices after administration of hypertonic sodium phosphate enemas, and those that did monitor these parameters did not, of course, employ the massive doses or the forced retention of enema fluid seen in the animal studies. The human studies nevertheless demonstrate that in persons without contraindicating conditions (and even in elderly persons with decreased creatinine clearance), use of sodium phosphates enemas at the recommended dose, or even higher doses than recommended, results in only small, clinically inconsequential

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movements of fluid into (or out of) the colon; some absorption of sodium; rapid development of small, transient increases in serum phosphate; slower and inconsistent development of decreases in serum calcium concentration and no evidence of significant hypernatremia, hypokalemia or acidosis.

The studies in animals and humans that included systematic monitoring of blood concentrations of the ionic constituents of hypertonic sodium phosphate enemas show that phosphate and sodium are absorbed, but that only relatively small, transient increases in serum phosphate concentration and smaller, reciprocal decreases in serum calcium concentration can be documented, even with large overdoses of these enemas in elderly patients with compromised renal function. Maximum increases in serum phosphate concentration and decreases in serum calcium concentration seen in two studies of oral administration of hypertonic sodium phosphate were, in fact, substantially greater than those seen after recommended doses of hypertonic sodium phosphate administered as an enema.

Results of small clinical trials of effectiveness and tolerability reviewed in Section 4 of the report do not show any evidence of significant adverse effects associated with hypertonic sodium phosphate enemas. Hence, they provide no basis for characterizing the

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presentation of such adverse events, and they are of limited utility in estimating the risk or potential severity of such events.

Finally, reports of adverse events associated with hypertonic sodium phosphate enemas in the published literature and those included in the spontaneous reporting databases maintained by Fleet, FDA, and Poison Control Centers have been summarized and analyzed in Section 4 of the report. These cases make clear that adverse events are almost always associated with overdosing or with use in patients with contraindicating conditions, or both. Thus, although a toxic syndrome can be associated with hypertonic sodium phosphate enemas, the syndrome appears to be caused primarily by absorption of too much phosphate caused by extreme overdose or by enema retention associated with physiological abnormality, where use of these enemas is contraindicated. In any case, the syndrome, even when the possibility of under-reporting is considered, is very rare and is almost never seen in healthy subjects. Fleet® enemas are currently labeled appropriately to address the risks described.

As described in Dr. Garvey's report, almost all of the reports of adverse events associated with the use of sodium phosphates enemas (other than nozzle-related injuries or adverse outcomes associated with misuse of these enemas by administration to patients with contra-indicating conditions) occurred either in young children (children under the age

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of five) or in the elderly. Because of the concerns as to the dosing for children raised in Dr. Garvey's report, Fleet is changing the labeling of its sodium phosphates enema for children to recommend that only one-half of the currently recommended dose be given to children two years of age up to under age five. The labeling will also continue to warn against use in children under the age of two. Fleet urges FDA to amend the Proposed Monograph to require that the labeling of *all* sodium phosphates enema products limit the recommended dose for children two years of age up to under age five to one-half of the dose for older children and to proscribe use of sodium phosphates enemas in children under the age of two.

For adult sodium phosphates enema products, Fleet urges FDA to amend the Proposed Monograph to require (1) that consumer directed labeling instruct that sodium phosphates enemas should not be used by patients on sodium-restricted diets and (2) that professional use warnings include warnings against using the product in patients with bowel obstruction, or congestive heart failure, and to advise use with extreme caution in patients with impaired renal function, patients with pre-existing electrolyte disturbances and patients using diuretics or other medications that may affect electrolyte levels.^{2/}

^{2/} In the preamble to the Proposed Rule, FDA took the position that "[p]rofessional labeling . . . should not appear on the retail package." 63 Fed. Reg. 27886, 27888 (May 21, 1998). Fleet is unaware of any prohibition in the Federal Food, Drug, and Cosmetic

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Reports of toxicity in children and the elderly virtually all involve patients who were administered the product at the direction of, and under supervision of, medical personnel, and Fleet believes that the proposed labeling changes will be sufficient to address the problem. Fleet is not aware of any reason for believing that revising labeling requirements either (1) to require warnings against use of two enemas within 24 hours or the use of daily enemas for more than three consecutive days "without asking a doctor" or (2) to instruct users to obtain medical help if an enema is retained for more than 30 minutes would result in any significant reduction in toxicity associated with use of the enemas in either adults or children. There is nothing in Dr. Garvey's report or in the literature to support such restrictions.

III. CONCLUSION

The Final Rule is seriously flawed because the new warnings and directions for use that the Rule impose are unsupported either by the information in the administrative record or by the scientific literature cited in support of these requirements.

Act or in any regulation that prohibits putting professional labeling directly on the package of an OTC product. Furthermore, Fleet's experience shows a dramatic reduction in the number of reported adverse events since 1987, when the company began placing professional warnings directly on the OTC label. See Summary of Published Reports attached at Tab A. For these reasons, Fleet believes that it is in the public interest for professional labeling, including warnings, to appear on the OTC labeling of sodium phosphates enemas.

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Based on the information submitted earlier and the enclosed analysis of existing safety data regarding the use of sodium phosphates enemas, Fleet again urges the Agency to reconsider those portions of the Final Rule that (1) require a warning on the labels of all rectal enemas containing sodium phosphates reading, "Using more than one enema in 24 hours can be harmful" and (2) require that the directions for use on the labels of such enema products contain a statement reading, "Do not" ("take" or "use") "more unless directed by a doctor". Fleet believes reconsideration is both legally required and scientifically appropriate. **Specifically, the warning should be revised to *eliminate* the statement regarding use of more than one enema in 24 hours.^{3/} Instead, the warning should read, simply, "Serious side effects may occur from excess dosage." The instructions for use should be revised to read, "Use recommended dose unless otherwise directed by a doctor."**

^{3/} In NDMA's July 1998 petitions, NDMA urged, with Fleet's concurrence, that the warning be revised to read, "Do not use more than one enema in a 24-hour period unless directed by a doctor. Serious side effects may occur from excess dosage" and that the instructions for use be revised to read, "Only use recommended dose unless directed by a doctor. See Warnings." However, Dr. Garvey's report now makes clear that the warning about using more than one enema in a 24 hour period is without scientific basis. Given FDA's long-standing and sound policy that warnings should be "scientifically documented" and "clinically significant", see 50 Fed. Reg. 54750, 54654 (December 3, 1982) and 53 Fed. Reg. 46204, 46213 (November 16, 1988), Fleet now believes that the warning must be deleted rather than revised.

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In addition, Fleet believes that the Proposed Rule, when finalized, should be revised because the Agency's proposed limitation of consecutive single daily use to three rather than seven days is also unsupported by the record or by the scientific literature. Fleet requests that the final laxative rule, when published, be amended as set forth in the company's comments of August 19, 1998.

Further, Fleet urges FDA to amend the Proposed Monograph to require that the labeling of all sodium phosphates enema products limit the recommended dose for children under the age of five, but over the age of two, to one-half of the dose for older children and to proscribe use of sodium phosphates enemas in children under the age of two. The Proposed Monograph should also be amended to require (1) that consumer directed labeling on adult dosage forms instruct that sodium phosphates enemas should not be used by patients on sodium-restricted diets and (2) that professional use warnings include warnings against using the product in patients with bowel obstruction, or congestive heart failure, and to advise use with extreme caution in patients with impaired renal function, patients with pre-existing electrolyte disturbances and patients using diuretics or other medications that may affect electrolyte levels.

Finally, Fleet urges FDA to reconsider the requirement in the Proposed Rule that the directions for use on the labels of such enema products instruct the user to contact a

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physician if the enema is retained for more than 30 minutes. **Specifically, Fleet believes that the instruction for users to contact a physician if the enema is retained for more than 30 minutes must be deleted because this instruction is lacking a scientific basis.**

It is well-settled principle of administrative law that agency decision-making must be rational in order to satisfy the requirements of the Administrative Procedure Act that agency action not be arbitrary and capricious. 5 U.S.C. § 706(2)(a). An “agency must examine the relevant data and articulate a satisfactory explanation for its action.” *Motor Vehicle Manufacturers Ass’n v. State Farm Mutual Automobile Insur. Co.*, 463 U.S. 29, 43 (1983). Although substantial deference is to be accorded to an agency decision, particularly where the administrative action is based on the expertise of the agency, a reviewing court will nevertheless conduct a “searching and careful” review of the record in order to “ensure that the agency’s decision was the product of reasoned decisionmaking based upon consideration of relevant factors.” *Abbott Laboratories v. Young*, 691 F. Supp. 462 (D.D.C. 1998), citing *Motor Vehicle Manufacturers Ass’n v. EPA*, 768 F.2d 385 n.5 (D.C. Cir 1985). See also *Small Refiner Lead Phase-Down Task Force v. EPA*, 705 F.2d 506 (D.C. Cir. 1983), *Natural Resources Defense Council, Inc. v. S.E.C.*, 606 F.2d 1031, 1039 (D.C. Cir. 1979).

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Because the Agency's actions with regard to the labeling of OTC sodium phosphates enema laxatives are not supported by science, they do not meet the basic legal requirement that agency decision-making be rational and fair. Fleet does not believe, therefore, that they would be sustainable on legal challenge, and the company urges the Agency to reconsider the relevant portions of the Final Rule and the 1998 Proposed Rule.

We thank you for your attention to this matter.

Sincerely,



Peter S. Reichertz
Naomi Joy Levan Halpern
Counsel to C. B. Fleet Company, Incorporated

ENCLOSURE