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January 19, 2004

VIA FEDERAL EXPRESS

Division of Dockets Management
(HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

Re: Laxative Drug Products for Over-the Counter Human Use; Reopening of the
Administrative Records
DOCKET 1978N-036L

Dear Sir/Madam:

We represent C.B. Fleet Company, Incorporated, of Lynchburg, Virginia 24502 ("Fleet"). Fleet is the manufacturer and distributor of a number of Over-the-Counter ("OTC") laxative drug products for human use, including Fleet® Enemas (both Sodium Phosphates and Mineral Oil), Fleet® Phospho-soda® (Sodium Phosphates Oral Solution, USP), Fleet® Glycerin Suppositories, Fleet® Bisacodyl laxatives (enema, suppositories, and tablets) and Fleet® bowel preparation kits. On behalf of Fleet, we hereby submit additional data in response to the reopening of the administrative record on OTC Laxative Drug Products for Human Use, in response to the notice dated October 22, 2003, at 68 Fed. Reg. 60302 ("the Notice").

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1. Enemas Containing Bisacodyl Should Be Found Generally Recognized as Safe and Effective and Included in Final Monograph on OTC Laxative Drug Products.

The Agency listed in Table 2 of the Notice a number of Citizen Petitions it had acted upon for which it sought no further comment. It did not list its response to Fleet's Citizen Petition (CP0007), dated November 12, 1987, requesting that Proposed 21 C.F.R. § 334.60(d) be amended to include an enema dosage form of bisacodyl, and conforming amendments to reflect the inclusion of that dosage form into the Final Monograph on Laxative Drug Products for Over-the-Counter Human Use ("Final Monograph").

On October 26, 1989, the Agency responded by letter (Exhibit A) from William E. Gilbertson, Pharm. D., Director, Division of OTC Drug Evaluation, Office of Drug Standards, Center for Drug Evaluation and Research, indicating that:

Based on the above, we plan to recommend to the Commissioner that proposed 21 C.F.R. 334.60(c)(1)(ii) be changed to read "Rectal dosage forms" from the currently proposed "Rectal suppository dosage forms," and that the following be added to proposed 21 C.F.R. 334.60(d)(2):

Rectal enema dosage: Adults and children 12 years of age and over: 10 milligrams bisacodyl in 37.5 milliliters of aqueous suspension in a single daily dose. Children under 12 years of age: Consult a doctor.

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The Division of OTC Drug Evaluation intends to recommend to the Commissioner that the agency respond to your petition 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 the post-evacuant claims for bisacodyl enema, as well as for use as a laxative in children under 12 years of age.

Since the Agency's action on that Petition was not listed in Table 2 of the Notice, Fleet hereby incorporates that Petition and the Agency's response by reference, and requests that this dosage form of bisacodyl be included in the Final Monograph when published, as the Agency has already acted upon this request and found this dosage form of bisacodyl to be generally recognized as safe and effective. Please note that Fleet has no knowledge of any studies published since the Agency's response addressing the safety and/or effectiveness of enemas containing bisacodyl, except as noted in Comment 3 hereafter. Please note the Agency confirmed its October 26, 1989, decision, following withdrawing it due to concerns about the safety of bisacodyl, in a letter dated January 16, 2001, from Linda M. Katz, M.D., M.P.H., Deputy Director, Division of OTC Drug Products, Office of Drug Evaluation V, Center for Drug Evaluation and Research responding to Fleet's Petition for Reconsideration dated March 17, 2000 (Comment PRC2). See Exhibit B.

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2. The Response Time for Rectally Administered Stimulant Laxative Products in an Enema Dosage Form Should be 5 to 20 Minutes

Table 2 of the Notice also did not list the Agency's action in response to Fleet's Citizen Petition (CP0010) dated April 22, 1991. In that Petition, Fleet requested that the response time for enema dosage forms of stimulant laxative products be listed separately from response times of rectal suppositories and that the response time for enema dosage forms of those laxatives (bisacodyl) should be 5 to 20 minutes.

On July 23, 1991, the Agency responded by letter (Exhibit C) from William E. Gilbertson, Pharm. D., Director, Division of OTC Drug Evaluation, Office of Drug Standards, Center for Drug Evaluation and Research, indicating that:

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.

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Since the Agency's action on that Petition was not listed in Table 2 of the Notice, Fleet incorporates that Petition and the Agency's response by reference, and requests that the Final Monograph include, as requested, separate time-to-response statements in 21 C.F.R. §334.60(b)(2) for suppositories (1/4 to 1 hour) and enemas (5 to 20 minutes) dosage forms of stimulant laxatives. Please note that Fleet has no knowledge of any studies since the Agency's response addressing the difference in response time for enemas and suppository dosage forms of bisacodyl laxatives.

3. Bowel Cleansing Systems Containing Sodium Phosphates Oral Solution, Bisacodyl Tablets and either a Bisacodyl Enema or Suppository Should Be Found Generally Recognized As Safe and Effective and Included in the Final Monograph.

Table 2 of the Notice also did not list the Agency's action in response to Fleet's Petition dated November 12, 1987 (CP0008) requesting that certain bowel cleansing systems consisting of Sodium Phosphates Oral Solution, Bisacodyl Tablets and either a Bisacodyl Enema or Suppository in sequential administration be found generally recognized as safe and effective and be included in the Final Monograph.

On October 26, 1989, the Agency responded by letter (Exhibit D) from William E. Gilbertson, Pharm D., Director, Division of OTC Drug Evaluation, Office of Drug Standards, Center for Drug Evaluation and Research including that Fleet Prep Kits 1 and 3 would be recommended for inclusion in the Final Monograph. He stated that:

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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 laxatives 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 laxatives 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)

Since the Agency's action on that Petition was not listed in Table 2 of the Notice, Fleet incorporates that Petition and the Agency's response by reference, and requests that these bowel cleansing systems be found generally recognized as safe and effective and included in the Final Monograph. Please note the Agency confirmed its decision, following withdrawing it due to concerns about the safety of bisacodyl, in a letter dated January 16, 2001, from Linda M. Katz, M.D., M.P.H., Deputy Director, Division of OTC Drug Products, Office of Drug Evaluation V, Center for Drug Evaluation and Research responding to Fleet's Petition for Reconsideration dated March 17, 2000 (Comment PRC2). (Exhibit B).

Please note that Fleet has no knowledge of any published studies or other information relating to the safety and effectiveness of either bowel cleansing kit listed above, except as follows.

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The safety and effectiveness of the prep kit containing a bisacodyl suppository as a final cleansing step was compared to use of a polyethylene glycol ("PEG") lavage (GoLyteLy®, Braintree Laboratories, Inc.) by Macari, et al. See Macari, M. et. al.: Effect of Different Bowel Preparations on Residual Fluid at CT Colonography. Radiology 218(1); 274-277 (January 2001). In this study, they found that use of the Fleet Prep Kit resulted in significantly less fluid than the PEG lavage and that it was safe and effective for colonography. See Exhibit E.

The safety and effectiveness of the prep kit containing the bisacodyl enema as the final cleansing step was compared to use of a PEG lavage by Hookey, et. al. The results of this study have not been formally published, but attached as Exhibit F is a poster presentation on the study which was entitled "A Prospective, Randomized, Controlled Trial Comparing One Bottle of Oral Sodium Phosphate and Stimulant Laxatives with Large Volume Polyethylene Glycol for Colon Cleansing." They concluded that the Fleet prep kit was as efficacious and safe as the PEG lavage and was significantly better tolerated. Only one adverse event from the prep kit was reported - one patient expressed dizziness, lightheadedness, attributed to a possible vasovagal reaction.

Both of these studies support the safety and effectiveness of these bowel cleansing kits, and Fleet requests their inclusion in the Final Monograph as previously requested by Fleet and recommended by the Agency.

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4. Bowel Cleansing Systems Consisting of Two 30 mL or 45 mL Doses of Sodium Phosphates Oral Solution Administered 10-12 Hours Apart Should be Found to be Generally Recognized as Safe and Effective and Included in the Final Monograph.

Table 2 of the Notice did list the Agency's denial of Fleet's Citizen Petition requesting the inclusion of a bowel cleansing system (and professional labeling) for the use of two 45 mL doses of Sodium Phosphates Oral Solution administered 10-12 hours apart by letter dated March 4, 1996. (Exhibit G). Please note that Fleet submitted data in response to the denial of that Citizen Petition on June 25, 2003 (CP28), requesting that dosing, as well as dosing of two 30 mL doses, administered 10-12 hours apart, be included in professional labeling in the Final Monograph for bowel cleansing purposes prior to diagnostic procedures such as colonoscopy or x-ray, and prior to surgery.

Fleet incorporates that Petition by reference and requests that the Agency find that product with such professional labeling to be generally recognized as safe and effective for professional labeling use and included in the Final Monograph when published.

As indicated, Fleet has submitted data requesting professional labeling for this dosing. Fleet believes that, for patient convenience and for compliance and safety associated therewith, the Agency should provide for the use of a bowel cleansing kit consistent with this labeling in the Final Monograph. If the professional labeling requested in CP28 is granted as Fleet believes it should be, this kit would be consistent with the professional labeling, with the only difference

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being the possible inclusion of anesthetic pads to treat anal irritation that is associated with use of purgative dose of laxative such as Sodium Phosphates Oral Solution. The pads are added again solely for patient convenience, and do not affect the safety or effectiveness of the system as they are externally applied. Fleet requests that such a bowel cleansing system, consistent with professional labeling to be added to the Final Monograph per CP28, be found generally recognized a safe and effective and included in the Final Monograph.

Based on the data submitted, Fleet requests that Proposed 21 C.F.R. §334.32 be amended to include a bowel cleansing system as follows:

A kit containing the following laxative drug products for sequential administration: 30 or 45 mL of Sodium Phosphates Oral Solution in two doses to be administered 10-12 hours apart, and with the second dose administered at least 3 hours before the scheduled x-ray or examination, with or without anesthetic pads containing pramoxine hydrochloride 1% and glycerin 12% meeting the requirements of 21 C.F.R. § 346 for treatment of associated anal irritation.

5. The Laxative Dose of Sodium Phosphates Oral Solution, USP, Should Be Limited to 10-20 mL.

The Tentative Final Monograph on Laxative Drug Products for Over-the-Counter Human Use, ("Tentative Final Monograph") currently provides for the use of approximately 20 to 45 mL (4 to 9 teaspoons) of Sodium Phosphates Oral Solution for use as a laxative. See proposed 21 C.F.R. §334.58(d)(5)(i), 50 Fed. Reg. 2154 (January 15, 1985). In investigating matters to be addressed

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during the reopening of the administrative record, Fleet reviewed the issue of the laxative dose of Sodium Phosphates Oral Solution, *USP*. What Fleet found is as follows.

In response to the call for data from the FDA, Fleet submitted data on its Sodium Phosphates Oral Solution product Fleet® Phospho-soda® on May 8, 1973. See C090011. Included in that submission was labeling for Fleet® Phospho-soda® which is Sodium Phosphates Oral Solution. See Exhibit H. That labeling indicates that 4 teaspoonfuls was the most effective laxative dose; other labeling submitted demonstrated the product was recommended as a laxative at “two to four teaspoonfuls.” (It was recommended as a **purgative** at 4 to 8 teaspoonfuls).

Fleet has reviewed its records and FDA records about the issue of the laxative dose of this ingredient and can find no document describing why and how the laxative dosing changed from 2 to 4 teaspoonfuls to 4 to 9. There is nothing in this docket. There is only one mention of dosing of the product in the minutes of the OTC Advisory Review Panel on Laxatives, Antidiarrheals, Antiemetics, and Emetic Drug Products. In that document, the dosage is listed as 4-8 grams with a comment that: “The dose of each compound relate to the weight of hydration, but there is insufficient data to define the range of dosage.” (Exhibit I). Without any further discussion of the issue on the record it is difficult, if not impossible, to determine why the dosing arrived at was 4 to 9 teaspoonfuls, not 2 to 9. Fleet has evidence going back to at least 1963 that 2 to 4 teaspoonfuls were the appropriate laxative dose. (Exhibit J).

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It thus appears possible that the change was due to inadvertence or mistake. Given the historical use of 2-4 teaspoonfuls of the Sodium Phosphate Oral Solution, as well as safety issues, Fleet believes it is appropriate that the **laxative** dose of the product be limited to 2 to 4 teaspoonfuls, or 10 to 20 mL, or at a minimum and in the alternative, that the **laxative** dose of the ingredient be limited to 20 mL, or 4 teaspoonfuls, of Sodium Phosphates Oral Solution, *USP*.

While Fleet believes that dosages above 20 mL are safe and effective, Fleet believes that above 20 mL the product has more of a purgative effect appropriate for bowel cleansing prior to medical procedures, but inappropriate for relief of occasional constipation. The product at dosages above 20 mL certainly relieves constipation, and is effective and appropriate for bowel cleansing (as demonstrated in CP28 and conceded in FDA's letter of March 1, 1996), but Fleet believes such dosage is not appropriate for strictly laxative use. Fleet, therefore, requests that Final Monograph provide that the laxative dosage of Sodium Phosphates Oral Solution, *USP*, be 10 to 20 mL, or, in the alternative, 20 mL.

6. The Suggested Dose Range for Sodium Phosphates Oral Solution in the Tentative Final Monograph Should Be Made Consistent with the *United States Pharmacopeia*.

The Tentative Final Monograph currently provides the following for the dose ranges for oral dibasic sodium phosphates/sodium biphosphates products:

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(5) For products containing sodium phosphate/sodium biphosphate identified in § 334.16(d) marketed as a solution - (i) Oral dosage. Adults and children 12 years of age and over; oral dosage is sodium phosphate 3.42 to 7.56 grams, and sodium biphosphate 9.1 to 20.2 grams in a single daily dose. Children 10 to under 12 years of age: oral dosage is sodium phosphate 1.71 to 3.78 grams and sodium biphosphate 4.5 to 10.1 grams in a single daily dose. Children 5 to under 10 years of age: oral dosage is sodium phosphate 0.86 to 1.89 grams and sodium biphosphate 2.2 to 5.05 grams in a single daily dose. Children under 5 years of age: consult a doctor.

Proposed 21 C.F.R. §334.58(d)(5), 50 Fed. Reg. 2155 (January 15, 1985).

Please note that these dosage ranges were proposed before the *USP* monograph for this product was adopted. They are inconsistent with the *United States Pharmacopeia XXVI* (Exhibit K), which provides that the ranges of the ingredients per 100 mL in the Oral Solution Product are:

Dibasic sodium phosphate 16.2 to 19.8 grams

Monobasic sodium phosphate 43.2 to 52.8 grams

which would be, in 45 mL:

Dibasic sodium phosphate 7.29 to 8.91 grams

Monobasic sodium phosphate 19.44 to 23.76 grams

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In order to maintain consistency between the *USP* and the Final Monograph, as well as to reflect the formulation marketed since 1869, Fleet requests that, assuming that the Agency agrees with the proposal in Comment 5 above, that the dose ranges be set at:

(5) For products containing dibasic sodium phosphate/monobasic sodium phosphate identified in § 334.16(d) marketed as a solution -
(i) Oral dosage. Adults and children 12 years of age and over; oral dosage is dibasic sodium phosphate 1.8 to 3.6 grams (10 to 20mL) and monobasic sodium phosphate 4.8 to 9.6 grams (10 to 20mL) in a single daily dose, or 3.6 to 8.1 grams (20 to 45mL) and monobasic sodium phosphate 9.6 to 21.6 grams (20 to 45mL) in a single daily dose. Children 10 to under 12 years of age: oral dosage is dibasic sodium phosphate 1.8 to 3.6 grams (10mL to 20 mL) and monobasic sodium phosphate 4.8 to 9.6 grams (10 to 20mL) in a single daily dose. Children 5 to under 10 years of age: oral dosage is dibasic sodium phosphate 0.9 to 1.8 grams (5 to 10mL) and monobasic sodium phosphate 2.4 to 4.8 grams (5 to 10mL) in a single daily dose. Children under 5 years of age: **Do not use.**

These dose ranges reflect the currently marketed product which is the subject of all clinical testing of Sodium Phosphates Oral Solution, which are set at the midpoints of the *USP* ranges.

Therefore, for consistency with the *USP* and testing of the products, Fleet requests that the dose ranges for oral dibasic sodium phosphate/monobasic sodium phosphate products be amended as requested when the Final Monograph is published.

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7. The Directions for Use for Sodium Phosphates Oral Solution Should Be Revised to Provide that the Product Should Not Be Used in Children Under Five Years of Age

At present, the Tentative Final Monograph provides that Sodium Phosphates Oral Solution should only be used in children under five years of age when a doctor is consulted. See Proposed 21 C.F.R. § 334.58(d)(5), 50 Fed. Reg. 2155 (January 15, 1985). Fleet requests that this be revised, as indicated in Comment 6 above, to:

Children under 5 years of age: **Do not use**

Please note that Fleet implemented this change beginning in July 2003, on packaging and in professional use labeling.

Fleet requests this change because it has evaluated the safety associated with use of this product in this population and does not believe the product can be safely used in this population. Most of the adverse events associated with use of this product involve overdosages, and the effect of an overdose in children under 5 years of age can be quite serious, if not fatal. To avoid the possibility of such overdosages, and since there are other more appropriate laxative products available for use in this population such as glycerin, Fleet believes it should be prominently stated on the directions that the products **should not be used in children under five years of age.**

Please note that the proposed Professional Labeling Fleet submitted in CP28 contained the Professional Use Warning:

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Do not use in patients with megacolon, gastrointestinal obstruction, ascites, congestive heart failure, kidney disease or in children under 5 years of age.

See Exhibit O of CP28. Fleet believes these changes are necessary to prevent the possibility of overdoses and their consequences in this population.

- 8. The Warning “Ask a doctor or pharmacist before use if you are taking any other drug. Take this product 2 or more hours before or after other drugs. Laxatives may affect how other drugs work.” Should Not Apply to Rectally Administered Laxatives.**

On March 28, 1996, the Procter & Gamble Company (“P&G”) submitted a Citizen Petition (CP22) requesting that the Agency reopen the administrative record for laxative drug products to include the statement “Laxatives may affect how well other medicines work. If you are taking a prescription medicine by mouth, take this product at least 2 hours before or 2 hours after the prescribed medicine.” By letter dated November 6, 2000, (Exhibit L), the Agency responded and indicated it would recommend the following warning be included in the Final Monograph:

“Ask a doctor or pharmacist before use if you are taking any other drug. Take this product 2 or more hours before or after other drugs. Laxatives may affect how other drugs work.”

The studies and other information supplied by P&G all reflect information on the effect of orally administered laxative drug products and possible drug interactions with other orally administered products. The statement itself is premised on the effect on oral medications. The rationale for the warning - that they affect gastrointestinal motility, and hence, the bioavailability of co-

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administered **oral** medications - is simply not applicable or substantiated for laxative drug products administered rectally. There is no evidence that rectally administered laxatives such as glycerin, mineral oil, dibasic sodium phosphates/monobasic sodium phosphates, bisacodyl or any other rectally administered laxative affect the bioavailability of concomitant medications. There is no such evidence in the scientific literature for these forms of products, nor does Fleet have any adverse event or other data indicating there is any interaction between rectally administered laxatives and other drug products, or that they have any affect on their bioavailability.

In the absence of such evidence, Fleet believes it is not appropriate to add such a warning for these products in the Final Monograph. St. James Hospital v. Heckler 760 F.2d. 1460 (7th Cir. 1985), invalidating an HHS rule for lack of substantial evidence to support the rule, and finding it arbitrary and capricious under 5 U.S.C. §553.

Fleet does not object to the proposed warning provided it is limited to laxatives taken by mouth. It proposes that the last sentence of the proposed warning read:

Laxatives taken by mouth may affect how other drugs work.

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CERTIFICATION

The undersigned certifies that, to the best knowledge and belief of the undersigned, this submission includes all information and views on which this submission relies, and includes representative data and information known to the submitter which are unfavorable to the submission.

Respectfully Submitted

SONNENSCHN NATH & ROSENTHAL LLP

By:



Peter S. Reichertz
Counsel for C.B. Fleet Company, Incorporated