DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

JUL 3 2003

Anthony L. Young, Esquire
American Herbal Products Association
International Aloe Science Council
1200 Nineteenth Street, N.W.
Washington, D.C. 20036-2412

Re: Docket No. 78N-036L
Comments No. CP25,
SUP14, and SUP15

Dear Mr. Young:

This responds to your citizen petition (CP25) submitted on June 11, 2002, requesting administrative reconsideration of action and administrative stay of action for a final rule that the Food and Drug Administration (FDA) published on May 9, 2002 (67 FR 31125). This letter also responds to the supplemental information you submitted on October 28, 2002 (SUP14) and December 19, 2002 (SUP15).

I. PETITIONERS' REQUEST AND FDA'S DECISION

In the May 9, 2002 final rule, FDA declared the stimulant laxative ingredients aloe (including aloe extract and aloe flower extract) and cascara sagrada (including casanthranol, cascara fluidextract aromatic, cascara sagrada bark, cascara sagrada extract, and cascara sagrada fluidextract) in over-the-counter (OTC) drug products as not generally recognized as safe and effective (GRASE) or misbranded. You requested that FDA stay the effective date of this final rule and that FDA and a relevant advisory committee evaluate new information regarding the safe and effective use of these ingredients.

As grounds for your petition, you contend that FDA 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. You cite the agency's regulation for general recognition of safety of an OTC drug in 21 CFR 330.10(a)(4)(i) and state that the agency's proposed and final Federal Register notices regarding aloe and cascara sagrada fail to meet or consider that standard. You also contend that, in concluding that aloe and cascara sagrada are no longer GRASE laxative ingredients, the agency failed to consider relevant conclusions by others. You also contend that 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. You claim that FDA failed to make a proper analysis as required by the Regulatory Flexibility Act because it considered only the "direct" effects of the rule and not its "collateral" effects.

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

II. DISCUSSION

A. Background

1. Legal Authority

FDA has the statutory authority under the Federal Food, Drug, and Cosmetic Act (FFDCA) (21 U.S.C. 321 et seq.) to ensure that drug products sold in the United States are safe and effective and not misbranded. The final rule issued on May 9, 2002 falls squarely within that authority. FDA established its OTC drug review in 1972 as a mechanism to evaluate the safety and effectiveness of OTC drugs that would not be considered new drugs, as defined in section 201(p) of the FFDCA (21 U.S.C. 321(p)).

The OTC drug review determines 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.

As part of the OTC drug review, a panel of experts (the Advisory Review Panel on OTC Laxative, Antidiarrheal, Emetic, and Antiemetic Drug Products) (the Panel) reviewed the ingredients in OTC laxative drug products and recommended to FDA that the stimulant laxative ingredients aloe, bisacodyl, cascara sagrada [preparations], danthron, phenolphthalein, and senna could be GRASE. The Panel's report was published in the Federal Register of March 21, 1975 (40 FR 12902). The agency agreed with the Panel's recommendations for these ingredients in the tentative final monograph (TFM)[1] for OTC laxative drug products, which was published in

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[1] A TFM is a proposed rule stating the agency's proposed conditions, based on the information considered up to that time, under which a category of OTC drugs or specific OTC drugs are GRASE. This status does not become final until the agency publishes the final monograph.

the Federal Register of January 15, 1985 (50 FR 2124). In this TFM, the agency proposed GRASE status for these stimulant laxative ingredients.

After publication of the TFM, FDA became aware of studies concerning the potential carcinogenic risk of danthron, which subsequently led FDA to send a recall letter to all registered drug firms and distributors stating that "danthron toxicity in humans has not been specifically demonstrated, but because of potential risk, FDA requested an immediate halt to all manufacturing, relabeling, repackaging, and further distribution of human drug products containing danthron as an ingredient." Danthron was removed from OTC drug products in 1987.

Subsequently, in 1996 FDA became aware of data indicating that phenolphthalein is a potential carcinogen in humans. In the Federal Register of September 2, 1997 (62 FR 46223), FDA discussed the removal of danthron from OTC laxative drug products as a potential carcinogen in 1987. The agency noted that danthron had not been specifically included in part 310 (21 CFR 310) as a new drug and proposed to amend § 310.545 to include danthron as a nonmonograph ingredient. In the same notice, the agency discussed new information on phenolphthalein studied for its carcinogenic potential in rats and mice. Based on rodent carcinogenicity and genotoxicity in several test systems, FDA was concerned that these findings indicate that chronic use of phenolphthalein could lead to damage to the human genome (including p53, which is known to be a tumor suppressor gene) and could increase the risk of malignancy. FDA believed that such genetic damage and increased risk could occur at phenolphthalein doses that are likely to be used by humans. Because of this concern, FDA proposed to declare all drug products containing phenolphthalein "new drugs" per section 201(p) of the FFDCA. Accordingly, FDA amended the laxative TFM at that time to classify both ingredients as nonmonograph (not GRASE). FDA issued a final rule on this proposal in the Federal Register of January 29, 1999 (64 FR 4535). The final rule was effective January 29, 1999, based on the safety problem identified for OTC drug products containing phenolphthalein.

In the Federal Register of June 19, 1998 (63 FR 33592), FDA reopened the administrative record for the rulemaking for OTC laxative drug products and reclassified the stimulant laxatives aloe, bisacodyl, cascara sagrada, and senna from proposed GRASE status to "further testing is required." The agency discussed the chemical similarity of these anthraquinone ingredients to each other and to phenolphthalein, mutagenicity studies that had been conducted on bisacodyl, and metabolic, genotoxicity, and carcinogenicity data on senna and its components. The agency noted that it had received no data on mutagenicity, genotoxicity, or carcinogenicity for aloe and cascara sagrada. Based on the similarity of these ingredients to danthron and phenolphthalein, which had been found to be carcinogens after the TFM was published, the agency determined that these other stimulant laxative ingredients needed additional safety data and stated that aloe, bisacodyl, cascara sagrada, and senna needed to have the same types of data (mutagenicity, genotoxicity, and carcinogenicity) and other toxicity data using tests similar to those used and found positive for phenolphthalein. Based on the potential risks, the agency determined it needed such data to make a final determination on the GRASE

status of these ingredients for use in OTC laxative drug products and stated that if these data are not provided or are inadequate for any of these ingredients, they would be placed in nonmonograph status in a final rule.

In the final rule published on May 9, 2002, FDA stated that it had received data on bisacodyl and senna, which it would discuss in future issues of the Federal Register, but that no comments or data had been submitted for aloe or cascara sagrada ingredients. Based on this lack of data and information and the failure of interested persons to submit any new data from carcinogenicity studies during the almost 4 years since the agency requested that information, FDA considered the potential risk of these products as outweighing the benefits. Further, FDA was not aware of any ongoing studies being conducted. Thus, FDA determined that aloe and cascara sagrada ingredients should be deemed not GRASE for OTC use before a final monograph is established for OTC laxative drug products. Accordingly, the agency finalized the GRASE evaluation of these ingredients and classified them as nonmonograph (not GRASE). FDA considered this action to be in accord with its safety standards for OTC drug products in 21 CFR 330.10(a)(4)(i) because it lacked sufficient information to find these ingredients "safe" under their conditions of OTC use.

2. New Data Provided

You cite a number of publications that included: the American Herbal Products Association Botanical Safety Handbook (1997); The Complete German Commission E Monographs, Therapeutic Guide to Herbal Medicines (1998), containing an aloe monograph published in 1985 and replaced in 1993 and a cascara sagrada bark monograph published in 1984 and replaced in 1993; Herbal Medicine, Expanded Commission E Monographs (no date provided); and World Health Organization (WHO) reviews of aloe and aloe vera (undated). You noted that WHO discusses carcinogenesis, mutagenesis, impairment of fertility, and genotoxicity of aloe [references 32 to 38]. You conclude that the agency's failure to cite these references vitiates the agency's determination that aloe and cascara sagrada are not GRASE for their intended laxative use.

The OTC drug review administrative procedures in 21 CFR 330.10 invite interested persons to submit data and information for the agency to consider to establish GRASE status for OTC drug ingredients. While the agency may include other information in the administrative record for an OTC drug rulemaking, it is not required to do so. Nor is the agency required to do an exhaustive literature search to try to find all data that exist on a particular ingredient. In the case of aloe, bisacodyl, cascara sagrada, and senna, the agency informed all interested parties what additional information it needed to make a GRASE determination. Interested parties provided information on bisacodyl and senna, but not on aloe or cascara sagrada before the final rule was published on May 9, 2002.

Nonetheless, the agency evaluated the additional information that you provided and finds

it inadequate to support GRASE status for aloe and cascara sagrada for OTC drug use as a laxative. The Botanical Safety Handbook, German Commission E Monographs, and Herbal Medicine, Expanded Commission E Monographs contain general information about these ingredients, similar to the Panel's report published in 1975. While the German Commission E Monographs contain some pertinent information [e.g., the statements in the aloe monograph about mutagenic effects], no supporting references are provided to allow assessment of the statements. We note that the Commission E monographs state that since 1995 Commission E has not issued any new monographs and that its monograph on cascara sagrada bark states: "Experiments pertaining to the genotoxicity of cascara sagrada and its preparations are not available. Some positive data were obtained for aloe-emodin, emodin, physicon and chrysphanol. No data are available for carcinogenicity."

We evaluated the pertinent WHO references [numbers 32 to 38] on carcinogenesis, mutagenesis, impairment of fertility, and genotoxicity for aloe and find the data therein insufficient to support GRASE status. These references include seven literature reports - three original studies, three review articles, and one case report - published between 1980 and 1994 [before our 1998 request for data]. Although no WHO review of cascara sagrada was provided, we note that some of the chemical components of cascara sagrada were tested and discussed in the WHO reference articles on aloe. Our assessment of the WHO data on aloe follows.

Reference 32 (Siegers, C. P., "Anthranoid laxative abuse--a risk for colorectal cancer," Gut, 1993, 34:1099-1101) reported two clinical case-series, or descriptive, epidemiology studies to determine the association between colic abnormality and pseudomelanosis coli, a reliable indicator of chronic anthranoid laxative abuse. In case-series study #1 ("retrospective" study), colic abnormality was presented in 3,049 patients who underwent endoscopy between 1981 and 1987. The incidences of diagnosed gastrointestinal abnormalities with pseudomelanosis coli were determined. A statistically significant increase in pseudomelanosis coli was found in adenoma patients [59 out of 683, 8.64%, p value (Fisher test) < 0.01] as compared to patients without endoscopic abnormality. In case-series study #2 ("prospective" study), endoscopic and pathologic data from 1,095 patients were collected between October 1989 and March 1991. The difference between this study and the first study was that the identification of pseudomelanosis coli was prospectively searched for during endoscopy and found in 22 of 225 adenoma patients [9.8%, p value (Fisher test) 0.07] and in 11 of 59 carcinoma patients [18.6%, p value < 0.001]. All 33 patients with adenoma (22) and carcinoma (11) were asked about laxative use history; 31 of them had abused anthranoid laxatives for 10 to 30 years (the actual laxatives used were not specified in the report). The agency finds that the results of this study suggest an association of laxative abuse with colon tumors, such as adenoma and carcinoma, based on indirect evidence of laxative abuse and pseudomelanosis coli. The correlation of the colon tumors with particular anthranoid-containing laxatives was not known.

Reference 33 (Siegers, C. P., "Anthranoid laxatives and colorectal cancer," Trends in Pharmacological Sciences," 1992, 13:229-231) was a review article that discussed genotoxicity

and carcinogenicity of anthranoids, including aloe and cascara. Several in vitro genotoxicity tests were positive with aloe-emodin, a component of both aloe and cascara: Ames (metabolic activation reduced mutation), UDS, and V79 mutation assay. The in vivo genotoxicity tests were contradictory (no details were discussed in the article). Tests on chrysophanic acid, one of cascara's chemical constituents, were positive in the bacterial mutation assay but negative in the mammalian cell assay. A carcinogenicity study in rats fed a diet containing 1% 1-hydroxyanthraquinone (a similar ingredient in aloe) for 480 days showed in the tested diet group 86% (25 of 29) developed adenoma or adenocarcinomas cecum and upper colon, 41% (12 of 29) developed liver tumor, and 17% (5 of 29) developed benign gastric tumor. These tumor types were not found in the control rats fed a basal diet. Several epidemiological studies were also discussed. The agency finds that the information summarized in this review article does not alleviate the concern of potential carcinogenicity of anthranoid laxatives, including aloe and cascara, in humans.

Reference 34 (Patel, P. M., et al., "Anthraquinone laxatives and human cancer," Postgraduate medical journal, 1989, 65:216-217) was a case report involving danthron, an anthraquinone laxative the agency removed from the market in 1987 as a potential carcinogen in humans. This reference is not directly related to aloe or cascara sagrada.

Reference 35 (Loew, D., "Pseudomelanosis coli durch Anthranoide," Zeitschrift fur Phytotherapie, 1994, 16:312-318) was an article about pseudomelanosis coli induced by anthranoids that was written in German with a brief abstract in English. The abstract did not clearly describe the type of study and conclusion and was not helpful.

Reference 36 (Lang, W., "Pharmacokinetic-metabolic studies with 14C-aloe emodin after oral administration to male and female rats," Pharmacology, 1993, 47 (Suppl. 1):73-77) was a study in which rats received orally (by gavage) 14C-labeled aloe-emodin followed by monitoring 14C radioactivity in plasma and organs/tissues up to 168 hours. The metabolites of aloe and emodin in plasma were measured. The study showed aloe-emodin can be absorbed after oral administration [at least 30% (plasma terminal half-life was 50 hours)], is highly bound to plasma protein [> 95%], and is rapidly metabolized. The absorbed aloe-emodin was mainly eliminated through urine, although biliary elimination may be possible [not determined in this study]. The major target organs were the liver and the kidneys after absorption. The long-term effects of this systemic exposure after aloe-emodin and its metabolites are not known. The agency finds this study does not eliminate the need for a carcinogenicity study, and this reference does not support GRAS status.

Reference 37 (Brown, J. P., "A review of the genetic effects of naturally occurring flavonoids, anthraquinones and related compounds," Mutation Research, 1980, 75:243-277) was a review article in which the second part discussed genetic effects of anthraquinone laxatives, which included aloe (aloe-emodin and aloin) and cascara sagrada (chrysophanol and physicon). Bacterial reverse mutation assays from literature reports showed that TA1537 was positive for

aloe-emodin, rhein, chrysophanol, and physicon. There were no mammalian cell mutation assays or animal carcinogenicity studies available when this article was prepared. The author suggests that the structural similarity between the phenolic anthraquinones and the carcinogenic mycotoxins (-)-luteoskyrin and (+)-regulosin, together with positive bacterial mutation tests, should encourage a cautious attitude regarding undue exposure to these agents. The agency finds that this review article suggests that the chemical constituents in aloe and cascara sagrada may be genotoxic and does not support GRAS status.

Reference 38 (Westendorf, J., et al., "Genotoxicity of naturally occurring hydroxyanthraquinones," Mutation Research, 1990, 240:1-12) was an original study in which four in vitro genotoxicity assays were conducted with 16 anthraquinones, including aloe-emodin and cascara sagrada (chrysophanol and physicon). The assays were the Ames test, unscheduled DNA synthesis (primary rat hepatocytes), V79 mutation assay, and malignant transformation assay (C3H/M3 mouse fibroblast). All four assays on aloe-emodin were positive. Cascara was positive using the Ames tests (positive TA1537 and TA102 on chrysophanol and positive TA1537 + S9 on physicon). The agency notes that cascara sagrada contains an aloe-emodin-type anthranoid, which was positive on all four genotoxicity assays. The agency finds that this study indicates that aloe and cascara sagrada are genotoxic.

It is our view that the WHO monograph on aloe made an incorrect conclusion based on the findings from this study and the other reference articles mentioned above. In conclusion, our review of the WHO data does not change our decision that aloe and cascara sagrada ingredients are not GRASE for OTC laxative use.

We have also reviewed the supplemental information that you submitted on October 28, and December 19, 2002. The October 28, 2002 submission provides a literature search on genotoxicity and carcinogenicity of chemical constituents contained in aloe and cascara. The search was performed on the chemical substances "aloe-emodin," "barbaloin," "casanthranol," "cascara," "cascaroside," "chrysaloin," "chrysophanol," and "emodin" in a number of databases. However, you did not specify the searching methodology that was used. You provided only a brief summary of mutagenicity data and a list of literature references, which were directly retrieved and printed out from the databases. You did not provide any summary of the literature references and interpretation of the study results. Thus, we consider this supplemental submission to be incomplete and not reviewable. You should have conducted and submitted a review of the literature references, including strategies for the literature search and the coverage of the literature databases.

Further, we note that the printouts from the chemical carcinogenesis research information system (CCRIS) show positive mutagenicity findings for aloe-emodin and emodin using the Ames test and the mammalian cell assay. We conclude that the positive genotoxic results from the limited mutagenicity summary included in this submission suggest that aloe and cascara sagrada are potentially carcinogenic to humans and that additional studies are needed to

support GRASE status.

The December 19, 2002 submission provides a review [conducted by the Toxicology Group, LLC, Ann Arbor, Michigan] of genotoxic and carcinogenicity studies on emodin published by the National Toxicology Program (NTP) of the National Institutes of Health to assess the carcinogenic risk of cascara sagrada and compared the studies with a NTP study on phenolphthalein. The two technical reports published by NTP are entitled "TR-465: Toxicology and Carcinogenesis Studies of Phenolphthalein (CAS No. 77-09-8) in F344/N Rats and B6C3F1 Mice" (November 1996) and "TR-493: Toxicology and Carcinogenesis Studies of Emodin (CAS No. 518-82-1) in F344/N Rats and B6C3F1 Mice" (June 2001). The review discusses the chemistry and pharmacology of cascara sagrada followed by a comparison of genotoxicity and carcinogenicity between emodin and phenolphthalein. The results suggest that emodin, one of the constituents of cascara sagrada, is less genotoxic than phenolphthalein and that there is equivocal evidence of carcinogenic activity in rats and mice treated with emodin but clear evidence in those treated with phenolphthalein. You contend that the toxicity of emodin is relevant to the toxicity of cascara sagrada because the chemical structure of the other hydroxyanthracene derivatives of cascara sagrada is very similar to emodin and this should support maintaining the inclusion of at least cascara sagrada bark in the monograph.

We do not find the genotoxicity and carcinogenicity results from the NTP study on emodin extrapolatable to the other anthraquinone derivatives contained in cascara sagrada preparations. The literature suggests that the genotoxicity of anthraquinone derivatives is clearly structure dependent. We are aware of genotoxicity and carcinogenicity results from other NTP studies, which you did not provide or discuss, on anthraquinone related to cascara sagrada. The report, entitled "Toxicology and Carcinogenesis Studies of Anthraquinone (CAS No. 84-65-1) in F344/N Rats and B6C3F1 Mice" (draft, May 1999, at http://ntp-server.niehs.nih.gov), indicates that there is clear evidence of carcinogenic activity of anthraquinone in rats and mice. As you note on page 5 of your submission, anthraquinone glycosides (the primary constituents of cascara sagrada) are hydrolyzed by the gastrointestinal flora to produce anthraquinone. This suggests that cascara sagrada may be a potential human carcinogen.

We conclude that the information in these two supplemental submissions does not rule out the possibility that aloe and cascara sagrada preparations are genotoxic and/or carcinogenic and that additional animal carcinogenicity and/or epidemiology studies need to be conducted for further risk assessment. The information you provided does not change our decision, as expressed in the final rule, that there are insufficient data to support GRASE status for both aloe and cascara sagrada.

3. Aloe as an Ingredient for OTC Laxative Use

You mention the United States Pharmacopoeia (U.S.P.) definition of aloe and WHO monographs for aloe and aloe vera gel, specifically noting that WHO provides a separate listing

for each of the two ingredients. You also pointed out that the WHO monograph states that aloe vera gel is not to be confused with the juice, and the drug aloe consists of the dried juice. You stated that your clients were not aware of aloe flower extract. You asked the agency to reconsider the definitions for aloe and clarify that aloe vera gel is not intended to be covered in any way by the final rule.

The final rule issued on May 9, 2002 addresses only OTC drug products. There was no need and no basis for the agency to describe aloe marketed as a food or as a dietary supplement for non-laxative use because those products were not within the scope of the rule. Further, neither the administrative record for this rulemaking nor your petition contain information on aloe marketed as a food or as a dietary supplement for non-laxative use.

The agency has again reviewed the types of aloe ingredients. The final rule applies primarily to aloe as defined in the U.S.P. used in OTC laxative drug products. U.S.P. 25 defines aloe as "the dried latex of the leaves of *Aloe barbadensis* Miller (*Aloe vera* Linne), known in commerce as Curacao Aloe, or of *Aloe ferox* Miller and *Aloe spicata* Baker, known in commerce as Cape Aloe (Fam. Liliaceae). Most of the aloe-containing laxative products in the agency's Drug Listing System (DLS) identify their active ingredient as "aloe." One product in the agency's DLS identifies its active ingredient as "aloe extract" and four products in the agency's DLS identify their active ingredient as "aloe flower extract." Two of the products containing aloe flower extract use "Aloe Vera Laxative Capsules" and "Cape Aloe 250 Capsules" as their respective product names. As noted above, the U.S.P. states that one of the aloe ingredients it describes is known in commerce as "Cape Aloe." Without further information, the agency cannot be certain about the actual source of the aloe in those products that list aloe extract and aloe flower extract as their active ingredient. However, as the manufacturers have listed the products in the DLS, the agency considers them as marketed for OTC laxative drug use and subject to the final rule.

We note that there is no U.S.P. monograph for aloe vera and that WHO has separate monographs for aloe and aloe vera gel. We also note that there is significant overlap in the synonyms listed for aloe and aloe vera gel in the WHO monographs. Finally, we note that the WHO monograph states that aloe vera gel is not approved as an internal medication, and internal administration of the gel has not been shown to exert any consistent therapeutic effect. In general, we do not consider aloe vera gel to be directly covered by this final rule because this ingredient was not considered in the agency's OTC drug review rulemaking for these laxative products and products containing this ingredient do not appear to have been marketed as OTC drug products for laxative use. Any marketing of aloe vera gel for internal use as an ingredient in OTC laxative drug products would cause such products to be considered unapproved new drugs as defined in the Federal Food, Drug, and Cosmetic Act (see 21 U.S.C. 321(p) and 355) because the agency has no evidence that aloe vera gel is GRASE for this use. Such OTC drug products would be subject to appropriate regulatory action by the agency.

4. FDA's Analysis Under the Regulatory Flexibility Act

You contend that the basic premise of the agency's regulatory flexibility analysis was wrong because it did not discuss aloe in its non-laxative form sold as a food and as a dietary supplement and did not discuss cascara sagrada sold as a dietary supplement to address temporary or occasional constipation. You stated that the agency must consider the collateral as well as the direct effects of the final rule before it may be implemented, and that this has not been done with respect to food and dietary supplement manufacturers and marketers. You mention that under the final rule it is lawful to market food or dietary supplement products containing aloe vera and to market dietary supplement products containing cascara sagrada.

We disagree with your position about the scope of the agency's regulatory flexibility analysis in the final rule. As we noted above, this final rule addressed only OTC drug products containing aloe and cascara ingredients for laxative use and established that these ingredients in OTC drug products for this use are not GRASE or are misbranded. This final rule does not pertain to food or dietary supplement uses of these ingredients, and there was no basis or reason for the agency to discuss the economic impact on manufacturers of such products. The agency's analysis of impacts indicates that approximately 15 OTC laxative drug products that contain aloe and 160 OTC laxative drug products that contain cascara sagrada ingredients are affected by the final rule. The agency also stated that its DLS indicates that approximately 35 manufacturers and 70 distributors/repackers/relabelers market the 170 affected products [six products contain both ingredients]. The agency concluded that acting on the nonmonograph status of these stimulant laxative ingredients in advance of finalization of other monograph conditions would not be a significant regulatory action as defined by Executive Order 12866. The agency stated that it considered but rejected not acting on these ingredients in advance of the finalization of other monograph conditions because of the potential safety risks of these ingredients.

As you noted, under the final rule, it remains lawful to market food or dietary supplement products containing aloe vera and to market dietary supplement products containing cascara sagrada. Should the agency have concerns about the marketing of food or dietary supplement products containing these ingredients, those concerns would be addressed in the appropriate forum. However, the final rule does not apply to those uses of the ingredients; therefore, the agency did not discuss such uses in the final rule because it has no impact on manufacturers/distributors/repackers/relabelers of such food or dietary supplement products.

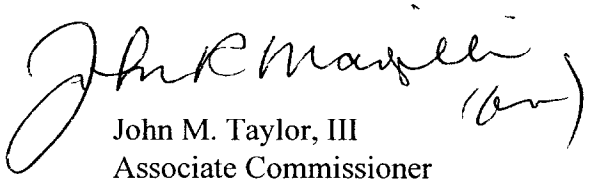
III. CONCLUSION

You asked that FDA reconsider the final rule in accord with your comments stated above, confer with your clients 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, and to stay the November 5, 2002 effective date of the regulation.

We have reconsidered the final rule in accord with your comments. We have also considered the new information that you provided and determined that it is not sufficient to support GRASE status of aloe or cascara sagrada ingredients for use as a laxative in OTC drug products. Thus, the agency confirms its determination of nonmonograph status for these laxative ingredients and the November 5, 2002 effective date of the final rule. Based on our review of the information you provided, we have determined that there are no controversial issues in those data that agency scientists have not been able to evaluate and that we need to present to an agency advisory committee for consideration. Finally, we see no need to confer with your clients 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 because the rule does not pertain to such uses.

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 Dockets Management Branch (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: JUL 9 2003

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

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

TO: Dockets Management Branch, HFA-305

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

[X] This material should be cross-referenced to Comment No. CP25 - SUP14 and SUP15

Charles J. Ganley, M.D.

Attachment