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Inside Aloe Online is the official publication of the International Aloe Science Council (IASC), the organization dedicated to serving the needs of the aloe industry. Inside Aloe Online is published quarterly (February, May, August, November). Although the information is believed to be correct, IASC disclaims all responsibility for any damage or liability that may result from any reliance on the information contained in this publication. Articles may not be reproduced or reprinted without written permission from IASC.

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DIRECTOR'S MESSAGE



A belated Happy New Year to all – and I hope your winter is going well and everyone is keeping themselves (and their aloe vera) warm! A severe cold weather system has been blanketing the United States in a unique way – poor souls in Texas and other similar areas are getting lots of snow and ice. Luckily (though not according to my daughter who I think would prefer to go sledding than to school) the Washington, D.C. area has been spared much of the snow and icy weather. I've also spoken with many members regarding the weather's effect in Mexico – and it will be interesting to see the potential damage to aloe vera crops and if there is any impact on supply. I've been crossing my fingers in the hopes that it will be minimal.

Speaking of supply, it's time for the annual "IASC aloe vera tonnage survey" to commence, and I will be emailing and calling those of you who have identified yourselves or your businesses as ones that are engaged in the commercial cultivation of aloe vera in order to create a picture of the industry's overall size and presence. This information is very useful for many reasons, including the obvious (size of the industry, etc.) as well as details such as extrapolations on the overall amount of juice in the marketplace, acreage, and economic impact. It's a wonderful set of data that make it so we are able to quantify the industry in a meaningful way, and I'll look forward to hearing from those of you who grow aloe vera and thank you for your cooperation in advance.

I'm happy to report the IASC Board of Director's has been active lately, meeting regularly to discuss several items that are likely of interest, including the development of an industry standard for aloe vera. An outline for the items of interest has been established, which includes contaminants, microbial limits, etc. and is an ongoing project that will take some time to complete. This project should provide the industry with a more concrete set of standardization elements that, until now, have not been present.

The board has also continued to address issues related to the NTP study on "aloe vera whole leaf extract (native)" (and which has been seen in related items listed as "aloe vera whole leaf extract"), with a draft report expected to be released in the next few weeks prior to the Technical Review Committee meeting scheduled for April 5, 2011. The board has instructed me and Board Chairman Ken Jones to attend that meeting and present the IASC's positions and requests, which include:

- Ensure adequate clarification of the article/ingredient used in the study in such a manner that it does not confuse consumers with the ingredient primarily sold in the marketplace in both the title and body of the report
- Adequately describe the differences between the two ingredients (marketplace and the article used in the study) within the introduction
- Clearly define the article used in the study in the methods and materials section of the report

In light of the release of the report, members continuing to use the terms "whole leaf" on labels are reminded of the required compliance with the IASC Labeling Guidance, developed and established in 2009 and which indicates that use of those terms must be prefaced by a qualifier such as "purified" or "filtered". Considering the terminology we are likely to see come from the report, using these qualifiers (or following the recommendation to remove the terms entirely) is absolutely necessary in order to avoid potential consumer confusion.

Also in regards to the pending report, the board passed a motion in late January to engage a PR/crisis management firm, Bernstein Crisis Management, to assist the IASC and its members in dealing with any potential negative publicity that might accrue as a result of the study. Members are encouraged to contact me for details and the organization will be conducting fundraising for this purpose – contributions will be restricted for this purpose and are appreciated in any denomination.

Special thanks to the current contributors to the Crisis Management Fund:

- Aloecorp, \$30,000
- Lily of the Desert, \$15,000
- Aloe Vera Group, \$5,000
- Florida Food Products \$5,000
- Winning Solutions/Miracle of Aloe, \$5,000

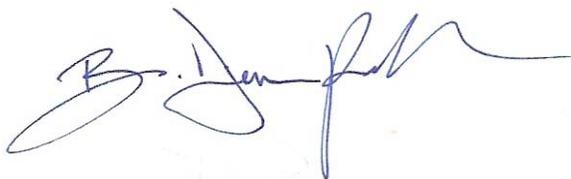
There are many other projects that continue to be developed during this period of heightened activity, such as the creation of a formal, written audit questionnaire for the IASC Certification Program, aloin testing of certified products for compliance with the parameter adopted by the board last year, the development of an aloe vera identification guidance document, and the production of a risk assessment, to name a few.

Finally – happy 30th anniversary! Many of you may not know it – I didn't realize it myself until I began writing this report – but the IASC has been active since 1981. I hope you are all as proud of how far the organization has come as I am and will continue to provide support as the association grows for the next 30+ years.

Clearly it continues to be a very busy time and I am hopeful that business for our members has been and continues to be the same. Though we maintain an optimistic outlook on the future and will keep the membership informed as these elements and projects progress, and take actions to ensure we are as prepared as possible – the next few months will be very telling ones.

A unified voice and efforts will be and is our best option for positive results during what could be a very difficult time for the industry, and I want to thank all IASC members in advance for their consideration, efforts, and support as we move forward.

And, as always, members are encouraged to contact the IASC with any questions.



Devon Powell
Executive Director





California Plaintiffs Can More Easily Sue Companies over Misleading “Made in U.S.A.” Claims

By Linda Dougherty, Esq.

Both federal law and California law prohibit the false or misleading use of “Made in U.S.A.” claims on product labels. Such claims include any indication on the label that the product is domestically made (such as “Made in U.S.A.”, “Made in America”, “U.S.A.”, an American flag symbol, etc.). Under the FTC’s standard, such a claim is deemed misleading unless “all or virtually all” of the costs associated with the product are domestic in origin. Thus, under federal law, it is possible for a product to lawfully make a “Made in U.S.A.” claim even if the product contains some minimal amount of foreign content. However, products sold or offered for sale in California must also comply with California’s standard, which is much more stringent than the FTC’s standard. Under California law, a “Made in U.S.A.” claim is deemed misleading whenever “the merchandise

■ “Under federal law, it is possible
 ■ for a product to lawfully make a
 ■ “Made in U.S.A.” claim even if the
 ■ product contains some minimal
 ■ amount of foreign content.
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 ■ for sale in California must also
 ■ comply with California’s standard,
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 ■ the FTC’s standard.”

or any article, unit, or part thereof, has been entirely or substantially made, manufactured, or produced outside of the United States.” In other words, if any one component or ingredient of the product is imported, the product may not make a “Made in U.S.A.” claim under California law, regardless of how minimal that one component or ingredient is in relation to the overall product.



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In addition to California’s stricter standard, California differs from federal law in that the California law provides for a private right of action. This means that a class action consumer lawsuit may be brought against a company that makes products sold in California if the products bear a “Made in U.S.A.” claim that does not comply with the California standard.

The *Kwikset* case is an example of such a lawsuit. (*Kwikset Corp. v. Super. Ct.*, No. S171845 (Cal. Jan. 27, 2011)). In *Kwikset*, a consumer in California bought a lockset sold by Kwikset Corporation that was labeled “Made in the U.S.A.” Upon learning that the lockset contained pins made in Taiwan, the consumer brought a lawsuit against Kwikset based on the California law prohibiting the use of “Made in U.S.A.” claims on products that contain any part that is made outside of the U.S.

In order to have standing to bring such a lawsuit in California, a plaintiff must show that he or she “lost money or property” as a result of the label misrepresentation. In *Kwikset*, the plaintiff argued that he satisfied this standing requirement insofar as he “lost” the money he paid for the product because he would not have bought it if he had known it contained foreign parts. The defendant company countered that a plaintiff has not “lost” any money so long as the product was not overpriced or defective. Arguing that the lockset, despite any label misrepresentation, was equal in value to the amount the plaintiff had paid for it, the defendant company alleged that the plaintiff had received the benefit of his bargain and therefore lacked standing to bring suit.

On January 27, 2011, the Supreme Court of California settled this question in the *Kwikset* case, ruling that a plaintiff has satisfied the “lost money or property” standing requirement so long as he or she would not have purchased the product absent the label misrepresentation. In other words, if a plaintiff in California alleges that he or she was induced to buy a product based on a “Made in U.S.A.” claim that is false or misleading under California’s strict standard, that plaintiff has standing to sue. This decision drastically relaxes the standing requirement, thereby making it easier for plaintiffs in California to sue companies over label misrepresentations.

While every company must be aware of the FTC standard, companies selling products labeled “Made in U.S.A.” in California are well advised to take steps to ensure that their products satisfy California’s stricter requirements for making such claims.

Linda Dougherty, Esq., is an associate of the law firm of Ullman, Shapiro & Ullman, LLP, whose practice concentrates in legal issues affecting the dietary supplements and natural products industry. (212) 571-0068 / ld@usulaw.com.

“Inside Law” is an *Inside Aloe: Online* exclusive column by IASC General Counsel Ullman, Shapiro and Ullman. Ullman, Shapiro and Ullman is a New York,

NY-based law firm that specializes in legal issues in the dietary supplement and natural products industry (www.usulaw.com).



IASC NEWS

Proposed Revisions to Bylaws: IASC Member Vote Required

December 14, 2010 - The International Aloe Science Council (IASC) Board of Directors met in late October, covering a variety of issues before the organization (details are available in the November issue of the newsletter - Inside Aloe Online - available on the IASC website). Included amongst these issues was a proposed revision to the organization’s bylaws in regards to votes conducted during Board of Director elections.

At the last Board of Directors election in March 2010, a membership quorum was not present and the election had to be delayed by some weeks as a result. With the amount of important business regularly before the board, it was considered to be more effective to have the election conclude in a timely manner and the proposed changes were drafted as a result. Under the proposed changes to the Bylaws, no delay to the election process would be experienced.

Any change to the association’s Bylaws requires a 2/3 majority vote of the membership. All members in good standing are being asked to please review the proposed revisions (available by download at [THIS LINK](#)) and then submit the ballot following the revisions, preferably by email. Only revised sections have been included and all the changes are marked in blue inside the document.

“The organization continues to work to improve internal processes in order to increase productivity and effectiveness on items of more pressing interest to the members,” said Devon Powell, IASC Executive Director.



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U.S. Senate & House of Representatives Succeeds on Second Attempt to Pass “Food Safety Modernization Act”

On Tuesday, December 21, the House of Representatives agreed with the U.S. Senate vote held on Sunday, December 19 passing S. 510, the FDA Food Safety Modernization Act. The Senate’s move put an end to much of the uncertainty that had surrounded the bill following its invalidation immediately after its passage weeks ago based on a disallowed revenue-raising measure.

The bill, which was signed into law by President Barack Obama, will give the Food and Drug Administration (FDA) authority to mandate a recall of any food (including a dietary supplement) when there is a “reasonable probability [of] serious adverse health consequences or death” associated with such food. The International Aloe Science Council has expressed support for this expanded recall power.

Under S. 510, FDA will also be provided with enhanced authority on records inspections, administrative detention, imported foods, and in numerous other areas. Other features of the legislation include:

- ◆ a minimum schedule for FDA inspections of all food and supplement manufacturers;
- ◆ a requirement that food facilities re-register biannually;
- ◆ accountability of companies for expenses borne by FDA related to facility re-inspections, and
- ◆ a requirement that food companies and dietary ingredient firms establish hazard analysis and risk-based preventive controls.
- ◆ Supplement companies would be exempt from this last requirement in recognition of their obligation to comply with the new dietary supplement cGMP regulation.

“IASC appreciates that the Food Safety bill exempts dietary supplement manufacturers from the HACCP portion of the law, but is reviewing the final language to

determine its full effect on ingredient manufacturers,” observed IASC executive director Devon Powell. IASC will continue to observe and report on progress related to its final passage.



IASC Annual Meeting & 2011 Board of Directors Election

The IASC announced today the opening of registration for the Council’s annual member meeting to be held on Monday, March 14, 2011 from 8am-10am at the Hilton Anaheim Hotel in Anaheim, California. All members are welcome and encouraged to register and attend the event, which will include presentations from key speakers on topics such as:

- ◆ How to evaluate if a method is fit for purpose for verifying identity
- ◆ IASC risk assessment on aloe vera – an overview and Q&A
- ◆ Legal & legislative report

To register for the event please [CLICK HERE](#).

The 2011 election for the Board of Directors will also take place at the meeting, and those interested in standing for election have until Monday, February 14 to submit their intent form and candidate statement. Please [CLICK HERE](#) to download the form and if you have any questions contact Devon Powell for more details (dpowell@iasc.org).



New York Recognizes Aloe Vera Is “Product Consumed for the Preservation of Health”

December 28, 2010 – In an article published today in the Wall Street Journal (*Answers to Many Taxing Questions*), it reported that throughout 2010, the New York state tax department has been handing down edicts on various products as to whether or not they would be subject to the new distinctions in the states sales-tax laws.

Aloe vera: “Product consumed for the preservation of health.”

- NY State Tax Department

One of these edicts happened to be regarding aloe vera, and as a result edible aloe vera leaves are not subject to sales tax – as long as they are not sold in potted form. Noting that the dried juice of the leaves “may be consumed as a laxative”, the state determined the plant is a “product consumed for the preservation of health” and therefore not subject to the 4% sales tax.

“The New York state tax department’s recognition of the benefits to health of aloe vera should be commended”, said IASC executive director Devon Powell. “Allowing consumers to continue to purchase aloe vera beverages and other products without additional taxation should make residents of that state very happy”.



Natural Products and Anti-Inflammatory Activity

Gossiau A, Li S, Ho CT, Chen KY, Rawson NE. [The importance of natural product characterization in studies of their anti-inflammatory activity.](#) *Mol Nutr Food Res.* 2011 Jan;55(1):74-82.

This paper contains a comprehensive illustration of known inflammatory human cellular pathways and discusses them in the context of natural products acting as anti-inflammatory agents. The need to properly chemically characterize materials is emphasized in this report as is the availability of bioassays to investigate their anti-inflammatory potential. Tea catechins and citrus peel flavones were provided as two examples. This paper should be required reading for anyone interested in understanding cellular mediators of inflammation and the study of how complex natural product mixtures (herbal extracts or compound classes extracted from herbs) affect them.

DNA ID Sorts Bean Family Species

Gao T, Sun Z, Yao H, Song J, Zhu Y, Ma X, Chen S. [Identification of Fabaceae plants using the DNA barcode *matK*](#). *Planta Med.* 2011 Jan;77(1):92-94.

These authors investigated the utility of a specific gene (*matK*) in determining the identity of plants in the Fabaceae (legume family), which includes important medicinal plants such as licorice (*Glycyrrhiza glabra*) and astragalus (*Astragalus membranaceus* and *A. mongholicus*), down to the species level. They were able to demonstrate that this gene was particularly accurate in some genera for differentiating some species and proposed that it may be used with other markers as a standard bar code. Their work was based on analysis of 53 samples from 42 medicinal plants in 29 genera.



... and Finds Indian Valerian Adulterant

Yang Y, Zhai Y, Liu T, Zhang F, Ji Y. [Detection of Valeriana jatamansi as an adulterant of medicinal Paris by length variation of chloroplast psbA-trnH region](#). *Planta Med.* 2011 Jan;77(1):87-91.

This work focused on one of the things that DNA analysis does best, using its exquisite sensitivity and specificity to detect trace DNA containing adulterants. The authors report that the dried rhizome of herb-paris (*Paris polyphylla* varieties *chinensis* and *yunnanensis*) is used as a raw material in Yunnan Baiyao, a Chinese traditional medicine valued for analgesic and hemostatic uses. Cultivation efforts for these plants have begun but it is still mostly wildcrafted and reportedly on the decline due to habitat destruction and overharvesting. Adulteration with an unrelated, but similar looking rhizome from *Valeriana jatamansi*, has appeared and presents a quality control issue because the adulterant has distinct chemical and medicinal differences from herb-paris, the genuine article.

While the rhizomes from the genuine article and the adulterant can be differentiated via organolepsis (smelling and tasting), not many people are skilled at this. I do not agree with the authors that this method is unreliable because it lacks scientific control.

Scientifically, the authors were able to detect the adulterant down to a 1:1000 concentration using the relatively simple techniques of DNA extraction, PCR (polymerase chain reaction) and electrophoresis that comprise a simple, cheap, and fast method.

IASC AND ALOE IN THE NEWS

The essential aloe vera – Zimbabwe Independent
<http://www.theindependent.co.zw/entertainment/29771-the-essential-aloe-vera.html>

Turkana [Kenya] women embrace aloe farming to combat drought – coastweek.com
http://www.coastweek.com/kenxin_110211_02.htm

Yeast Infections Treatments Involve Using Ingredients In Daily Life – Nutrition and Diet News
<http://nutritiondietnews.com/yeast-infections-treatments-involve-using-ingredients-in-daily-life/851551/>

Himachal's [India] aloe vera crop: In comes money, out goes monkey – newkerala.com
<http://www.newkerala.com/news/world/fullnews-128171.html>

3 Things You Need to Know Before Using Aloe on Sunburn – bellasugar.com (Australia)
<http://www.bellasugar.com.au/How-Use-Aloe-Vera-Sunburn-12461110>

Answers to Many Taxing Questions: In NY, Edible aloe leaves not subject to sales tax – The Wall Street Journal
<http://online.wsj.com/article/SB10001424052970203731004576046153457901280.html>

Healthlines: Aloe Vera – arabnews.com
http://arabnews.com/lifestyle/food_health/article220873.ece

Rare ingredient raises the value of your cosmetic product – The Economic Times
<http://economictimes.indiatimes.com/features/sunday-et/business/Rare-ingredient-raises-the-value-of-your->

[cosmetic-product/articleshow/7125944.cms](http://www.cosmetic-product/articleshow/7125944.cms)

What Conditions Aloe Vera Helps – newsmax.com

<http://www.newsmax.com/FastFeatures/Aloe-Vera-Helps-conditions/2010/11/16/id/370585>

Do You Have An Aloe Sensitivity?

<http://www.greenwala.com/profiles/danika-carter-your-organic-life/blog/10968-Do-You-Have-an-Aloe-Sensitivity>



LEGAL & LEGISLATIVE NEWS

Industry Joins FDA in Confronting Illegal Drug-Spiking

By Michael McGuffin, AHPA President.

Originally published in the January 2011 AHPA Report.

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On December 15, the Food and Drug Administration (FDA) issued communications [to consumers](#) and to the dietary supplement industry to call attention to its concern about products that are “tainted” with drug ingredients or other compounds, such as steroids.

Although many of these products are labelled as dietary supplements, FDA clearly stated that they are actually illegal due to the presence of these ingredients, which

“We have consistently communicated our concerns to FDA about the need for active and well-publicized enforcement in this area and we will support the agency’s use of its significant authority to get these illegal goods out of the market.”

- Tony Young

FDA said are generally not declared on product labels.

FDA Principal Deputy Commissioner Dr. Joshua Sharfstein held a press conference to call greater attention to this issue, and stated that these tainted products pose “significant public health problems.” The American Herbal Products Association (AHPA) and other trade associations were in attendance to demonstrate support for FDA to use its full enforcement authority to remove these illegal products from the marketplace. Dr. Margaret A. Hamburg, FDA’s Commissioner, also delivered [a letter](#) to AHPA and other associations to communicate the agency’s concerns directly to the trade.

“AHPA applauds FDA for acting to protect consumer safety and for sending a strong message to those who would ignore the law by spiking products with undeclared and illegal ingredients,” noted Anthony L. Young, AHPA General Counsel. “We have consistently communicated our concerns to FDA about the need for active and well-publicized enforcement in this area and we will support the agency’s use of its significant authority to get these illegal goods out of the market.” Dr. Sharfstein focused attention on the need to keep consumers informed, and announced new tools to alert consumers when FDA identifies tainted products. He stated that FDA will publish rapid notifications on its website and is making available a web widget that can be easily added to any web page. He also noted that the government may initiate criminal investigations against individuals and companies who violate the law and endanger the public health.

FDA’s letter placed significant emphasis on the “role and responsibilities” of the dietary supplement industry. It stated that companies must “take appropriate steps to ensure that their products do not contain active ingredients that may cause the product to be an unapproved new drug, a misbranded drug and/or an adulterated or misbranded dietary supplement.” It also noted that manufacturers are required under good manufacturing practice (GMP) rules for dietary supplement operations to establish specifications for contaminants that may adulterate finished dietary supplements. Further, it noted that FDA has found that these illegal products are often promoted for

weight loss, sexual enhancement, and body building, and emphasized that some GMP procedures may be of particular relevance in these product classes.

“I know I speak for all marketers of legitimate products in the sports nutrition supplement category in expressing appreciation for FDA’s strong message,” commented Erica Stump, chair of AHPA’s Sports Nutrition Committee and General Counsel of

Bodybuilding.com. “AHPA will continue to provide a forum for companies in this category to work together to implement FDA’s expressed guidance.”

In the above-cited letter, FDA made clear its interest in continued input and collaboration from the dietary supplement industry’s trade associations “to educate the industry about this problem and to develop strategies to combat it.” AHPA was requested to share this letter with

Why FDA’s “Tainted Products” Letter is a Big Deal

By Anthony L. Young, Esq., Partner, Kleinfeld, Kaplan and Becker, LLP, and AHPA General Counsel

In 35 years food and drug law, this is the strongest letter that I and my partners have ever seen FDA send to any part of the industry it regulates. Here are the notable points.

- 1. Undeclared ingredients.** The letter lists the various substances that FDA has found as adulterants in products labeled as dietary supplements and focuses on three primary product categories: weight loss, sexual enhancement, and body building. The letter also lists other substances not found in these product classes, including lovastatin, a “statin” drug that also appears in very small amounts in red yeast rice, and warfarin, also known as Coumadin, a blood thinning drug. The listing of any drug substance in FDA’s letter is intended as fair warning to supplement manufacturers and distributors that the ingredient should not appear in supplements at meaningful levels. And FDA promises more testing.
- 2. No Warning Letters and Criminal Consequences.** When adulterated products are found, FDA will contact responsible firms to get the products off the market. No warning letters will be issued. This means that FDA will begin investigations and may seek to impose strict criminal liability upon responsible individuals in the involved company or companies. Strict criminal liability means that if it happened, and you are the boss, you take the fall, even if you claim “I knew nothing” and there is no solid evidence you knew you were selling adulterated products. Simply put, “but I did not know my supplier was shipping me adulterated products” and “I just ordered the product and it sold well. That’s all I know,” are not good defenses. Guarantees from suppliers will not cut it.

- 3. Addressing the Problem and (Perhaps) Liability with Due Diligence.** FDA makes several recommendations as to what manufacturers and distributors can do to exercise due diligence, with emphasis on the three product categories identified above. These should be read carefully and within the context of FDA’s dietary supplement current good manufacturing practice (cGMP; i.e., 21 CFR 111) rule, and particularly where §§ 111.70 (b)(3) and (e) address “limits on those types of contamination that may adulterate” a dietary supplement. Manufacturers may consider the specific substances identified in the FDA letter, and substances similar to them, to be such contaminants. If there is a problem with an undeclared ingredient despite taking FDA’s several recommended steps, it is possible, but not certain, that strict liability may be avoided.
- 4. How the FDA and USDOJ Will Implement this Enforcement Program.** If your company is found to have distributed adulterated products, do not be shocked if FDA, using its inspection powers and with search warrants issued by US Magistrates and District Court Judges, seizes products and copies records, and then begins a detailed investigation to seek to prove a felony (intentional crime). Companies and their responsible officials will then need to hire defense counsel, leading to large legal fees. This will create pressure for a resolution that would include, in the usual course, a guilty plea by the company and several responsible officials to criminal misdemeanors.

our members and “remind them of their responsibility to comply with the law and support their members in their efforts to do so.” In addition, FDA encouraged industry to report any suspected tainted ingredients or finished products to FDA, and announced two new tools to receive such information — via email to TaintedProducts@fda.hhs.gov and/or via an anonymous reporting form “Report Suspected Criminal Activity” located at: <http://www.fda.gov/oci>.



FDA on Spiked Products, cGMP Small Entity Compliance Guidance Guide, More Warning Letters and Free Form Plant Phytosterols

By Anthony L. Young, Esq., AHPA General Counsel.
Originally published in the January 2011 AHPA Report.
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FDA educates through guidance documents and through enforcement actions (Warning Letters). On

December 15, FDA sent a [letter](#) to manufacturers of dietary supplements, as reported in the two articles above. It was an important message to manufacturers, distributors and retailers about spiked products masquerading as dietary supplements. Please read it and heed its teachings.

In a spiked product [Warning Letter](#) to dietary supplement manufacturer ProLatis, FDA warned that the Agency had found that “ProLatis” contains sulfoildenafil, an analogue of sildenafil, the active pharmaceutical ingredient in Viagra, an FDA-approved drug...” The Warning Letter follows an [FDA Safety Alert](#) on this product and a recall by the company. This letter is noteworthy in that a copy of it was sent to the Director and Chief Executive Officer of a major national retailer that carries this product line. This occurred two weeks prior to FDA’s industry letter, and is stark evidence that the FDA means what it says when it notes that “[M]anufacturers, distributors, importers and others in the supply chain of dietary supplements are responsible for ensuring that their products comply with the statutes and regulations FDA enforces.”

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The [cGMP Small Entity Compliance Guidance](#) follows the cGMP which was promulgated on June 25, 2007. This cGMP rule became effective for all dietary supplement manufacturers on June 25 of this year. The Small Entity Compliance Guide is prepared as required by the Small Business Regulatory Enforcement Fairness Act (Public Law 104-121) and is intended to restate the cGMP requirements in plain language. Comments on this guidance may be filed at any time, and manufacturers should read it and advise AHPA President Michael McGuffin of any matters that require clarification or correction. Noteworthy in FDA's Federal Register notice announcing the availability of this guidance, FDA noted that AHPA "submitted a petition for reconsideration on July 25, 2007, under 21 CFR 10.33, requesting reconsideration of certain provisions of the DS CGMP final rule. FDA is currently considering this petition and the SECG does not represent a response to such petition."

The guidance is written in question and answer format. One issue it addresses is "expiration" or "best if used by" dating of products. In Part IX B and C, FDA discusses expiration dating as follows:

- ◆ Does the DS CGMP rule require me to establish an "expiration date" (or a "shelf date" or "best if used by" date)?
- ◆ No.
- ◆ Should I have data to support any expiration date (or "shelf date" or "best if used by" date) that I will place on a product label?
- ◆ Yes. Although the DS CGMP rule does not require you to establish an "expiration date" (or a "shelf date" or "best if used by" date), you should have data to support any such date that you place on a product label.

At the outset of the guidance, however, there is an important caveat on page 5 – "The use of the word 'should' in Agency guidances means that something is suggested or recommended, but not required."

AHPA members who are concerned about whether FDA has the authority to review data supporting "best if used by" dating should keep this guidance and these references on hand if they would prefer not to volunteer

supporting data to FDA inspectors.

cGMP Warning Letters were sent to two companies. The first was to [Hain Celestial Group](#) and it followed an inspection that occurred in March and April of this year. The letter contains many observations and manufacturers should read it against their own procedures to assure their own compliance. Be concerned that these letters make bold statements that can be used by competitors vying for precious retail shelf space. How would your sales staff answer a major account that wants to know why FDA says, "Your quality control program is not adequate"?

"Members who are concerned about whether FDA has the authority to review data supporting "best if used by" dating should keep this guidance and these references on hand if they would prefer not to volunteer supporting data to FDA inspectors."

The second letter was to [New Life Alternatives](#) and discusses their Tongkat Ali product. Plainly, this inspection was predicated on products in the sexual enhancement category. During the inspection, it was noted that the company received products via international parcel post, and that "none of your imported shipments were declared" under the Bioterrorism Act. This is the first time we have seen a Warning Letter mention these prior notice provisions, and it is surprising that the products are not simply returned to the country from which they were sent.

The enforcement discretion that allows the coronary heart disease health claim to appear on free form plant phytosterol dietary supplements [has been set by FDA to expire](#) on February 22, 2011. This results from an FDA

decision to revoke the letter of enforcement discretion allowing such claims that was issued back in February 2003. With respect to products on the market, this may mean nothing, but manufacturers and distributors may have substantial inventories that are impacted by this decision. You can expect that the trade associations will be asking FDA for a more reasonable time frame to bring their products into compliance.



The 112th Congress: Outlook and Opportunities

By Pete Evich, Vice President, Van Scoyoc Associates.
Originally published in the January 2011 AHPA Report.
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2011 brings with it the start of a new Congress. As we know from the November election results, the congressional landscape will be undergoing a significant change. On January 5th, when the 112th Congress

convenes, the House of Representatives will be Republican-controlled. The power shift from Democrat to Republican means we will see a new set of leaders and federal priorities coming from the House. On the other side of the Capitol, while Senate Democrats will see their ranks slimmed from 59 to 53 seats, Democrats will retain structural control of the upper chamber.

An Obama White House, a Republican House of Representatives, a Senate controlled by a modest Democratic majority, and a high stakes presidential election in 2012: all taken together, this translates into a perfect recipe for legislative stalemate over the next two years.

Bringing it into focus for AHPA members, the question becomes: how are the pending political changes in Washington likely to impact the issues that are important to the herbal supplement trade?

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■ "As this industry well knows, warning letters and litigation against drug and supplement companies have increased significantly over the past two years."

While we don't know if FDA's activities or regulatory actions as it relates to supplements will be a factor in these pending hearings, we are certain to see a high level of scrutiny from House Republicans who believe the FDA has received little accountability from the Democratic-controlled 111th Congress.

As this industry well knows, warning letters and litigation against drug and supplement companies have increased significantly over the past two years as the Obama FDA has prioritized enforcement and compliance with regulations. Some industry stakeholders have expressed consternation that FDA has been overzealous in its enforcement scheme, allowing for only limited communication and little or no give-and-take. It is possible that this is an area in which House Republicans will question the agency on its tactics.

The Prescription Drug User Fee reauthorization legislation (PDUFA) is due for consideration in the 112th Congress. While Reps. John Dingell and Henry Waxman had plans for a massive drug safety reform measure which would have expanded FDA's jurisdiction, that effort is now considered off the table with the House Republican takeover. While supplements are not a part of PDUFA, that must-pass measure often carries FDA policy riders. The supplement industry needs to pay attention to PDUFA reauthorization legislation and the extraneous provisions that are often attached to it.

The small business-friendly predisposition of the new Congress might provide an opportunity for smaller

supplement facilities to voice concerns about regulations which potentially place an undue and unnecessary burden on their operations. Any regulatory relief petitions will need to be weighed against their potential impact on public safety.

Will the Other Shoe Drop?

The FDA is appropriately concerned about the rise of illegal drug spiking of products which are often falsely labeled as dietary supplements. These products are usually marketed for weight loss, muscle growth, and sexual enhancement. AHPA and the major trades recently joined with the FDA in a renewed voluntary effort to assist the agency in identifying and helping them prosecute unscrupulous actors who are illicitly marketing these dangerous products.

Despite the best intentions and FDA's commitment to bring resources to bear on this issue, we know that it only takes one or two high profile tragedies to lead to congressional scrutiny, which will be accompanied by misplaced calls to add further regulatory burdens to the supplement industry.

As we have seen in the past, it's the unpredictable and usually unpreventable events which throw the industry into defensive action in Washington. The point of outlining this potential scenario is to instruct the herbal supplement community to remain vigilant and avoid the trap of complacency when it comes to federal advocacy.

Time to Engage

Starting this month, there will be 96 newly elected officials in the House of Representatives and 16 new Senators. Last month, in addition to naming Rep.

■ "Building or fortifying relationships with one's members of Congress entails effort and a time commitment, but it's a worthwhile endeavor."

Fred Upton as the Chair of the House Energy and Commerce Committee, House Republicans added 13 new members to that committee.

This historic level of turnover in Congress provides a great opportunity for AHPA members to seek out and engage their federal representatives. The supplement industry is always in need of more congressional champions and these next few months are a perfect time to start this process. Building or fortifying relationships with one's members of Congress entails effort and a time commitment, but it's a worthwhile endeavor. With no pressing or specific legislative issue to address, "meet and greets" and general outreach meetings with congressional offices are very easy, and often more fruitful.

■ "The law requires FDA to clarify
■ and explain what a new dietary
■ ingredient is, when an NDI
■ notification is required, the
■ evidence that would show an NDI
■ to be "reasonably expected to be
■ safe," and the scientific methods
■ for establishing NDI identity."

In the next month, I will be providing AHPA President Michael McGuffin with detailed profiles of the new members of Congress, as well as of those who will be serving on the congressional committees which are important to the herbal supplement trade. For those AHPA members who have not already done so, I hope this information will serve as a starting point to begin the process of building relationships with your federal representatives. I would be happy to assist any AHPA member with a congressional outreach plan, or any other information that members might find helpful for engaging their congressional delegation.

I look forward to working with AHPA over these next two years as we educate the new Congress about the important role that herbal supplements play in the lives of millions of Americans, as well as to ensure access is not impeded by unnecessary and costly regulations. As always, both challenges and opportunities lie ahead, but I am confident that in working together we will continue to be effective and productive in our endeavors in Washington.



FDA Food Safety Modernization Act Provides FDA with New Regulatory Authority

NDI Guidance Mandated; New Powers Apply to Supplements and Foods—Most Rigorous Apply Only to Food and Dietary Ingredient Manufacturers

By Anthony L. Young, Esq., Partner, Kleinfeld, Kaplan and Becker, LLP, and AHPA General Counsel.

Originally published in the February 2011 AHPA Report. Reprinted by permission of AHPA.

President Barack Obama signed the [FDA Food Safety Modernization Act](#) into law on January 4, 2011. This legislation marks the first major change in the regulation of food manufacturing in more than fifty years. But even as passage of the law was completed at the end of the last Congress, some members of the new Republican majority in the House have questioned whether FDA's budget should be increased as much as will be needed to implement the new law. Below is an overview of the provisions of the new Act that will be of interest to AHPA members.

NDI Guidance

Only one provision of the law is specifically directed to the dietary supplement industry. Section 113 requires FDA to issue the long-awaited, new dietary ingredient notification (NDI) guidance. The law requires FDA to clarify and explain what a new dietary ingredient is, when an NDI notification is required, the evidence that would show an NDI to be "reasonably expected to be safe," and the scientific methods for establishing NDI identity. FDA also must notify the Drug Enforcement Administration (DEA) whenever it appears that an NDI

may be an anabolic steroid or analogue.

From a regulatory perspective, most of the new law applies to all manufacturers of foods and supplements. It has been FDA's practice to issue draft guidance documents spelling out its view of new legislative requirements and to then issue proposed regulations where required. AHPA closely monitors FDA's activities and will issue Legal Alerts as and when FDA implements this law.

"Hazard Analysis Critical Control Points (HACCP) is the centerpiece of the new food-safety law."

Applicable to Food and Dietary Ingredient Suppliers Only

The following sections are applicable to manufacturers of food and dietary ingredient suppliers only. The three-digit number represents the section of the Act being referenced.

103 – Hazard Analysis and Risk-Based Preventive Controls – Hazard Analysis Critical Control Points (HACCP) is the centerpiece of the new food-safety law. Dietary supplement manufacturing is exempted because of the comprehensive cGMP now in place for this class of goods. The statute is self-executing and does not depend on FDA regulations being proposed and made final for implementation. The core requirements are set out below, and dietary ingredient manufacturers should begin taking steps to assure compliance with the understanding that FDA will be providing clarifying information from time to time. The preventative control provisions go into effect in eighteen months.

"(a) In general.—The owner, operator, or agent in charge of a facility shall, in accordance with this section, evaluate the hazards that could affect food manufactured, processed, packed, or held by such facility, identify and implement preventive controls to significantly minimize or prevent the occurrence of such hazards and provide assurances that such food is not adulterated under section 402 or misbranded

under section 403(w), monitor the performance of those controls, and maintain records of this monitoring as a matter of routine practice.

"(b) Hazard analysis.—The owner, operator, or agent in charge of a facility shall—

"(1) identify and evaluate known or reasonably foreseeable hazards that may be associated with the facility, including—

"(A) biological, chemical, physical, and radiological hazards, natural toxins, pesticides, drug residues, decomposition, parasites, allergens, and unapproved food and color additives; and

"(B) hazards that occur naturally, or may be unintentionally introduced; and

"(2) identify and evaluate hazards that may be intentionally introduced, including by acts of terrorism; and

"(3) develop a written analysis of the hazards.

"(c) Preventive controls.—The owner, operator, or agent in charge of a facility shall identify and implement preventive controls, including at critical control points, if any, to provide assurances that—

"(1) hazards identified in the hazard analysis conducted under subsection (b)(1) will be significantly minimized or prevented;

"(2) any hazards identified in the hazard analysis conducted under subsection (b)(2) will be significantly minimized or prevented and addressed, consistent with section 420, as applicable; and

"(3) the food manufactured, processed, packed, or held by such facility will not be adulterated under section 402 or misbranded under section 403(w).

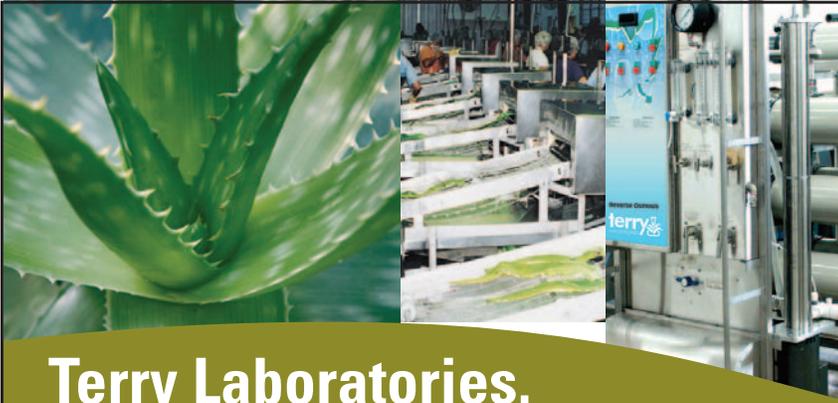
"(d) Monitoring of effectiveness.—The owner, operator, or agent in charge of a facility shall monitor the effectiveness of the preventive controls implemented under subsection (c) to provide assurances that the outcomes described in subsection (c) shall be achieved.

"(e) Corrective actions.—The owner, operator, or agent in charge of a facility shall establish procedures to ensure that, if the preventive controls implemented under subsection (c) are not properly implemented or are found to be ineffective—

"(1) appropriate action is taken to reduce the likelihood of recurrence of the implementation failure;

"(2) all affected food is evaluated for safety; and

"(3) all affected food is prevented from entering into commerce if the owner, operator or agent in charge of



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past, FDA has enlisted its state counterparts when this authority was needed.

301 – Foreign Supplier Verification – Effective in two years, FDA will provide guidance and promulgate regulations under which each importer (the owner of the food at the time of entry into the United States) must verify that its imported food is produced in accordance with US requirements, is not adulterated, and does not contain an undeclared allergen.

302 – Voluntary Qualified Importer Program – FDA is required within one year to establish, in consultation with DHS, a voluntary program whereby importers may achieve expedited review and importation of products. Those participating will provide notice to FDA and meet all requirements for the program.

303 – Authority to Require Import Certification for Food - This section authorizes FDA to require third-party certifications or other assurances for types or sources of imported food based on public health considerations, specific food or source risks, or a finding by FDA that a country-of-origin food-safety system is inadequate. As an example, FDA presently bars all beef imports from Europe.

304 – Food Import Prior Notice – Six months after enactment, prior notices for imported food must declare whether the food has ever been barred entry by any country.

■ "Companies that sell supplements
■ and foods in California in any of
■ the categories identified here can
■ best protect themselves from
■ Proposition 65 by analyzing their
■ products for chemicals that the
■ State has listed under this law."

307 – Accreditation of Third-Party Auditors – Requires FDA in two years to establish a system to accredit third-party auditors to inspect foreign food facilities and ascertain compliance with US law.



Sports Supplements, Green Foods Targeted by Proposition 65 in 2010; Attention Continuing in 2011

By Michael McGuffin, AHPA President.
Originally published in the February 2011 AHPA Report.
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California Proposition 65 Notices of Violation were issued against supplement companies in record numbers during 2010. Three private plaintiffs sent 172 such notices during the year and one of them—Environmental Research Center (ERC)—was responsible for 165 of these. For comparison, a total number of 131 such notices were issued in the prior decade. ERC has filed 28 additional notices already in 2011.

Each of these Proposition 65 notices have alleged that one or more of each recipient's marketed products were "exposing people to lead," and in a few cases "to arsenic," but had "failed to provide a ... clear and reasonable ... warning" to consumers, as required by California's Proposition 65. A warning is generally required on any product that contains more than 0.5 mcg of lead in the amount consumed daily.

The earliest Proposition 65 notices to target the dietary supplement category were directed to marketers of calcium tablets (and also OTC antacids) and herbal formulas in tablet and capsule form. A significant shift in this pattern can now be seen, as many of the products identified by ERC are protein powders, pre-workout drink mixes, green foods, and fruit-based liquids sold in large-format bottles or cans.

Companies that sell supplements and foods in California in any of the categories identified here can best protect themselves from Proposition 65 by

analyzing their products for chemicals that the State has listed under this law.

Please contact AHPA for introductions to analytical labs that can perform the types of testing needed for heavy metals, including lead. In addition, AHPA's educational symposium, Living with Proposition 65 – Preventative Measures & Defending Against a 60-Day Notice, can be purchased at the [AHPA Book Store](#), and provides excellent guidance on complying with this law.



THE SCIENCE OF ALOE RECENTLY PUBLISHED STUDIES

[In vitro study of the PLA2 inhibition and antioxidant activities of Aloe vera leaf skin extracts](#)

Abstract

BACKGROUND: In the present work we determined the total phenolic content of Aloe vera leaf skin (AVLS) extracts by using various solvents (hexane, chloroform-ethanol (1/1), ethyl acetate, butanol and water). We have also evaluated the antioxidant and the anti-PLA2 properties of these extracts by measuring their inhibition potency on the human pro-inflammatory phospholipase A2 (group IIA). **RESULTS:** The water extract exhibits the highest inhibitory effect with an $IC_{50} = 0.22$ mg/ml and interestingly no effect was observed on the digestive phospholipase A2 (group IB) even at a concentration of 5 mg/ml. Antioxidant activities were also analyzed and the most active extracts were observed when using chloroform ethanol (1/1) and ethyl acetate ($IC_{50} = 0.274$ and 0.326 mg/ml, respectively). Analysis of the total phenolic content reveals that the water extract, with the best anti-PLA2 effect, was poor in phenolic molecules (2 mg GAE/g). This latter value has to be compared with the chloroform-ethanol and the ethyl acetate extracts (40 and 23.8 mg GAE/g, respectively), mostly responsible for the antioxidant activity. **CONCLUSION:** A significant correlation was established between the total phenolic content and the antioxidant capacity but not with the anti PLA2 activity. Results from phytochemical screening suggest that the anti PLA2 molecules were probably catechin tannins compounds.

[Nutritional Supplements and Their Effect on Glucose Control](#)

Abstract

Type 2 diabetes is a growing health concern. The use of nutritional supplements by patients with type 2 diabetes is estimated at somewhere between 8% to 49%. The objective of this review was to search the scientific literature for advances in the treatment and prevention of type 2 diabetes with nutritional supplements. Twelve databases were searched with a focus on extracting studies published in the past 3 years. The following nutritional supplements were identified as potentially beneficial for type 2 diabetes treatment or prevention: vitamins C and E, α -lipoic acid, melatonin, red mold, emodin from Aloe vera and Rheum officinale, astragalus, and cassia cinnamon. Beta-carotene was shown to be ineffective in the prevention of type 2 diabetes. Ranging from preclinical to clinical, there is evidence that nutritional supplements may be beneficial in the treatment or prevention of type 2 diabetes. Health providers should investigate drug-nutritional supplement interactions prior to treatment

[Polymer fraction of Aloe vera exhibits a protective activity on ethanol-induced gastric lesions](#)

Abstract

For centuries, Aloe has been used as a herbal plant remedy against skin disorders, diabetes, and for its cardiac stimulatory activity. Here, we examined the gastroprotective effects of an Aloe vera polymer fraction (Avpf; molecular weight cut-off ≥ 50 kDa; 150 mg/kg body weight, p.o.) on an ethanol-induced gastric lesion mouse model. Mice pre-treated with Avpf had significantly fewer gastric lesions than their respective controls. To further examine the potential mechanism underlying this effect, we used reverse transcription-polymerase chain reaction to examine nitric oxide synthase and matrix metalloproteinase (MMP)mRNA expression on tissues from gastric lesions. Our results revealed that the mRNA expressions of inducible nitric oxide synthase (iNOS) and neuronal nitric oxide synthase (nNOS) were each reduced by ~50% in Avpf-treated mice vs. the

controls, whereas, the mRNA expression levels of endothelial nitric oxide synthase remained unchanged. MMP-9, an index for gastric lesions, also alleviated the ethanol-treated gastric ulceration during Avpf treatment. These findings collectively suggest that Avpf significantly protects the gastric mucosa against ethanol-induced gastric damage, at least in part, by decreasing mRNA expression levels of not only iNOS and nNOS, but also MMP-9.

Destabilization of CARP mRNAs by aloe-emodin contributes to caspase-8-mediated p53-independent apoptosis of human carcinoma cells

Abstract

Using short hairpin RNA against p53, transient ectopic expression of wild-type p53 or mutant p53 (R248W or R175H), and a p53- and p21-dependent luciferase reporter assay, we demonstrated that growth arrest and apoptosis of FaDu (human pharyngeal squamous cell carcinoma), Hep3B (hepatoma), and MG-63 (osteosarcoma) cells induced by aloe-emodin (AE) are p53-independent. Co-immunoprecipitation and small interfering RNA (siRNA) studies demonstrated that AE caused S-phase cell cycle arrest by inducing the formation of cyclin A-Cdk2-p21 complexes through extracellular signal-regulated kinase (ERK) activation. Ectopic expression of Bcl-X(L) and siRNA-mediated Bax attenuation significantly inhibited apoptosis induced by AE. Cyclosporin A or the caspase-8 inhibitor Z-IETD-FMK blocked AE-induced loss of mitochondrial membrane potential and prevented increases in reactive oxygen species and Ca⁽⁺⁺⁾. Z-IETD-FMK inhibited AE-induced apoptosis, Bax expression, Bid cleavage, translocation of tBid to mitochondria, ERK phosphorylation, caspase-9 activation, and the release of cytochrome c, AIF, and endonuclease G from mitochondria. The stability of the mRNAs encoding caspase-8 and -10-associated RING proteins (CARPs) 1 and 2 was affected by AE, whereas CARP 1 or 2 overexpression inhibited caspase-8 activation and apoptosis induced by AE. Collectively, our data indicate AE induces caspase-8-mediated activation of mitochondrial death pathways by decreasing the stability of CARP mRNAs in a p53-independent manner. *J. Cell. Biochem.* © 2011 Wiley-Liss, Inc.

Dietary aloin, aloesin, or aloe-gel exerts anti-inflammatory activity in a rat colitis model

Abstract

AIMS: Aloe has been a very popular folk remedy for inflammation-related pathological conditions despite the lack of studies reporting its efficacy in vivo. The present study evaluated the anti-inflammatory effects of aloe components (aloin, aloesin and aloe-gel) known to be biologically active in the rat model of colitis.

MAIN METHODS: Male Sprague Dawley rats were fed experimental diets for 2 weeks before and during the induction of colitis. Drinking water containing 3% dextran sulfate sodium (DSS) was provided for 1 week to induce colitis. At the end of the experimental period, clinical and biochemical markers were compared.

KEY FINDINGS: Plasma leukotriene B₄ (LTB₄) and tumor necrosis factor- α (TNF- α) concentrations were significantly decreased in all groups supplemented with aloe components compared to the colitis control group ($p < 0.05$). Animals fed both a 0.1% and 0.5% aloesin supplemented diet showed colonic myeloperoxidase (MPO) activities which were decreased by 32.2% and 40.1%, respectively ($p < 0.05$). Colonic mucosa TNF- α and interleukin-1 β (IL-1 β) mRNA expressions were significantly reduced in all animals fed aloin, aloesin, or aloe-gel ($p < 0.05$). **SIGNIFICANCE:** Dietary supplementation of aloe components ameliorates intestinal inflammatory responses in a DSS-induced ulcerative colitis rat model. In particular, aloesin was the most potent inhibitor. Further studies are required for a more complete understanding of the specific mechanism of the action of these supplements.

Protective effects of Aloe vera-based diets in Eimeria maxima-infected broiler chickens

Abstract

Aloes have been widely used for a broad range of pharmacological activities, including parasitic problems. Avian coccidiosis is the most costly and wide-spread parasitic disease in the poultry industry, and has been mainly controlled by the use of chemotherapeutic agents. Due to the emergence of

drug-resistant strains, alternative control strategies are needed. In this study, the protective effects of Aloe vera-based diets were assessed in broiler chickens following oral infection with *Eimeria maxima*. Chickens were fed a regular diet supplemented with ground Aloe vera throughout the duration of the experiment beginning 2 days prior to infection with 1×10^4 sporulated oocysts of *E. maxima*. No significant differences were found in body weight gain or loss between the Aloe vera-supplemented and unsupplemented groups with or without *E. maxima* infections. Fecal oocyst shedding decreased significantly ($p < 0.05$) in all of the treatment groups that were supplemented with Aloe vera as compared to the unsupplemented group. Furthermore, the Aloe vera-supplemented group showed significantly fewer intestinal lesions ($p < 0.05$) than the unsupplemented group following infection. The findings of this study suggest that Aloe vera could be used an alternative treatment for controlling avian coccidiosis.

Isolation and characterization of novel protein with anti-fungal and anti-inflammatory properties from Aloe vera leaf gel

Abstract

The Aloe protein of 14 kDa from the Aloe vera leaf gel was isolated by an ion exchange chromatography using DEAE-cellulose and CM-cellulose column. The purified Aloe protein exhibited a potent anti-fungal activity against *Candida parapsilosis*, *Candida krusei* and *Candida albicans*. In addition, the purified Aloe protein also showed an anti-inflammatory property against pure lipoxygenase and cyclooxygenase-2 with 84% and 73% inhibition, respectively, and was verified by binding with these proteins by real time method by the phenomenon of surface plasmon resonance. This Aloe protein is a novel protein possessing antifungal and anti-inflammatory properties and thus sets a platform to be used as a medicinal plant product.

The Effect of Aloe Vera Oral Administration on Cutaneous Wound Healing in Type 2 Diabetic Rats

Abstract

Delayed wound healing is one of the complications of diabetes mellitus. The present study was planned to investigate the effect of Aloe vera oral administration on open wounds in type 2 diabetic rats. Full thickness open wounds (1.5×1.5 cm) were created under general anesthesia on the back of the rats. These rats were divided into two groups; control group (Group C) and Aloe vera oral administration group (Group A). Each wound area was measured on days 1, 2, 4 and 8 post-wounding. The stages of wound granulation tissues were evaluated histopathologically. The expression of transforming growth factor (TGF)- β 1 and vascular endothelial growth factor (VEGF) were determined by immunohistochemically. The wounds were contracted significantly in Group A on days 2, 4 and 8 post-wounding. Histological results revealed that the inflammatory cell infiltration, angiogenesis, extracellular matrix deposition and epithelialization were promoted in Group A, respectively. The immunohistochemical results revealed that both TGF- β 1 and VEGF protein positive cells increased in Group A on day 4 post-wounding. We concluded that Aloe vera oral administration accelerated wound healing in type 2 diabetic rats.

A novel sensitive detection platform for antitumor herbal drug aloe-emodin based on the graphene modified electrode

Abstract

This paper has presented a novel strategy to carry out direct and sensitive determination of antitumor herbal drug aloe-emodin in complex matrices based on the graphene-Nafion modified glassy carbon (GN/GC) electrode. This proposed modified electrode showed good electrochemical response towards aloe-emodin (AE). Compared with the multiwall carbon nanotubes (MWCNTs) modified electrode, the GN/GC electrode has the advantages of higher sensitivity and lower cost. Under the optimized conditions, the

calibration curve for AE concentration was linear in the range from 5 nmol/L to 1 µmol/L with the detection limit of 2 nmol/L. In addition, the practical analytical performance of the GN/GC electrode was examined by evaluating the selective detection of AE in natural aloe extracts and human urine samples with satisfied recovery. Therefore, the GN/GC electrode may hold great promise for fast, simple and sensitive detection and biomedical analysis of AE in complex matrices.

Simultaneous quantification of twelve active components in Yiqing granule by ultra-performance liquid chromatography: application to quality control study

Abstract

An ultra-performance liquid chromatography (UPLC) method coupled with photodiode array (PDA) detection has been developed and validated for simultaneous quantification of 12 active components (berberine, palmatine, jatrorrhizine, aloe-emodin, rhein, emodin, chrysophanol, phycion, baicalin, baicalein, wogonoside and wogonin) in Yiqing granule. Optimum separation were achieved on a C(18) column (50 × 2.1 mm i.d., 1.7 µm particle) through a 7.5 min gradient delivery of a mixture of A (acetonitrile) and B (0.1% aqueous phosphoric acid containing 1.8 mmol/L sodium dodecyl sulfonate and 10% acetonitrile, v/v) at a flow rate of 0.3 mL/min at 30°C. Because of the different UV characteristics of these components, three detection wavelengths were used for quantitative analysis. All of the analytes showed good linearity (r of >0.999). The method was validated for repeatability, precision, stability, accuracy and selectivity. The validated method was applied to quality control of Yiqing granule from different production batches.

Interventions for preventing oral mucositis for patients with cancer receiving treatment

Abstract

BACKGROUND: Treatment of cancer is increasingly more effective but is associated with short and long term side effects. Oral side effects remain a major

source of illness despite the use of a variety of agents to prevent them. One of these side effects is oral mucositis (mouth ulcers).

OBJECTIVES: To evaluate the effectiveness of prophylactic agents for oral mucositis in patients with cancer receiving treatment, compared with other potentially active interventions, placebo or no treatment.

SEARCH STRATEGY: Electronic searches of Cochrane Oral Health Group and PaPaS Trials Registers (to 1 June 2010), CENTRAL (The Cochrane Library 2010, Issue 2), MEDLINE via OVID (1950 to 1 June 2010), EMBASE via OVID (1980 to 1 June 2010), CINAHL via EBSCO (1980 to 1 June 2010), CANCERLIT via PubMed (1950 to 1 June 2010), OpenSIGLE (1980 to 2005) and LILACS via the Virtual Health Library (1980 to 1 June 2010) were undertaken. Reference lists from relevant articles were searched and the authors of eligible trials were contacted to identify trials and obtain additional information.

SELECTION CRITERIA: Randomised controlled trials of interventions to prevent oral mucositis in patients receiving treatment for cancer.

DATA COLLECTION AND ANALYSIS:

Information regarding methods, participants, interventions, outcome measures, results and risk of bias were independently extracted, in duplicate, by two review authors. Authors were contacted for further details where these were unclear. The Cochrane Collaboration statistical guidelines were followed and risk ratios calculated using random-effects models.

MAIN RESULTS: A total of 131 studies with 10,514 randomised participants are now included. Nine interventions, where there was more than one trial in the meta-analysis, showed some statistically significant evidence of a benefit (albeit sometimes weak) for either preventing or reducing the severity of mucositis, compared to either a placebo or no treatment. These nine interventions were: allopurinol, aloe vera, amifostine, cryotherapy, glutamine (intravenous), honey, keratinocyte growth factor, laser, and polymixin/tobramycin/amphotericin (PTA) antibiotic pastille/paste.

AUTHORS' CONCLUSIONS: Nine interventions were found to have some benefit with regard to

preventing or reducing the severity of mucositis associated with cancer treatment. The strength of the evidence was variable and implications for practice include consideration that benefits may be specific for certain cancer types and treatment. There is a need for further well designed, and conducted trials with sufficient numbers of participants to perform subgroup analyses by type of disease and chemotherapeutic agent.

Photodynamic activity of aloe-emodin induces resensitization of lung cancer cells to anoikis

Abstract

Aloe-emodin was found to be a photosensitizer and possess anti-tumor activity. However, the detailed mechanism underlying the biological effects of aloe-emodin remains unknown. In this study, we explored the mechanisms of photocytotoxicity induced by aloe-emodin in lung cancer H460 cells. According to the results of the photoactivated aloe-emodin-induced disruption of cytoskeleton, we verify that aloe-emodin with irradiation induces anoikis of H460 cells. Photosensitized aloe-emodin-induced anoikis is associated with the protein expression of α -actinin and mitogen-activated protein (MAP) kinase members. In this study, a rapid opening of the mitochondrial permeability transition pore and the change in apoptosis-related protein expression were involved in photoactivated aloe-emodin-induced cell death. We also demonstrated that anoikis induced by aloe-emodin with irradiation is mediated through the intrinsic and extrinsic death pathways in a caspase-dependent manner in H460 cells.

Anti-adhesive effect of an acidic polysaccharide from Aloe vera L. var. chinensis (Haw.) Berger on the binding of Helicobacter pylori to the MKN-45 cell line

Abstract

OBJECTIVES: The emergence of antibiotic-resistant *Helicobacter pylori* strains has necessitated a search for alternative therapies for the treatment of this infection. The aim of this study was to evaluate whether or not polysaccharide fractions from Aloe

vera are effective in inhibiting the adherence of *H. pylori* in vitro.

METHODS: Polysaccharide fractions were extracted from *A. vera* and subjected to carbohydrate analysis. The adhesive effect was determined by co-incubation of *H. pylori* and cells with polysaccharides followed by fluorescein isothiocyanate labelling and Gram staining in vitro. Inhibition of *H. pylori* growth and cellular viability was tested by agar diffusion and MTT assay.

KEY FINDINGS: APS-F2 contained significant amounts of galacturonic acid, galactose and arabinose. APS-F1 was galacturonic acid-free and consisted of mannose, glucose and galactose. APS-F2 (0.1, 0.5 and 1.0 mg/ml) reduced the count of *H. pylori* attached to MKN45 cells to 88, 76 and 64%, respectively. APS-F1 did not show the same effect. Neither polysaccharide revealed an inhibitory effect on the growth of *H. pylori* or cell viability. In addition, APS-F2 was shown to have a potent anti-adhesive effect against *Escherichia coli*.

CONCLUSIONS: The results show that the acidic polysaccharide from *A. vera* has a potent anti-adhesive effect against *H. pylori* in vitro. However, there have yet to be any in-vivo studies to demonstrate the clinical relevance of this finding.

Anisotropy and nonlinear properties of electrochemical circuits in leaves of Aloe vera L

Abstract

Plant tissue has biologically closed electrical circuits and electric fields that regulate its physiology. The biologically closed electrochemical circuits in the leaves of *Aloe vera* were analyzed using the charge stimulation method with Ag/AgCl electrodes inserted along a leaf at 1-2cm distance. The electrostimulation was provided with different timing and different voltages. Strong electrical anisotropy of the leaves was found. In the direction across the leaf the electrical circuits remained passive and linear, while along the leaf the response remained linear only at small voltages not exceeding 1V. At higher potentials the circuits became strongly non-linear pointing to the opening of voltage gated ion channels in the plant tissues. Changing the polarity of electrodes located along conductive bundles led to a strong rectification

effect and to different kinetics of capacitor discharge. Equivalent electrical circuit models of the leaf were proposed to explain the experimental data.

Diabetes is an inflammatory disease: evidences from traditional Chinese Medicines

Abstract

Diabetes is usually associated with inflammation. Inflammation contributes to the development of diabetes. Traditional Chinese Medicines (TCM) play an important role in lowering blood glucose and controlling inflammation. Many studies show that TCM with hypoglycemic effects, eg. Radix Astragali, Radix Rehmanniae, Radix Trichosanthis, Panax Ginseng, Fructus Schisandrae, Radix Ophiopogonis, Rhizoma anemarrhenae, Radix Puerariae, Fructus Lycii, Poria, Rhizoma Coptidis, Rhizoma Dioscoreae, Rhizoma Polygonati, Radix Salviae Miltiorrhizae, Radix Glycyrrhizae, Semen Trigonellae, Momordica charantia, Allium sativum, Opuntia stricta, Aloe vera, Cortex Cinnamomi, Rhizoma curcumae longae, etc., have nearly independent anti-inflammatory action.

Anti-hyperglycemic compounds, eg. beberine, puerarin, quercetin, ferulic acid, Astragaloside IV, curcumin, epigallocatechin gallate, resveratrol, tetrandrine, glycyrrhizin, emodin, baicalin used in TCM also have anti-inflammatory effects. These studies suggest that TCM might exert hypoglycemic effects that are partly mediated by the anti-inflammatory mechanisms. However, small amounts of TCM with potent anti-inflammatory action does not have any hypoglycemic effect. This indirectly indicates that diabetes may be a low-grade inflammatory disease and potent regulation of inflammatory mediators may not be required. Studies of TCM add new evidences, which indicate that diabetes may be an inflammatory disease and slight or moderate inhibition of inflammation might be useful to prevent development of diabetes. Through this review, we aim to develop more perspectives to indicate that diabetes may be an inflammatory disease and diverse TCM may share a common antidiabetic property: anti-inflammatory action. Further studies should focus on and validate inflammation-regulating targets of TCM that may be involved in inhibiting the development of diabetes.



The International Aloe Science Council

Presents an

Aloe Scientific Primer



Effects of oral Aloe vera on electrocardiographic and blood pressure measurements

Abstract

PURPOSE: The effects of oral aloe vera on electrocardiographic and blood pressure measurements were evaluated.

METHODS: In this double-blind, placebo-controlled, crossover study, healthy volunteers over age 18 years received either 1200 mg of oral aloe vera powder or matching placebo on day 1 of the study and the treatment not received during the first phase on day 8. In each phase, electrocardiographic variables, systolic blood pressure, and diastolic blood pressure were evaluated at baseline and one, three, five, and eight hours after treatment. The primary endpoint was the maximum posttreatment Q-Tc interval over eight hours in both groups.

RESULTS: Sixteen participants were enrolled in the study, with a mean \pm S.D. age of 25 ± 5 years. No significant differences in electrocardiographic or blood pressure measurements were observed. The maximum Q-Tc interval was 419 ± 17 milliseconds in the placebo group and 422 ± 17 milliseconds in the aloe-treated group. The maximum P-R intervals in the placebo- and aloe-treated groups were 166 ± 22 and 169 ± 25 milliseconds, respectively. The maximum QRS complex duration did not significantly differ between the placebo- and aloe-treated groups (89.4 ± 9 and 89.3 ± 9 milliseconds, respectively). The maximum systolic blood pressures in the placebo- and aloe-treated groups were 120 ± 16 and 120 ± 14 milliseconds, respectively. The maximum diastolic blood pressures in the placebo- and aloe-treated groups were 74 ± 10 and 75 ± 9 milliseconds, respectively.

CONCLUSION: A single dose of oral aloe vera had no effect on electrocardiographic or blood pressure measurements in young healthy volunteers.

Effects of Scutellariae radix and Aloe vera gel extracts on immunoglobulin E and cytokine levels in atopic dermatitis NC/Nga mice

Abstract

AIM OF THE STUDY: The present study aimed to investigate the effects of Scutellariae radix (SR) and Aloe vera gel (AV), alone or in combination, on levels of immunoglobulin E (IgE) and inflammatory cytokines in spontaneous atopic dermatitis(AD)-like skin lesions.

MATERIALS AND METHODS: After spontaneous AD-like skin lesion was developed by adaptation to conventional conditions, mice were randomly assigned to control, SR (50 mg/kg, p.o.), AV (0.8 mg/kg, p.o.) and SRAV (50 mg of SR and 0.8 mg of AV/kg, p.o.) groups, and were treated for 6 weeks.

RESULTS: SR and SRAV suppressed IL-5 levels compared with control, but had no effects on IgE levels ($P < 0.05$). AV increased IgE levels, but decreased both IL-5 and IL-10 compared with control ($P < 0.05$).

CONCLUSION: These results suggest that SR and AV modulate immunological responses in AD, mainly through influencing IL-5 or IL-10 levels.

Efficacy of topical Aloe vera in patients with oral lichen planus: a randomized double-blind study

Abstract

BACKGROUND: Different treatments have been used in application to symptomatic oral lichen planus (OLP), with variable results, perhaps caused by the refractory nature of the disease. The objective of this study was to evaluate the efficacy of the topical application of aloe vera (AV) in OLP compared with placebo.

METHODS: A total of 64 patients with OLP were randomized in a double-blind study to either AV (32 patients) or placebo (32 patients), at a dose of 0.4 ml (70% concentration) three times a day. A Visual Analog Scale was used for rating pain, with the application of a clinical scale for scoring the lesions, the Oral Health Impact Profile 49 (OHIP-49), and the Hospital Anxiety-Depression (HAD) scale. The patients were evaluated after 6 and 12 weeks.

RESULTS: No statistically significant differences were recorded between both groups in relation to pain after 6 and 12 weeks. In the AV group, complete pain remission was achieved in 31.2% of the cases after 6 weeks, and in 61% after 12 weeks. In the placebo group, these percentages were 17.2% and 41.6%, respectively. There were no adverse effects in any of the groups. In relation to quality of life, significant differences were observed between the two groups in the psychological disability domain and total OHIP-49 score.

CONCLUSION: The topical application of AV improves the total quality of life score in patients with OLP.

[Molecular biology, phytochemistry and bioactivity of three endemic Aloe species from Mauritius and Réunion Islands](#)

Abstract

INTRODUCTION: Aloe tormentorii, A. purpurea and A. macra are used as multipurpose folk medicines in Réunion and Mauritius Islands and are mistaken for the introduced Aloe vera.

OBJECTIVE: To compare the phytochemical, antimicrobial and DNA profiles of Aloe endemic to Mauritius and Réunion with the profiles of A. vera. **Methodology -** Leaf extracts of these Aloe species were analysed using standard phytochemical screening techniques, TLC and by HPLC. These extracts were also assayed for antimicrobial activity using microdilution techniques. Genetic diversity was studied using RAPD markers.

RESULTS: Phytochemical and antimicrobial assays and RAPD analysis showed that Mascarene Aloe species were very different from A. vera.

CONCLUSION: This study is the first report highlighting the differences between Aloe sp.p from Mascarene and Aloe vera at the metabolic and genomic level.

[A multi-analytical approach for the identification of aloe as a colorant in oil-resin varnishes](#)

Abstract

Aloe plants have been widely documented in artists'

treatises dating from the sixteenth to the nineteenth century as a source of colorant to achieve lustrous golden glazes on tin- and silver-foiled objects and warm-toned finishes on musical instruments, such as violins. Aloe extracts contain characteristic anthraquinone and phenolic components which impart a distinctive orange tone and fluorescence to mixtures containing them. Because of the low concentration of colorant in the coatings and its probable degradation by high temperature during manufacture, the identification of aloe in heated oil-resin mixtures represents an analytical challenge. For this reason, the possible presence of aloe in glazes and coatings has been largely overlooked. This paper describes various analytical approaches to the identification of aloe in historic samples, from comparison with results obtained from reference standards and mock-up samples. Complementary analytical techniques including thermally assisted hydrolysis and methylation-gas chromatography-mass spectrometry, high-performance liquid chromatography, laser desorption-mass spectrometry, matrix-assisted laser desorption-ionization-mass spectrometry and surface-enhanced Raman scattering were used. Different chemical markers were identified by the individual methods and the advantages and limitations of each technique for the identification of aloe in oil-resin varnishes are discussed.



REGULATORY NEWS

FDA Warning Letters Teach Old Lessons

By Anthony L. Young, Esq., partner, Kleinfeld, Kaplan and Becker and AHPA General Counsel.

Originally published in the December 2010 AHPA Report. Reprinted by permission of AHPA.

Three warning letters in the last month to dietary supplement manufacturers teach that the cGMPs are here to stay and that there are no easy answers to the deficiencies most often noted by FDA. Warning Letters to Vita-Herb Nutraceuticals, <http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/ucm231342.htm>, Swedish Bitters Herbs Company, <http://www.fda.gov/ICECI/EnforcementActions/>

[WarningLetters/ucm233370.htm](#), and Kabco Pharmaceuticals, Inc., <http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/ucm234131.htm>, emphasize the importance of attention to the detail of the dietary supplement cGMPs. Manufacturers, and those who have products manufactured by others, should click on the links above and use the observations in these letters as auditing tools.

FDA's observations are set out below along with some of the responses made by the affected company and FDA's responses back. These too are instructive regarding what information must be provided to FDA in order to have the response deemed adequate.

The following were some of the most problematic areas highlighted by FDA:

Failure to conduct finished product testing on each batch to determine if established product specifications for identity, purity, strength, and composition, as required by 21 CFR 111.75(c) have been met. FDA noted that manufacturers must establish product specifications for each dietary supplement

manufactured (21 CFR 111.70(e)) and determine whether these specifications are met (21 CFR 111.73) by testing the finished batch of dietary supplement in accordance with testing requirements in 21 CFR 111.75(c).

FDA deemed one company's post-inspection response to be inadequate because "Your letter stated that you will increase the scope of testing 'to capture a wider slice of the products manufactured,' but you did not provide documentation that the . . . batches had finished product testing conducted and [you] did not provide documentation on how you plan to ensure finished product testing is conducted for future batches." What this teaches is that FDA expects a company's response to address the actual products noted with evidence, as well as how the situation is to be addressed in the future. This means that the company must test the batches noted during the inspection and that FDA will review documentation (e.g., SOPs and results) for such testing in the future.

Another company responded that the cost of ingredient



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and finished product testing would be prohibitive. FDA dismissed this response by noting that, “As a manufacturer of dietary supplements, you are required to comply with 21 CFR 111.75(c).”

Failure to verify the identity of each dietary ingredient by conducting at least one appropriate test or examination, prior to its use, to comply with 21 CFR 111.75(a)(1)(i). In response, one company noted it would in the future “increase the scope of testing.” FDA found this response inadequate because the company “did not specify and submit supporting documentation on how you intend to ensure that you will verify the identity of each dietary ingredient used in these dietary supplements you manufacture.” Again, FDA wants the proof submitted in such responses. Another company responded that the dietary ingredient identity testing requirement is unnecessary because their ingredients are considered “generally recognized as safe” (GRAS) and their suppliers test them and provide a Certificate of Analysis (COA) for each ingredient. FDA dismissed this response by noting that “under 21 CFR 111.75(a)(1), a manufacturer must conduct at least one appropriate test or examination to verify the identity of any component that is a dietary ingredient prior to its use.”

Failure to qualify suppliers of components (other than dietary ingredients) by establishing the reliability of the suppliers’ certificate of analyses through confirmation of the results of their tests or exams, prior to their use. FDA deemed a company’s response to be inadequate because it did not provide documentation that it had begun identity testing as described, and did not provide a completion date for the identification of the dietary ingredients in its warehouse that had not been previously tested. Surprisingly, FDA questioned whether certain products that had been distributed should remain in distribution: “You did not indicate what steps you intend to take regarding already distributed dietary supplements, which were manufactured using dietary ingredients and other components for which your firm did not conduct identity testing or for which you failed to qualify the suppliers, as applicable.” FDA did note that a company is not required to continue qualifying the suppliers of components if it is currently conducting appropriate

tests or examinations on all such components.

Failure to approve and release from quarantine all components before use, as required by 21 CFR 111.120(e). FDA states that an adequate response must commit to “fully complying with the regulation by approving and releasing all components before they are used.”

Failure to document that quality control personnel approved and released or rejected, in the batch production record, at the time of performance, the batch for distribution, including any reprocessed batch, to comply with 21 CFR 111.260(1)(3) and 21 CFR 111.123(a)(8). In response to the company’s statement that it would “make an effort to decrease occurrences of this type,” FDA stated that this was insufficient and provided no assurances “that you will review the batch records and make a determination on the batch of product (e.g., approved and released or rejected) prior to it being released.”

Failure to document the addition of an ingredient during blending to compensate for leaky capsules. FDA described in the Warning Letter the extensive documentation required when there are deviations from SOPs.

Failure to prepare and follow a written master manufacturing record (MMR) for each unique formulation of dietary supplement manufactured, and for each batch size, to ensure uniformity in the finished product from batch to batch, as required by 21 CFR 111.205(a). No written master manufacturing records for any of the dietary supplements manufactured at the facility were available. The company’s response was not recounted, but it was deemed inadequate because the company did not include MMRs with their response. The message here is that promising compliance is not enough; FDA wants to be shown the compliance documentation.

Failure to prepare a batch production record every time a batch of dietary supplement is manufactured, as required by 21 CFR 111.255(a). There were no batch records and the company response was deemed inadequate because it did not provide any batch records

for the dietary supplements it manufactures as evidence that it had implemented this requirement.

Failure to establish and follow written procedures for the responsibilities of the quality control operations, as required by 21 CFR 111.103. The company's response was deemed inadequate because no written QC procedures were provided.

Failure to maintain, clean, and sanitize equipment and utensils used to manufacture, package, label, or hold components or dietary supplements as required by 21 CFR 111.27(d). A build-up of residual powders from previous manufacturing activities was observed. The response was deemed inadequate because no records to support the maintenance, cleaning, and sanitizing of equipment and utensils were provided.

Failure to include required elements master manufacturing record (MMR), required by 21 CFR 111.210. This refers to the weight or measure of each dietary ingredient and component used in the production of certain products, as required by 21 CFR 111.210(a) and 21 CFR 111.210(c) and procedures for sampling in the MMRs. The company responded but the response was deemed inadequate because it was not documented by including the new MMR or the new SOP.

Failure of batch production records (BPRs) to include complete information as required by 21 CFR 111.255(b) and 21 CFR 111.260. Documentation was missing supervisor signatures, had been edited with "whiteout," was missing data, used incorrect units of measure, and included errors in the placement of decimal points. Also, BPRs did not include documentation at the time of performance that quality control reviewed the BPRs for the results of any tests and examinations on the finished batches of dietary supplements and approved and released, or rejected the batches for distribution to comply with 21 CFR 111.260(1)(1)(ii) and 21 CFR 111.260(1)(3). FDA deemed the response inadequate because the response appeared to FDA to show that quality assurance personnel had approved and released batches that did not meet identity specifications.

Failure to fit each freezer, refrigerator, and other cold storage compartment used to hold components or dietary supplements with an indicating thermometer, temperature measuring device, or temperature recording device that indicates and records, or allows for recording by hand, the temperature accurately within the compartment as required by 21 CFR 111.27(a)(5)(i). This was corrected and FDA promised to verify the adequacy of the correction during the next inspection.

Expiration Dating. In one Warning Letter, FDA noted that there was expiration dating placed on product labels and that such dating needed to "be supported by data." FDA cited to the preamble to the final cGMP rule and advised the company that it "should continue to work with your customers to provide supporting data for the expiration dates placed on the products you manufacture."

This last observation is surprising because FDA rarely cites the preambles of its regulations in enforcement matters. Preambles are not regulations. FDA chose not to require expiration dating in the cGMPs for dietary supplements, and citing a preamble that was written in the context of the failure to impose this requirement is disingenuous, at best.



FDA Warns Companies Away from Drug Claims

By Anthony L. Young, Esq., AHPA General Counsel.
Originally published in the December 2010 AHPA Report.
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If you want to be in the drug business, follow the drug rules. If you want to market dietary supplements, stay within the dietary supplement rules.

FDA issues Warning Letters to companies found to make such claims and FDA demands a response within fifteen working days. Failure to respond can lead to eventual seizure or other action against the company receiving the Warning Letter.

The Warning Letter to Swedish Bitters Herbs Company

■ "Remember, any testimonial that is
■ used in the advertising of a dietary
■ supplement is a claim for the
■ product."

<http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/ucm233370.htm>, teaches that telling a story ("Small Flowered Willow: herb-was used for years in Europe for the treatment of Prostate Disease which includes Benign Prostatic Hyperplasia (usually a bacterial infection of the prostate) and Prostate Cancer") is a drug claim. And it teaches that support claims such as "Natural Support for Heart Disease/Stroke Sufferers ... " are also drug claims. FDA found many testimonials on this company's website that included drug claims. Remember, any testimonial that is used in the advertising of a dietary supplement is a claim for the product.

Vitality Products Company <http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/ucm232504.htm> was warned by FDA that various of its products make unlawful drug claims for diseases such as arthritis, chronic fatigue syndrome, fibromyalgia, hardening of the arteries, allergies, asthma, attention deficit disorder, anxiety, depression, heart disease, high blood pressure, heart attack, stroke, diabetes, urinary tract infections, yeast infections, benign prostatic hyperplasia, cancer (especially of the colon), hemorrhoids, diverticulosis, varicose veins, and obesity.

FDA noted that the company informed investigators that "you are revising all of your labeling, which will take you at least one year," and stated that "this amount of time appears to be excessive to make these corrections." FDA asked for a response which showed completion of labeling corrections, or a revised date in which the company anticipates making these label corrections.

Another FDA Warning Letter went to Bioenergy, Inc., a Minneapolis manufacturer of ribose-

containing products. <http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/ucm232086.htm>.

The company markets these products in various forms, including as medical foods. FDA noted that certain products are labeled and marketed as medical foods for the conditions of fibromyalgia, chronic fatigue syndrome, and cardiovascular disease, but do not meet the statutory definition of a medical food set forth in the Orphan Drug Act [21 U.S.C. § 360ee(b)(3)]. FDA's letter described the requirements for a medical food.

Disease or drug claims can be made for medical foods and medical foods do not require FDA preclearance. But the category is very limited. Any company that intends to use the medical food category to make claims for their product should examine this Warning Letter carefully.

So, you want to be in the drug business? FDA knows this and is watchful of the claims made for products and how they are labeled and otherwise marketed.

For more information about claims and claim substantiation visit the [IASC Bookstore](#) and purchase: **Allowable Claims and Claim Substantiation Webinar: How to Comply with the Law & Maximize your Marketing**



AHPA Comments on FTC "Green Guides"

By Michael McGuffin, AHPA President.
Originally published in the January 2011 AHPA Report.
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On December 10, the American Herbal Products Association (AHPA) communicated to the Federal Trade Commission its comments on that agency's proposal to revise its Guides for the Use of Environmental Marketing Claims ("Green Guides").

FTC identifies the Green Guides as helpful to marketers that make environmental marketing claims to avoid making these claims in any manner that could be ruled as deceptive. They address claims such as recyclable,

“FTC identifies the Green Guides as helpful to marketers that make environmental marketing claims to avoid making these claims in any manner that could be ruled as deceptive.”

degradable, or refillable packaging, carbon offsets, renewable energy, and other environmental benefit claims. The Guides were originally issued in 1992 and revised by FTC in 1996 and again in 1998.

AHPA’s comments suggest that FTC recognize:

- ◆ Non-deceptive general claims. That there may be conditions under which an unqualified general environmental benefit claim (e.g., “environmentally friendly”) is not deceptive. AHPA provided as an example an organic farm that produces its own energy (or purchases carbon offsets) and uses only recycled packaging.
- ◆ Carbon offsets that include legally required emission reductions. That a carbon offset claim can be truthful and not deceptive even if some of the offsets are related to legally required emission reductions, for example from renewable energy production in states that require its utilities to produce some portion of its energy by renewable means.
- ◆ Commonly recyclable materials. That most consumers already know whether commonly recycled materials, such as aluminum, glass, and plastic bottles, can be recycled in their communities, even without having this information provided on package labeling. Analysis of the adequacy of recycling facilities is therefore not required in every community where such materials are identified as recyclable.
- ◆ Compostable claims. That a compostable claim for a material for which facilities are not readily

available for a substantial majority of consumers can be adequately qualified either by describing the required capabilities for composting the material or with a statement that appropriate facilities may not be available. Both such statements, however, should not be needed.

- ◆ Organic claims for non-agricultural products. That AHPA agrees with FTC’s decision to refrain from offering guidance on organic claims for non-agricultural products. AHPA’s comments note that significant expertise on this topic exists at USDA’s National Organic Program and on the National Organic Standards Board.

The Green Guides are a useful regulatory tool for marketers that make environmental benefit claims. Enforcement of the principles set forth in these guidelines protects companies that have well substantiated claims from those who would be deceptive. AHPA’s comments to FTC are provided to seek clarification on a few specific issues and to prevent unnecessary restrictions when not required.



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AHPA's comments also request that FTC consider whether its position that truthful carbon offset claims are necessarily deceptive if they are related to legally required emission reductions may inadvertently serve as a disincentive to companies that might otherwise promote laws that mandate emission reductions in their municipalities or states. Similarly, AHPA calls attention to FTC's position that marketers should not make unqualified general claims under any circumstances, and suggests that this could also disincentivize marketers from investing in making their products comply with more strict environmental standards.

"While it is outside of the scope of FTC's role to take actions that explicitly or implicitly encourage strict environmental standards or that advocate for laws that mandate emission reductions, neither should the agency take actions that might have the opposite effect," AHPA went on to say in its comments.

To read the full text of AHPA's comments, click [here](#).



AHPA Comments on USDA's Draft Guidance on Organic Wild Crops

By Michael McGuffin, AHPA President.
Originally published in the January 2011 AHPA Report.
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On December 13, the American Herbal Products Association (AHPA) submitted comments to the USDA's National Organic Program (NOP) in which it provided several suggestions on recently released draft guidance titled "Wild Crop Harvesting." AHPA made the following suggestions on subject areas addressed in the draft guidance:

- ◆ That the guidance clarify that it is acceptable to produce organic wild crops and organic cultivated crops on the same certified farm or site.
- ◆ That the presence of an endangered species in the same habitat where a wild crop is harvested restrict the wild crop harvest only if the harvest is detrimental to that endangered species.

- ◆ That a certifier's interviews with wild crop collectors be carried out by contacting a representative portion of these collectors, as it is neither necessary nor pragmatic to attempt to interview all collectors.

NOP's guidance on organic wild crops should provide clear information to ensure that all wild-harvested plants identified as organic meet the same standards. Consistent implementation of the guidance will provide consumers with confidence in the integrity of the USDA organic brand, and companies that are making the extra effort to certify wild crops as organic with an even playing field. AHPA applauds NOP's attention to this issue and hopes that our few suggestions to clarify the draft will be well received.

AHPA will report to members on the final content of the NOP "Wild Crop Harvesting" guidance when it becomes available.

To read the full text of AHPA's comments, click [here](#).

To read USDA's Federal Register notice on its proposed revisions to the NOP's draft guidance on Organic Wild Crops, click [here](#).



FDA Warning Letters Teach Old Lessons

By Anthony L. Young, Esq., AHPA General Counsel.
Originally published in the February 2011 AHPA Report.
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Same old, same old. That is what the Warning Letters teach. And when one relates the Warning Letters back to the websites of the companies targeted, it is clear that companies wrongly believe that if the items noted in an FDA Warning Letter are addressed, that the job is over. NOT. Those responsible for compliance at supplement companies need to read the FDA Warning Letters completely:

"The above violations are not meant to be an all-inclusive list of deficiencies in your products and their labeling. It is your responsibility to ensure that all products marked by your firm comply with the Act and its implementing

regulations. You should take prompt action to correct these violations. Failure to promptly correct these violations may result in regulatory action, including seizure and/or injunction, without further notice.”

■ “Stacking a large number of
 ■ citations, all of which make implied
 ■ disease claims for a product, can
 ■ cause a product to be considered a
 ■ drug.”

For companies that use the Internet to offer a wide variety of different products and that have determined to use the Internet to communicate everything it knows or has heard about these products, it is important to review *all* website copy, not just the items listed in the FDA Warning Letter, for compliance with the law. This can be a huge task. And remember, FDA does not need to visit your facility to measure compliance—FDA inspectors can sit in their offices and cruise your website to determine whether the site has been brought into compliance.

Natural Zing LLC appears to be an electronic retailer. Its website describes the products it sells, many of them organic foods and botanicals but also many supplements, as well. FDA inspected the Natural Zing facility and its website and sent a [Warning Letter](#). The Warning Letter first cataloged unlawful drug claims such as these for raw, organic milk thistle powder: “[A] remedy for snake bites. They [milk thistle seeds] are also used as a preventive antidote to poisoning by death-cap mushroom,” and for yacon powder: “[Y]acon ... safeguards against colon cancer. ...”

The Natural Zing Warning Letter also cataloged some unlawful nutrient content claims for goji berries: “rich source of ... germanium” and of “selenium.” Germanium is not a Daily Value (DV) nutrient and therefore a nutrient content claim is not permitted for it, and selenium is a DV nutrient but the product

label did not declare how much selenium is in the goji berries. The Warning Letter went on to note that several food products did not declare Nutrition Facts on their labels.

The lessons here are old. Drug claims are not permitted for foods or supplements. That has been the law since 1938. And the nutrient-content claim regulations and nutrition-labeling regulations have been on the books for more than 15 years. Compliance with the law is an effort, but it is required.

Even some old and established pharmaceutical companies are also clueless when it comes to compliance with the law. Upshur-Smith Laboratories markets a slow-release form of niacin, Slo-Niacin, as a dietary supplement. But the claims on its website caused FDA to send a [Warning Letter](#).

Following are some of the claims that caused FDA to issue the Warning Letter: “Reduced risk of cardiovascular events when combined with a statin.” “Halted stenosis progression when combined with a statin.” “Niacin is clinically proven to help manage cholesterol levels, a major factor in heart health.” “Offers an affordable option for Cholesterol Management.” “[N]iacin is the oldest of today’s commonly used agents for lowering cholesterol.” “See how ... niacin complements statin therapy for heart health.”

FDA also noted many citations to published literature on the website, so many in fact that the agency determined that the literature constituted drug claims. FDA set out the principles covering this as follows: “A citation of a publication or reference in the labeling of a product is considered to be a claim about disease treatment or prevention if the citation refers to a disease use, and if, in the context of the labeling as a whole, the citation implies treatment or prevention of a disease.” Companies that use literature citations on their websites should keep this in mind. Stacking a large number of citations, all of which make implied disease claims for a product, can cause a product to be considered a drug.

Dr. John Christopher is no longer living, but that does not mean that the claims he made for his product

line do not merit FDA attention. FDA's [Warning Letter](#) to the company details disease claims that simply are not acceptable for dietary supplements. For example, claims for bilberry eye capsules that bilberry is "traditionally used for: ... Cataracts, Conjunctivitis ... Glaucoma, Macular Degeneration ... Retinopathy ...," just does not pass the red face test. Nor do claims for cayenne pepper extract: "Ailments traditionally used for: ... Arthritis, Atherosclerosis ... Bursitis, Cancer ..., Cold Sores, Colitis, Common Cold ... Constipation, Coronary Artery Disease ... Cystitis ... Flu ... Gout ... Heart Disease ... Herpes Simplex 1 ... Hypercholesterolemia[sic], ... Influenza ... Irritable Bowel Syndrome ... Measles ... Mitral Valve Prolapse ... Pleurisy ... Stroke ... Urinary Tract Infection ... Yellow Fever." Again, many claims on this company's websites are beyond those cited by FDA, indicating a major fix is in order if compliance is a goal.

Back in August of last year, FDA inspected Novacare LLC, in Salt Lake City, and found a drug ingredient in the manufacturing process (sulfoildenafilafil, an analogue of sildenafilafil). In response, the company recalled "Stiff Nights" and a host of other adulterated and misbranded products. Now, Kelly D. Harvey, the company's president, and the company have gotten a stiff [Warning Letter](#) from FDA. And it might expect more. FDA announced January 20, that Tribavus Enterprises, LLC, dba IForce Nutrition, pled guilty in federal court to causing purported dietary supplements to be unlawfully manufactured and distributed in interstate commerce. According to the plea agreement, the products, called "17aPheraFLEX," "Dymethazine" and "Methadrol," contained synthetic steroids and were unapproved drugs under the Food, Drug and Cosmetic Act. According to the plea agreement, the parties have agreed to recommend that the defendant pay a \$125,000 fine. Also as part of the plea, Tribavus has agreed to implement a testing protocol for its products to ensure future products sold as dietary supplements do not contain synthetic steroids.

Spiking is illegal. And the stakes are going up. At some point, someone is going to be doing time. FDA's signals in this regard are becoming loud and clear. This kind of conduct has no lawful place here or anywhere else in the world.