

ANTHONY L. YOUNG  
anthony.young@piperrudnick.com  
direct 202.861.3882 fax 202.223.7642

June 10, 2002

**BY UPS AND E-MAIL**

Dockets Management Branch (HFA-305)  
Food and Drug Administration  
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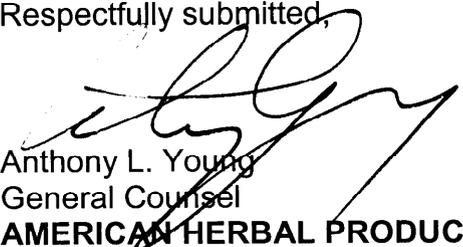
fdadockets@oc.fda.gov

Re: Docket No. 78N-036L  
OTC Laxative  
Drug Product Ingredients  
Aloe Vera and Cascara Sagrada

Dear Sir:

Please accept for filing the original and four copies of the enclosed Petition for Reconsideration and Petition for Stay of Action in the above-captioned docket.

Respectfully submitted,

  
Anthony L. Young  
General Counsel

**AMERICAN HERBAL PRODUCTS ASSOCIATION**  
Special Counsel  
**INTERNATIONAL ALOE SCIENCE COUNCIL**

ALY/jjb

Enclosures (4)

The e-mail version of this document does not include compendial enclosures.

78N.036L

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**BEFORE THE  
UNITED STATES OF AMERICA  
DEPARTMENT OF HEALTH AND HUMAN SERVICES  
FOOD AND DRUG ADMINISTRATION**

**PETITION FOR RECONSIDERATION  
AND  
PETITION FOR STAY OF ACTION**

**BY THE  
AMERICAN HERBAL PRODUCTS ASSOCIATION  
AND THE  
INTERNATIONAL ALOE SCIENCE COUNCIL**

**STATUS OF ALOE INGREDIENTS AND CASCARA SAGRADA INGREDIENTS  
AS OVER-THE-COUNTER DRUG ACTIVE INGREDIENTS**

**June 10, 2002**

Pursuant to 21 C.F.R. § 10.33 ("Administrative reconsideration of action") and 21 C.F.R. § 10.35 ("Administrative stay of action"), the undersigned American Herbal Products Association ("AHPA") and International Aloe Science Council ("IASC"), submit this petition to request a stay and reconsideration of the provisions of 21 C.F.R. § 310.545(a)(12)(iv)(C) and (d)(30) regarding the status of aloe vera ingredients (aloe, aloe extract, aloe flower extract) and cascara sagrada ingredients (casanthranol, cascara fluidextract aromatic, cascara sagrada bark, cascara sagrada extract, cascara sagrada fluidextract) which were purportedly made final in a Federal Register notice published May 9, 2002 (67 Fed. Reg. 31125). The relief requested is that the Food and Drug Administration ("agency") stay the November 5, 2002 effective date of this regulation and that the agency reconsider the regulation in light of new information not previously considered by the agency or its Advisory Review Panel on OTC Laxative, Antidiarrheal, Emetic, and Antiemetic Drug Products or, insofar as the associations are aware, by its OTC Drug Product staff.

AHPA is the national trade association and voice of the herbal products industry, which is comprised of domestic and foreign companies doing business as importers, growers, manufacturers, and distributors of herbs and herbal products. AHPA serves its members by promoting the responsible commerce of products which contain herbs and which are used to enhance health and quality of life. AHPA members manufacture and sell cascara sagrada-containing dietary supplements as dietary supplements for the relief of temporary or occasional constipation.

IASC is the international trade association and voice of the aloe vera products industry, which is comprised of growers, processors, manufacturers, wholesalers and retailers of aloe vera product from around the world. The IASC

was organized in 1981 to promote the quality of aloe vera products, encourage aloe vera product research and to address the business and regulatory needs of the growing aloe vera industry. IASC members manufacture and distribute aloe vera products from which the anthraquinone-containing aloin has been processed out, as liquid dietary supplement products.

A. Decision Involved

In the Federal Register of May 9, 2002, 67 Fed. Reg. 31125, FDA Docket No. 78N-036L, the agency published a final rule purporting to classify aloe vera and cascara sagrada ingredients stating that aloe vera and cascara sagrada will not be included in the final monograph for OTC laxative drug products because FDA has concluded that they “should be deemed not generally recognized as safe and effective for OTC use before a final monograph is established for OTC laxative drug products.” 67 Fed. Reg. At 31126. The rule purports to require that these ingredients be eliminated from OTC laxative drug products by November 5, 2002. AHPA and IASC seek a stay of the effective date of that rule and its reconsideration.

B. Action Requested

IASC and AHPA request that the purported final rule be stayed until the agency and a relevant Advisory Committee have reconsidered the action based on readily available information regarding the safe and effective use of these botanicals as well as the other positions, information and requests for clarification contained in this petition.

C. Statement of Grounds

1. The Proposed and Final Rule Fail to Establish that the Failure to Perform the Testing Requested by the Agency Vitiates the Well-Established General Recognition of the Safety and Effectiveness of Aloe and Cascara Sagrada as Laxative Ingredients.

There has long been general recognition of the safety and effectiveness aloe and cascara sagrada for use as laxative ingredients. This general recognition of safety and effectiveness was confirmed 27 years ago by the agency's Advisory Committee on OTC Laxative, Antidiarrheal, Emetic, and Antiemetic Drug Products. 40 Fed. Reg. 12902 (Mar. 21, 1975). That Advisory Committee conclusion was concurred in by the agency after a decade of thorough review and consideration of the available data and information regarding these ingredients. 50 Fed. Reg. 2124 (Jan. 15, 1985).

In the Federal Register of June 18, 1998 the agency reported that an internal agency Carcinogenicity Assessment Committee had recommended that aloe vera and cascara sagrada be tested in a standard battery of genotoxicity and, possibly, carcinogenicity tests. The agency then proposed to declare these ingredients Category II, nonmonograph, if such tests were not performed. The May 9, 2002 Federal Register notice against which this petition for reconsideration and stay is submitted carried out that proposal.

It is the position of IASC and AHPA that the agency does not have the legal right to require tests to be performed on drugs that are not new drugs and then summarily order those drugs to be removed from the market if such tests are not performed. Yet the agency has done just this; "any drug product

containing aloe or cascara sagrada will be considered nonmonograph and misbranded, \*\*\* and a new drug \*\*\* for which an approved new drug application under \*\*\* the act and \*\*\* the regulations is required for marketing.” 67 Fed. Reg. At 31126.

The appropriate legal test for the continued marketing of aloe and cascara sagrada is whether there is general recognition of their safety and effectiveness for laxative use. See 21 C.F.R. §330.10(a)(4)(I). According to the agency, the failure to perform the requested studies means that “they have not been shown to be generally recognized as safe and effective for their intended use.” 67 Fed. Reg. At 31126. But this rationale stands the concept of general recognition on its head. In essence, the agency has said that the determination by its internal committee that these studies should be performed and their failure to be performed meets that criteria. If that were so, the statute would not use the term and would set the agency up as the decisionmaker. This was done for new drugs but not for drugs that are not new drugs.

In addition to the lack of statutory authorization, the agency’s OTC drug review regulations regarding the general recognition of safety and effectiveness of OTC drug products nowhere provide that the agency has the power unilaterally to declare the requirements of general recognition of safety and efficacy. To the contrary, in 21 C.F.R. §330.10(a)(4)(I) those regulations spell out the test for general recognition of safety as follows:

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.

The agency's proposed and final Federal Register notices regarding aloe and cascara sagrada fail to meet or consider that standard.

2. In Concluding That Aloe and Cascara Sagrada are No Longer Generally Recognized as Safe and Effective Laxative Ingredients, the Agency Failed to Consider Relevant Conclusions by Others.

The safety and effectiveness of aloe and cascara sagrada has been generally recognized and well-established for decades. In AHPA's *Botanical Safety Handbook*, published in 1997, aloe and cascara sagrada are classified as Class 2 herbs, "Herbs for which the following use restrictions apply, unless otherwise directed by an expert qualified in the use of the described substance," which, in the case of these two herbs consist of the following label for products containing this herb in sufficient quantity to warrant the labeling: "Do not use this product if you have abdominal pain or diarrhea. Consult a health care provider prior to use if you are pregnant or nursing. Discontinue use in the event of diarrhea or watery stools. Do not exceed recommended dose. Not for long-term use." Attachment A, pp 7-8, 96. This caution substantively makes the points required by the State of California for such products.

In Germany, botanical drugs are regulated through a review that was conducted by the German Commission E which is described in the introduction to *The Complete German Commission E Monographs, Therapeutic Guide to Herbal Medicines* edited by Mark Blumenthal. Attachment B, pp. 27 –70. Aloe

and cascara sagrada bark are both approved herbs for which there are monographs. The Aloe monograph was published in 1985 and replaced in 1993. The Commission E aloe monograph provides for its use in the treatment of constipation. Such products are not for use for over two weeks without medical advice and is recommended for use only if no effects can be obtained by diet or the use of bulk forming laxatives. Attachment B, pp. 73, 80-81. Similarly, with respect to cascara sagrada, the Commission E monograph provides for its use in the treatment of constipation and the same restrictions as for aloe are applied to its use. Attachment B, pp. 73, 104-105. The Commission E monograph also provides other useful information regarding the appropriate use of these ingredients.

In *Herbal Medicine, Expanded Commission E Monographs*, Blumenthal et al further describe the evidence reviewed by Commission E as well as other evidence regarding cascara sagrada (aloe was not included). As pointed out in the introduction by the late Varro Tyler, Ph.D., of Purdue University, the Commission E monographs contained no references. Attachment C, pp. i and ii. One purpose of *Herbal Medicine* was to provide those references as well as discussion of the information contained in them. The discussion of cascara sagrada in the text points out that its first use in western medicine was reported by an Eclectic physician in 1877 and that it was later introduced as a product by Parke-Davis & Co. and then by Eli Lilly & Co. and that the European Scientific Cooperative on Phytotherapy has a monograph on this herb. Attachment C, pp 47 – 51.

The World Health Organization (“WHO”) has reviewed aloe (Attachment D) and aloe vera (Attachment E). Aloe is recognized by WHO as supported by clinical data for the short-term treatment of occasional constipation. Attachment

D, p. 37. WHO also discusses carcinogenesis, mutagenesis, impairment of fertility as follows [Attachment D, p. 39]:

Data on the carcinogenicity of Aloe are not available. While chronic abuse of anthranoid-containing laxatives was hypothesized to play a role in colorectal cancer, no causal relationship between anthranoid laxative abuse and colorectal cancer has been demonstrated. (Citations omitted.)

*In vitro* (gene mutation and chromosome aberration tests) and *in vivo* (micro-nucleus test in murine bone marrow) genotoxicity studies, as well as human and animal pharmacokinetic data, indicate no genotoxic risk from Cape Aloe (citations excepted).

Notably, WHO also evaluated aloe vera gel for topical use. In that evaluation WHO made clear that the gel is not to be confused with the juice which in its dried form is the laxative aloe ingredient. Attachment E, p. 43.

The above-cited evaluations of aloe and cascara sagrada have been available since they were published. The agency has not cited them at all. It is IASC's and AHPA's position that this failure vitiates the agency's determination that aloe and cascara sagrada are not generally recognized as safe and effective for their intended laxative use.

3. The Final Rule Fails Properly to Describe Aloe Suitable for Laxative Use as Compared to Aloe That is Marketed as a Food or as a Dietary Supplement for Non-Laxative Use.

The final rule fails to recognize and identify that the stimulant laxative ingredient aloe is not the same ingredient as the aloe ingredients that are sold as or contained in foods and dietary supplements. These are also aloe ingredients that are obtained from the leaves of one or more cultivated species of Aloe.

With respect to aloe flower extract, IASC and AHPA are not aware of this ingredient and it is not mentioned in either historical or modern botanical texts.

“Aloe” is defined in the current edition of the United States Pharmacopoeia as “the dried latex of the leaves of *Aloe barbadensis* Miller (*Aloe vera* Linné)...or of *Aloe ferox* Miller and hybrids of this species with *Aloe africana* Miller and *Aloe spicata* Baker...” (*United States Pharmacopeia 25 INational Formulary 20*. 2001. Rockville, MD: United States Pharmacopoeial Convention, Inc.).

“Aloe” is defined in the WHO monograph for aloe vera as “the dried juice of the leaves of *Aloe vera* (L.) Burm. f. or of *A. ferox* Mill. and its hybrids with *A. africana* Mill. and *A. spicata* Baker (Liliacea) ....” Attachment D, p. 33. This monograph goes on to describe the “plant material of interest” as the “dried juice,” and more specifically as the “[s]olidified juice originating in the cells of the pericycle and adjacent leaf parenchyma...allowed to dry...It is not to be confused with Aloe Vera Gel, which is the colourless mucilaginous gel obtained from the parenchymatous cells in the leaves of *Aloe vera* (L.) Burm. f.” (Attachment D, p. 34, *WHO Monographs on Selected Medicinal Plants*, vol. 1. 1999. Geneva: World Health Organization.) As set forth above, WHO provides a separate listing for each of the two ingredients.

Thus, “Aloe vera gel” is defined by WHO as “the colourless mucilinous gel obtained from the parenchymatous cells in the fresh leaves of *Aloe vera* (L.) Burm. (Liliaceae).” Attachment E, p. 43. It specifically states that “Aloe Vera Gel is not to be confused with the juice, which is the bitter yellow exudate originating from the bundle sheath cells of the leaf. The drug Aloe consists of the dried

juice...” (Id., *WHO Monographs on Selected Medicinal Plants*, vol. 1. 1999.

Geneva: World Health Organization.)

The agency should reconsider the definitions that have been provided for aloe and clarify that aloe vera gel is not intended to be covered in any way by the final rule.

4. The Agency Failed to Make a Proper Analysis as Required by the Regulatory Flexibility Act.

The Regulatory Flexibility Act (“RFA”) (5 U.S.C. § 601-612), requires an agency to consider the impact of its rulemaking on small businesses and to consider less burdensome alternatives. Under the RFA, agencies must prepare both an initial and final regulatory flexibility analysis for rules that may have a significant economic impact on a substantial number of small entities.<sup>1</sup> In practice, this requires agencies to prepare an analysis whenever a rule’s impact on small entities cannot be described as *de minimis*. This regulatory flexibility analysis must be undertaken, unless an agency head provides a “certification,” which is a finding of no significant impact on a substantial number of small entities.

FDA, in both its proposed and final rule implementing the final rule, concluded that its rulemaking would *not* have a significant economic impact on a

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<sup>1</sup> According to the Small Business Administration (SBA), distributors of drugs with 100 or fewer employees are considered small entities. In its final rule, FDA states that 94 percent of the drug distribution firms, or approximately 4,000 firms, are small. 64 Fed. Reg. 67720, 67753 (December 3, 1999).

substantial number of small entities. 63 Fed. Reg. 33592, 33594 (June 19, 1998); 67 Fed. Reg. 31125, 31126 (May 9, 2002). FDA came to this determination simply by analyzing the impacts on OTC drug product manufacturers and marketers of products containing aloe and cascara sagrada and concluding that the regulatory costs would be less than \$100 million. This basic premise is wrong because aloe in its non-laxative form is widely sold as a food and as a dietary supplement. Moreover, cascara sagrada is widely manufactured and sold as a dietary supplement to address temporary or occasional constipation.

Under the final rule, it is wholly lawful to market food or dietary supplement products containing aloe vera and to market dietary supplement products containing cascara sagrada. This fact is nowhere noted in the final rule. Accordingly, the impact of the final rule on those who manufacture and distribute foods and dietary supplements containing aloe or cascara sagrada was not considered at all. The agency has recognized that most of the manufacturers and distributors of dietary supplements meet the definition of small businesses. 60 Fed. Reg. At 67211 (Dec. 28, 1995).

It is the position of the IASC and AHPA that the agency must consider the collateral as well as the direct effects of the final rule before it may be implemented. This has not been done at all with respect to food and dietary supplement manufacturers and marketers. Because most of these are small businesses, this analysis is important and should be done.

Certification in Lieu of a Full Analysis. An agency must undertake a preliminary threshold analysis to determine the economic impact of a proposed rule on small food and dietary supplement entities before it can make a “certification,” like the one made by FDA in this instance. 5 U.S.C. § 605(b). To “certify,” an agency head provides certification that the rulemaking will not have a significant economic impact on a substantial number of small entities. *Id.* If the agency makes such a determination, it need not undertake an initial regulatory flexibility analysis, however, it must provide “a statement providing the factual basis for such certification” in the Federal Register at the time it proposes its rulemaking. *Id.* The RFA does not state what constitutes a significant economic impact on a substantial number of small entities, but cases decided under the law teach that rules have been set aside in circumstances similar to those in the FDA’s PDMA rulemaking.

In North Carolina Fisheries Ass’n, Inc. v. Daley, 16 F. Supp.2d 647 (E.D. Va. 1997), *remanded* 27 F. Supp.2d 650 (E.D. Va. 1998), the court invalidated a certification made by the National Marine Fisheries Service (NMFS) regarding a 1997 flounder fishery quota. NMFS recommended a new quota “no different” from the previous year’s quota without undertaking any analysis to determine if it had a significant economic impact on a substantial number of small entities. The NMFS’s statement of “no difference” did not provide a factual basis demonstrating that there would be no impact. 16 F.Supp.2d at 652. Here, the statement by FDA that its proposed and final rule simply implemented prior

practice, a statement that was not supported by any analysis and was flatly wrong, also does not provide the requisite factual basis.

The Initial Regulatory Flexibility Analysis. Where an agency cannot certify the lack of a significant economic impact, the RFA requires federal agencies to consider the impact of regulations on small entities at the proposal stage by conducting an initial regulatory flexibility analysis. 5 U.S.C. § 603(a). This analysis ensures that the agency has considered all reasonable regulatory alternatives that would minimize the rule's economic burdens or increase its benefits for the affected small entities, while achieving the objectives of the rule.

Under 5 U.S.C. § 603(b), an agency's initial regulatory flexibility analysis must contain:

- (1) the reasons why action by the agency is being considered;
- (2) the objectives and legal basis for the rule;
- (3) an estimate of the number of small entities to which the proposed rule will apply;
- (4) the reporting or recordkeeping the proposed rule would require;
- (5) all Federal rules that may duplicate, overlap or conflict with the proposed rule.

The requirement of 5 U.S.C. § 603(c) that each initial regulatory flexibility analysis contain a description of *any significant alternatives* to the proposal that accomplish the statutory objectives and *minimize* the significant economic impact of the proposal on small entities is detailed and specific. The analysis should discuss *significant alternatives* such as:

- (1) differing compliance or reporting timetables;
- (2) clarification, consolidation or simplification of compliance and reporting requirements;
- (3) the use of performance rather than design standards; and
- (4) an exemption from coverage of the rule, or any part thereof.

5 U.S.C. § 603(c).

In the FDA's proposal and in its final rule, there is no discussion whatsoever of the use of aloe in food and aloe and cascara sagrada in dietary supplements. Moreover, the proposal never discusses the fact that the FDA has recognized that laxative structure-function claims may be made for dietary supplements containing laxative dietary ingredients. Similarly, there is no discussion whatsoever of the impact of the proposal or final rule to require data and information for these ingredients for their OTC drug use and how that request and the conclusion that followed will affect these other uses of the ingredients.

The Final Regulatory Flexibility Analysis. The RFA also requires an agency, when it issues a final rule, to prepare a final regulatory flexibility analysis or to certify the lack of a significant economic impact on small businesses. The final regulatory flexibility analysis must discuss the comments received, the significant alternatives considered and the rationale for the final rule. 5 U.S.C. § 604. The law requires that each final regulatory flexibility analysis contain:

- (1) a statement of the need for and objectives of the rule;
- (2) a summary of the issues raised by the public comments in response to the initial regulatory flexibility analysis, the agency's assessment of these comments, and a statement of any changes made;
- (3) the number of small entities to which the rule will apply;
- (4) the projected reporting, recordkeeping and other compliance requirements of the rule; and
- (5) a description of the steps the agency has taken to minimize the significant economic impact on small entities consistent with the stated objectives of applicable statutes, including a statement of the factual, policy and legal reasons for selecting the alternative

adopted in the final rule and why each one of the other significant alternatives to the rule was rejected.

5 U.S.C. § 604(a).

Importantly, as in the initial regulatory flexibility analysis, the agency must analyze the relative merits and demerits of the alternatives and explain the rationale for the final agency action. An agency may not simply rely on its preamble to the final rule to comply with the requirements for a final regulatory flexibility analysis. Agencies must provide specific discussion of small entity alternatives designed to reduce adverse impacts or enhance the beneficial impacts of a rulemaking. Small Business Administration, *Guide to the Regulatory Flexibility Act* (May 1996) at 12.

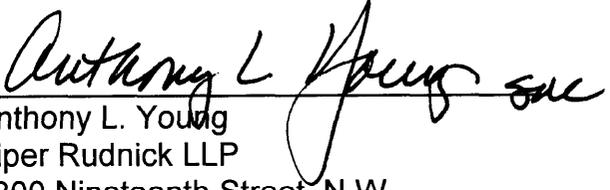
In the FDA's final rule, no such analysis was made with respect to the food or dietary supplement uses of these ingredients and this failure of analysis occurred despite the fact that the agency's drug regulatory staff is highly involved in the review of dietary supplement products. Thus, it is surprising that the agency fails completely to discuss the economic impact this interpretation will have on the small food and dietary supplement businesses.

#### D. CONCLUSION

AHPA and IASC requests that FDA reconsider the final rule regarding the use of aloe and cascara sagrada in OTC drug products as requested herein. In addition, IASC and AHPA request a stay of the final rule until the agency has had the opportunity to confer with AHPA and IASC regarding the collateral effect of the rule on the use of aloe as a food or in dietary supplements and of cascara

sagrada as a dietary supplement. A stay of the regulation would not adversely effect the public interest because the agency has cited no information whatsoever that these ingredients pose any health risks to consumers when the products are used as directed.

Respectfully submitted,

  
Anthony L. Young  
Piper Rudnick LLP  
1200 Nineteenth Street, N.W.  
Washington, DC 20036  
(202) 861-3882  
General Counsel  
American Herbal Products Association  
Special Counsel  
International Aloe Science Council

Mr. Michael McGuffin  
President  
American Herbal Products Association  
8484 Georgia Avenue  
Suite 370  
Silver Spring, MD 20910  
301/588-1171

Gene Hale  
Managing Director  
International Aloe Science Council, Inc.  
415 E. Airport Freeway  
Suite 250  
Irving, Texas 75062  
972/258-8772