



**Pharmaceutical
Company, Inc.**

January 13, 2003

VIA EXPRESS COURIER

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

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Re: Comments on the Citizen Petition Requesting that FDA Modify the Tentative Final Monograph on Laxative Drug Products for Over-the Counter Human Use Submitted by Peter S. Reichertz on behalf of the C.B. Fleet Company, Inc., dated June 25, 2003, and Additional Comments on the Tentative Final Monograph (Docket No. 78N-036L)

These comments, filed under 21 C.F.R. Part 10, are submitted on behalf of InKine Pharmaceutical Company, Inc. (InKine) in response to FDA's reopening of the administrative record until January 20, 2004 for the OTC laxative rulemaking. 68 Fed. Reg. 60303 (October 22, 2003). More specifically, these comments are submitted in regard to the above-referenced Citizen Petition submitted on behalf of the C.B. Fleet Company, Inc. ("C.B. Fleet" or "Fleet"), which seeks to change the OTC laxative drugs Tentative Final Monograph (TFM) to include professional labeling for "2 x 30 mL to 2 x 45 mL dosing of sodium phosphates oral solution, administered 10-12 hours apart." InKine respectfully requests that FDA reject the changes proposed in the C.B. Fleet Citizen Petition. On balance, we believe that the data demonstrate that sodium phosphates oral solution should be subject to prescription control when indicated for colon cleansing. As an alternative to prescription status for sodium phosphates oral solution when it is indicated for colon cleansing, we suggest that FDA modify the provision in the TFM regarding professional labeling of sodium phosphates oral solution products to limit the OTC colon cleansing indication for this product to situations where sodium phosphates oral solution is part of bowel cleansing kit and is administered at a total dose of no more than 7.56 g sodium phosphate and 20.2 g sodium biphosphate, as described below.

78N-036L

C 208

FDA should note that the safety information discussed in these comments and the arguments raised here are new information that was not raised by Braintree Laboratories in its Citizen Petition of August 23, 2000 regarding the OTC status of sodium phosphates oral solution. In fact, at the time that Petition was submitted, Visicol Tablets, InKine's sodium phosphate tablet product, had not yet been approved for marketing by FDA. Thus, this information has never before been considered by FDA in connection with the OTC status of sodium phosphates oral solution. The fact that FDA rejected Braintree's Petition should not influence FDA's consideration of these comments.

InKine is the manufacturer of Visicol Tablets (sodium phosphate monobasic monohydrate, USP and sodium phosphate dibasic anhydrous, USP)¹, a prescription product marketed in the U.S. under NDA 21-097 for cleansing of the bowel as a preparation for colonoscopy, in adults 18 years of age or older.

A. Action Requested

InKine respectfully requests that FDA:

- Reject all actions requested in the Citizen Petition on behalf of C.B. Fleet dated June 25 and submitted to Docket No. 78N-036L by Peter S. Reichertz, counsel for C.B. Fleet; and
- Take one of the following two (mutually exclusive) actions with respect to proposed 21 C.F.R. § 334.80(a)(2), the provision in the laxative drugs TFM dealing with professional labeling of certain laxative products:
 - Delete the following phrase: "*For products containing sodium phosphate/sodium biphosphate identified in § 334.16(d)*,". This would have the effect of eliminating the OTC colon cleansing indication for sodium phosphates oral solution.
 - Immediately after the phrase "*For products containing sodium phosphate/sodium biphosphate identified in § 334.16(d)*", insert the following: "*when used at a dose not exceeding 7.56 g sodium phosphate and 20.2 g sodium biphosphate as part of a bowel cleansing system defined in § 334.32*". This would have the effect of limiting the OTC bowel cleansing indication for sodium phosphates oral solution to the situation described in the added text.

B. Statement of Grounds

1. **The benefits of OTC availability of sodium phosphates oral solution for use as a colon cleansing agent do not outweigh the risks of access without a prescription**

¹ "Sodium phosphate monobasic" is the USP term equivalent to the monograph term "sodium biphosphate," and "sodium phosphate dibasic" is the USP term equivalent to the monograph term "sodium phosphate."

The typical over the counter (OTC) drug is one with a favorable risk benefit profile with labeling that can be understood by the lay public that is used for a disease or condition that can be self-diagnosed and self-treated by patients. Thus, the medical aspects of a drug's indication play an important role in determining whether a drug should be marketed OTC. Typical OTC indications include occasional constipation, heartburn, rhinitis, headache, and other minor aches and pains. Experience has shown that in many cases, patients can manage these conditions without a physician's intervention, and thus benefit from the convenient availability of OTC medications.

However, bowel cleansing prior to colonoscopy is unlike these other indications. Colonoscopy is a diagnostic and sometimes therapeutic procedure that is performed by a physician with specialized training, usually with the patient sedated; it is not performed by the patient. The procedure is performed in a colonoscopy suite, generally with an intravenous line inserted and the patient's vital signs electronically monitored. After the procedure, the patient is generally taken to an anesthesia recovery area until he/she is able to leave the area. The patient is generally warned not to drive home from the procedure because of residual effects of the sedation.

Most importantly, elective colonoscopy procedures (the overwhelming majority of procedures) are always scheduled in advance. Accordingly, there is always communication between the patient and the physician's office prior to the procedure, allowing for a prescription to be provided to the patient or called in to a pharmacy with no additional need to contact the physician's office.

Thus, the patient derives no benefit from having a colon cleansing agent available OTC for elective procedures. In the case of emergency procedures in patients who have not contacted a physician before arriving at a physician's office or ER, which are rare, the number of patients who actually have the foresight to purchase and use an OTC colon cleansing product prior to seeing a physician is virtually, if not actually, zero. Again, there is no benefit to the patient in having colon cleansing agents available OTC.

Indeed, most physicians performing colonoscopy already provide patients with detailed written instructions regarding pre-procedure dietary restrictions and prep dosing. It would be a trivial matter to provide a prescription as well, and most physicians already do.

The above facts should be important to FDA in considering OTC status for a colon cleansing indication for any drug. The essence of FDA's consideration of OTC vs. prescription status was recently summarized by Dr. R. William Soller, Senior Vice President and Director of Science & Technology for the Consumer Healthcare Products Association, as follows.

“Based on this framework, the compulsory benefit/risk assessment integrates safety, effectiveness and labeling within the question: **Is the benefit of self-care**

**through OTC availability worth the risk of access without a prescription?”
(emphasis added)²**

Dr. Soller's organization represents the companies that market OTC drugs, and one would expect him to formulate a standard for determining OTC status that is at least as permissive as the one typically used at FDA. This suggests that any drug product that fails to meet the test formulated by Dr. Soller is a very poor choice for OTC status. Significantly, the answer to Dr. Soller's question in the case of Phospho-Soda's indication for use in bowel cleansing is clearly "No," demonstrating that a drug for colon cleansing is not a good candidate for OTC marketing. As discussed above, there is no additional benefit for "self-care" in this setting because in every case, the patient will have contact with a physician's office or endoscopy center prior to her colonoscopy (as well as before any colonic x-ray exam or any elective surgery procedure). Thus there is no offset for any added "risk of access without a prescription" in this setting. This added risk is not trivial due to the various fluid and electrolyte abnormalities and their sequelae that have been reported with the use of sodium phosphate colon cleansing agents at doses above 30 g.

The fact that the Citizen Petition by C.B. Fleet and these comments concern professional labeling (as opposed to consumer labeling) should not affect how FDA assesses the risks and benefits of OTC status for the colon cleansing indication for sodium phosphates oral solution. Despite the new precautions proposed by C.B. Fleet for the professional labeling of sodium phosphates oral solution, the product would still be available over the counter for purchase and use by any person. The important controls of prescription drug dispensing (with the frequent use by pharmacies of computerized recognition of hazardous co-medications and co-morbid conditions) would not apply. The perception that the product has the benign safety profile of other OTC products would not change; in fact, the new dosing instructions proposed by C.B. Fleet are less restrictive than the current ones mandated by FDA, a fact that would surely be noted by physicians. Promotion of the product would still be regulated by the FTC, not by FDA. There would still be no requirement to report adverse events to FDA. The monograph process would still make it difficult for FDA to effect changes in adverse event information in labeling or to once again change dosing recommendations if that were deemed to be appropriate. In short, all the issues inherent in OTC distribution and control of labeling and promotion are just as relevant to a drug with both professional and consumer labeling as one with just consumer labeling. These issues are discussed further below.

Sodium phosphate at the dose suggested by Fleet has the safety profile of a prescription drug

Sodium phosphate has been marketed as a laxative for over 100 years. It has been used extensively as a bowel cleansing agent prior to colonoscopy since about 1990, when a paper by Vanner et. al. indicated that a dose of about 60 grams of sodium phosphates

² Remarks of R. William Soller, FDA open public hearing regarding the regulation of OTC drug products. June 28,2000.

solution (45 mL of Fleet ® Phospho-Soda® given twice) was effective for colon cleansing in this setting.³

The recent safety review of sodium phosphate for use in colon cleansing by Hookey, Depew, and Vanner, indicates that sodium phosphate has a steep dose response for adverse events.⁴ Medically important adverse events appear to be rare when sodium phosphates oral solution is given to adults at its currently labeled maximum dose (no more than 45 mL (about 30 g) in a 24 hour period, consistent with its status as an OTC product. However, the risk of adverse events is higher when about 60 g, the dose shown to be effective in the study performed by Fleet, is given in a roughly 12 hour window, and appears to escalate rapidly with even higher doses or very short intervals between the two 30 g doses that are usually given (i.e., intervals less than about 5 hours.) This dose response relationship formed the basis of FDA's 1998 Federal Register notice imposing the current 45 mL maximum dose in a 24 hour period in the OTC labeling of Phospho-Soda.⁵

Electrolyte abnormalities with sodium phosphate

Use of sodium phosphate at a dose of 60 g, given in two divided doses separated by 6 to 12 hours, has been shown to be associated with transient electrolyte disturbances that resolve spontaneously and that are rarely of clinical consequence.⁶ These transient electrolyte disturbances include increases in serum concentrations of sodium and phosphate (inorganic phosphorus) and decreases in serum potassium and calcium. However, the risk of medically important adverse events is increased in patients with the following conditions:

- Previously existing electrolyte abnormalities (generally associated with use of certain medications or metabolic disturbances)
- Renal failure
- Heart failure
- Gut conditions predisposing to excess absorption of sodium or phosphate

These risks are discussed in the labeling for Visicol Tablets.

A precaution in the labeling of Visicol Tablets describes a newly recognized risk of purgatives that was observed with both Visicol Tablets (at a total dose of 60 g sodium

³ Vanner SJ, MacDonald PH, Paterson WG, 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. *Am J Gastroenterol.* 1990;85:422-427.

⁴ Hookey LC, Depew WT, Vanner S. The safety profile of oral sodium phosphate for colonic cleansing before colonoscopy in adults. *Gastrointest Endosc* 2002;56:895-902.

⁵ 63 FR 67399, 67400, December 7, 1998.

⁶ Kastenberg D, Chasen R, Choudhary C, Riff D, Steinberg S, Weiss E, Wruble L. Efficacy and safety of sodium phosphate tablets compared with PEG solution in colon cleansing: two identically designed, randomized, controlled, parallel group, multicenter phase III trials. *Gastrointest Endosc.* 2001; 54:705-713. This publication describes the Phase III studies that supported the approval of Visicol Tablets.

phosphates) and the PEG/salt comparator (NuLYTELY®) that was used in the Phase III trials conducted by InKine – transient QT interval prolongation. In patients treated with Visicol, these changes were closely associated with transient hypokalemia and hypocalcemia. Not surprisingly, **similar ECG changes were also observed in patients taking 90 mL (60 g) of Phospho-Soda.**⁴ Thus, a precaution regarding use of colon cleansing agents in patients taking drugs that prolong the QT interval is appropriate.⁷ InKine is unaware of any OTC drug with such a precaution, suggesting that OTC status is not appropriate for such drugs. Moreover, patients are typically referred to gastroenterologists and colorectal surgeons for colonoscopy. These physicians may not be aware of what drugs a referred patient is taking, so that prescription status is plainly advisable for any colon-cleansing drug that might interact with drugs that prolong the QT interval in order to take advantage of the controls inherent in pharmacy dispensing, which often include computerized recognition of risks relating to concurrent medications and co-morbid conditions.

Hyponatremia, which has recently been recognized as a class risk of purgative use, in severe cases can lead to encephalopathy, including coma, seizures, or death.^{8,9,10} Cases of serious encephalopathy associated with hyponatremia have been reported in the literature following use of Visicol Tablets¹¹ and PEG/salt solution.^{9,12,13} Serious hyponatremia has also been reported after use of sodium picosulfate, a colon cleansing product closely related to bisacodyl that is not approved in the US but is used in the UK.⁸ Seizures related to hypocalcemia have been reported after use of Phospho-Soda.¹⁴

Hyponatremia following purgative use is believed to result from excessive excretion of antidiuretic hormone (ADH) coupled with excessive ingestion of free water, leading to dilutional hyponatremia. ADH secretion may be stimulated by hypovolemia, nausea, or vomiting, which may occur after the use of any purgative, or the colonoscopy procedure itself. ADH is a powerful stimulus for renal tubular reabsorption of water, and severely limits the kidney's ability to excrete free water (i.e., make dilute urine). Ingestion of water or other hypotonic fluids (such as soft drinks or Gatorade®) at a time when circulating ADH levels are elevated may result in impaired free water excretion, leading to dilution of the extracellular fluid and depressed levels of serum sodium.⁹ Factors that

⁷ For reasons that are not clear to InKine, PEG products do not yet have a precaution regarding QT prolongation.

⁸ Lewis M, Rugg-Gunn F, Don C, Woods W. Bowel preparation at home in elderly people. Patients should be warned not to drink too much or too little fluid. *BMJ* 1997; 314:74.

⁹ Ayus JC, Levine R, Arief AI. Fatal hyponatremia caused by elective colonoscopy. *BMJ*. 2003; 326:382-384.

¹⁰ Rose M, Jacob LS. Seizure associated with use of Visicol for colonoscopy. *N Engl J Med*. 2002;347:295-296.

¹¹ Mackey AC, Shaffer D, Prizont R. Seizure associated with the use of Visicol for colonoscopy. *N Engl J Med*. 2002;346:2095.

¹² Schroppel B, Segerer S, Keuneke C, Cohen CD, Schlondorff D. Hyponatremic encephalopathy after preparation for colonoscopy. *Gastrointest Endosc*. 2001;53:527-529.

¹³ Cohen CD, Keuneke C, Schiemann U, Schroppel B, Siegert S, Rascher W, Gross M, Schlondorff D. Hyponatremia as a complication of colonoscopy. *Lancet*. 2001;357(9252):282-283.

¹⁴ FDA Science Backgrounder: Seizure Associated with the Use of Visicol for Colonoscopy--Additional Information. <http://www.fda.gov/cder/drug/safety/visicol.htm>, accessed December 30, 2003.

might increase the risk for hyponatremia in a patient undergoing colon cleansing include those that are known to independently produce or contribute to hyponatremia, such as inadequately treated hypothyroidism, use of drugs that induce hyponatremia such as thiazide diuretics or tricyclic antidepressants, excessive fluid intake, unreplaced salt and water (i.e., perspiration) losses resulting from intense exercise before taking a purgative, or a prior history of hyponatremia with purgative use.

To date, serious hyponatremia has not been reported following the use of Phospho-Soda. However, until recently, the labeling for Phospho-Soda has not recommended the ingestion of large volumes of fluid during the colonoscopy prep. The labeling proposed by Fleet in their petition suggests the ingestion of 48 ounces of liquid or more, with no upper limit. Another possibility for the lack of reports of hyponatremia with Phospho-Soda may relate to the general under-reporting of adverse events for this product, as discussed below. In any event, medically important hyponatremia appears to be a rare complication of the use of all marketed classes of colon cleansing agents, and should be a concern of physicians who recommend the use of Phospho-Soda as a colon cleansing agent. An OTC drug product should not have a risk as serious and complex as this one. As with QT prolongation, the controls inherent in prescription drug dispensing are advisable for drugs that might induce hyponatremia.

Phospho-Soda adverse events are very likely to be underreported to FDA

In its Citizen Petition, Fleet emphasizes the safety record of Phospho-Soda, which Fleet characterizes as benign. However, there are several very strong reasons to believe that adverse events associated with the use of Phospho-Soda are substantially underreported to FDA in comparison to prescription drugs. First, Phospho-Soda is an OTC drug without an approved NDA. Manufacturers of such products have no legal obligation to report adverse events to FDA, although they may do so at their option. InKine has no direct knowledge of the reporting practices of the CB Fleet Company, the manufacturer of Phospho-Soda.

However, even if the manufacturer of Phospho-Soda reported every adverse event that it became aware of to FDA, we are confident that there would still be substantial under-reporting for Phospho-Soda **because knowledge of comparatively few adverse events would reach the company.** At InKine, which is subject to and complies with FDA's adverse event reporting requirements for drugs with approved NDAs, we first learn of most adverse events through our field sales staff that visit physician's offices. About 70% of adverse events that are reported to InKine are reported initially to our sales representatives, who then report the cases to our Medical Affairs staff at our corporate offices. A member of our Medical Affairs staff (a registered nurse or a physician) then contacts the physician's office, collects information on the adverse event, enters it into our electronic database, and reports the data to FDA as required by regulation. We understand that most other prescription drug companies have similar programs. However, to our knowledge, the CB Fleet Company does not have a field staff that visits the offices of physicians who perform colonoscopies or other procedures for which

Phospho-Soda is used. Thus, we believe that many adverse events occur that never reach the awareness of CB Fleet.

The importance of InKine's sales staff in collecting AE information is demonstrated by a recent unpublished analysis of Visicol adverse event information in FDA's AERS database performed by InKine with the assistance of the Degge Group, who are consultants in drug safety issues. The adverse event reports available to us at the time this study was performed (August 2003) cover the period from the launch of Visicol in January 2001 through June 31, 2002. Of the 31 Visicol adverse events in the AERS database in this period, 17 (55%) met both of the following criteria: (1) information about the adverse event was spontaneously communicated to FDA by InKine but to our knowledge, by no other person, and (2) the adverse event was reported to InKine headquarters by field sales staff, without spontaneous reporting to InKine by other persons (such as health care professionals or the patient).

These data indicate that over half of the adverse events associated with Visicol in FDA's AERS database in the relevant time period came to FDA's awareness because someone in a physician's office mentioned an adverse event to a visiting InKine sales representative. We believe that this situation is typical for drugs marketed by pharmaceutical companies with sales staffs.

These data strongly suggest that if a colon cleansing agent is marketed by a company without a sales force that regularly visits the offices of the physicians who perform procedures requiring colon cleansing, more than half of adverse events will be missed. Fleet Phospho-Soda is such a drug.

The pattern of reporting of seizures following use of purgatives supports our conclusion that Phospho-Soda adverse events are under-reported to FDA. An article published in June 2002 by FDA authors, based on data from FDA's AERS database, indicated that there were no reports of seizures in AERS associated with Phospho-Soda.¹¹ However, a subsequent examination of the published literature performed several weeks after publication of the article indicates that FDA had become aware of three cases of seizures following use of Phospho-Soda.¹⁴ Until recently, there were no cases of seizures associated with PEG products reported in the literature by health care providers, but there were five cases in FDA's AERS database in June 2002.^{10,11} There were two cases of seizures following use of GoLYTELY that were reported in the medical literature in 2003, along with other serious sequelae of electrolyte disturbances, including three deaths.⁹ In the case of Visicol, the publication cited above indicates that FDA's AERS database contained four cases of seizures. The medical literature still contains no cases of seizures associated with Visicol that were reported by health care providers.

This information indicates that for Visicol and the marketed PEG products (all prescription drugs with approved NDAs or ANDAs, and for the branded products, with sales forces that visit physician's offices), the number of cases of purgative-associated seizures reported to FDA is larger than the number of cases reported in the literature by health care providers. However, for Phospho-Soda, the number of seizure cases reported

in the literature is larger than the number of cases reported to FDA, which is zero. These data are consistent with the data discussed above showing the important contribution of a pharmaceutical sales force that visits physician's offices in collecting adverse events, and they support the conclusion that adverse events are substantially underreported to FDA for Phospho-Soda.

Some may argue that several years ago InKine stated in documents submitted to FDA regarding the risks of sodium phosphate that Fleet Phospho-Soda had an excellent safety record. At that time, we had no experience with the adverse event reporting rules for OTC products, and thus we did not appreciate that Fleet was not required to report adverse events associated with Phospho-Soda to FDA. Likewise, we did not take into consideration the important contribution of a sales force to collecting adverse event information. We now know better, and firmly believe that adverse events are substantially under-reported for Phospho-Soda, especially when it is used at the doses needed for adequate colon cleansing.

2. Prescription status for the colon cleansing indication of Phospho-Soda will allow more efficient and rapid communication of emerging safety information by requiring AE reporting and establishing greater controls over risk information in labeling and promotion

Sponsors of prescription drugs typically perform large, well-controlled studies to get their drugs approved, and submit study data to FDA, where the data undergo rigorous review. After approval, these sponsors are required to monitor the safety of their products and submit periodic safety updates to FDA.

One outcome of this exacting regulatory regime is that the most common safety risks of a drug are generally identified before approval. Less common risks are generally identified in the first few years of marketing, if not sooner. The requirement of quarterly safety updates in the first three years after approval and yearly updates thereafter is a powerful tool in identifying safety risks that are too rare to be picked up in the clinical studies supporting approval. The data from these updates can be used by FDA and the sponsor to change labeling to promote safe use of the drug.

The situation for OTC monograph products is very different. Manufacturers are not required to submit safety information collected during commercial use. Labeling, which is determined by Federal Register notices, is difficult to change. Risk information may be poorly communicated to physicians and consumers. This is especially true for subtle and complex risks, such as QT interval prolongation and hyponatremia, which have been identified as class risks of purgative products.

Requiring prescription status for sodium phosphates oral solution when used as a sole pharmacologic agent for colon cleansing will make it easier for FDA to promote the safe use of this product. Risks arising from the use of sodium phosphates oral solution will more likely be recognized and dealt with in labeling. Safety information in labeling can be modified without the substantial burden of changing an OTC monograph.

It is telling that despite decades of marketing Phospho-Soda since the invention of the ECG machine, Fleet apparently did not perform the studies necessary to determine the effects of Phospho-Soda on the QT interval until very recently. They had no incentive to do so. The relevant study was performed only after a clinical trial performed for NDA approval by a competitor – InKine – suggested that QT prolongation is a class effect of colon cleansing agents. Making sodium phosphates oral solution a prescription drug when used for colon cleansing will require manufacturers of this product to adopt the rigorous controls required of NDA applicants and NDA holders. In this way, the public health will be protected by making sure that the safety information about the most widely used colon cleansing agent is available to FDA.

3. All the other widely used colon cleansing agents are prescription drugs, and making sodium phosphates oral solution a prescription drug will level the playing field for promotion and erase the false impression that sodium phosphates solution is safer than the available prescription agents

Market information purchased by InKine indicates that the most widely used colon cleansing products are Phospho-Soda, NuLYTELY and other branded and generic PEG products, and Visicol. With the exception of Phospho-Soda, all of these are prescription products in the U.S. Thus, promotion of all major colon cleansing products other than Phospho-Soda is subject to regulation by FDA. Promotion of Phospho-Soda is regulated by the Federal Trade Commission, whose rules regarding the quantity and quality of evidence required to back up promotional claims, including comparative claims, are more lenient than those of FDA. Thus, Phospho-Soda is able to disseminate promotional pieces aimed at its competitors backed up by one study performed at a single center that has never been subjected to regulatory review, while competitors of Phospho-Soda must ordinarily back up competitive promotional claims with data from at least two well-controlled studies. Making Phospho-Soda a prescription product for its colon cleansing indication would remedy this obvious inequity.

4. There are no data in the Citizen Petition filed by Fleet to support use of sodium phosphates oral solution for colon cleansing prior to surgery or radiologic procedures

In the Citizen Petition filed by Fleet, the company requests indications for colon cleansing prior to colonoscopy, abdominal surgery, and radiologic procedures. However, the data backing up the petition come from a single study of the use of Phospho-Soda for colon cleansing prior to colonoscopy. There are no data to support use of the proposed regimen in patients having surgery or undergoing radiologic procedures. **FDA should recall that beginning with the approval of NuLYTELY in 1991, FDA has allowed colon cleansing studies performed in patients undergoing colonoscopy to support claims only for that specific use, and not for use prior to surgery or radiologic procedures.** Accordingly, sodium phosphates oral solution should not be approved for use in colon cleansing prior to surgical or radiologic procedures until it is shown to be

safe and effective for such uses in appropriately designed clinical studies at the intended dose.

5. The efficacy data for the 60 mL Phospho-Soda dose are inadequate to support a colon cleansing indication for this dose.

In its Petition, Fleet requests labeling indicating that Phospho-Soda at a total dose of 60 to 90 mL (roughly 40 to 60 g of sodium phosphates) is effective for colon cleansing. The only study with detailed data on the efficacy of the 60 mL dose is Study 9902, which is discussed at some length in the petition; the report of this study is included in an appendix to the petition. In this study, the 90 mL dose of Phospho-Soda was significantly more effective than either the 60 mL dose of Phospho-Soda or GoLYTELY. The efficacy of the 60 mL dose was not significantly different from that of GoLYTELY. However, the study data do not support approval of this indication for the 60 mL dose.

As a preface to our discussion of the data submitted by Fleet in its Petition, we note that achieving adequate colon cleansing prior to colonoscopy is very important. The dominant use of colonoscopy today is for colon cancer screening. If a colon is poorly prepared, and a pre-malignant polyp or early stage cancer is missed, the patient is at risk for death or serious morbidity due to colon cancer, since the next colonoscopy may not be performed for 10 years. Hence, the evaluation of data regarding colon cleansing efficacy should be rigorous, and certainly has been rigorous in the case of NDAs reviewed by the Division of Gastrointestinal and Coagulation Drug Products.

In general, FDA has concluded that drugs are effective for use for a given indication upon a showing that they are superior to placebo or to an approved product, or that they are not inferior to an approved product. The 9902 study established none of these showings with respect to the 60 mL dose of Phospho-Soda. The 60 mL dose was inferior to the 90 mL dose, so that a showing of efficacy, if it is based on anything, must be based on non-inferiority to GoLYTELY. In the Division of Gastrointestinal and Coagulation Drug Products (as well as in all other New Drug Review Divisions that we are aware of) non-inferiority is typically established by prospective delineation of a "margin of non-inferiority" and examination of the lower or upper (as appropriate) limit of the confidence interval (generally the 95% to 97.5% confidence interval) of the difference between the efficacy of the comparator (GoLYTELY) and the experimental agent (the 60 mL dose of Phospho-Soda.). Such an analysis is entirely data-dependent and generally requires a large study (or a large difference in favor of the experimental agent) in order to keep the confidence interval within the required, pre-set boundary. Note that the *a priori* power of the study to detect a difference between the treatment groups plays no role in the interpretation of the results in this type of analysis. In the case of the Visicol NDA, in which this statistical approach was used to establish the non-inferiority of Visicol to NuLYTELY, each of the two studies had well over 200 patients per study group. There were a total of 859 patients treated in the two Visicol studies.

By contrast, the study relied upon by Fleet to support the efficacy of the 60 mL dose of Phospho-Soda had only 75 patients in the 60 mL group and 73 patients in the

GoLYTELY group in the intent to treat analysis, the one most heavily emphasized in the study report. Neither the petition nor the study report mentions a pre-specified margin of inferiority or the confidence interval of the difference between the 60 mL group and the GoLYTELY group with respect to any efficacy parameter. We think that it is very likely that this type of analysis, if performed, would have failed to demonstrate the non-inferiority of the 60 mL dose. In any event, there are no data in the Fleet petition or the study report from which to conclude that the 60 mL dose of Phospho-Soda is effective for colon cleansing.

6. As an alternative to eliminating the OTC colon cleansing indication for sodium phosphates oral solution, FDA may want to preserve the OTC use of this product for colon cleansing at a reduced dose as part of a bowel cleansing system

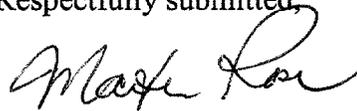
As discussed above, the 90 mL dose of Phospho-Soda (containing just under 60 g of sodium phosphates) is effective for colon cleansing, but does not have the safety profile of an OTC product. Since 90 mL of Phospho-Soda is the only dose that has been shown to be effective for colon cleansing as monotherapy, there is no appropriate OTC use of this product as monotherapy for colon cleansing.

As stated earlier, InKine believes that an OTC colon cleansing indication for sodium phosphate provides no benefits for patients. Accordingly, the risks inherent in marketing without a prescription outweigh the benefits, indicating that there should be no OTC colon cleansing indication for sodium phosphates oral solution. However, we recognize that the risks of sodium phosphates at total doses of about 30 g or less are small. As an alternative to completely eliminating the OTC marketing of sodium phosphates oral solution for colon cleansing, FDA may find it appropriate to limit such marketing to the situation where sodium phosphates oral solution is sold as a component in an OTC "bowel cleansing system" defined in 21 C.F.R. § 334.32 (i.e., a multi-component kit) containing no more than 7.56 g sodium phosphate and 20.2 g sodium phosphate (the amounts contained in about 45 mL of Phospho-Soda). As noted earlier, this dose of sodium phosphates may be safe enough for OTC use, although it has not been shown to be effective as monotherapy for colon cleansing. However the colon cleansing kit would contain one or more other purgative products, so that the contents of the kit, taken as directed, would provide effective colon cleansing. Accordingly, under heading "**B. Action Requested**" we provide language implementing the above change in the TFM as an alternative to eliminating the colon cleansing indication for sodium phosphates oral solution.

C. Conclusion

For the reasons discussed above, we respectfully request that FDA reject the Citizen Petition filed on behalf of C.B. Fleet on June 25, 2003, and additionally modify the OTC laxative drugs TFM to either eliminate the colon cleansing indication for sodium phosphates oral solution or limit the colon cleansing indication for sodium phosphates oral solution to situations where sodium phosphates oral solution is part of a bowel cleansing system and is administered at a total dose of no more than 7.56 g sodium phosphate and 20.2 g sodium biphosphate, as discussed above.

Respectfully submitted,

A handwritten signature in black ink, appearing to read "Martin Rose". The signature is written in a cursive style with a large, stylized initial "M".

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