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IASC Staff

Devon Powell,
Executive Director
dpowell@iasc.org

Rosie Ysasi,
Certification Program Coordinator
rysasi@iasc.org

Send inquiries, comments or requests to:

International Aloe Science Council
8630 Fenton Street, Suite 918
Silver Spring, MD 20910
Ph: 301-588-2420
Fax: 301-588-1174
Email: info@iasc.org
Website: www.iasc.org
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DIRECTOR'S MESSAGE



GMP Regulations & Aloe Vera: How Your Business May Be Affected

We're just about to the middle of the summer, and according to the NOAA, this past June was the hottest on record worldwide (I won't be surprised to find July was, as well). It's a good thing aloe vera plants thrive in such hot climates! Now, if someone could just figure out how to control frost/freezing temperatures...

Speaking of "records", I'm compelled to remind the membership that as of June 25, 2010 the Good Manufacturing Practices for Dietary Supplements (21 CFR 111 - DS-GMP) are now in effect for all manufacturers, and for those of you making and selling dietary supplements, I hope your GMP systems are in place or well on the way to being so. As the FDA likes to say, "If it isn't documented, it didn't happen," and based on feedback from the agency, we can likely expect to see the number of inspections of manufacturers of dietary supplements increasing in frequency near the very end of 2010 or early 2011.

The DS-GMP regulations have also placed some significant changes on suppliers' business operations - albeit indirectly. The DS-GMP places many burdens on manufacturers in many areas of manufacturing operations, but one of the most impactful, and also most ambiguously described within the regulations, has to be Section 111.75 (a)(1) and (2), which deal with verifying the identity of components and those elements that constitute qualification of a vendor when choosing to rely on a vendor's Certificate of Analysis (COA).

Suppliers are required to comply with 21 CFR 110, the food GMP, but under 21 CFR 111, manufacturers are given the responsibility to ensure ingredients used in dietary supplements meet specifications for purity, strength, and composition, as well as identity (those other than identity being established by the manufacturer in accordance with section 111.70 (b)). Because of the disparity in the regulatory requirements between 21 CFR 110 and 111, many manufacturers are pushing some of the burden downstream to suppliers, and from what I've heard many suppliers who are working to assist their manufacturing business partners

An excerpt from 21 CFR 111 - Section 111.75:

§ 111.75 What must you do to determine whether specifications are met?

(a) Before you use a component, you must:

(1)(i) Conduct at least one appropriate test or examination to verify the identity of any component that is a dietary ingredient; and
(2) Confirm the identity of other components and determine whether other applicable component specifications established in accordance with § 111.70(b) are met. To do so, you must either:

(i) Conduct appropriate tests or examinations; or
(ii) Rely on a certificate of analysis from the supplier of the component that you receive, provided that:

(A) You first qualify the supplier by establishing the reliability of the supplier's certificate of analysis through confirmation of the results of the supplier's tests or examinations;

(B) The certificate of analysis includes a description of the test or examination method(s) used, limits of the test or examinations, and actual results of the tests or examinations;

(C) You maintain documentation of how you qualified the supplier;

(D) You periodically re-confirm the supplier's certificate of analysis; and

(E) Your quality control personnel review and approve the documentation setting forth the basis for qualification (and requalification) of any supplier.

are solidifying those relationships, whereas those who are not are, or may soon, find themselves losing significant portions of their business to their more cooperative competitors.

Providing methods of analysis along with the results on C of A's, particularly in regards to verifying identity, seems to be one of the items most often requested of suppliers by manufacturers. The IASC is developing guidance regarding potential methods of analysis for this purpose, which will hopefully prove useful. As we saw from the FDA inspection of an aloe vera manufacturer conducted in 2009 - the first observation made was in regards to the failure of the manufacturer to effectively verify the identity of the dietary ingredient. Clearly, this is going to be an area of particular focus in future FDA inspections.

Other resources that are currently available on this topic include:

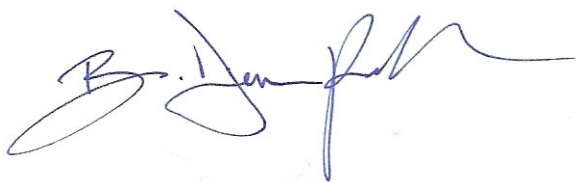
AHPA Educational Seminar: cGMP Compliance Series: Establishing Identity & Vendor Qualification. This seminar, originally presented in June 2010, provides the primary considerations that make up the details of a vendor qualification program. Presentations from industry experts. Available online and for secure purchase from the [AHPA Bookstore](#) (IASC members receive the AHPA member discount!).

SIDI Working Group - A joint-industry trade group effort currently focused on the development of tools to assist industry in complying with the Dietary Supplement GMP - specifically in regards to vendor qualification. Currently available tools include a COA guidance & templates; SIDI documents; Please visit <http://www.vendorqualification.com>

Whatever method(s) you use, it's important to be able to demonstrate that they are scientifically valid - which means the test does what it's supposed to do - and what it's supposed to do is verify the ingredient is what it is and not something else.

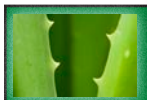
On October 13, 2010 from 8:30-9:30am, together with Dr. Steven Dentali & Tony Young, I'll be hosting a Q&A panel discussion on this topic in Boston during EXPO East as part of their educational programming. If you'll be in Boston, please join us!

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



Devon Powell
Executive Director





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INSIDE LAW**

FTC'S Revised Guides on the Use of Endorsements and Testimonials in Advertising

By Linda M. Dougherty, Esq., of Ullman, Shapiro & Ullman, LLP

The Federal Trade Commission (FTC) recently revised the guidance it provides to advertisers with respect to the use of endorsements in advertising. Endorsements, which include testimonials, are defined by the FTC to mean any advertising message that consumers are likely to believe reflects the opinions of a party other than the sponsoring advertiser. The Endorsement Guides explain FTC's interpretation of how the FTC Act's prohibition of "unfair or deceptive acts or practices in commerce" applies to endorsements and provide examples of advertising practices that would be considered deceptive under the FTC Act. Two significant changes affected by the revised Endorsement Guides are the elimination of the "results not typical" disclaimer as a safe harbor and the extension of disclosure requirements to sponsorship of studies.



Elimination of "Results Not Typical" Safe Harbor

Product advertisements often utilize endorsements in the form of testimonials that describe the positive results the endorser achieved while using the product. In some cases, the endorser's experience with the product may be atypical (i.e., not representative of what consumers can generally expect to achieve). Under the FTC's previous rules, an advertisement containing such an endorsement could likely avoid being considered deceptive by simply stating the fact that the endorser's experience is atypical. This was often done by including a disclaimer such as "Results Not Typical" or "Individual Results May Vary."

The revised Endorsement Guides now make clear that simple disclaimers do not suffice. Under the new rules, if an advertiser cannot substantiate that the endorser's experience is representative of what consumers can

generally expect to achieve, the advertisement must affirmatively state what consumer can generally expect to achieve. For example, an endorser might state that he lost 50 pounds in six months using a particular product. The ad containing this endorsement will be deemed deceptive unless (a) the advertiser has substantiation that consumers can generally expect to lose 50 pounds in six months, or (b) the advertisement explicitly describes the results consumers can generally expect (e.g., "Most people who use the product for six months lose less than 20 pounds.")

Even in the presence of a disclosure of generally expected results, the advertiser must have substantiation for the claim that the product can produce the specific results claimed by the endorser (even though it cannot substantiate that these specific results can be generally expected). And of course, the advertiser must have substantiation for the separate claim with regard to what consumers can generally expect.



ULLMAN, SHAPIRO & ULLMAN LLP

Ullman, Shapiro & Ullman attorneys have long established nationwide reputations in the areas of Food and Drug Law, Intellectual Property and Trade Reputation Litigation.

299 Broadway Suite 1700

New York, NY 10007

Ph: 212-571-0068 • Fax: 212-571-9424

usulaw@usulaw.com

IASC members receive a 10% discount



Disclosure of Study Sponsorship

The law has always required the disclosure of certain connections between the endorser and the marketer. For example, if an ad includes a product endorsement by a person who is a relative or employee of the product's marketer, or who

has been paid or otherwise given something of value in exchange for the endorsement, the ad must disclose that fact. This is because a consumer may give less weight to a rave review offered by someone with a personal stake in the product's success.

Previously, the FTC did not interpret this disclosure requirement to extend to situations where an ad cites a study that the advertiser has itself sponsored or paid for. Under the revised Endorsement Guides, however, an advertiser's sponsorship of a study is a fact that must be disclosed. An advertisement that fails to disclose that a study it references was paid for by the advertiser will be deemed deceptive.

The above is only a brief summary of two important points. Anyone who works in advertising would be well advised to read the Endorsement Guides in their entirety. The revised Endorsement Guides, codified as 16 C.F.R. Part 255, are available at: <http://www.ftc.gov/os/2009/10/091005revisedendorsementguides.pdf>.

"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

IASC Provides Information on NTP Study Targeted for Consumers

The International Aloe Science Council (IASC) announced the availability of a recently developed position paper on the National Toxicology Program's (NTP) 2-year oral consumption study on an aloe vera ingredient. The position paper was developed in order to educate consumers, retailers, and the industry at-large on the potential issues that could arise upon the publication of the NTP study results, which are

expected in or after 2011.

The NTP is an interagency program whose objective is to evaluate substances of possible public health concern by developing and applying tools of modern toxicology and molecular biology. Aloe vera was nominated along with several other substances for review by NTP in the late 1990s for analysis. In 2009, the IASC was informed of the high probability that the study results will conclude that there is clear evidence of carcinogenic activity in test animals. "With so much misinformation available, the IASC recognized the need for absolute clarification amongst consumers, retailers and the industry in general as to the ingredient used in the study vs. what is in consumer products," said Devon Powell, IASC executive director.

The paper clearly defines the ingredient used in the NTP study (aloe vera whole leaf extract native), a sample of which the IASC analyzed and is now known to be an unfiltered aloe vera. The paper further outlines and describes the difference between that ingredient and the aloe vera available in consumer products.

"We want to be sure that consumers, retailers, and the general population know and understand that what the NTP fed to test animals is not the ingredient being used, sold and consumed in the vast majority of products available in the marketplace," said Powell.

The paper is available on the IASC website and can be downloaded [HERE](#).



IASC Clarifies REACH Applicability to Aloe Vera

The International Aloe Science Council (IASC) announced the availability of a newly developed position paper on the applicability of the REACH Regulations to aloe vera raw materials.

REACH is the acronym for the European Union (EU) regulation **R**egistration, **E**valuation, **A**uthorization and **R**estriction of **C**hemicals. The law took effect on June

1, 2007 and will be phased in over an 11 year period. It was developed and implemented to replace about 40 other legislative controls in an effort to streamline and improve the former legislative framework on chemicals marketed in the EU. The program is managed by the [European Chemicals Agency \(ECHA\)](#), who handles the registration, evaluation, authorization and restriction processes for chemical substances.

The IASC position paper clearly and concisely demonstrates the inapplicability of the REACH regulations and requirements to register to aloe vera raw materials. “Members were contacting the IASC requesting clarification of the regulations applicability due to questions they were receiving from downstream users of the ingredient within the EU member states,” said IASC Executive Director Devon Powell. The IASC had the position paper reviewed by Mark Mansour, partner with Bryan Cave, LLP, an international legal expert with intimate knowledge of the regulations, who expressed his agreement with the position taken by the Council.

“The regulation is highly complex, and even more so as they weren’t written specifically for the food, dietary supplement or natural products industry; it was intended for other materials and equipment containing or made with chemicals such as computers and furniture,” said Powell.

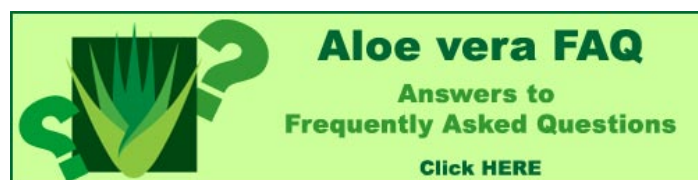
For more information, interested parties are encouraged to review the IASC Draft guidance on REACH – *“[Understanding the Reach Regulations and Their Impact on the Herbal Products Industry](#)”*. For more specific questions, the IASC recommends seeking assistance from knowledgeable consultants and taking advantage of the ECHA regional helpdesks. A list of EU national helpdesks can be found at [THIS LINK](#), which, along with the ECHA website, is available in multiple languages.

The Position Paper is available for download on the IASC website’s Policies page or by following [THIS LINK](#).

IASC Launches FAQ on Aloe Vera to Educate Consumers, Industry

The International Aloe Science Council (IASC) announced the availability of its “Aloe Vera FAQ” in June.

The FAQ answers such questions as “Are there standards established defining what is and isn’t aloe vera?” and “How can I tell if a product truly contains aloe vera?” The document also answers questions related to the cultivation and processing of aloe vera.

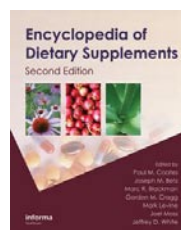


“IASC’s new FAQ provides industry and consumers with reliable and accurate answers to commonly asked questions and further establishes IASC as the source of information on aloe vera,” said Executive Director Devon Powell.

The “IASC Aloe Vera FAQ” is available online: <http://iasc.org/faq.html>.



Definitive Aloe Vera Resource Published by NIH-ODS



The Office of Dietary Supplements (ODS), a division of the National Institutes of Health (NIH), recently announced the publication of its Encyclopedia of Dietary Supplements, 2nd Edition. This new edition contains a chapter on aloe vera that provides the global industry with definitive language and information on the botanical and its products, including nomenclature that clarifies the difference between the often confused aloe vera leaf juice and aloe latex components.

Co-authored by IASC member and President-Elect Santiago Rodriguez, Ph.D. of Lorand Laboratories, IASC Executive Director Devon Powell, and Steven Dentali, Ph.D., Chief Science Officer at AHPA, the aloe vera chapter presents a definitive description of the plant derived ingredients used in commerce, and information on cultivation, processing, clinical studies, global regulatory status, and other relevant scientific data.

“The IASC is very pleased to have contributed to this project,” said Devon Powell, “having clear and consistent information on aloe vera in this authoritative publication will greatly benefit the industry and is consistent with the organization’s regulatory and scientific efforts.”

According to the publisher, the book “presents peer-reviewed, objective entries that rigorously examine the most significant scientific research, and thereby provides evidence-based information on the major vitamin and mineral micronutrients, single herbs and botanicals, phytochemicals, and other bioactive preparations.” Describing the work as “useful to a broad spectrum of healthcare professionals, researchers and educated, health-conscious consumers,” the publisher also states that the new edition “is the definitive guide for anyone interested in a scientific and balanced presentation of both the science behind and the possible benefits (or not) of dietary supplements.”

The title is available from Informa Healthcare Books at a retail price of \$1,000. IASC members receive a 15% discount by ordering online at <http://www.informahealthcarebooks.com/> and using coupon code “COLLEAGUE” (case sensitive) or via the order form located [HERE](#). For more information please contact the publisher or the IASC.

IASC Improves Website with Translation into 52 Languages

The IASC website has been updated with new features to better assist members and the industry. Updates include the addition of Google Translator to many pages, as well as reorganization of much of the menu items to more easily locate information.

“As an international organization with members in countries around the world, it is important that we are able to communicate with our membership and the industry as broadly as possible,” said IASC Executive Director, Devon Powell. “The incorporation of Google Translator on the site will make it easier and more user-friendly for many non-English reading users. Though not a perfect solution in regards to translation services, it certainly is a good step forward in providing more value to our international constituents and the industry at-large.”



Available languages included with the translator include the more commonly found languages such as French, Italian, German, Spanish and Chinese (simplified & traditional), as well as Danish, Finnish, Korean, Japanese, Russian and Swedish, among others.

The website menu navigation has also been updated to make locating information contained within the site more intuitive. A new section was also recently added to the site under the Certification Program heading, the [“Not Certified List”](#). The IASC maintains lists of products and companies currently as well as no longer participating in the program. Current program participants, upon completion, are granted usage of a seal for their products that demonstrates that it truly contains aloe vera. However, there had not been a way to alert consumers directly to known, fraudulent products.

“We continue to receive regular communications



from consumers regarding whether or not a product is certified,” said Powell. “Companies whose products illegally display the seal or utilize IASC Certification Seal the program language without authorization or participation in the program will be added to this new “Not Certified List” - making it easy for consumers to know if a product is legitimate and make a decision as to whether or not to purchase it.” Powell further indicated that the IASC communicates with and takes legal action against companies who infringe upon the seal trademarks, but that often it can take weeks before the seal is fully removed from illegal products in the marketplace.

“The list and the certification program itself is a great way for participants in the program to differentiate themselves from their competition and for consumers to get the best possible aloe vera products,” said Powell.



Further Research on Topical Aloe Vera for Burns and Wound Healing

Hosseiniemehr SJ, Khorasani G, Azadbakht M, Zamani P, Ghasemi M, Ahmadi A. Effect of aloe cream versus silver sulfadiazine for healing burn wounds in rats. *Acta Dermatovenereol Croat.* 2010;18(1):2-7.

Eshghi F, Hosseiniemehr SJ, Rahmani N, Khademloo M, Norozi MS, Hojati O. Effects of Aloe vera cream on posthemorrhoidectomy pain and wound healing: results of a randomized, blind, placebo-control study. *J Altern Complement Med.* 2010 Jun;16(6):647-50.

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

The first citation above complements earlier research by this group as reported in a previous AHPA Report (October 2009, Volume 24, Number 10, p. 21). The earlier paper compared the effects of aloe vera versus silver sulfadiazine (SSD) cream products in a randomized controlled study on 30 patients with second degree burns. This newly reported study provides additional proof of principle whereby the aloe vera product was compared to SSD in wound healing

from second degree burns in an animal model. The preparation of aloe vera cream employing a 200:1 aloe inner leaf fillet to powder material was again described.

The results are consistent to what was found in humans; that is the aloe vera cream product showed significantly better wound healing than the antimicrobial SSD treatment. Notably no bacteria were found in the biopsy of the aloe vera treated skin unlike the skin treated with the cream base only. Curiously the authors apparently seem to have written “saffron” in a few places in their article when they meant aloe!

The second citation is yet another paper by this research group, this time for the use of aloe vera cream in wound healing and pain reduction following hemorrhoid surgery. The same product was employed in a randomized study following 49 patients for 4 weeks after surgery. The aloe vera cream treated patients had significantly lower pain scores from 12 hours post surgery through two weeks. All of the aloe vera cream treated patients had complete skin covering the surgical wound at two weeks compared to only one of the patients receiving the placebo cream. The rest of the placebo group was split half and half between fresh wounds with inflammations and wounds with granulated tissue.

The reported consumption of 500-mg acetaminophen tablets (for pain) was also significantly lower for the aloe vera cream treated group at two weeks (18 tablets for 24 patients) compared to the placebo group who reported consuming 53 tablets among 25 patients. The authors suggested that the beneficial effects of topical aloe vera on wound healing may be due to antimicrobial and anti-inflammatory effects, and the promotion of collagen production.



Aloe Vera Food and Supplement Ingredient Reviews

Rodríguez Rodríguez E, Darias Martín J, Díaz Romero C. Aloe vera as a functional ingredient in foods. *Crit Rev Food Sci Nutr.* 2010 Apr;50(4):305-26.

Rodriguez S, Dentali S, Powell D. (2010). Aloe vera. In Coates PM, Blackman M Encyclopedia of Dietary Supplements (2nd ed., pp. 7-14). London: Informa Healthcare.

The first citation above, a 22 page review of aloe vera as a functional food ingredient, covers the major papers of the last 30 years on the chemical composition of aloe vera exudate and inner leaf gel, medicinal uses and applications, biologically active compounds and therapeutic properties, and quality control and legal issues. It begins by addressing the confusion that often arises between aloe vera leaf exudates and gel, pointing out that while different parts of the leaf can yield different types of polysaccharides it is appropriate to draw a clear distinction between the anthraquinone rich yellow leaf exudate and the carbohydrate rich inner leaf gel.

The wound healing and anti-inflammatory properties of topically applied aloe vera are discussed as well as its immunologic, antioxidant, gastrointestinal, and other beneficial effects. Attention is given to factors that may influence the quality of aloe vera leaf juice and that authenticity testing and determination of aloin content are important considerations. The advisability of seeing products marked with the logotype of the International Aloe Science Council (IASC) was mentioned as was the problem with adulteration of commercial materials, most commonly with maltodextrin.

Issues regarding contamination of aloe vera gel derived materials with aloin from the leaf rind were also covered and the maximum threshold for aloin content in food products for human consumption set by the European Council of 0.1 mg/l (0.1 ppm) was mentioned. While aloe vera concentrates may exceed this limit by a considerable margin it was pointed out that their addition to food products or beverages is generally below a 1% concentration. This results in products that are well below the European regulatory limit that was established with food flavoring applications in mind.

The last of the aloe vera references presented here is a chapter in the second edition of the Office of Dietary Supplements Encyclopedia of Dietary Supplements that was the subject of a July 14, 2010 IASC Update. This resource clearly delineates aloe vera juice materials

(differentiating between filtered aloe vera juice and purified whole leaf aloe vera juice) and aloin-rich materials based on the different industrial processes employed to create them. A more detailed description of this text can be found in this edition of the newsletter in the article titled, "Definitive Aloe Vera Resource Published by NIH-ODS."



IASC AND ALOE IN THE NEWS

Florida Bottling Label Claims Attract FDA Attention

<http://www.foodproductdesign.com/news/2010/08/florida-bottling-label-claims-attract-fda-attenti.aspx>

Horse tranquilizer ketamine found in aloe vera drink

<http://www.bbc.co.uk/news/uk-england-leicestershire-10687488>

Office of Dietary Supplements ~ Encyclopedia of Dietary Supplements, 2nd Ed.

<http://www.naturalproductsinsider.com/news/2010/07/office-of-dietary-supplements-encyclopedia-of-dietary-supplements-2nd-ed.aspx>

India shows the way for natural skincare

<http://www.indiannewslink.co.nz/index.php/communitylink/4667.html>

Beware those herbal remedies

http://www.jamaicaobserver.com/magazines/allwoman/Beware-those-herbal-remedies_7766676

Which Naturals Are Backed By Serious Science?

<http://www.good.is/post/which-naturals-are-backed-by-serious-science/>

Aloe Vera--Soothing to the Skin, From Burns to Psoriasis

<http://www.empowher.com/skin-hair-amp-nails/content/aloe-vera-soothing-skin-burns-psoriasis?page=0,0>

Aloe Vera-As Healing to Our Insides as it is to Our Outsidess

<http://www.empowher.com/wellness/content/aloe-vera-healing-our-insides-it-our-outsides>

Biologist Kees Nooren Conducts Investigation for National Park

<http://www.aruba.com/news/general-news/biologist-kees-nooren-conducts-investigation-for-national-park/>

Easy Home Remedies for Healthy Looking Hair

<http://www.empowher.com/skin-hair-amp-nails/content/easy-home-remedies-healthy-looking-hair>

Natural Sunburn Treatments and Remedies

<http://health.gather.com/viewArticle.action?articleId=281474978312196>

Relief for radiation regimen

<http://gazettextra.com/news/2010/jun/14/relief-radiation-regimen/>

How I saved my skin after radiotherapy

<http://blogs.telegraph.co.uk/news/judithpotts/100043038/how-i-saved-my-skin-after-radiotherapy/>

Mystery ingredient / Aloe vera

<http://www.winnipegfreepress.com/life/food/95172359.html>

(DSHEA) and requires not less than \$20 million of funds appropriated to FDA in 2010 be allocated for this purpose.

“IASC recognizes that this bill will protect consumer access to dietary supplements by providing FDA with better resources to enforce the many regulations that govern this class of goods, and thanks Senators Hatch and Harkin for introducing this important piece of legislation,” said IASC Executive Director Devon Powell.

The bill also establishes additional requirements, such as mandating FDA provide industry with guidance on existing rules that apply to new ingredients. IASC will be actively engaged in commenting on any proposed guidance.

Additionally, the bill requires FDA to submit to Congress an annual accountability report including information on the number of dietary supplement manufacturers inspected under FDA’s Good Manufacturing Practice (GMP) regulation, the number of new dietary ingredient (NDI) notifications reviewed, a brief summary of all enforcement actions taken in relation to dietary supplements, and other specific data related to the agency’s regulation of dietary supplements.

“Such an annual accountability report to Congress will provide a written record of FDA’s continuing regulation of dietary supplements,” said Powell. “Building a collection of facts and figures related to FDA’s enforcement of DSHEA is key to setting the record straight when it comes to the regulation of this class of goods.”



GAO Report Finds Heavy Metals in Herbal Supplements at Levels That Do Not Raise Safety Concerns for FDA

The U.S. Government Accountability Office (GAO) provided testimony during a Senate Special Committee



LEGAL & LEGISLATIVE NEWS

Senators Hatch, Harkin Introduce “Dietary Supplement Full Implementation and Enforcement Act of 2010”

On May 25, 2010, Senators Orrin Hatch (R-UT) and Tom Harkin (D-IA) introduced the “Dietary Supplement Full Implementation and Enforcement Act of 2010,” which calls for the Food and Drug Administration (FDA) to implement and enforce regulatory requirements established by the Dietary Supplement Health and Education Act of 1994

Aloecorp's Qmatrix® Aloe Now Has GRAS Status!

Qmatrix®
PROPRIETARY PROCESSING

The Generally Recognized as Safe (GRAS) status of Aloecorp's Qmatrix aloe has been affirmed by an independent panel of scientific experts for use in a broad range of foods and beverages.

Qmatrix is a proprietary high-purity aloe vera inner leaf fillet preparation that is high in soluble fiber and minerals. It is simply the most extensively tested aloe vera available.

We invite you to visit our website at www.aloecorp.com for more information.



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on Aging hearing entitled, “Dietary Supplements: What Seniors Need to Know” in May. The testimony focused on herbal dietary supplements and GAO’s investigative findings with regards to marketing claims and “harmful substance contamination.”

GAO reported that none of the 40 herbal products tested were found to contain heavy metals in amounts exceeding either Food and Drug Administration (FDA) or Environmental Protection Agency (EPA) regulations governing dietary supplements or raw ingredients used in supplements. Additionally, the report states, “FDA and EPA officials did not express concern regarding any immediate health consequences from consuming these 40 supplements.” This sentiment is reiterated in a May 25 article in New York Times, which reports FDA Deputy Commissioner Dr. Joshua Sharfstein stated in an interview he “was not concerned about the safety of the supplements tested by the G.A.O. investigators.”

“IASC is pleased manufacturers of all tested products appear to be aware of the ways good agriculture and manufacturing practice can minimize the level of trace amounts of these naturally-occurring metals in their products,” said Executive Director Devon Powell.

GAO reported that investigators posing as elderly customers received potentially harmful medical advice from retail sales staff. Upon review, FDA and FTC informed GAO many of the claims were “largely improper.” GAO also reported, “in several cases, written sales materials for products sold through online retailers claimed that herbal dietary supplements could treat, prevent or cure conditions such as diabetes, cancer or cardiovascular disease.” Under the Dietary Supplement Health and Education Act of 1994 (DSHEA), claims that a dietary supplement can treat, prevent or cure a disease are illegal.

In one example provided by GAO, a ginseng product bears labeling stating the product possesses “Powerful Anti-cancer Function.” An Internet search conducted by the American Herbal Products Association (AHPA) finds this claim and other illegal disease claims being made by China-based Internet-marketer KunMing LingCao-Dali Industry and Trade Company.

“In the past, FDA has taken enforcement action against companies making the kinds of claims noted in the GAO report,” Powell said. “IASC supports active enforcement of DSHEA and is always pleased to see FDA exercise its enforcement authority when warranted.”

A press release from the Special Committee on Aging is available here:

http://aging.senate.gov/hearing_detail.cfm?id=325240&

A Webcast of the hearing is now available on the committee’s web site: <http://aging.senate.gov/>.



Safe Cosmetics Act Introduced in U.S. House

By Stacy L. Ehrlich, Kleinfeld, Kaplan and Becker, LLP
Originally published in the August 2010 AHPA Report. Reprinted by permission of AHPA.

On July 21, 2010, Reps. Jan Schakowsky (D-IL), Ed Markey (D-MA) and Tammy Baldwin (D-WI), introduced in the House of Representatives H.R. 5786, the Safe Cosmetics Act of 2010. If enacted, this would significantly increase FDA’s regulatory authority over cosmetics.

The proposed legislation includes the following provisions:

- **FDA Registration:** Requires domestic and foreign establishments that manufacture, package, or distribute cosmetics to register annually (including the number of workers, gross receipts of sales, and the name and address of companies that supply the establishment with any ingredient) and list products with FDA.
- **User Fees:** Establishes cosmetic user fees based on an establishment’s gross receipts or sales, applicable only to companies with annual gross receipts or sales of more than \$1 million.

- **Ingredient Disclosure:** Requires, within one year after the date of enactment, identification of all ingredients on cosmetic labels in descending order of predominance, including contaminants present at levels above technically feasible detection limits, fragrances, flavors and preservatives, declared individually. Fragrances, flavors, and colorants will not be considered confidential business information. In addition, Internet vendors of cosmetics would be required to display the ingredient list on their website.

- **Data Submission to FDA:** Requires manufacturers and distributors of cosmetics and ingredients to submit electronically, not later than one year after enactment, “all reasonably available information in the possession or control of the manufacturer or distributor that has not previously been submitted to [FDA] regarding the physical, chemical, and toxicological properties of single or multiple chemicals listed on the cosmetic labels,” including function and uses, exposure and fate information, and tests of finished cosmetics. This information (except for confidential information) will be published in a public database.

- **FDA Regulation on Safety of Ingredients:** Requires FDA to issue regulations not later than two years after enactment identifying ingredients as “prohibited,” “restricted,” or “safe without limits” for use in cosmetics. Within 18 months of enactment, FDA must develop a “priority assessment list of not less than 300 ingredients” that cannot be included on the above-referenced lists “because of a lack of authoritative information on the safety of the ingredient” and must conduct safety determinations for these ingredients. FDA must add at least 100 ingredients to the priority assessment list each year. Within 24 months of placement on this list, FDA must issue, by regulation, a safety determination for the ingredient. FDA is also required to consider petitions on ingredient safety.

- **CEO Certification:** Requires, within 18 months of enactment, each cosmetic manufacturer/marketer to submit to FDA a statement signed by the CEO that, based on available information after a good faith inquiry, “the cosmetic and its ingredients meet

the safety standard” or “there is insufficient data to determine whether the cosmetic and its ingredients meet the safety standard.”

- **FDA Order to Cease Distribution:** Gives FDA the authority to issue an order requiring a company to immediately cease distributing a cosmetic if it may cause serious adverse health consequences to humans, is misbranded, or was manufactured, packaged or distributed by an unregistered facility.

- **FDA Recall Authority:** Gives FDA the authority to require a cosmetic product recall if the product presents an imminent threat of serious adverse health consequences or death to humans.

- **Nanomaterials:** Gives FDA the authority to require that cosmetics containing nanomaterials be labeled with information regarding such ingredients;

- **Adverse Event Reporting:** Requires the submission of reports containing information received concerning any serious adverse event associated with the use of a cosmetic within 15 days of receipt.

- **Alternative Testing Methods:** Requires FDA to publish a list of “alternative testing methods” that do not involve the use of animals or use fewer animals to test a chemical substance and that must be used in ingredient testing where practicable.

Companies that sell cosmetic products may wish to maintain attention on the progress, if any, of this legislation. There is no related bill in the Senate.



THE SCIENCE OF ALOE RECENTLY PUBLISHED STUDIES

Quantitative 1H-NMR spectrometry method for quality control of Aloe vera products.

<http://www.ncbi.nlm.nih.gov/pubmed/20629385>

Abstract

An 1H-NMR spectrometry method was developed and validated to quantify acetylated polysaccharides, glucose, malic acid, lactic acid, and acetic acid in

Aloe vera products. Nicotinamide was selected as an internal standard (IS) in this quantification method. The quantity of marker compounds was calculated by the relative ratio of the integrals of each compound to the IS. The method validation included specificity, linearity, accuracy, robustness, reproducibility, LOD, and LOQ on two samples--A. vera inner leaf standard and decolorized aloe whole leaf Standard from the International Aloe Science Council. Eighteen A. vera commercial products were analyzed with this NMR spectrometry method.

Innovations in natural ingredients and their use in skin care.

<http://www.ncbi.nlm.nih.gov/pubmed/20626172>

Abstract

Natural ingredients have been used traditionally for millennia and their application in topical creams, lotions and preparations within the traditional medicines and healing traditions of many cultures has been observed. Over the last 20 years, clinical and laboratory studies have identified the benefits of an array of natural ingredients for skin care. Consequently, a number of these ingredients and compounds are today being developed, used or considered not only for anti-aging effects, but also for use in dermatologic disorders. Certain ingredients, such as colloidal oatmeal and aloe vera, have been identified as beneficial in the treatment of psoriasis and atopic dermatitis, respectively, due to their anti-inflammatory properties. For combating acne and rosacea, green tea, niacinamide and feverfew are considered efficacious. As to hyperpigmentation and antioxidative capabilities, licorice, green tea, arbutin, soy, acai berry, turmeric and pomegranate are among those plants and compounds found to be most beneficial. Additional research is needed to determine to confirm and elucidate the benefits of these ingredients in the prevention and management of skin disease.

Antitumor properties of aloe-emodin and induction of transglutaminase 2 activity in B16-F10 melanoma cells.

<http://www.ncbi.nlm.nih.gov/pubmed/20624404>

Abstract

AIMS: Aloe-emodin (AE), a natural hydroxyanthraquinone compound, has been reported as a potential anticancer agent. We studied the antineoplastic properties of AE on highly metastatic B16-F10 melanoma murine cells. **KEY FINDINGS:** Our results demonstrated inhibitory effects of AE on melanoma cell proliferation and invasion power, accompanied by the stimulation of cell differentiation parameters. Cell differentiation correlated with a remarkable increase of the activity of the transamidating form of TG2, with a significant enhancement of cell adhesion and aggregation. Impaired invasion was paralleled by the decrease of the secretion of matrix metalloproteinase-9. **SIGNIFICANCE:** The overall data confirm a remarkable antiproliferative, antimetastatic and differentiative capability of this anthraquinone. Results suggest that AE appears particularly promising for its potential application in the newborn differentiation therapy of cancer.

[Theoretical and experimental studies on apparent solubility parameters of multiple components for Chinese materia medica with HPLC fingerprint.]

<http://www.ncbi.nlm.nih.gov/pubmed/20617675>

Abstract

OBJECTIVE: To establish the theories and methods to determine apparent solubility parameters of multiple components for the Chinese materia medica (CMM) with HPLC fingerprint. **CONCLUSION:** The TQGART of HPLC fingerprint can be used to determine simultaneously the apparent or single intrinsic solubility parameters for total quantum or intrinsic solubility parameters for single in multiple constitute systems, by which theoretical and technologic platform to study the compatibility rule and dosage form reform of the single CMM will be

established.

Mouthwash solutions with microencapsuled natural extracts: Efficiency for dental plaque and gingivitis.

<http://www.ncbi.nlm.nih.gov/pubmed/20605180>

Abstract

Mouthwash solutions are mainly used for their antiseptic properties. They currently include synthetic agents (chlorhexidine, triclosan, etc.) or essential oils (especially Listerine). Many natural extracts may also be used. These associate both antiseptic effects and direct action on host response, due to their antioxidant, immunoregulatory, analgesic, buffering, or healing properties. The best known are avocado oil, manuka oil, propolis oil, grapefruit seed extract, pycnogenol, aloe vera, Q10 coenzyme, green tea, and megamin. The development of new technologies, such as microencapsulation (GingiNat((R)) concept), may allow an in situ slow release of active ingredients during several hours, and open new perspectives for mouthwash solutions. Copyright © 2010 Elsevier Masson SAS. All rights reserved.

Anti-tuberculosis activity of selected medicinal plants against multi-drug resistant *Mycobacterium tuberculosis* isolates.

<http://www.ncbi.nlm.nih.gov/pubmed/20571171>

Abstract

INTERPRETATION & CONCLUSION: Our findings showed that all these plants exhibited activity against MDR isolates of *M. tuberculosis*. While the anti-TB activity of *A. vera*, *A. vasica* and *A. sativum* against MDR isolates confirm earlier results, activity of the extracts of *A. indica* and *A. cepa* is reported for the first time. Further studies aimed at isolation and identification of active substances from the extracts which exhibited promising activities, need to be carried out.

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Effects of Aloe vera cream on posthemorrhoidectomy pain and wound healing: results of a randomized, blind, placebo-control study.

<http://www.ncbi.nlm.nih.gov/pubmed/20569031>

Abstract

OBJECTIVE: Aloe vera is an herbal medicine, which has wound healing effects in burn injury. This study assessed the effects of Aloe vera cream in reducing postoperative pain, postdefection pain, and its promotion of wound healing after open hemorrhoidectomy. **CONCLUSIONS:** Application of Aloe vera cream on the surgical site is effective in reducing postoperative pain both on resting and during defecation, healing time, and analgesic requirements in the patients compared with the placebo group.

Antidiabetic screening of commercial botanical products in 3T3-L1 adipocytes and db/db mice.

<http://www.ncbi.nlm.nih.gov/pubmed/20521979>

Abstract

Numerous botanicals are purported to improve glucose metabolism and diabetic risk factors with varying degrees of supportive evidence. We investigated 203 commercially available botanical products representing 90 unique botanical species for effects on lipogenic activity in differentiating 3T3-L1 adipocytes. Anti-inflammatory activity of 21 of these products was further assessed in tumor necrosis factor alpha (TNFalpha)-stimulated, mature 3T3-L1 adipocytes. From these results, rho-isoalpa acids, *Acacia nilotica* bark, fennel, and wasabi were tested in the db/db mouse model. Fifty-nine percent of the 90 unique botanicals increased adipogenesis as did the standard troglitazone relative to the solvent controls. Botanical species with the greatest percentage of positive products were *Centella asiatica*, *Panax quinquefolius*, and *Phyllanthus amarus* at 100%, *Vitis vinifera* at 80%, *Humulus lupulus* at 71%,

Aloe barbadensis at 66%, and *Momordica charantia*, *Phaseolus vulgaris*, and *Punica granatum* at 60%. All 21 subset samples inhibited TNFalpha-stimulated free fatty acid release and attenuated TNFalpha inhibition of adiponectin secretion. Both rho-isoalpa acids and *A. nilotica* reduced nonfasting glucose in the db/db mouse model, whereas *A. nilotica* also decreased nonfasting insulin levels. A post hoc analysis of the screening results indicated that the positive predictive value of the lipogenesis assay alone was 72%, while adding the criterion of a positive response in the anti-inflammatory assays increased this figure to 82%. Moreover, this large-scale evaluation demonstrates that antidiabetic, in vitro efficacy of botanicals is more a function of manufacturing or quality control differences than the presence of marker compounds and further underscores the need to develop functional as well as analytical bases for standardization of dietary supplements.

Antioxidant/lipoxygenase inhibitory activities and chemical compositions of selected essential oils.

<http://www.ncbi.nlm.nih.gov/pubmed/20499917>

Abstract

Twenty-five essential oils were tested for antioxidant activities using a conjugated diene assay, the aldehyde/carboxylic acid assay, the DPPH free radical scavenging assay, and the malonaldehyde/gas chromatography (MA/GC) assay. They were also tested for lipoxygenase inhibitory activities using the lipoxygenase inhibitor-screening assay.

...Aloe vera oil exhibited the greatest lipoxygenase inhibitory activity (96%), followed by thyme oil (86%) and bergamot oil (85%) at a concentration of 0.5 microg/mL. The results obtained in the present study suggest that some essential oils possess strong medicinal activities, which can be utilized for treatment of certain diseases.

Toxicological evaluation of aqueous extract of *Aloe ferox* Mill. in loperamide-induced constipated rats.

<http://www.ncbi.nlm.nih.gov/pubmed/20498033>

Abstract

Aloe ferox Mill. is a widely used medicinal plant in South Africa for the treatment of many ailments including constipation. The present study evaluated the toxicological effect of aqueous leaf extract of the herb at 50, 100 and 200 mg/kg body weight for 7 days on the haematological parameters as well as liver and kidney function indices in loperamide-induced constipated rats. The available evidence in this study suggests that *A. ferox* may be safe as an oral remedy for constipation. Generally, the effect of the extract compared favourably well with senokot, a recommended drug for the treatment of constipation.

Aloe vera as a Functional Ingredient in Foods

<http://www.informaworld.com/smpp/content~content=a919986540~db=all~jumtype=rss>

Abstract

The main scientific discoveries on Aloe vera published mainly in the last three decades are presented in this work. After describing Aloe from a botanical point of view, the papers related with the chemical composition of different parts of the leaf of Aloe, particularly those in which the gel is described and are presented in a synthetic manner. The chemical analyses reveal that Aloe gel contains mannose polymers with some glucose and other sugars, among which the most important is Acemannan. Besides these, other components such as glycoproteins, enzymes, amino acids, vitamins, and minerals are described. Different factors also affecting the chemical composition of the gel, such as species and variety, climatic and soil conditions, cultivation methods, processing and preservation, are enumerated and discussed.

On the other hand, the main therapeutic applications have been revised and the possible damaging effects of Aloe are also commented upon. A special emphasis is placed on the biologically active

compounds or groups of compounds responsible for the therapeutic applications and which are their action mechanisms. The paper concludes that more research is needed to confirm the therapeutic and beneficial effects and to definitively clarify the myth surrounding Aloe vera. A general view on the problem of the commercialization and establishment of the quality and safety of Aloe products in the food industry has been offered here. The main points and European regulations that need to be considered regarding the quality control of prepared Aloe products are presented in this paper.

The Effects of Aloe Vera on Pain and Wound Healing

<http://nhiondemand.com/hsjarticle.aspx?id=862>

Abstract

A wound is a physical injury that results in an opening or break of the skin. There are several types of wounds, including surgical, traumatic and chronic wounds. Traumatic wounds may be caused by mechanical, traumatic or thermal injury, including contusions, abrasions, punctures, fractures, burns and frostbite. The surgical wound is usually clean and easiest to heal. By definition, chronic wounds may be more difficult to heal, and include pressure sores and diabetic ulcers.

Aloe is a succulent plant, mostly found in East and South Africa that has been used medicinally for centuries. Traditional applications abound, including topical use in wounds, burns, rashes, and internal use as a laxative. While the gel from the aloe leaf may provide the wound healing properties, the bitter, yellow latex from the plant contains a bowel stimulant that may function as a laxative.

A study published in the Journal of Alternative and Complementary Medicine assessed the effects of aloe vera cream versus a placebo cream in reducing pain, infection and wound healing after an open hemorrhoidectomy. Researchers recruited 49 patients who were randomly assigned to receive aloe vera cream (24 patients) or placebo (25 patients) which was topically applied to the surgical site 3 times per day for 4 weeks. The aloe vera group had significantly less postoperative pain than the placebo group. Also, they experienced significantly greater wound healing

than the placebo group. The aloe vera group also required fewer pain killers. The conclusion of these findings suggests that aloe vera is effective in reducing postoperative pain, healing time and analgesic requirements.¹

¹ Eshghi F, Hosseinimehr SJ, Rahmani N, et al. Effects of Aloe vera Cream on Posthemorrhoidectomy Pain and Wound Healing: Results of a Randomized, Blind, Placebo-Control Study. J Altern Complement Med. Jun2010;16(6):647-50.

Aloe Vera Enhances Bioavailability of Vitamins C and B12

<http://nhiondemand.com/hsjarticle.aspx?id=870>

Abstract

Aloe Vera is a species of succulent plant that probably originated in the southern half of the Arabian Peninsula, Northern Africa, the Canary Islands and Cape Verde. Aloe vera's use can be traced back 6,000 years to early Egypt, where the plant was depicted on stone carvings. Known as the "plant of immortality," aloe was presented as a burial gift to deceased pharaohs.

Aloe Vera has been used for: Traditionally, aloe was used topically to heal wounds and for various skin conditions, and orally as a laxative.

Today, aloe is used to treat a variety of conditions such as: diabetes, asthma, osteoarthritis, burns, and sunburns.

Aloe vera gel can be found in hundreds of skin products, including lotions and sunblocks. The Food and Drug Administration (FDA) has approved aloe vera as a natural food flavoring.

A recent study published in the Journal of Dietary Supplements examined the effect of two different aloe vera preparations (aloe inner leaf gel and aloe whole leaf gel) on the bioavailability of vitamins C and B12. Fifteen healthy volunteers were enrolled and were randomly given either aloe inner leaf gel with 1 mg B12 and 500 mg vitamin C or aloe whole leaf extract with 1 mg B12 and 500 mg vitamin C or placebo (water with 1 mg B12 and 500 mg vitamin C). Both aloe preparations significantly increased absorbance of vitamins C and B12 in comparison to placebo. Also, both aloes significantly increased plasma levels

of vitamin C and both significantly increased serum levels of vitamin B12. In conclusion the researchers indicated that both aloe preparations were safe, well tolerated and enhanced the bioavailability of vitamins C and B12 and increased antioxidant status.¹

¹ Yun JM, Singh S, Jialal R, et al. A Randomized Placebo-Controlled Crossover trial of Aloe Vera on Bioavailability of Vitamins C and B12, Blood Glucose, and Lipid Profile in Healthy Human Subjects. J Dietary Suppl. Jun2010;7(2):145-53.

Aloe May Induce Hepatitis

<http://nhiondemand.com/hsjarticle.aspx?id=865>

[Editors Note: The IASC has submitted a letter to the editor on this article, which has been accepted for publication]

Abstract

Hepatitis is a term used to describe inflammation of the liver. Hepatitis can be a result of chronic alcohol abuse, certain medications, trauma, or viral infection. Viral hepatitis is caused by infection from one or more viruses, including hepatitis A, B, C, D, and E. These viruses all differ in nucleic acid structure, modes of infection, incubation, pathogenicity, and prognosis. All forms of viral hepatitis can cause acute illness; some may result in cirrhosis or carcinoma of the liver.

Toxic hepatitis resembles viral hepatitis in onset. Obtaining a history of exposure to hepatotoxic chemicals, medications, or other agents assists in early initiation of treatment and removal of the offending agent. Anorexia, nausea, and vomiting are the usual symptoms; jaundice and hepatomegaly are noted on physical assessment.

Aloe, a genus with over 150 species, is mostly native to East and South Africa. Aloe is a succulent plant that has been used medicinally for centuries. Records of its use date back to 1750 BC. The plant has a variety of uses, including topical application for traumatic wounds (from mechanical, traumatic, or thermal injury, including contusions, abrasions, punctures, fractures, sunburn, burns, and frost bite), and chronic wounds (including pressure and diabetic ulcers). Aloe can also be used internally as a laxative and cathartic.

Aloe is described as having anti-inflammatory,

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¹ Yang HN, Kim DJ, Kim YM, et al. Aloe-induced toxic hepatitis. J Korean Med Sci. 2010;25(3):492-5.

These statements were quite strong and seemed to indicate a change in enforcement strategy by FDA. In the usual course, FDA uses Warning Letters to induce compliance rather than court enforcement because court enforcement utilizes substantially more of the agency's scarce enforcement resources. So in my role as AHPA General Counsel I asked Dr. Moore for clarification and received the following response:



FDA's Moore Clarifies Statement on NDI Enforcement

An article in the June 21, 2010 edition of “The Tan Sheet” reported on comments made by the Food and Drug Administration’s Dr. Robert Moore at the Drug Information Association’s Annual Meeting on June 15. The article was headlined, “FDA Will Enforce NDI Notification Requirement Without Warning,” and generated anxiety by some who thought this represented a shift in FDA’s long-standing enforcement policies with regard to new dietary ingredients (NDIs). Dr. Moore’s presentation was of particular interest in light of recent comments made by Dr. Joshua Sharfstein, FDA Principle Deputy Commission, on the agency’s intention to complete NDI Guidance as a priority (see AHPA Report, July 2010, page 4).

Dr. Moore's title is Supervisor of the Regulations Implementation Team at FDA's Division of Dietary Supplement Programs. He was quoted in the June 21 article as stating, "Once there is [an NDI] guidance then there is a lot of low hanging fruit for us to pick" from an enforcement perspective. He was further

- Robert Moore, FDA

“And yes, I did say that it would be likely that, given that the purpose of enforcement actions is to induce

voluntary compliance, we likely would try to pick targets that would be more likely to result in the rest of the industry sitting up and taking notice. I don't know that that is anything new."

Forewarned is forearmed. Manufacturers and distributors of dietary supplements know best whether they are utilizing new dietary ingredients that might be at enforcement risk once an NDI Guidance comes out. At a recent Food and Drug Law Institute luncheon, FDA Deputy Commissioner for Foods Michael Taylor reaffirmed that NDI Guidance is a high priority for FDA. Taylor was FDA Deputy Commissioner for Policy at the time the Dietary Supplement Health and Education Act was under consideration by Congress and became law.



Warning Letter Addresses Unpermitted Irradiation, Labeling of Excipients in Extracts, and Application of Food cGMP to Ingredient Suppliers

By Anthony L. Young, Kleinfeld, Kaplan & Becker, LLP
Originally published in the August 2010 AHPA Report. Reprinted by permission of AHPA.

[In a Warning Letter to Pharmline, Inc.](#), dated May 25, 2010 the Food and Drug Administration raised three important issues for dietary supplement ingredient suppliers.

First, FDA warned that the company had received gamma radiation-treated spirulina powder and had also sent spirulina powder out to a contract facility to be irradiated. FDA pointed out that "a food is adulterated if it has been intentionally subject to radiation, unless the use of the radiation was in conformity with a regulation or exemption in effect." FDA went on to note that there is "no regulation or exemption in effect pursuant ... for spirulina powder (see 21 CFR 179.26)" and that "your spirulina powder is adulterated under section 402(a)(7) of the Act because it received radiation treatment and there is no FDA regulation or exemption

permitting the use of radiation for this product."

As a matter of background, the issue of irradiation of dietary ingredients is pending before FDA. FDA noted this in the June 2007 preamble to its issuance of the final rule on current good manufacturing practice (cGMP) for dietary supplement:

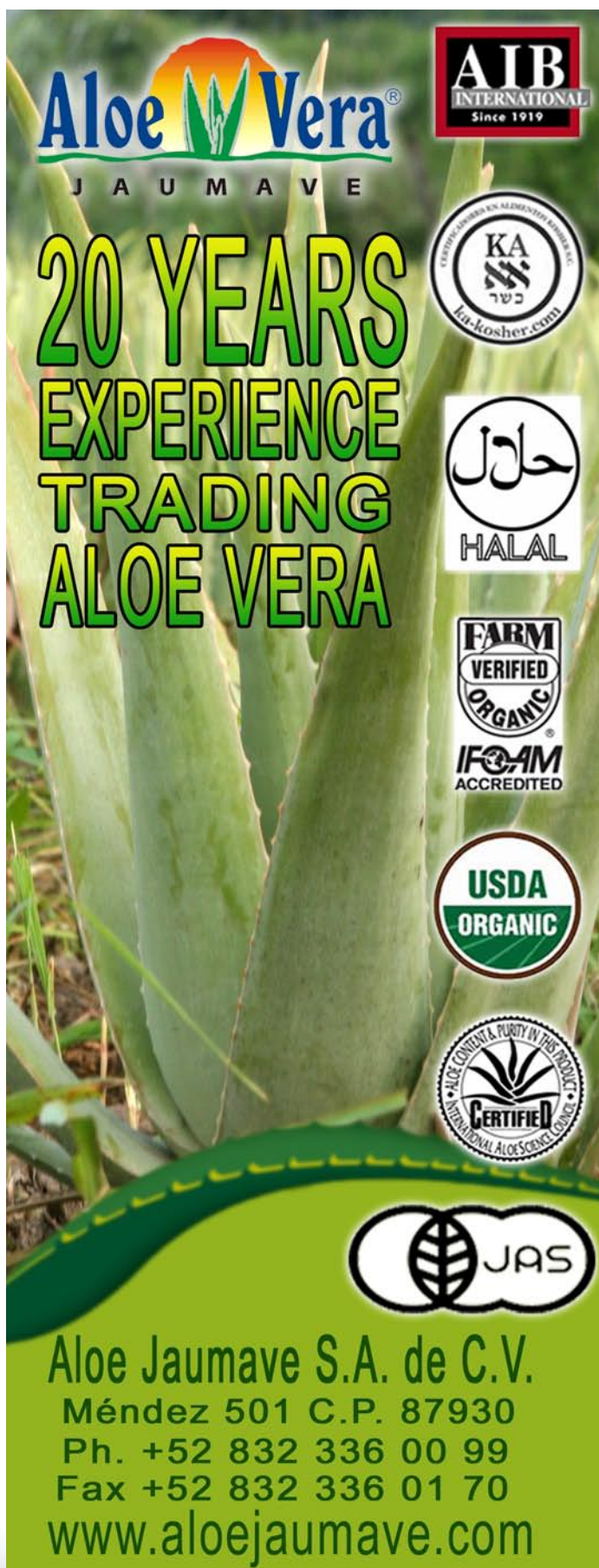
"Under section 201(s) of the act, irradiation intended for use in producing, manufacturing, packing, processing, preparing, treating, packaging, transporting, or holding food is a food additive that requires premarket review and approval before it can be used in food. Our Office of Food Additive Safety is currently reviewing a food additive petition for the use of irradiation on dietary ingredients and dietary supplements. Until that review process is completed and we have authorized this use of irradiation through a final rule codified in part 179, irradiation of dietary ingredients and dietary supplements as a means to reduce or eliminate microbial loads is not permitted. However, you may use an irradiated component (such as a spice that is used to flavor a dietary supplement) when the irradiation of that component is allowed under § 179.26."

"There are important distinctions between the cGMPs for dietary supplements and foods."

- Tony Young

Note that the food additive petition referred to above is apparently still under review by FDA, and that AHPA has filed comments to oppose FDA approval of the petition (see AHPA Report, January 2008, page 13). While this is the first Warning Letter to warn against the use of irradiation for certain food or dietary ingredients, it is not new news.

Second, FDA warned that the company's "Saw Palmetto Extract 30% product is misbranded under section 403(i)(2) of the Act [21 U.S.C. 343(i)(2)] because it



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is fabricated from two or more ingredients, but the label fails to bear the common or usual name of each ingredient, as required by 21 CFR 101.4(a)(1).” FDA noted that the product contains “dicalcium phosphate dihydrate, sorbitol, maltodextrin, and calcium silicate, but these ingredients are not declared on the label of the product.”

The short story is this - a food ingredient, or an ingredient intended for use in the manufacture of a dietary supplement, is a food. Accordingly, such ingredients or blends must be labeled as food, at least with respect to common and usual name, ingredient labeling in descending order, net quantity of contents, and name and place of business of the manufacturer and distributor. There is a provision in the FDA’s regulation exempting foods for processing, labeling or repacking at other establishments. 21 CFR 101.100(d). Ingredient suppliers might consider using this provision to continue the general practice to put minimal labeling on the outer containers and to provide ingredient information and Certificates of Analysis for their ingredients.

Third, the FDA’s Warning Letter to Pharmline appears to recognize that as a dietary ingredient manufacturer, the company is not subject to the cGMPs for dietary supplements and instead is subject to the cGMPs for foods, i.e., 21 CFR Part 110. In its letter, FDA states “In addition, if you are manufacturing a dietary supplement, including a dietary supplement that you manufacture but that is packaged or labeled by another person, you are subject to 21 CFR Part 111, Current Good Manufacturing Practice in Manufacturing, Packaging, Labeling, or Holding Operations for Dietary Supplements.” There are important distinctions between the cGMPs for dietary supplements and foods.



52 New Proposition 65 Complaints Filed Against Supplements Companies; Settlements Now Exceed \$4 Million

By Michael McGuffin, AHPA President

Originally published in the August 2010 AHPA Report.

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In a striking increase in attention to the dietary supplement category, a private plaintiff in California has issued a Notice of Violation to each of 52 dietary supplement marketers since May to inform them of purported noncompliance with the State's Proposition 65. The plaintiff, the Environmental Research Center in San Diego, alleges that one or more products marketed by each of these companies are "exposing people to lead," and in one case "to arsenic," but have "failed to provide a ... clear and reasonable ... warning" to consumer, as required by this law.

The first Proposition 65 notices against dietary supplement companies were filed in December 1996 when 6 companies marketing either calcium supplements or OTC antacids were confronted due to the inadvertent lead content of these products. (See sidebars below and on page 24 for more details on these cases and for a short review of Proposition 65 as it may apply to supplement marketers.) In the intervening years until May, 2010 there have been 129 notices issued to supplement brands claiming that the targeted products contained lead, and sometimes arsenic,

cadmium or mercury. The 52 new notices, all issued between May 24 and July 9, thus represent in this six-week period nearly 30 percent of all such Proposition 65 notices ever issued to supplement brands and focused on heavy metals.

"Companies that sell dietary supplements in California can best protect themselves from Proposition 65 complaints by analyzing their products for chemicals that the state has listed under this law."

Only about 40 of the Proposition 65 notices filed to date against supplement companies have been followed up with complaints and reached settlements. The cumulative total for all settled cases has now reached over \$4.6 million, and the cost borne by individual companies have ranged as high as \$685,000. These fees have been paid to cover civil penalties, as additional payments that may be directed to non-profit organizations, and to reimburse plaintiffs' legal expenses.

Lead in conventional foods: an emerging Prop 65 target

For more than a decade AHPA and its members have learned to deal with the Proposition 65 ramifications of lead in herbal products and other dietary supplements. Though a number of complaints were filed against marketers of nutrition bars in 2002 and of vinegar (especially balsamic vinegar) beginning in 2003, until now there has been little attention to the presence of this ubiquitous heavy metal in conventional foods.

There are now signs that the plaintiffs' bar has recognized that lead may also be present in conventional foods at a daily consumption level above the 0.5 mcg that triggers a warning requirement as a reproductive toxin. Notices of Violation were issued in June by the Environmental Law Foundation alleging failure to warn of the presence of lead in 125 specific fruit juice and canned fruit products, including many nationally-distributed brands. The same private plaintiff also sent notices to 17 companies that market protein powders, largely based on whey protein, as foods rather than as dietary supplements.

Contact Michael McGuffin (mmcguffin@ahpa.org) if you would like to receive copies of these notices.

The notices filed in the past few months by the Environmental Research Center appear to be focused on different products and channels of trade than earlier notices. For example, many of these were sent to companies that distribute through direct selling to consumers rather than through retail stores, a channel of distribution that has been largely overlooked until this time. In addition, the plaintiff identified not only tablet and capsule products, but also directed considerable attention to protein powders and fruit-based liquids sold in large-format bottles or cans. Because the limits imposed by Proposition 65 on quantities of listed chemicals are calculated on daily consumption, the concentration of any such chemical must be lower in any product that is consumed in a large daily quantity.

Companies that sell dietary supplements in California can best protect themselves from Proposition 65 complaints by analyzing their products for chemicals that the State has listed under this law. As it is lead that has been identified by plaintiffs as the main focus of their attention to this class, marketers in California will regret being the second person to know how much lead is in their product if a plaintiff is the first.

Prop 65: A Quick Summary

Consumer goods sold in the California, with certain exceptions, are subject to Proposition 65, the Safe Drinking Water and Toxic Enforcement Act of 1986. The regulations that have been implemented in the years since this law was passed place specific labeling requirements on products sold in the state if the product contains chemicals listed by the State as carcinogens or reproductive toxicants above specified limits. Failure to provide such warnings can result in action by the California Attorney General or by “any person in the public interest.”

Lead is listed under Proposition 65 both as a carcinogen and as a reproductive toxin, with a no significant risk level (NSRL, relevant to carcinogens) of 15 mcg/day and a maximum allowable daily level

(MADL, for reproductive toxins) of just 0.5 mcg. Most actions against supplement companies have focused just on the MADL, and products that present more than 0.5 mcg of lead at the highest labeled

daily consumption level must provide a “clear and reasonable” warning that it “contains a chemical known to the State of California to cause birth defects.”

The earliest supplement-related Proposition 65 complaints, filed in 1996 and 1997, were focused on nationally sold calcium products, including both supplements and OTC antacids. These actions led to a settlement with the Attorney General that established a naturally-occurring tolerance of 1.0 mcg of lead after April 1, 1999 and since that time calcium products have been able to bear as much as 1.5 mcg per daily serving (the MADL plus the naturally-occurring amount) without requiring any consumer warning. Though this decision was limited to the handful of settling companies it has nonetheless served as something of an industry standard for products that contain calcium for over a decade. But the Attorney General informed the settling parties in May 2009 of its intention to seek to modify this agreement in light of new evidence on the normal range of lead in multivitamin-mineral products.

Not all Notices of Violation lead to settlements or even to formal complaints by the plaintiff. In some cases the Attorney General acts to bring complaints against companies that received notice from a private plaintiff, and did so against 56 supplement brands that were identified as noncompliant due to lead in their products as recently as December 2008. (See the January 2009 AHPA Report, pages 3-4).

AHPA provides as a member benefit an authoritative document with important information to assist in complying with this law (McGuffin M. and Norris T. December 2008. Background on California

Proposition 65: Issues related to heavy metals and herbal products.) Contact Michael McGuffin (mmcguffin@ahpa.org) to request a copy of this document.



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Government Gets Tough with Purveyors of Drug-Spiked “Dietary Supplements”

By Anthony L. Young, AHPA General Counsel & Michael McGuffin, AHPA President.

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

Using their substantial enforcement powers, FDA and the Department of Justice have brought criminal actions against an Orange County, California man and his daughter for distributing misbranded drugs called “Vitalex” (or “Vitalex for men” and “Vitalex for women”).[1] The products were labeled as consisting of Chinese herbs and were marketed as “all-natural” versions of sexual enhancement drugs such as Viagra®. It is alleged that these products were not spiked with “real” Viagra (i.e., sildenafil citrate) but with analogs, which means that the ingredients were untested, unapproved new drugs. See FDA’s press release [HERE](#).

In a separate case, FDA and other United States law enforcement officials arrested two people and charged them with illegally trafficking counterfeit and unapproved weight loss medication. The government alleges that the two, a Chinese national and a resident of Plano, Texas, imported and distributed products labeled with names such as “2 Day Diet”, “Meitzitang”, and “Superslim” that were found by FDA to contain the weight loss drug sibutramine as an undeclared ingredient. Two of these were among 28 such products identified by FDA in a December 22, 2008 consumer advisory, a list that FDA has now expanded to include 72 products. FDA’s press release on these arrests is posted [HERE](#).

These aggressive enforcement actions are of particular interest in light of a statement made by Dr. Joshua Sharfstein, FDA Principle Deputy Commissioner, before the Senate Special Committee on Aging on May 26, 2010. At the committee’s hearing Sharfstein identified the area of dietary supplement regulation “that gives the FDA the most concern” as “without question ... the pharmaceutical spiking of dietary supplements because we’re talking about very serious risk and injuries that can happen to people.” (See AHPA Report, July 2010, pages 3-5 for a full report of

Sharfstein’s May testimony at this hearing).

The dietary supplement industry clearly shares Dr. Sharfstein’s concern for consumers of drug-spiked products, and also recognizes the damage to the reputation of this trade that occurs when adulterated products masquerade as dietary supplements. There is no doubt that adding an undeclared drug ingredient to a product is illegal, and these recent actions show that FDA is proceeding to bring alleged criminals to justice when they are identified. These cases are felony indictments and it appears from the allegations that these individuals knew that they were distributing spiked products. But they are a warning as well to companies that may inadvertently market products in these categories that contain drugs due to illegal actions by a remote manufacturer. The Federal Food, Drug, and Cosmetic Act is a strict criminal liability statute, and just distributing an adulterated or misbranded product is a crime.

FDA now has a website that consolidates all of the alleged “dietary supplements” that are spiked drugs, found at [HERE](#). As this list grows, FDA might well need to use its strict criminal liability powers to assure that this practice of drug-spiking does not continue to put consumers at risk. And because this is an international problem, do not be surprised if Interpol and other international law enforcement agencies begin to move in concert against those who are perpetrating it.

[1] This is not the same product as Vitalex™ sold under the MMS Pro brand as a standardized extract of chaste tree fruit (*Vitex agnus-castus*).



Aloe Vera Juice Manufacturer Receives Warning Letter from FDA

The FDA recently issued a [Warning Letter](#) to the manufacturer of the Lakewood Juice brand, Florida Bottling, Inc. The company has an aloe vera juice product, Pure Aloe, among many others, and was the subject of much of the contents of the Warning Letter and the company’s infractions. We have distilled the letter to include here the components relevant to

LABELING RESOURCES

The FDA produced guidance for the labeling of dietary supplements, and can be found on the FDA website [HERE](#). The FDA Food Labeling Guide is also available [HERE](#). The FDA has also published food labeling guidance and other regulatory information, which can also be found on the FDA website [HERE](#), and includes links to the following: Title 21, parts 100-199; the Federal Food, Drug and Cosmetic Act (FD&C Act), Chapter IV: Food; and the Fair Packaging and Labeling Act of 1966. The IASC has also developed labeling guidance to assist members with some aspects of regulatory compliance that can be found [HERE](#).

members and have called attention to these sections in particular, adding bold type font to the most relevant text.

The FDA has informed the company that they have found the pure aloe product to be in violation of the Federal Food, Drug & Cosmetic Act for the following reasons:

Your product labels and your websites at www.lakewoodjuices.com and www.floridabottling.com, promote your juice beverage products for conditions that cause them to be drugs under section 201(g)(1) of the Act [21 U.S.C. § 321(g)(1)]. The therapeutic claims on your website establish that the products are drugs because they are intended for use in the cure, mitigation, treatment, or prevention of disease. The marketing of these products with these claims violates the Act.

Pure Aloe:

Label:

- ***“Reduce Swelling in Joints”***
- ***“Healing Bums and Wounds”***
- ***“Effective Skin Emollient with Antibacterial, Antifungal and Antiviral Properties”***

Website:

- ***“Drinking aloe vera juice can aid in the healing of ... ulcers”***

Your products are not generally recognized as safe and effective for the above referenced, uses; therefore, the products are “new drugs” under section 201(P) of the Act [21 U.S.C. § 321(P)].

This should be taken as an indication that the FDA will be more heavily scrutinizing beverage products marketed as a conventional food going forward,

including aloe vera beverages, and members should keep label and marketing claims made on websites and in other materials to those that comply with federal labeling law. Structure/Function claims that are made for products marketed as conventional beverages must not make “drug” claims and are limited to the nutritive value of the product or its ingredients. We should also assume that a high level of scrutiny will also apply to aloe vera dietary supplements.

Unauthorized Nutrient Content Claims

*Nutrient content claims using the terms “high,” “rich in,” or “excellent source of” may be used on the label and in the labeling of foods provided that the food contains 20 percent or more of the reference daily intake (RDI) or the daily reference value (DRV) per reference amount customarily consumed (RACC) [21 CFR 101.54(b)(1)]. **Therefore, claims made on the label and website for your Pure Aloe juice beverage product are unauthorized nutrient content claims because, according to the label, the product contains less than the required 20 percent RDI or DRV per RACC of the nutrient for which the claim is made.** Specifically, your Pure Aloe product label and webpage bear the claim “Excellent sources of ... Fiber” The Nutrition Facts panel declares that a 4 fl oz serving of the product contains 8% of the Daily Value for fiber. The RACC for fruit juices is 240 mL, or 8 fl oz; therefore, this product contains only 16% of the Daily Value for fiber per RACC.*

Nutrient content claims using the term “antioxidant” must also comply with the requirements listed in 21 CFR 101.54(g). These requirements state, in part, that for a product to bear such a claim, an RDI must have been established for each of the nutrients that are the subject of the claim [21 CFR 101.54(g)(1)], and these nutrients must have recognized antioxidant activity [21 CFR 101.54(g)(2)]. The level of each nutrient that is the

subject of the claim must also be sufficient to qualify for the claim under 21 CFR 101.54(b), (c), or (e) [21 CFR 101.54(g)(3)]. Such a claim must also include the names of the nutrients that are the subject of the claim as part of the claim or, alternatively, the term “antioxidant” or “antioxidants” may be linked by a symbol (e.g., an asterisk) that refers to the same symbol that appears elsewhere on the same panel of the product label, followed by the name or names of the nutrients with recognized antioxidant activity [21 CFR 101.54(g)(4)]. The use of a nutrient content claim that uses the term “antioxidant” but does not comply with the requirements of 21 CFR 101.54(g) misbrands a product under 403(r)(1)(A) of the Act. **Therefore, the claims “Super Anti-Oxidant” and “Tremendous Source of Anti-Oxidants” for your Pure Aloe product are unauthorized nutrient content claims because the source of the antioxidant is not identified with use of the term as required in 21 CFR 101.54(g)(4).**

Other Food Labeling Violations

Your...Pure Aloe...juice beverage products are further misbranded within the meaning of Section 403(q)(1) of the Act [21 U.S.C. 343(q)(1)] because the nutrition facts

information is not in the proper format as defined in 21 CFR 101.9. **Specifically, the Pure Aloe...product labels fail to properly declare the serving size as specified by 21 CFR 101.9(b) and 101.12(b). The serving size for a fruit juice product is based on the RACC, which is 240 mL, or 8 fl oz. However, the Pure Aloe...product labels declare a serving size of 4 fl oz.**

“...FDA will be more heavily scrutinizing beverage products marketed as a conventional food going forward, including aloe vera beverages.”

Your Organic Pure Aloe juice beverage product is misbranded within the meaning of section 403(i)(2) of the Act [21 U.S.C. § 343(i)(2)] because the percentage of fruit juice is declared in the incorrect format. **Specifically,**



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Manufacturing Practices (cGMPs);

4) Manufacturers must submit to FDA all reports that they receive of serious adverse events associated with a product that it manufactures; and

5) A manufacturer must submit a notification to FDA before it markets a dietary supplement containing a 'New Dietary Ingredient'."

cGMPs are in place:

"Since the rule went into effect in June 2008, we have conducted approximately 55 inspections for compliance with the new regulations. The majority of facilities have been found to be in substantial compliance."

FDA has identified enforcement priorities:

Adulteration with Drug Substances

"Products that are marketed as dietary supplements but contain active ingredients in FDA-approved drugs, analogs of approved drugs, and other compounds that do not qualify as dietary ingredients, present an emerging and expanding challenge. FDA has found that certain products in the following categories have been illegally represented as dietary supplements: sexual enhancement or erectile dysfunction, weight loss, cholesterol reduction, and body building products. These products have been found to be intended for use as drugs and to contain active prescription pharmaceutical ingredients including PDE-5 Inhibitors (e.g., sildenafil or Viagra), controlled substances for obesity (e.g., sibutramine or Meridia), lovastatin, and synthetic steroids or steroid-like substances. These products are often sold with misleading labeling and are frequently manufactured without quality controls."

Illegal Claims

"Dietary supplements with unsubstantiated and illegal claims may encourage consumers to self-treat for a serious disease without the benefit of a medical diagnosis or treatment. FDA conducts enforcement activities against supplements that make these types of claims."

Unsafe Ingredients

"A dietary supplement is adulterated, and subject to enforcement action, 'if it bears or contains any

poisonous or deleterious substance which may render it injurious to health' or if it presents a 'significant or unreasonable' risk to consumers. DSHEA allows the HHS Secretary to ban a dietary supplement if she finds it to be an 'imminent hazard.' Under the current regulatory framework, FDA looks for such problems after marketing through reviewing the medical literature and analyzing adverse event reports."

Dr. Sharfstein also commented specifically on the findings of the GAO report.

Heavy Metals

"GAO ... analyzed 40 dietary supplements for heavy metal contaminants. All of the products were found to contain trace amounts of lead, cadmium, arsenic and mercury. Given the expected generally small consumption of the supplements, we do not believe these levels represent a significant risk to health. For example, the cadmium levels reached to about 1.4 µg/day (micrograms per day). This compares to FDA's tolerable daily intake level of 60 µg/day. The lead levels reached to 1.9 µg/day, which is about a third of FDA's tolerable daily intake. While this is a not a dangerous level, it is a significant fraction of daily intake."

Pesticides

"GAO also analyzed supplements for pesticide residues. The 41 residues listed in Appendix IV of GAO's statement of facts fall into four groups.

Seven residues were found at levels within the Environmental Protection Agency (EPA) tolerances for dietary supplements. For example, two samples of ginseng had residues of metalaxyl at .01 and .03 parts per billion (ppb), while the tolerance level for metalaxyl in ginseng is set by EPA at 3.0 ppb.

Thirty-one (31) residues were at levels within tolerances used for fruits and vegetables, but there are no tolerances in the law for dietary supplements. For example, the pesticide chlorpyrifos has no set tolerance level for residue in Echinacea, where it was found at a level of .01 ppm. However, residue levels for chlorpyrifos have been set for celery at 15 ppm and for tomatoes at 5 ppm.

One residue found was a low level of carbofuran, a pesticide that had its tolerances canceled by EPA in 2009.

Two residues were low levels of pesticides that were either never approved for use in the United States (tolclofos-methyl) or had their use banned in the United States over 40 years ago (hexachlorobenzene, or HCB). These findings are within or very close to the allowable residue levels set by the European Union.”

Dr. Sharfstein put the GAO’s findings into a public health perspective context, and he did the same with FDA’s enforcement priorities. This is a good communication.

¹ A Webcast is available online at http://aging.senate.gov/hearing_detail.cfm?id=325265.

² <http://aging.senate.gov/events/hr221gk.pdf>



FDA Issues CFR 111 Guidance for Inspectors, Prioritizes Botanicals

By Katia Fowler, Director of Communication, AHPA
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FDA recently issued guidance to the field with respect to dietary supplement manufacturer inspections. Under FDA’s Compliance Program Guidance Manual, botanicals have a priority status over vitamins and minerals. Specifically, FDA instructs inspectors:

Select firms for inspection in the following order of priority:

1. Firms producing both dietary supplements such as botanicals (e.g., ginseng, yohimbe), animal and plant extracts (e.g., garlic extracts and glandulars), fats and lipid substances (e.g., oil of evening primrose, fish oils, essential fatty acids) *and also producing* dietary supplements such as vitamins, minerals, and proteins;
2. Firms producing dietary supplements such as botanicals (e.g., ginseng, yohimbe), animal and plant

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extracts (e.g., garlic extracts and glandulars), fats and lipid substances (e.g., oil of evening primrose, fish oils, essential fatty acids) **but not producing** any dietary supplements of vitamins, minerals, or proteins;

3. Firms producing only dietary supplements of vitamins, minerals, or proteins.

The agency notes, however, that “because of its focus on firms manufacturing ‘non-traditional’ products,’ the above prioritization scheme may hinder district office’s ability to “meet the threshold for sample collection and analyses under the program, i.e., products which contain 25% of the Reference Daily Intake (RDI) or Daily Reference Value (DRV) of a vitamin, mineral, or protein.” For this reason, FDA encourages sample collection “from other establishment types visited for purposes of conducting field exams.”

The Compliance Program Guidance Manual also provides inspectors with a list of priority botanicals (see table at right). It is clear from this list that FDA’s focus is on safety, and that this focus draws the agency’s attention to botanicals it believes to be at higher risk for adulteration, especially adulteration with toxic material. It is also notable that FDA makes a point to identify several of the botanicals – namely, *Withania somnifera* and *Bacopa monnieri* – as being sourced from developing countries.

The Compliance Program Guidance Manual is worth reading if only to provide manufacturers with an understanding of how FDA sets the general priorities for inspection of manufacturers. It is accessible online at: <http://www.fda.gov/Food/ GuidanceComplianceRegulatoryInformation/ ComplianceEnforcement/ucm071547.htm>. The list below is reproduced directly from that site under Attachment E.

Acacia rigidula (Other common names: Black brush or Chaparro Prieto)

Scientific Name: *Acacia rigidula* Benth.

Interest: New dietary ingredient for which a notice is required; possible toxicity issue

Caralluma fimbriata (Other common names: Indian Hoodia ; *Caralluma cactus*)

Scientific Name: *Caralluma fimbriata* , *Caralluma adscendens*

Interest: Identity; substitution by other ingredients

Hoodia gordonii (Other common names: African Hoodia cactus; Bokhorings; Bushmen’s hat)

Scientific Name: *Hoodia gordonii*

Interest: Identity; substitution by other ingredients

Withania somnifera (Other common names: Indian ginseng, Ashwagandha, Winter Cherry)

Scientific Name: *Withania somnifera*

Interest: Identity and contamination (origin in third world countries)

Bacopa monnieri (Other common names: Brahmi, Water hyssop)

Scientific Name: *Bacopa monnieri*

Interest: Identity and contamination (origin in third world countries)

Black cohosh (Other common names: black snakeroot, macrotys, bugbane, bugwort, rattleroot, rattleweed)

Scientific Name: *Actaea racemosa*, *Cimicifuga racemosa*

Interest: Identity. (substituted for with other plants; economic adult.)

Scutellaria: (Other common names: skullcap, mad dog)

Scientific name: *Scutellaria lateriflora* L.

Interest: Identity (substituted for with other plants; economic adult.)

Memordica Chrantia (Other common names: bitter Guard/bitter melon)

Scientific Name: *Memordica Charantia*

Interest: Identity and contamination (origin in third world countries)

Milk thistle

Scientific Name: *Silybum marianum* (L.) Gaertn.

Interest: Identity and contamination. (origin in third world countries)

Goldenseal

Scientific Name: *Hydrastis canadensis* L.

Interest: Substitution by, or contamination with, *Berberis*/Mahonia species, *Coptis groenlandica* L. *C. trifolia* (L.) Salisb; or *Xanthorhiza simplicissima* Marshall, all of which shares a yellow color (Wendy) (econ. adulteration)

Akebia (Three-leaf akebia)

Scientific name: *Akebia trifoliata* (Thunb.) Koidz.

Interest: Substitution by, or contamination with, *Aristolochia* spp. (which is toxic)

Stephania

Scientific name: *Stephania tetrandra* S. Moore

Interest: Substitution by, or contamination with, *Aristolochia* spp. (which is toxic)

Plantain

Scientific Name: *Plantago major* L.

Interest: Substitution by, or contamination with, *Digitalis lanata* (which is a toxic plant)

Source: Compliance Program Guidance Manual, Dietary Supplements – Import and Domestic

"The way I think about DSHEA is that it balances access against risk..."

- Dr. Joshua Sharfstein,
Principal Deputy FDA Commissioner

Sharfstein on DSHEA:

Law Balances Access and Risk

In response to a question from Sen. Herb Kohl (D-Wisc.) on the topic of pre-market approval, Principal Deputy FDA Commissioner Dr. Joshua Sharfstein explained his understanding of the Dietary Supplement Health and Education Act of 1994 (DSHEA):

"I think that the framework that DSHEA puts on dietary supplements is very different than prescription drugs, and Congress's thinking about dietary supplements was very different than the framework for prescription drugs. The way I think about DSHEA is that it balances access against risk, and there is a very clear feeling in the law, by Congress and the public, that they want access to supplements that are important to people ... so ... people can put [supplements] on the market without pre-review by FDA – particularly for the products that have been marketed historically – and that's not the case at all for drugs. On the other hand, there are provisions in the law that mitigate risk. So you could have a situation where you only care about risk – and it would be very hard to have access – or you could say, 'we will let everything on there,' and there would be no risk provisions. But, I think DSHEA tries to strike a balance.

FDA needs to do a few things to maximize the risk part of the equation, I think, when the law permits, and that includes getting out the guidance on the new dietary ingredients; we have to do our enforcement – like you've heard; we need to fully implement the good manufacturing principles. I think, if you think about that balance, the question is, 'are we striking the right balance.' I think for the most part the answer to that is 'yes.'

The area ... that gives the FDA the most concern, without question, relates to the pharmaceutical spiking of dietary supplements because we're talking about very serious risk and injuries that can happen to people. Often [the people taking these products] are young people who don't really understand that what they're taking are actually prescription drugs or steroids [marketed as] dietary supplements. And there has been testimony by FDA that, while we are being as aggressive as we can with enforcement, we are very concerned about the state of the market for these products. And I think that's the area that gives us the most concern."



FDA's First cGMP Warning Letter Goes to Herbal Supplement Manufacturer

By Anthony L. Young, Esq., Partner, Kleinfeld Kaplan & Becker and AHPA General Counsel. Originally published in the August 2010 AHPA Report. Reprinted by permission of AHPA.

FDA released its first dietary supplement cGMP [Warning Letter](#) to Coats International Holdings, Inc., manufacturer of two aloe products for Herbalife. These are relatively simple products, and the FDA Warning Letter describes the cGMP regulations and concepts that the Coats company is said to have failed to meet. What the Warning Letter teaches can be evaluated by reading the letter and attending one of the many seminars that have sprung up since the Warning Letter was made public. AHPA's seminar, "Meeting Specifications: Identity Testing and Vendor Qualification," touched on these issues. Here are the concepts:

1. Conduct at least one appropriate test or examination to verify the identity of a dietary ingredient. Situation - you receive the dietary ingredient but how do you know it is a) the dietary ingredient or b) the dietary ingredient plus thickeners or other ingredients. Need to have appropriate tests and examinations.
2. Document why meeting in-process specifications and component specifications help ensure the product meets specifications and why the results of the tests and examinations performed ensure specifications are met. This means that there must be a predicate rationale for the specifications and how they assure the integrity of the product. Specifications alone are not enough.
3. Follow your written procedures for collecting representative samples of each unique shipment of components. This means that when you have a procedure in place, it must be followed. If each shipment of components is to be tested, this must be done and the procedure must make clear what a "shipment" means, e.g., one sample from each batch, or one sample from each container.
4. Have a complete quality control program

including, periodic instrument calibration, written instructions for manual operations and witnessing such operations, quality control approval and release of each manufactured batch at the time of manufacture.

5. The master manufacturing record must include a statement of the theoretical yield of a manufactured dietary supplement expected at each point, step, or stage of the manufacturing process where control is needed to ensure the quality of the dietary supplement, and the expected yield when you finish manufacturing the dietary supplement. Essentially this means you need to assure that your yields are as expected. Batch production records must include a statement of the percentage of theoretical yield at appropriate phases of processing.
6. The written instructions in master manufacturing records must corrective action plans to use when a specification is not met. It is not sufficient to simply state that a product investigation will be initiated to determine the root cause on the batch record. The master manufacturing records must set out the response.

The Coats Warning Letter is a signal that that dietary supplement cGMP are in place and must be adhered too. There have been other inspections of dietary supplement manufacturers with similar findings. When you read this Warning Letter you will see that Coats responded to FDA's 483 and that FDA has evaluated their response and come back with further comments. And, while the Warning Letter is revealing with respect to level of response required to satisfy FDA observations, the cryptic language of the letters and restatement of the regulations is often difficult to decipher. What is often needed is dialog, and dialog is usually lacking in a regulatory setting.

A link to the Warning Letter is here:

<http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/ucm210182.htm>

For more information on AHPA's Identity Testing and Vendor Qualification seminar, visit: <http://www.ahpa.org/Default.aspx?tabid=68#semvendorqualfctn>

