DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

SEP 2 2003

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Alan G. Minsk, Esquire
Arnall Golden Gregory LLP
2800 One Atlantic Center
1201 West Peachtree Street
Atlanta, Georgia 30309-3450

Re: Docket No. 78N-036L
Comment No. CP27

Dear Mr. Minsk:

This responds to your citizen petition submitted on August 30, 2002, requesting that the Food and Drug Administration (FDA) refrain from taking enforcement action after November 5, 2002, against any manufacturer of an over-the-counter (OTC) stimulant laxative drug product containing casanthranol or cascara sagrada (hereafter "cascara sagrada").

I. PETITIONER'S REQUEST AND FDA'S DECISION

You requested FDA to refrain from taking enforcement action based on a new final rule published in the Federal Register on May 9, 2002, (67 FR 31125), which as of November 5, 2002, does not allow the initial introduction or initial delivery for introduction into interstate commerce of OTC laxative drug products that contain the aloe and cascara sagrada ingredients listed in 21 CFR 310.545(a)(12)(iv) (C). You also requested, alternatively, that FDA stay and reconsider its decision regarding these products, even though it has been more than 30 days since the agency issued the Federal Register notice on May 9, 2002. You made this request so that manufacturers may have sufficient time to reformulate these products, which you stated have been on the market as safe and effective products for over 40 years.

You summarized FDA's actions on cascara sagrada in the agency's OTC drug review and noted that FDA had published a tentative final monograph (TFM) but had not completed its review of OTC laxative drug products. You mentioned that FDA has an enforcement policy under which the agency will not take action against a manufacturer of an OTC drug product whose ingredients and claims are included in the review, unless there is a safety problem or a substantial effectiveness question. You contended that failure to perform FDA-requested testing does not negate the fact that OTC stimulant laxatives containing cascara sagrada have been on the market for more than 40 years, without presenting a public health risk, and contended that cascara sagrada is a generally recognized as safe and effective (GRASE) OTC stimulant laxative ingredient. You also contended that OTC stimulant laxative drug products containing cascara sagrada ingredients have been marketed to a material extent and for a material time and, thus, are not "new drugs" as defined in section 201(p) of the Federal Food, Drug, and Cosmetic Act [FFDCA] (21 U.S.C. 321(p)).

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You mentioned the lack of serious adverse event reports for cascara sagrada laxative products and referred to another citizen petition on this ingredient submitted by the American Herbal Products Association and the International Aloe Science Council on June 10, 2002.[1] You mentioned a recent toxicity study by Borelli et al., Life Sciences, 69:1871-1877 (2001), as support that cascara sagrada is not a carcinogen. You concluded that there will be no adverse effect if FDA refrains from taking enforcement action against manufacturers of OTC stimulant laxative drug products that contain cascara sagrada after November 5, 2002. Finally, you contended that if FDA chooses not to issue an interim enforcement policy, it should reconsider its decision. You suggested that FDA consider imposing certain labeling restrictions for these products so they could remain available, noting that FDA permits the sale of OTC drug products when the benefits outweigh the risks and adequate directions and warnings can be provided in the product labeling.

The agency has reviewed your petition and arguments and denies your requests. The basis for these decisions is set forth below.

II. DISCUSSION

A. Background

The agency established the OTC drug review in 1972 to determine the GRASE status of ingredients like cascara sagrada that had been in the OTC marketplace for a number of years. The OTC drug review was designed to implement both the misbranding and the new drug provisions of the FFDCA. (See 21 CFR 330.10; 37 FR 9466 comment 23, May 11, 1972.) During the course of the review, a number of ingredients that have been marketed to a material extent and for a material time have been determined not to be GRASE for various reasons, including lack of adequate data to support safety and/or effectiveness, and new information that shows that the ingredient can no longer be considered safe for OTC use. Cascara sagrada has been found to be one of those ingredients as a result of new information that has arisen during the course of the review process, as discussed below. Many of these active ingredients are listed in 21 CFR 310.545, where aloe and cascara sagrada ingredients are also listed. Ingredients in this section are considered "new drugs" per section 201(p) of the FFDCA.

The agency acknowledges that the Advisory Review Panel on OTC Laxative, Antidiarrheal, Emetic, and Antiemetic Drug Products (the Panel) recommended monograph status for cascara sagrada ingredients (40 FR 12902, March 21, 1975). In the TFM for OTC Laxative Drug Products (50 FR 2124, January 15, 1985), the agency reviewed the Panel's recommendations and proposed monograph status for these ingredients.

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[1]The agency will address that petition separately.

However, based on subsequent events, which the agency discussed in the Federal Register of June 19, 1998 (63 FR 33592), FDA proposed to amend the TFM to reclassify the stimulant anthraquinone laxative ingredients aloe, bisacodyl, cascara sagrada, and senna (including sennosides A and B) from proposed GRASE status (Category I) to the status of "further testing is required (Category III)." The agency noted the carcinogenic risk of two chemically related stimulant anthraquinone laxative ingredients, danthron and phenolphthalein (which it had discussed in the Federal Register of September 2, 1997 (62 FR 46223). The agency noted that its Center for Drug Evaluation and Research (CDER) Carcinogenicity Assessment Committee (CAC) had recommended that the anthraquinone laxatives (aloe, cascara sagrada, and senna) and bisacodyl (which has a similar chemical structure and pharmacological characteristics to phenolphthalein) be tested in the standard battery of genotoxicity tests and under the test conditions by which phenolphthalein was found to be positive. The agency discussed data it had reviewed on bisacodyl and senna and stated that it had not received any mutagenicity, genotoxicity, or carcinogenicity data for aloe and cascara sagrada ingredients. The agency concluded that these two ingredients needed to have these types and other toxicity data using tests similar to those used and found positive for phenolphthalein. The agency stated that if these data are not provided or are inadequate for any of these ingredients, these ingredients will be placed in Category II (nonmonograph) in a final rule. This information had not been provided when the final rule on aloe and cascara sagrada ingredients was published on May 9, 2002.

In summary, as discussed above, new information about related anthraquinone laxative ingredients (danthron and phenolphthalein) resulted in additional information being needed about the safety of cascara sagrada ingredients. Without information from studies conducted to show that aloe and cascara sagrada are not mutagenic, genotoxic, or carcinogenic, FDA could not conclude that the ingredients are GRASE. As no information had been submitted and no testing was being conducted, the agency classified these ingredients as nonmonograph and, therefore, "new drugs." The agency considers this action to be in full accord with its interim enforcement policy [Compliance Policy Guide 7132b.15] under the OTC drug review.

B. Data

We have reviewed the recent toxicity study in rats, entitled "Effect of bisacodyl and cascara on growth of aberrant crypt foci and malignant tumors in the rat colon," by Borelli et al., Life Sciences, 69(16):1871-1877, 2001. The objective of this study was to assay carcinogenicity and tumor-promoting activity of cascara (13-week treatment) in rats by observation of pre-neoplastic changes (aberrant crypt foci) and tumors in the colon.

Rats (10 in each group) were treated with cascara (140 or 420 mg/kg) or bisacodyl (4.3 or 43 mg/kg) orally daily for 13 weeks for carcinogenicity evaluation. The rats were co-treated with azoxymethane (AOM, a carcinogen) intraperitoneally at day 1 and day 5 as an initiating agent to evaluate tumor promotion potential of the cascara and bisacodyl. Aberrant

crypt foci (ACF, a putative pre-neoplastic lesion) and tumors in the colon were determined microscopically at the end of the study.

ACF results are summarized in Table 1. After the 13-week treatment, neither dose of cascara induced ACF in rats or increased ACF in rats co-treated with AOM. Bisacodyl at both doses plus AOM increased the number of crypts per focus ($p<0.05$) but decreased the total number of ACF (*no explanation was provided in the report*).

In a previous rat study, the same research group reported[2] that an 8-week daily treatment of 0.1% cascara glycosides (a mixture of cascarosides A, B, C, and D) increased aberrant crypts per focus in rats co-treated with another carcinogen, dimethylhydrazine. The authors concluded that cascara could act as a tumor promoter in rat colon carcinogenesis.

Table 1. **Induction of aberrant crypt foci (ACF) in rats treated with cascara for 13 weeks with and without co-treatment of azoxymethane (AOM)**

Treatment	No of Rats	ACF per rat*		Crypt/Focus
		Total	Large ACF	
Vehicle Control	10	0	0	0
AOM alone	20	135.2 ± 49.0	41.8 ± 26.5	3.0 ± 0.8
Cascara, 140 mg/kg/d				
-AOM	10	0	0	0
+AOM	10	151.6 ± 44.9	39.3 ± 27.3	3.0 ± 0.9
Cascara, 420 mg/kg/d				
-AOM	10	0	0	0
+AOM	10	139.1 ± 44.1	43.3 ± 27.5	3.9 ± 0.9
Bisacodyl, 4.3 mg/kg/d				
-AOM	10	0	0	0
+AOM	10	100.0 ± 46.3	41.2 ± 21.5	4.4 ± 0.6#
Bisacodyl, 43 mg/kg/d				
-AOM	8	0.25 ± 0.7	0.12 ± 0.4	0.5 ± 1.4
+AOM	9	105.1 ± 34.8	62.0 ± 23.3	4.4 ± 0.9#

[2] Mereto, E. et al., "Evaluation of the potential carcinogenic activity of senna and cascara glycosides for the rat colon," Cancer Letter, 101:79-83, 1996.

* Mean ± SD of tested animals; Large ACF is the ACF containing 4 or more crypts.
# $p<0.05$ *vs* AOM alone with ANOVA followed by Dunnett's test.

Tumor results are summarized in Table 2. Cascara alone at both doses after the 13-week treatment did not induce tumors in the colon. However, cascara treatment tended to increase tumors in animals co-treated with AOM, although there was no statistical significance. Bisacodyl at the high dose significantly increased the incidence of adenocarcinoma.

Table 2. **Incidence of colon tumors in rats treated with cascara for 13 weeks with and without co-treatment of azoxymethane (AOM)**

Treatment	No of Rats	Tumor (% Rats)	Tumor/Rat	Tumor Type	
				Adenoma	Adenocarcinoma
Vehicle Control	10	0	0	0	0
AOM alone	20	20	0.25 ± 0.55	2H, 1L	2
Cascara, 140 mg/kg/d					
-AOM	10	0	0	0	0
+AOM	10	30	0.40 ± 0.70	2H	2
Cascara, 420 mg/kg/d					
-AOM	10	0	0	0	0
+AOM	10	30	0.50 ± 0.97	3H	2
Bisacodyl, 4.3 mg/kg/d					
-AOM	10	0	0	0	0
+AOM	10	30	0.50 ± 0.85	2H	3
Bisacodyl, 43 mg/kg/d					
-AOM	8	0	0	0	0
+AOM	9	78	2.33 ± 1.87*	0	21

* $p<0.05$ *vs* AOM alone with ANOVA followed by Dunnett's test.
H: high grade of dysplasia and L: low dysplasia.

In summary, cascara treatment at daily oral doses of 140 and 420 mg/kg for 13 weeks inrats did not significantly increase azoxymethane-induced colonic aberrant crypt foci. These results are inconsistent with results from a study in rats co-treated with dimethylhydrazine previously reported by the same research group. Cascara treatment alone did not induce colonic aberrant crypt foci or tumors, but tended to increase the incidence of azoxymethane-induced colon tumors in rats.

Bisacodyl treatment at daily doses of 4.3 and 43 mg/kg for 13 weeks in rats significantly increased azoxymethane-induced aberrant crypt foci in the colon and significantly increased the incidence of azoxymethane-induced adenocarcinoma in the high dose group. However, bisacodyl treatment alone did not induce aberrant crypt foci or colon tumors.

Regarding the data on cascara, the inconsistency in ACF-promoting effects of cascara between the results of the two studies reported by these authors suggests that cascara-induced tumor promotion may vary depending on the presence of different types of carcinogens. Also, various cascara preparations and treatment procedures (optimal dosages and treatment duration) may lead to different results.

In conclusion, we have determined that the data presented in this article do not adequately address the risk of potential carcinogenicity and tumor promotion risk of cascara. The data do not warrant a stay and reconsideration of the final rule. A long-term (2-year) carcinogenicity study (including promoter activity evaluation) on cascara with the same preparation used for humans and at appropriate dosages is still needed to help FDA evaluate the safety and effectiveness of this ingredient.

C. Enforcement Action

You stated that you failed to understand the urgent nature of the agency's 6-month effective date of the final rule and that FDA has offered no evidence that would lead to a conclusion that the continued marketing of cascara sagrada-containing OTC laxative drug products presents an imminent health risk. You asked that the agency exercise enforcement discretion as companies attempt to reformulate their products to comply with the agency's decision.

As discussed in the May 9, 2002, final rule, the agency requested additional data on cascara sagrada ingredients in June 1998, and no data were received. In the June 19, 1998, proposed rule, the agency alerted manufacturers that if the additional data are not provided, these ingredients would be placed in Category II (nonmonograph) in a final rule. As no data had been provided and the final monograph for OTC laxative drug products was not imminent in 2002, the agency did not wish to allow OTC laxative drug products containing these ingredients to continue to be initially introduced into interstate commerce until the final monograph is published and becomes effective, especially when any potential health risks from using such products could not be adequately determined. Manufacturers of OTC drug products containing cascara sagrada ingredients were provided 6 months to continue to initially introduce or initially deliver these products for introduction into interstate commerce. Manufacturers should have begun implementing product reformulations during this 6-month period. Given the potential risk to the public health and the prior notice the agency provided to manufacturers of these products in 1998, the agency declines to allow more time for manufacturers to continue to introduce additional drug products containing cascara sagrada ingredients into interstate commerce while they complete their product reformulations.

Therefore, the agency will not continue to exercise its enforcement discretion with regard to these products.

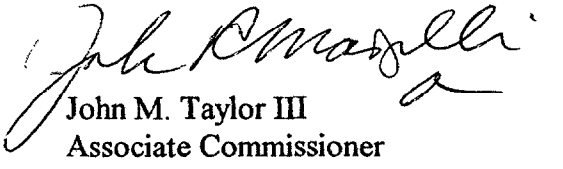
Further, the agency has evaluated additional data that were provided by the American Herbal Products Association and the International Aloe Science Council in a citizen petition to which you referred. The agency has determined that those data do not support GRASE status for cascara sagrada ingredients because they do not rule out the possibility that cascara sagrada preparations are genotoxic and/or carcinogenic. Thus, the agency has reconsidered its decision announced in the May 9, 2002, final rule and reaches the same conclusions. Finally, FDA does not believe that labeling restrictions relating to use of OTC laxative drug products containing these ingredients would be adequate to address the safety concerns related to these ingredients, especially when any potential health risks from using such products can not be adequately determined. The agency does not find that the benefits of using cascara sagrada laxative ingredients outweigh the risks and does not find that it could provide consumers adequate warnings when it does not have the information upon which to determine what those warnings should state. Accordingly, we reject these options.

III. CONCLUSION

After considering the information you presented, the agency declines to stay its decision that was published in the Federal Register on May 9, 2002, or to refrain from taking enforcement action against OTC laxative drug products that contain cascara sagrada ingredients and that are initially introduced or initially delivered for introduction into interstate commerce on or after November 5, 2002. This decision is based on continuing safety concerns, as described above, about OTC laxative drug products that contain cascara sagrada ingredients.

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, MD 20852.

Sincerely yours,



John M. Taylor III
Associate Commissioner
for Regulatory Affairs

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: SEP 2 2003

FROM: Director
Division of OTC Drug Products, HFD-560

SUBJECT: Material for Docket No. 78N-036L

TO: Dockets Management Branch, HFA-305

☑ The attached material should be placed on public display under the above referenced Docket No.

☑ This material should be cross-referenced to Comment No. CP27

Charles J. Ganley, M.D.

Attachment