

PURDUE

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January 16, 2004

SUBMITTED IN TRIPLICATE

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

RE: Docket No. 1978N-036L

Dear Sir or Madam:

The Purdue Frederick Company ("Purdue") is grateful for the opportunity to provide comment on and data in response to FDA's decision to reopen the administrative record for the above rulemaking proceeding. Reference is made to the Laxative Drug Products for Over-the-Counter Human Use; Tentative Final Monograph ("TFM" or "the monograph") issued by FDA on January 15, 1985.

Item 1 Sennoside Active Ingredient Labeling

Background

We understand that in the United States Pharmacopeia (USP) XXII, the official title was changed from "Sennosides A and B" to "Sennosides" to acknowledge that, although sennosides A and B are considered the primary active constituents as described in the Tentative Final Monograph, there are other sennosides present in senna that can be isolated. The USP assay was primarily designed to detect sennosides A and B, the major constituents, however, we have found it is not specific for sennosides A and B and includes other sennoside constituents.

We also understand that it has been the Agency's policy not to include an active ingredient in a Final Monograph unless USP standards for the ingredient exist or are under active development by the United States Pharmacopeial Convention (USPC). The TFM for OTC Laxative drug products (50 FR 2124) proposed that senna preparations be standardized to the sennosides A and B content, and, accordingly, the TFM provides only for a sennosides A and B.

In conjunction with the requested action below, Purdue intends to petition the USPC Council to alter its current definition to more accurately reflect the results achieved with the current Sennoside USP assay.

Requested Action

Based upon the background information provided above, Purdue respectfully requests that proposed §334.18 in the tentative final monograph be amended to change the name of the stimulant laxative ingredient from "sennosides A and B" to "sennosides" to more accurately

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reflect the results obtained from the USP "Sennosides" assay. In addition, to clarify the sennosides content implied in the TFM, Purdue requests that FDA clarify which components should be considered as "sennosides".

Item 2 100% Combination Rule as proposed §334.31

Background

On March 21, 1974 (40 FR 12902), FDA published a Proposal to Establish Monographs for OTC Laxative, Antidiarrheal, Emetic, and Antiemetic Products. The Proposed Rule included specific criteria for determining Category I combinations. The Panel developed the following concept as a reasonable means of expressing the sum of the percentage amounts of the effective dosage rate (EDR) of each active ingredient which must not exceed 100, as calculated by the following formula:

$$\frac{L \text{ max d-EDR (min)}}{\text{EDR (max)} - \text{EDR (min)}} \times 100 = \% \text{ EDR of each ingredient}$$

"Where: L max d is the labeled maximum daily dosage obtained from the labeling information for the product, EDR (min) is the minimum effective dosage range set by the Panel and EDR (max) is the maximum effective dosage range set by the Panel.

The purpose of the above formula is two-fold:

1. to assist the manufacturer in determining which combination products require reformulation and/or testing;
2. to encourage the use of ingredients in amounts at the minimum end of the dosage range rather than at the maximum effective range dosage."

On January 15, 1985 (50 FR 2124), FDA published a tentative final monograph on Laxative Drug Products. The TFM stated the following:

"If a manufacturer can show that a laxative combination meets the general guidelines for OTC combination drug products, the agency will have no objection to the product contain two or more Category I laxative ingredients...Also, the agency has evaluated the Panel's combination formula in recommended §334.31(b) in relation to marketed combination laxative products, the regulations (§330.10(a)(4)(iv)), and the combination guidelines and concludes that the formula allows those combinations of Laxative ingredients identified in §334.32 to meet these criteria for safe and effective OTC use. Combinations containing more than two laxative ingredients would also have to comply with the requirement of this formula. Any manufacturer wishing to market a product that is not within the specifications of the formula may submit data to support such a request."

Requested Action

Purdue sold 14,401,802 units of Senokot-S Tablets from 1994 to 2003. There were 72 Lack of Efficacy cases, equaling 0.0005% of total sales during the period, and 170 Adverse Events (excluding Lack of Efficacy cases), equaling 0.0012% of total sales during the period (see Attachment 1). Based upon the minimal amount of adverse events associated with the dosing regimen of 2-8 tablets/day of Senokot-S and the almost 30 years of successful marketing, Purdue requests that the combination of 8.6mg sennosides and 50mg DSS when provided as 2-8 tablets in an adult dose be exempt from complying with §334.31.

Item 3 Bowel Cleansing Systems as proposed §334.32

Background

The 'Laxative Drug Products for Over-the-Counter Human Use; Tentative Final Monograph' (Federal Register, Vol. 50 No. 10; January 16, 1985) allowed the monograph to be extended to include bowel cleansing systems which consisted of several different laxative ingredients for sequential administration at specified intervals, for use in evacuating the bowel prior to surgery, colon x-ray, or endoscopic examination. The monograph required the manufacturer to supply information concerning fluid intake and dietary restrictions along with the warning, "Do not use this product unless directed by a doctor". Purdue has marketed 2 bowel cleansing systems for over 20 years. X-Prep Bowel Evacuation Kit-1 consists of a Rectolax Suppository (10mg bisacodyl suppository), X-Prep liquid (130mg sennosides), and 2 Senokot-S tablets (docusate sodium 50mg and sennosides 8.6mg per tablet). X-Prep Bowel Evacuation Kit-2 consists of Citrilax Granules (effervescent citrate/sulfate of magnesium – 8.0g magnesium citrate and 5.3g magnesium sulfate), X-Prep liquid (130mg sennosides) and a Rectolax suppository (10mg bisacodyl). Each kit contains adequate warnings per the monograph and a dietary/fluid intake regimen based on time of the medical procedure. Purdue has marketed these two products for over 20 years with virtually no safety or efficacy issues. Purdue sold 229,903 units of X-Prep Bowel Evacuant Kit-1 between the years of 1994 and 2003. There were 0 Lack of Efficacy cases, and 1 Adverse Events (excluding Lack of Efficacy cases), equaling 0.0004% of total sales during the period (see Attachment 1). Purdue sold 176,970 units of X-Prep Bowel Evacuant for Barium Enema Kit-2 between the years of 1994 and 2003. There were 2 Lack of Efficacy cases, equaling 0.0011% of total sales during the period, and 4 Adverse Events (excluding Lack of Efficacy cases), equaling 0.0023% of total sales during the period (see Attachment 1).

Requested Action

Based on the low incidence of adverse events (see Attachment 1) and the 25 years of successful marketing of X-Prep Bowel Evacuation Kit-1 and 22 years of successful marketing of X-Prep Bowel Evacuation Kit-2, Purdue proposes that the following combinations be added to the monograph as Category I combinations for bowel cleansing systems under §334.32:

- a) 10mg bisacodyl suppository, standardized senna concentrate liquid (130mg sennosides), and 2 docusate sodium 50mg and sennosides 8.6mg tablets;

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- b) effervescent citrate/sulfate of magnesia – 8.0g magnesium citrate and 5.3g magnesium sulfate, standardized senna concentrate liquid (130mg sennosides) and one 10mg bisacodyl suppository.

Item 4 "Faintness" Warning associated with Bisacodyl

Background

The 'Laxative Drug Products for Over-the-Counter Human Use; Tentative Final Monograph' (Federal Register, Vol. 50 No. 10; January 16, 1985) requires a warning specific to enteric-coated bisacodyl tablet dosage forms for oral use (proposed §334.60(c)(1)(i)(d). This warning states " This product may cause abdominal discomfort, faintness, and cramps." Neither the Advance Notice of Proposed Rulemaking nor TFM provide support for this warning statement.

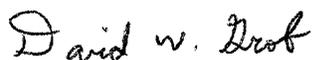
Requested Action

Purdue requests FDA provide the basis for the necessity and appropriateness of this statement with regards to "faintness".

In closing, Purdue would like to thank the agency for this opportunity to provide comments and additional data on the items included above and respectfully requests that FDA accept the actions requested for inclusion in the Final Monograph for Laxative Drug Products for Over-the-Counter Human Use.

Sincerely,

The Purdue Frederick Company
By



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Enclosures

Adverse Event (AE) Data Normalized for Sales

Product	Initial Marketing Date	Sales Totals (Units) 1994-2003	Total Lack of Efficacy (LOE) Cases 1994 - 2003 YTD	LOE as a Percent of Unit Sales	Total Adverse Event cases excluding LOE 1994 - 2003 YTD	AE as a Percent of Unit Sales (Excluding LOE)
Senokot-S Tablets (all SKUs) sample(s) 10 count 30 count 60 count 100 count HUD 1000 count	n/a May-94 October-74 October-74 April-90 January-75	14,401,802	72	0.0005%	170	0.0012%

Product	Initial Marketing Date	Sales Totals (Units) 1994-2003	Total Lack of Efficacy (LOE) Cases 1994 - 2003 YTD	LOE as a Percent of Unit Sales	Total Adverse Event cases excluding LOE 1994 - 2003 YTD	AE as a Percent of Unit Sales (Excluding LOE)
X-Prep Liquid Bowel Evacuant 2.5 oz	January-65	1,983,576	8	0.0004%	42	0.0021%

Product	Initial Marketing Date	Sales Totals (Units) 1994-2003	Total Lack of Efficacy (LOE) Cases 1994 - 2003 YTD	LOE as a Percent of Unit Sales	Total Adverse Event cases excluding LOE 1994 - 2003 YTD	AE as a Percent of Unit Sales (Excluding LOE)
X-Prep Bowel Evacuant Kit-1	June-78	229,903	0	0.0000%	1	0.0004%
X-Prep Bowel Evacuant for Barium Enema - Kit 2	September-82	176,970	2	0.0011%	4	0.0023%