

August 30, 2002

BY FEDERAL EXPRESS

Dockets Management Branch (HFA-305)
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

CITIZEN PETITION

The undersigned, on behalf of our client, submits this petition under the Federal Food, Drug, and Cosmetic Act (the "FDC Act") and 21 C.F.R. § 10.30 to request that the Commissioner of Food and Drugs, or Deputy Commissioner in the absence of a Commissioner, refrain from taking enforcement action against any drug manufacturer of a stimulant laxative product, sold over-the-counter, that markets a casanthranol or cascara sagrada-containing OTC laxative drug product, after November 5, 2002.

A. Action Requested

Petitioner requests that the Food and Drug Administration refrain from taking enforcement action against any drug manufacturer that markets casanthranol or cascara sagrada-containing OTC stimulant laxative drug products after November 5, 2002, the effective date of a new rule published in the Federal Register, dated May 9, 2002. Alternatively, petitioner requests that FDA stay and reconsider its decision concerning these products, even though it has been more than 30 days since FDA issued its Federal Register notice. This request is made to allow manufacturers sufficient time to reformulate these products, which have been on the market as safe and effective products for more than forty years.

The relevant portions of the applicable statutory and regulatory provisions are included in Attachment A.

78N-036L

CP 27

B. Statement of Grounds

1. Introduction

Our client is a drug company that manufactures and markets an OTC laxative product that contains casanthranol as an ingredient. Cascara sagrada, Spanish for "sacred bark," is the dried, aged bark of a small tree in the buckthorn family native to the Pacific Northwest. Encyclopedia of Herbs, www.allnatural.net; Natural Medicines Comprehensive Database: Monograph, www.naturaldatabase.com/monograph.asp?mono-id=773&hilite=1. Attachment B. The bark is harvested mostly from wild trees in Oregon, Washington, and southern British Columbia. Id. Casanthranol is obtained from cascara sagrada. It contains in each 100g not less than 20% of total hydroxyanthracene derivatives calculated on the dried basis, calculated as cascaroside A. Not less than 80% of the total hydroxyanthracene derivatives consists of casacarosides, calculated as cascaroside A. See USP 25/NF20. Attachment C.

For a number of business reasons unrelated to the safety or efficacy of the products, the company did not submit testing data to FDA after issuance of a Federal Register notice, dated June 19, 1998, where the agency proposed to declare cascara sagrada ingredients to be outside of the laxative monograph unless testing was performed.

Our client is currently in the process of reformulating its laxative product with ingredients found in the monograph. However, it is unlikely that the reformulation will be completed by the November 5, 2002 deadline. The product that our client markets has been sold for many years without receiving consumer complaints concerning safety or efficacy.

2. Statutory and Regulatory Background

i. **Regulation of New Drugs**

The FDC Act defines a "new drug" as a drug that is not generally recognized among scientifically qualified experts as safe and effective for use under the conditions stated in its labeling (GRASE). 21 U.S.C. § 321(p)(1). A drug may also be a new drug if it has not been used, outside of clinical investigations, "to a material extent or for a material time under [labeled] conditions." 21 U.S.C. § 321(p)(2).

Under the FDC Act, all new drugs are subject to premarket approval by FDA. There are three types of premarket applications for new drugs. The most onerous is the

"full" NDA, under section 505(b)(1). Full NDAs, in particular, require extensive clinical data. 21 C.F.R. § 314.50. Another form of "full" NDA is established by section 505(b)(2) of the FDC Act, which permits the inclusion of safety and effectiveness studies that the applicant has not conducted or been granted a right of reference by the sponsor of the studies. This usually requires published studies or similarly available information. FDA also expressly recommends an application under section 505(b)(2) for a modification, such as a new dosage form, of a previously approved drug, which requires more than just bioequivalence data. 21 C.F.R. § 314.54.

The least burdensome application is the ANDA, which may apply to a new drug that is bioequivalent to a "listed" drug (a new drug approved by FDA for safety and effectiveness). 21 U.S.C. § 355(j). The ANDA requires bioequivalence data and other technical and manufacturing information but no safety and effectiveness studies.

The FDC Act does not differentiate between prescription and OTC drugs with respect to new drug status. See 21 U.S.C. §§ 321(p) and 353(b)(1). An OTC new drug requires premarket approval. However, FDA has adopted an administrative process, the OTC Drug Review, to determine which active ingredients and indications are GRASE for use in OTC drugs. 21 C.F.R. § 330.1. With the aid of independent expert advisory review panels, FDA is developing final rules, referred to as monographs, that define categories of GRASE and not misbranded OTC drugs. Once a monograph is final, any drug within the category may be marketed only in compliance with the monograph or under an approved NDA. Id. FDA does provide for an abbreviated form of NDA where the drug would deviate in some respect from the monograph. 21 C.F.R. § 330.11. This so-called "NDA deviation" need include only information "pertinent to the deviation." Id.

In some cases, like the one at issue, FDA has not completed its review and, thus, has only published a Tentative Final Monograph (TFM). OTC laxative drug products fall into this category. See Proposed 21 C.F.R. Part 334; 50 Fed. Reg. 2124 (Jan. 15, 1985), revised 51 Fed. Reg. 35136 (Oct. 1, 1986); 58 Fed. Reg. 46589 (Sept. 2, 1993). Attachment D. While the OTC Drug Review is pending, FDA has established an interim enforcement policy under which the agency will not take action against a manufacturer of an OTC drug whose ingredients and claims are included in the Review, unless there is a safety problem or a substantial effectiveness question. 21 C.F.R. § 330.13; FDA Compliance Policy Guide No. 450.200. Attachment E.

ii. **FDA action on cascara sagrada**

On March 21, 1975, FDA published, under 21 C.F.R. § 330.10(a)(6), an advance notice of proposed rulemaking to establish a monograph for OTC laxative, anti-

diarrheal, emetic, and antiemetic drug products. 40 Fed. Reg. 12902. Attachment F. In addition, the agency included the recommendations of the appropriate advisory review panel responsible for evaluating data on the active ingredient in these drug classes. FDA published its proposed regulation, in the form of a TFM, for OTC laxative drug products on January 15, 1985. 50 Fed. Reg. 2124. In the TFM, FDA concurred with the panel's classification of cascara sagrada preparations as Category I. Id.

On June 19, 1998, FDA reopened the administrative record, originally opened in 1990, and reclassified the stimulant laxative ingredients aloe, bisacodyl, cascara sagrada (including casanthranol, cascara fluidextract aromatic, cascara sagrada bark, cascara sagrada extract, and cascara sagrada fluidextract), and senna (including sennosides A and B) from category I (in the monograph as GRASE) to category III (more data needed). 63 Fed. Reg. 33592. Attachment G. In that June 19 notice, FDA requested mutagenicity, genotoxicity, and carcinogenicity data on aloe and cascara sagrada ingredients and carcinogenicity data on bisacodyl and senna. Id. The agency noted that, if data was not provided, FDA would place these ingredients in category II (non-monograph or misbranded). Id.

On May 9, 2002, FDA said that no comments or data were submitted for aloe or cascara sagrada ingredients and, thus, concluded that these ingredients will not be included in the final monograph for OTC laxative drug products because they have not been shown to be GRASE for their intended use. 67 Fed. Reg. 31125; see new 21 C.F.R. § 310.545(a)(12)(iv)(C). Attachment H. Companies that want to continue to market laxative products with these ingredient after November 5, 2002, the effective date, must submit an NDA or risk enforcement action. Id.

3. Cascara Sagrada is a GRASE OTC stimulant laxative ingredient

We recognize that FDA did not receive any data from any party, including our client, to support a determination that cascara sagrada is a GRASE ingredient in OTC stimulant laxative products. However, the failure to perform the FDA-requested testing does not negate the fact that cascara sagrada-containing OTC stimulant laxatives have been on the market for more than forty years, without presenting a public health risk. In our client's case, since December 1, 1999, the company has received two adverse event reports, neither of which presented serious health risks. The company sells more than 1.7 million capsules per month, so the two events, pale in comparison to the millions of casanthranol-containing OTC laxative products sold without complaint or incident. In this regard, we agree with the comments made in section C.1. of a Citizen Petition, submitted by Piper Rudnick on behalf of the American Herbal Products Association and the International Aloe Science Council, dated June 10, 2002.

Attachment I.¹ We do not believe that the failure to conduct testing requested by FDA is dispositive of whether cascara sagrada is indeed GRASE. If FDA were the sole arbiter of GRASE determinations, Congress would not have included the phrase "among scientifically qualified experts as safe and effective" in the FDC Act. 21 U.S.C. § 321(p)(1).

In addition, FDA's own regulations make clear that "safety" is not merely what the agency says it is:

Safety means a low incidence of adverse reactions or significant side effects under adequate directions for use and warnings against unsafe use as well as low potential for harm which may result from abuse under conditions of widespread availability. Proof of safety shall consist of adequate tests by methods reasonably applicable to show the drug is safe under the prescribed, recommended, or suggested conditions of use. This proof shall include results of significant human experience during marketing. General recognition of safety shall ordinarily be based upon published studies which may be corroborated by unpublished studies and other data.

21 C.F.R. § 330.10(a)(4)(i). As implied by the regulation, the lack of consumer complaints should be considered when evaluating product safety and, in this case, there are minimal reports of adverse safety events.²

In fact, it is widely accepted in the medical and scientific community that cascara sagrada is safe and effective as an OTC stimulant laxative product. According to the Encyclopedia of Herbs, Native American groups of the northwest Pacific coast long used cascara sagrada as a laxative, but cascara sagrada bark was not introduced into formal medical practice in the United States until 1877. In 1890, the product replaced the berries of the European buckthorn as an official laxative, and "it is still used in over-the-counter laxatives available in every pharmacy in the United States." Id. In short, according to the Encyclopedia of Herbs, "dried, aged cascara sagrada bark is widely accepted as a mild and effective treatment for chronic constipation." Id. Similarly, in the Handbook of Nonprescription Drugs (12th ed., pp. 287-288), published by the American Pharmaceutical Association (2000), it is noted that, "the drugs of choice in this group

¹ That June 2002 Citizen Petition raises other issues, such as the FDA action's effect on botanicals, which are beyond the scope of this Citizen Petition.

² We are aware that, for OTC laxative products and the type of safety concern that FDA has, consumer complaints might take longer to become apparent. However, cascara sagrada-containing OTC laxatives have been on the market for so long that, if indeed there was a public health risk, any negative health effects would have been seen by now, but it has not proven to be the case.

[stimulant laxatives] are cascara, casanthranol, and senna compounds." Attachment J.³ In addition, cascara sagrada and casanthranol both have official monographs listed in the United States Pharmacopeia.

In a recent toxicity study relating to rats, published in Life Sciences, the authors concluded that, unlike bisacodyl, cascara was not a carcinogen. See "Effect of bisacodyl and cascara on growth of aberrant crypt foci and malignant tumors in the rat colon," by F. Borelli et al., Life Sciences 69:1871-1877 (2001) 1871-1877. Attachment L. The study concluded: "our results outline the clear-cut possible promoting effect of bisacodyl on colon rat carcinogenesis especially at higher (diarrhogenic) dose and absence of any promoting or initiating activity of a laxative and diarrhogenic dose of cascara." Id. at 1876.

Finally, FDA should not dismiss the real-world practice of healthcare professionals. Specifically, based on informal discussions with many healthcare professionals who work in and around pain control and labor-delivery services, drug products containing cascara are frequently on standard order forms for postpartum vaginal and C-section deliveries. The use of a mild stimulant is preferred with or without a stool softener as a prophylactic measure to maintain bowel function. In addition, this type of product is often the agent of choice in patients receiving patient-controlled opioid analgesia, again as a prophylactic laxative.

4. OTC stimulant laxative drug products containing cascara sagrada ingredients have been marketed for a material extent and time and, thus, are not "new" drugs.

According to section 201(p)(2) of the FDC Act, a drug is not "new," therefore not requiring FDA premarket approval, if it has been used, outside of clinical investigations, "to a material extent or for a material time under [labeled] conditions." 21 U.S.C. § 321(p)(2). Manufacturers of OTC stimulant laxative drug products containing cascara sagrada ingredients have sold these products for years without incident. Therefore, because the products have been used for material extent and time, we believe that an NDA is not required because they are not "new" drugs.

³ It is also noteworthy that cascara is available as a dietary supplement in the United States and is sold in Canada and in many Western European countries, such as Belgium, France, Germany, and Spain. See, e.g., MICROMEDEX[®] Healthcare Series, at Section 4.3.D; MICROMEDEX[®] Healthcare Series, Cascamax; www.willpharma.com/uk/medicament/default.htm; www.petrone.it/cgi-bin/spa/main.cgi?act=sost&stq=O&str=DOCUSATOSODICO. Attachment K.

5. There will be no adverse effect if FDA refrains from taking enforcement action against a manufacturer of an OTC stimulant laxative drug product that contains cascara sagrada after November 5, 2002.

For the reasons previously described, petitioner contends that FDA should not require manufacturers of cascara sagrada-containing OTC stimulant laxative drug products to submit an NDA because these products are not "new" drugs. However, if FDA concludes otherwise, we recommend that the agency refrain from taking enforcement action against these manufacturers, pending publication of the final monograph on laxatives.

The evidence suggests that the products are safe and effective for their intended use. FDA should not assert, as it has done, that the absence of data given to FDA means the products are unsafe or ineffective. Companies have years of marketing history to suggest otherwise. Thus, we fail to understand the urgent nature of the agency's action. FDA has offered no evidence that would lead to a conclusion that the continued marketing of cascara sagrada-containing OTC stimulant laxatives presents an imminent health risk. Absent data from FDA, we recommend that the agency exercise enforcement discretion as companies attempt to reformulate their products to comply with FDA's decision.

6. If FDA chooses not to issue an interim enforcement policy, it should reconsider its decision.

If FDA decides not to issue an interim enforcement policy that it will refrain from taking action against manufacturers of cascara sagrada-containing OTC stimulant laxative drug products, we request that the agency reconsider its decision for the reasons described. We recognize that, according to 21 C.F.R. §§ 10.33 and 10.35, a petition for stay of action or reconsideration should be submitted within 30 days after the date of the decision involved, and this deadline has passed in this case. However, the regulations also permit FDA to consider the request after that 30-day period. 21 C.F.R. §§ 10.33(g) and 10.35(g). Another option for FDA to consider is imposing certain labeling restrictions relating to the product's use, so that the product remains available but is labeled according to FDA's prescribed conditions. While no drug product is perfect and almost all have limitations, FDA permits the sale of OTC products when the benefits outweigh the risks and adequate directions and warnings can be provided in the product labeling.

Because we do not believe that an FDA stay or reconsideration presents a public health concern, we respectfully request that the agency consider these options.

C. Environmental Impact

According to 21 C.F.R §§ 25.30(k) and 25.31(a), (c), this petition qualifies for a categorical exclusion from the requirement for submission of an environmental assessment.

D. Economic Impact

According to 21 C.F.R. § 10.30(b), petitioner will, upon request by the Commissioner, submit economic impact information.

E. Certification

The undersigned certifies, that, to the best knowledge and belief of the undersigned, this petition includes all information and view on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

Respectfully submitted,



Alan G. Minsk
Arnall Golden Gregory LLP
2800 One Atlantic Center
1201 West Peachtree
Atlanta, Georgia 30309-3450
Telephone: (404) 873-8690
Facsimile: (404) 873-8691

Attachments