DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

NOV 17 2003

Donna Lee, R.Ph.
Director of Regulatory Affairs and Project Management
Banner Pharmacaps, Inc.
P.O. Box 2210
4125 Premier Drive
High Point, North Carolina 27261-2210

Re: Docket No. 78N-036L
Comment No. CP26

Dear Ms. Lee:

This is in response to your citizen petition dated August 8, 2002, filed August 15, 2002, under Docket No. 78N-036L in the Division of Dockets Management (formerly the Dockets Management Branch). Your petition requests that the Food and Drug Administration (FDA) amend the tentative final monograph (TFM) for over-the-counter (OTC) laxative drug products to state that docusate calcium (dioctyl calcium sulfosuccinate) is an interchangeable ingredient with docusate sodium (dioctyl sodium sulfosuccinate) in the proposed monograph combination products.

I. PETITIONER'S REQUEST AND FDA'S DECISION

You cited a final rule, published in the Federal Register on May 9, 2002 (67 FR 31125), that eliminates from OTC laxative drug products (effective November 5, 2002) the cascara sagrada ingredients (casanthranol, cascara fluidextract aromatic, cascara sagrada bark, cascara sagrada extract, cascara sagrada fluidextract) listed in 21 CFR 310.545(a)(12)(iv)(C). You pointed out that the final rule stated that "approximately 125 OTC drug products contain casanthranol and docusate sodium, a proposed monograph laxative ingredient. These combination products could be reformulated to eliminate the casanthranol, replace the casanthranol with sennosides A and B or sodium carboxymethylcellulose (proposed monograph combinations with docusate sodium in § 334.30(i)(3) and (j) (58 FR 46589 at 46595, September 2, 1993)), or possibly increase the quantity of docusate sodium in the product, in conformance with the proposed monograph." Your petition requests that FDA allow the use of docusate calcium as an interchangeable active ingredient with docusate sodium in the proposed monograph combination products.

FDA has reviewed your petition and arguments and denies your request. The basis for this decision is set forth below.

II. DISCUSSION

A. Background

In the advance notice of proposed rulemaking (40 FR 12902, March 21, 1975), the Advisory Review Panel on OTC Laxative, Antidiarrheal, Emetic, and Antiemetic Drug Products (the Panel) recommended monograph status (Category I) for docusate calcium, docusate potassium, and docusate sodium in the recommended dosages. The Panel also recommended the following docusate salt combinations as Category I: 1. docusate sodium combined with any one of the following: casanthranol, phenolphthalein, sennosides A and B, or sodium carboxymethylcellulose for oral use; 2. docusate calcium combined with danthron for oral use; and 3. docusate potassium combined with glycerin or sorbitol for rectal use. However, based on subsequent events, danthron and phenolphthalein (discussed in the Federal Register of September 2, 1997 (62 FR 46223)) and cascara sagrada ingredients (including casanthranol) (discussed in the Federal Register of May 9, 2002 (67 FR 31125)) are nonmonograph (no longer proposed as generally recognized as safe and effective OTC laxative drug product ingredients). At this stage of the rulemaking, the following docusate salt combinations are proposed as Category I: docusate sodium and sodium carboxymethylcellulose; docusate potassium and glycerin; and docusate potassium and sorbitol. In the proposed rule of June 19, 1998 (68 FR 33592), senna (including sennosides A and B) was reclassified from Category I to Category III (more data needed). Thus, the combination of docusate sodium and sennosides A and B is currently a Category III combination.

B. Data

In the amendment to the TFM for OTC laxative drug products (58 FR 46589, September 2, 1993), the docusate salts [sodium (oral use), calcium (oral use), and potassium (rectal use)] are proposed as Category I stool softener laxative active ingredients. As stated in that amendment, FDA is unaware of any data demonstrating that the substitution of the calcium or potassium ion for the sodium ion in a docusate formulation would have a significant effect on the biological activity of the docusate anion (58 FR 46592). However, no data have been submitted to show that the individual docusate salts are bioequivalent and/or have the same bioavailability when used

interchangeably in the proposed combinations in oral or rectal dosage forms.

We have reviewed the information provided in your petition, which includes articles from Martindale: The Extra Pharmacopeia, Remington's Pharmaceutical Sciences, and Goodman and Gilman's The Pharmacological Basis of Therapeutics. You also provided product label information on Surfak® LiquiGels (docusate calcium 240 mg). The information you presented discusses the use of the individual docusate salts as stool softener laxatives, but does not provide any data to support the interchangeable use of docusate calcium with docusate sodium in the proposed monograph combination products.

III. CONCLUSION

You asked that FDA allow docusate calcium to be interchangable with docusate sodium in the proposed OTC laxative drug product monograph combinations. We have considered your request and the information that you provided. We have determined that data are needed to show that the bioavailability of docusate calcium relative to docusate sodium is not affected when combined with sennosides A and B or sodium carboxymethylcellulose. Information may be provided from clinical studies and/or suitably designed and validated in vitro studies. We recommend that you consult with our Division of OTC Drug Products before proceeding with any studies.

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

Sincerely yours,

John M. Taylor, III
Associate Commissioner
for Regulatory Affairs