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## DIRECTOR'S MESSAGE



Devon Powell,  
Executive Director

The last few months have been busy ones here, and I hope they've been busy for IASC members, as well (which hopefully translates to "profitable"). As such, this will be a shorter-than-usual Director's Message.

That said, please review the special feature, "It's Not Over 'til the Fat Lady Sings: Ongoing FDA/NTP Studies," cowritten by IASC General Counsel Marc Ullman, Linda Dougherty, and me in this issue of *Inside Aloe Online* on page 3.

I am compelled to mention a few other items that should be of interest, including that litigation against Fruit of the Earth regarding trademark infringement/illegal usage of the IASC certification seal continues, and we are also addressing illegal seal usage against other companies around the globe.

The board of directors met in March and elected new officers, including President-Elect Jeff Barrie (Aloecorp), Secretary Roger Poore (Aloe Vera of America), Treasurer Bob Smith (Aloecorp), and Executive Committee members at-large Ken Jones (Aloecorp), Charlie Metcalfe (Custom Analytics), and Bill Pine (Improve USA).

At the March meeting, the board discussed ways to increase global exposure of the certification program and seal. A Certification Committee meeting was held in early May to discuss this and several other topics.

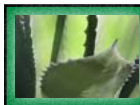
The Aloe Symposium, held in conjunction with VIRGO's SupplySide West trade show in Las Vegas in November, seems like it could be a reality this year, as well, which is an exciting opportunity for a gathering of all-things-aloe in November in Las Vegas and definitely something to look forward to!

Finally, the situation in Brazil, which has banned the sale of aloe vera in orally consumed products since late 2011, continues to be a priority. Staff has been instructed to gather all available safety and toxicology data, and this process is ongoing. Members with any data on individual products and raw materials are asked to please submit them for review.

I hope the summer months continue to treat everyone well.

Devon Powell  
Executive Director





## SPECIAL TOPICS

### It's Not Over 'til the Fat Lady Sings: Ongoing FDA/NTP Studies

By Devon Powell, Linda Dougherty, and Marc Ullman

Although we'd all prefer to never see the acronym NTP again, it's certain we haven't seen the last of the National Toxicology Program (NTP) and its efforts with regards to aloe.

As most will recall, NTP released its draft technical report on a two-year study of "non-decolorized whole leaf extract of *Aloe barbadensis* Miller," an unpurified aloe ingredient that contained 13,000-16,000 ppm of aloin and was fed to mice and rats for two years, with the draft report stating that ingredient was responsible for causing damage to the colon of the male rats. (See related story, page 5.) Now, the Food and Drug Administration (FDA) has indicated that it will be co-principal investigator with NTP in ongoing studies on aloe with one objective: to determine what constituent caused the results of this two-year study.

IASC met with FDA in May of 2011, where the association was asked to provide U.S. market data (volume/quantity) on those raw materials most often present in finished products for sale in the United States, as well as specifications for those materials. The requested data was presented to FDA on May 1, 2012, at which time the agency indicated it would be used in the determination and procurement of new test ingredients in its upcoming 13-week studies.

At the meeting, FDA personnel relayed their opinion that there are two constituents of aloe that are of principal interest to the FDA/NTP: aloin and polysaccharides. Though industry's position has been and continues to be that the aloin was the likely cause of any issues with the rats in the two-year study, the agency is clearly not going to accept this conclusion unless it is verified by the new studies. It's also clear

the studies will be designed to focus on polysaccharide content as well, and from the questions asked by agency personnel, Dalton size and how industry controls polysaccharides will likely be of interest.

It's likely the agency has already tested the majority of aloe vera products that are readily available in the U.S. marketplace and had an understanding of what raw materials are present in them before our meeting and before IASC provided the requested market data. It's also likely that FDA will use the market data IASC supplied simply as a way to verify its own information.

At the meeting, FDA also indicated that once all the information is vetted, the agency would be interested in connecting with raw material suppliers to request test materials. It will be up to individual suppliers to determine whether or not they want to have their specific raw material products tested.

There are several good reasons for suppliers to consider assisting in this process. NTP essentially wasted millions of taxpayers' dollars with the last study and by testing an ingredient that isn't actively sold in the U.S. marketplace. With FDA now directly involved, that won't happen again, and the two agencies will focus on the "right" ingredient this time around. By providing the ingredient, if requested, at least there will be some measure of control in the process, and there's a sense that by doing so, industry stands a chance of being kept apprised of the status of the new studies.

Although the IASC hypothesis is that FDA and NTP will find that the aloin content was and is the cause for concern, and the IASC position on aloin content of  $\leq 10$  ppm aloin at single-strength is a reasonable one, we're not out of the woods by any means. In the meantime, IASC members and others in the aloe industry should not only be considering how to best protect themselves from possible regulatory scrutiny in the future, but hopefully they have been engaged in those activities, such as toxicological studies on branded products or in obtaining generally recognized as safe (GRAS) status for raw materials.

## GRAS Status and Aloe Vera

The Federal Food, Drug, and Cosmetic Act (FDCA) requires that any substance that is intentionally added to food be subject to premarket review and approval by FDA, unless the substance is GRAS. To meet this standard, it must be generally recognized among qualified experts that the substance is safe under the conditions of its intended use. Under the FDCA and FDA regulations, a substance may be determined to be GRAS either through scientific evidence or, if the substance has been commonly used in food since before 1958, through general experience based on that prior use.

For substances requiring scientific evidence in order to prove GRAS status, FDA has defined “safe” to mean a reasonable certainty in the minds of competent scientists that the substance is not harmful under its intended conditions of use. This finding of safety must be based on information and data that is generally publicly available (usually published studies) so that it can be reviewed and considered by qualified experts in order to establish whether there is a consensus as to the substance’s safety.

Undertaking a GRAS self-affirmation requires that a panel of qualified experts be assembled to review and assess the substance’s safety. The panel of experts should include toxicologists, biologists, and food scientists. The sponsoring company should also make use of counsel

and consultants to interact with FDA. These GRAS assessments generally cost the sponsoring company around \$50,000 or more if additional testing is needed.

Once the GRAS affirmation is completed, companies have the option of notifying FDA of their GRAS determination and submitting the data to FDA for review. This is not a mandatory approval process, but rather for the purpose of providing FDA with an opportunity to review the data and publish the notification and its response. Ideally, FDA’s response will indicate that FDA has no further questions as to the substance’s GRAS status—it will not provide “approval.”

Several IASC members have claimed to have achieved self-affirmed GRAS status for their raw materials, including Aloecorp and Terry Laboratories. It should be noted that although a company may have claimed GRAS for its raw materials, this is not transferrable or applicable to a similar ingredient from another supplier.

## Getting Help with Self-Affirmed GRAS

There are firms that are capable of assisting members with achieving self-affirmed GRAS status, and members interested in the process are encouraged to discuss the options with IASC General Counsel Marc Ullman.

## Toxicological Studies on Finished Products

Those finished product marketers who are looking to build some protection for their products and businesses may want to consider undertaking 13-week toxicological studies on their own finished goods, especially those who are not using raw materials that are self-affirmed GRAS.

IASC can recommend firms capable of assisting with this work and interested members are encouraged to contact staff for additional details.

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## Aloe Vera: From Standards to Science

By Sandy Almendarez

Aloe vera may be one of the most well-known ingredients in the personal care aisle. From tissues and toilet paper to skin care and cosmeceuticals, aloe vera is almost as pervasive as the personal care products themselves. SPINS reported (52 weeks ending Feb. 18, 2012 versus the prior year) body care items with aloe vera as the primary ingredient grew 2.3 percent in the combined (natural and conventional Food Drug Mass) channel.

While other applications may be burgeoning, Patrick Anderson, Western regional sales manager for Terry Labs, said beverages and cosmetics are still the most popular delivery forms. “These two components involve consumers’ everyday movements,” he said. “The latest movement within the nutraceutical and cosmeceutical industry involves beauty from within. This involves taking capsules and/or drinks to improve the internal body as well as improving outward beauty.”

Anderson is spot on, as SPINS reported the combined channel experienced a 58 percent increase in sales (52 weeks ending Feb. 18, 2012 versus the prior year) of food items with aloe vera as the primary ingredient; and an 18.9 percent increase in sales of vitamins, supplements, herbs, and homeopathic aids with aloe vera as the primary ingredient.

As aloe vera expands its delivery forms into the nutricosmetic category, quality control is more important than ever, as is the issue of toxicity. While aloe vera is a botanical most consumers would say they know very well, it’s actually quite complicated, as “aloe” can refer to more than 400 species. Because of its health properties and low toxicity levels, aloe vera, aka aloe vera (L.) Burm. f., *Aloe barbadensis*, barbadensis (Mill.) or Miller, is the most commonly used aloe in consumer products; but, many confuse and combine the properties of the different species of aloe and components of aloe vera.

Thus, one of the most-pressing issues in the aloe industry is a study conducted in the spring of 2011 by the National Toxicology Program (NTP), an interagency program with the objective of evaluating substances

of possible public health concern, in collaboration with FDA’s National Center for Toxicology Research. It created quite a commotion. The two-year study reported aloe was linked to carcinogenic activity in male and female rats, based on tumors of the large intestines. But what’s important here is that this study was not conducted on the type of aloe found in the natural products market.

The study used a non-decolorized, whole-leaf extract of *Aloe barbadensis* Miller that did not undergo charcoal filtration during processing, a popular filtration method; in other words, it was filled with latex, which contains anthraquinones that cause a laxative effect in humans, and aloin. In a consumer information pamphlet, NTP said it used this aloe form because it wanted to test a preparation that included all components that may be in the products on the market.

The NTP studies consisted of a 14-day study on mice, a 13-week study on rats, a 13-week study on mice, a two-year study on rats and a two-year study on mice. In each study, the lab animals were administered the aloe preparation in various concentrations (1 percent, 2 percent or 3 percent wt/wt) or placebo. The two-year study on rats was the most damaging because it showed “clear evidence” of carcinogenic activity based upon increased incidence of adenomas and carcinomas of the large intestine. Data from the other studies revealed exposure resulted in increased incidences of non-neoplastic lesions of the large intestine in male and female rats, the large intestine in both rats and mice, the small intestine of rats, the stomach in rats and mice, the mesenteric lymph nodes in rats and mice, and the noses of mice.

In its consumer pamphlet, NTP reported it suspects the aloin content caused the tumors, but it said it does not know for sure. NTP said the aloe rat studies give cause for at least three serious concerns: the aloe types currently on the market, the aloin levels in these products, and the patterns of human exposure. The agency said it hopes to do more studies.

“FDA is after what caused damage to the rats,” noted Devon Powell, executive director of the International Aloe Science Council (IASC). “I’m not a scientist, but I think it’s because the aloe wasn’t filtered. Thinking logically, if you feed a rat aloe that’s laced with aloe latex for two years, you are going to put them in a

diarrhea state for two years. If you had diarrhea for your lifetime, I'm pretty sure you'd have some problems."

Powell noted the NTP draft report, which he expects will be finalized at some point, did not adversely affect the market. "We thought it would; we were definitely afraid that it would," he said. "When you say something like 'carcinogenic,' that causes people's ears to prick up."

It may just be the intervening work of the IASC that helped to keep the reports from causing the damage they could have. According to Powell, NTP was originally calling the preparation used in the studies "whole-leaf extract of aloe vera," but that's not what it tested. "They actually tested the non-decolorized form, which means they did not filter it," Powell said. "Our industry filters it."

To help NTP and FDA better differentiate between the preparations used in the study and those that are on the market, the IASC met with FDA officials on May 10, 2011, and provided them with analytical results of an NTP study sample obtained by the council. The analytical results of the study material showed it contained 10,000 ppm to 13,000 ppm of aloin,

which is 1,000 to 1,300 times the less than 10-ppm limit established by the IASC in 2009.

At that meeting, FDA officials informed IASC participants that the agency would be a co-principal investigator on a new 13-week study on aloe vera as a follow up to the NTP study.

Players in the aloe market don't seem to be too concerned with the NTP study's effect on the industry. "I do not expect the study to adversely affect the aloe market," said Santiago Rodriguez, Ph.D., and CEO of Lorand Laboratories LLC. "People have been using aloe vera for millennia, and so it is pretty evident in the people's minds that the product is safe."

Some even praise the study. "The NTP study is welcome as with any study done on aloe vera," Anderson said. "We do not expect any unusual outcomes. This type of study will only strengthen the safety and efficacy of aloe vera in the marketplace. The original NTP study focused on how the majority of processors within the aloe vera industry do not process aloe. With the new NTP study, we can now see true results because we have been asked to participate in how aloe is truly processed.



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Again, we expect great outcomes.”

Bill Pine, vice president of Improve USA Inc., has a wait-and-see attitude. “The first study was conducted on an ingredient that is not normally available in the consumer market, so we can only respond by assuring the consumer that aloe has been consumed for approximately 50-plus years with little or no indications of contraindications,” he said.

Rewind to 2010 when another study conducted by NTP examined the effects of synthetic solar light on the skin of hairless mice that had been treated with creams containing various aloe vera extracts.<sup>1</sup> Researchers applied creams containing aloe vera plant extracts (aloe gel, whole leaf or decolorized whole leaf) or aloe-emodin to groups of 36 male and female hairless mice in the morning; other groups received creams containing no aloe. In the afternoon, groups of animals were exposed to synthetic solar light for four hours. Other groups were not exposed to light and were control groups. The treatments and exposures were performed five days per week for 40 weeks, during which the animals were monitored for development of skin cancers. Mice exposed to synthetic solar light developed significant increases in squamous cell neoplasms and squamous cell nonneoplastic lesions of the skin whether or not they received treatment with cream. Female mice, but not male mice, treated with aloe gel or aloe-emodin and exposed to simulated solar light had increased numbers of squamous cell neoplasms when compared with mice treated with the carrier cream without the aloe gel or aloe-emodin and exposed to the same intensity of light. For both male and female mice, inclusion of aloe whole leaf extract or decolorized leaf extract in the cream increased the number of squamous cell neoplasms when the animals were exposed to simulated solar light. Researchers therefore concluded aloe gel or aloe-emodin had a weak enhancing effect on the photocarcinogenic activity of simulated solar light in female but not male hairless mice.

However, Powell said these results don't warrant concern. “NTP hazard analyses on rodents do not directly translate into a risk for humans,” he said. “The weak results found in the photosensitivity studies for the tested aloe vera materials were not sufficiently strong

enough for the IASC to consider them as hazardous or to trigger an official response.”

## A Lot on Aloe

Fortunately, the good outweighs the bad, as numerous studies have been conducted on aloe's ability to soothe and moisturize dry skin, as well as offer antibacterial and wound-healing benefits. A Brazilian study of 20 women found freeze-dried aloe vera extract was an effective ingredient for improving skin hydration and suggested it may be used in moisturizing cosmetic formulations and also as a complement in the treatment of dry skin.<sup>2</sup>

Expanding beyond dry skin, a 40-study review of dermatology-oriented *in vitro* and *in vivo* experiments and clinical trials of aloe vera determined oral administration of aloe vera in mice is effective on wound healing, can decrease the number and size of papillomas, and can reduce the incidence of tumors and leishmania parasitemia by more than 90 percent in the liver, spleen, and bone marrow.<sup>3</sup> The Iranian researchers reported aloe vera can be effective for genital herpes, psoriasis, human papilloma virus (HPV), seborrheic dermatitis, aphthous stomatitis, xerosis, lichen planus, frostbite, burn, wound healing, and inflammation. However, they noted evidence does not support the topical application of aloe vera as an effective prevention of radiation-induced injuries and has no sunburn or suntan protection.

In a 2007 systematic review, clinical trials for burn healing examined aloe vera's effects in four studies with a total of 371 patients.<sup>4</sup> The Thai researchers reported the average difference in healing time of the aloe vera groups was 8.79 days shorter than those in the control groups ( $P=0.006$ ). An *in vivo* human study with aloe vera gel found it to be effective on partial-thickness burn wounds<sup>5</sup>; and in a separate randomized, placebo-controlled study, aloe cream offered greater efficacy over silver sulfadiazine cream for treating second-degree burns.<sup>6</sup>

Similarly, post surgery, aloe can also offer relief. A 2010 study from Iran assessed the effects of aloe vera cream in reducing postoperative and post-defecation pain, and its promotion of wound healing after hemorrhoid-removal surgery.<sup>7</sup> Researchers found, using a prospective, randomized, double blind, placebo-controlled trial



# Aloe

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with 49 patients, those in the topical aloe cream group (n=24) had significantly less postoperative pain at 12, 24, and 28 hours, and two weeks after surgery compared to placebo (n=25). Aloe cream reduced the pain after defecation in 24 and 48 hours post surgery ( $P<0.001$ ). Wound healing at the end of the second postoperative week was significantly greater in the aloe group compared with the placebo group ( $P<0.001$ ).

Both topical and oral treatments with aloe vera were found to have a positive influence on the synthesis of glycosaminoglycans, which maintain and support collagen and elastin, and thereby beneficially modulate wound healing.<sup>8</sup> Orally, aloe also has an antifungal and antibacterial effect, as Brazilian researchers found aloe vera fresh leaves plant extract inhibited both the growth and the germ tube formation by *Candida albicans*, suggesting its use as a promising novel antifungal treatment.<sup>9</sup> Additionally, aloe vera tooth gel and toothpastes were effective against *Candida albicans*, *Streptococcus mutans*, *Lactobacillus acidophilus*, *Enterococcus faecalis*, *Prevotella intermedia*, and *Peptostreptococcus anaerobius* in a 2009 study.<sup>10</sup>

Aloe vera has also been tested in its ability to help specific skin ailments, such as psoriasis and erythema (reddening of the skin). A randomized, double blind, placebo-controlled Danish trial that included 41 patients reported aloe vera gel's effects on stable plaque psoriasis was modest and not better than placebo.<sup>11</sup> However, they noted the high response rate of placebo indicated a possible effect in its own right, which would make the aloe vera gel treatment appear less effective. The plant fared better in a German study of 40 volunteers, which found aloe vera gel (97.5 percent) significantly reduced UV-induced erythema after 48 hours, and was superior to the 1 percent hydrocortisone in the placebo gel.<sup>12</sup>

### The Need for Standards

As aloe shifts its beauty weight into the nutricosmetics category (in addition to considering how pervasive aloe is in the marketplace), manufacturers need to assure consumers by testing their products for aloin content. The IASC says aloe vera products meant for consumption should have an aloin content of 10 ppm or less, and companies should be able to provide that information to consumers upon request. Powell said the



IASC came up with that number based on adverse event report (AER) data.

Aloe's benefits can only be realized if products actually contain enough active ingredients. Rodriguez said the lack of consistent quality among both raw material producers and finished product makers is the biggest issue facing the aloe industry. "Many people use aloe as a 'label claim,' but don't really put a significant amount of it or use a good enough quality to produce an effect," he said. "This backfires in the long run, since consumers become disappointed after using the products and not getting the expected effects."

Shaun Bozorg, Eastern regional sales manager for Terry Labs, said some manufacturers can go even further than not containing enough active aloe; he said the greatest concern in the industry is the issue of adulteration. "Many so-called aloe products are adulterated by maltodextrin or other cheap fillers," he said. "The biggest issue is making sure aloe products are undiluted, unadulterated, and of high quality."

Powell noted IASC has also seen maltodextrin as a common adulterant, so it tests its member companies for purity. "It's important for any ingredient to have a framework of what's sold and what's not sold," he said.

To that end, the IASC established a certification program in the 1980s so aloe growers, processors, and manufacturers could show their products contain an efficacious amount of aloe vera. The IASC program verifies products that contain a string of sugars—acemannan, or beta 1-4 acetylated glucomannan—among other components. Acemannan is naturally occurring in the plant and is measured by IASC using a nuclear magnetic resonance method. The certification also requires an on-site audit for good manufacturing practices.

"This seal of certification provides the consumer confidence that the product they are purchasing contains pure, quality aloe ingredients in conformance with the label," Pine said, adding, "Consumers should look for the seal."

But aloe vera is more than just acemannan, and depending on what other components are found in products, safety can be an issue. If the industry had

a standard, Powell argued, FDA and NTP wouldn't question the safety of products on the market.

Therefore, the IASC is also developing an aloe vera monograph it hopes to have published in 2012.

"Standardization is a huge issue for this industry," Powell said. "It becomes difficult when something like the NTP study comes up because FDA wants to know what is in this stuff." The initial monograph will focus on standards and compliance, but the council hopes to add a therapeutic compendium in the near future.

## Manufacturing Matters

Obtaining a third-party certification and following a monograph can help differentiate a quality product from an inferior one, but manufacturing practices may play an even bigger role.

Pine said Improve USA's quality control starts at the field, as the company owns and manages almost 2,000 acres of aloe. "Improve employs agronomists to monitor the aloe and recommend improvements in the fields, we maintain harvesting crews that work only for us and know the quality we require, and all aloe harvested is processed in 12 hours or less," he said.

According to Anderson, "Aloe has two enemies: heat and time." He said when heat is applied to aloe vera, the long-chain polysaccharides (aka the active ingredients) start to break down into smaller chains. "We process our aloe with low temperatures, which keeps the long-chain polysaccharides intact." Further, he noted Terry Labs uses reverse osmosis during the processing phase, which allows for no heat during the concentrating of aloe. "By not using heat to concentrate, we preserve the long-chain polysaccharides," he said.

Taking too long to process the aloe can lead to degradation, Anderson continued. "We process our aloe immediately, so there is no degradation taking place with the raw plants." He said Terry Labs processes the aloe within a two-hour period.

For Rodriguez, the key to creating a stellar aloe product is a deep understanding of the chemistry and bioactivity of acemannan. "The primary concerns are in terms of the potential damage the processing can do to the acemannan chemically and to the biological activity of it as well. There are many aloe products in the market with

very little or no acemannan at all as a consequence of a poorly designed process.” He said Lorand Labs’ flagship product BiAloe was conceived to deliver a large amount of bioavailable acemannan. “These considerations are very important, as we do no good if we have a large amount of acemannan, but it turns out the form of this acemannan is not bioavailable due to structure features related to processing among other factors.”

An aloe product without enough acemannan would be a shame, but a product with too much aloin could be deadly, which is why manufacturers need to be on top of their aloe game. They need to test raw materials and finished goods, and have their marketing teams ready to discuss how their products differ from the one in the FDA/NTP study, should consumers ask. Seeking resources such as the IASC can help, but it’s the onus of each company to make sure its aloe contains enough of the good, not too much of the bad, and that its manufacturing processes create consistent products.

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*Sandy Almendarez is the editor of Natural Products Insider, published by VIRGO Publishing LLC. This article originally appeared in the May 2012 issue of Inside Cosmeceuticals, published by VIRGO Publishing LLC. Copyright 2012 by VIRGO Publishing LLC.*

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## ***Ancient Medicines* Lecturer Developing New Database from 2,400 Years of Traditional Medical Techniques**

*by Merle Zimmermann, Ph.D., AHPA Information Analyst*

*Ancient Medicines in the Modern Era*, a lecture discussing remedies from traditional Mediterranean medicine, was presented by Alain Touwaide, Ph.D., on March 6 at the George Washington University medical school. Touwaide is an esteemed researcher and cofounder of the [Institute for the Preservation of Medical Traditions](#) (IPMT) of the National Museum of Natural History at the Smithsonian Institution.

In his lecture, Touwaide described the development of a resource combining digitized original documents, written in ancient Greek, and an index database including symptoms, conditions, and the prescribed treatments as described in more than 3,100 individual formulas spanning 24 centuries of medical traditions.

This database allows IPMT researchers to examine overarching patterns of treatment strategies and approaches, as well as their development as the methods were distributed throughout the ancient world.

Touwaide underscored the usefulness of returning to the original sources throughout his presentation, discussing how differing marginal notations in each manuscript provided additional context and information about development of the traditions, as well as information about the adaptation of treatment methods to local medical and environmental conditions.

Furthermore, by comparing illustrated botanicals in original texts with modern botanical reference examples from the same geographic areas, many apparent inconsistencies could be identified as confusions over terminology. For example, ancient Greek monographs indicated apparently contradictory uses for sage, but examination of the sources unearthed an explanation: the same ancient Greek word for *sage* was being used in separate texts to refer to two distinct species that did not share natural environments in ancient Greece and were identified by IPMT research as *Salvia fruticosa* and *Salvia officinalis*.

An ongoing goal of the database project is to add this locational information to correlate the variety of treatments used for each medical condition across both time and space, to represent ancient therapies as they developed across three dimensions. Touwaide noted that by including frequency of use, date, and the locations where the therapies were applied, the database provides a new model of medicine development, which takes advantage of personalization that took place based on local populations and conditions.

“This type of resource would be an invaluable tool for both the historian and the modern herbalist interested in traditional methods,” American Herbal Products Association President Michael McGuffin said. “Having easy access to this extant but difficult-to-reference material will allow for a much deeper understanding of the traditional roots of a large variety of medicinal techniques than would be possible without such a compilation.”

This modern index is currently focused on ancient Mediterranean medicine, but the same approach could also be applied to other medical traditions, Touwaide said, including historical Traditional Chinese, Arabic, and Ayurvedic medicines, with the assistance and help of linguists trained in those areas.

Touwaide expressed IPMT’s interest in cooperating with other groups to secure additional support to expand its scope and accelerate completion of the project.

In closing, Touwaide explained that the information in this database could be applied in the modern era to bring to light local beneficial uses for herbals that are naturally present in the Mediterranean region and have been overlooked through the passage of time. This approach to treatment might be both more environmentally sustainable and economically affordable for some local populations than other options available for these locations.

For more information, contact the Institute for the Preservation of Medical Traditions, 202.633.0967, or visit [IPMT’s website](#).

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## SCIENCE & ALOE: LITERATURE CITATIONS BY STEVEN DENTALI, PH.D.

### Traditional Herbal Medicinal Products: Food or Medicine or Both?

- ♦ Quintus C, Schweim HG. [European regulation of herbal medicinal products on the border area to the food sector](#). *Phytomedicine*. 2012 Feb 15;19(3-4):378-381.

This article focuses on the place of Traditional Herbal Medicinal Products within the European Union regulations governing herbal medicinal products. The simplified registration procedure is discussed based on proof of safety and efficacy, which can be established via product-specific documentation, community monographs, and list entries that are published by the European Commission and are widely accepted as legally binding. Particular attention is also paid in this article to when products would be considered as food or as medicine and the regulatory differences between these categories.

### Herb-Drug Interaction Mechanisms Explained

- ♦ Gurley BJ. [Pharmacokinetic herb-drug Interactions \(Part 1\): Origins, mechanisms, and the impact of botanical dietary supplements](#). *Planta Med*. 2012 Feb 9. doi: 10.1055/s-0031-1298273. [Epub ahead of print]

This review begins by pointing out that the ability to metabolize modern-day drugs arises from our past evolutionary exposure to plants as food or medicine. Therefore, it should come as no surprise that some botanicals may impact the metabolism of some drugs. Such interactions can be divided into pharmacokinetic ones, where the action of xenobiotic (outside the body) metabolizing enzymes and/or drug transporters are affected, and pharmacodynamic ones, where the pharmacological effects of herbs and drugs may tend to enhance or negate each other.

Part 1 of this review focuses on pharmacokinetic herb-drug interactions emphasizing their source, mechanisms, and clinical relevance. With its extensive

and detailed coverage of the synthesis of plant secondary metabolites (PSMs) versus their metabolism by humans, mechanisms of drug disposition and how PSMs can affect them, and human genetic variations with respect to drug metabolizing enzymes, differentiating between *in vitro* predictions and *in vivo* realities, and more, this is by far the best and most thorough review on the topic that I have seen.

### Quick Primer on Herbal Product Quality Issues

- ♦ Zhang J, Wider B, Shang H, Li X, Ernst E. [Quality of herbal medicines: Challenges and solutions](#). *Complement Ther Med*. 2012 Feb;20(1-2):100-106.

This article, which focuses primarily on identified quality issues with Eastern herbal medicines, is a good introduction for herb industry beginners to acquaint them with possible problems of external contamination, such as may happen with heavy metals, microbial toxins, misidentification, and intentional adulteration. The authors suggest these risks can be minimized via the rigorous implementation of good agricultural and collection practices and good manufacturing practices.

### Aloe Vera Leaf Juice Enhances Drug Passage Through Buccal Membranes

- ♦ Ojewole E, Mackraj I, Akhundov K, Hamman J, Viljoen A, Olivier E, Wesley-Smith J, Govender T. [Investigating the effect of Aloe vera gel on the buccal permeability of didanosine](#). *Planta Med*. 2012 Mar;78(4):354-361.

This study evaluated the effects of aloe vera inner leaf juice on the permeability of the mucosa lining the cheeks of the mouth for a drug used for anti-HIV and AIDS therapy. The researchers reported that lower aloe concentrations enhanced the passage of the drug while higher concentrations reduced the tissue permeability.

### Aloe Vera Leaf Juice

- ♦ Huseini HF, Kianbakht S, Hajiaghaee R, Dabaghian FH. [Anti-hyperglycemic and anti-hypercholesterolemic effects of Aloe vera leaf gel in hyperlipidemic type 2 diabetic patients: A randomized double-blind placebo-controlled clinical trial](#). *Planta Med*. 2012 Mar;78(4):311-316.



The results of this trial suggest that use of freeze-dried aloe vera inner leaf juice may be safe and effective for reducing blood sugar and total and HDL cholesterol in patients with type 2 diabetes with elevated blood lipids.

## Aloe Attributes Studies with Regard to Potential Anticancer Activity

- ♦ Harlev E, Nevo E, Lansky EP, Ofir R, Bishayee A. [Anticancer potential of aloes: Antioxidant, antiproliferative, and immunostimulatory attributes](#). *Planta Med.* 2012 Apr 19. doi: 10.1055/s-0031-1298453. [Epub ahead of print]

This review article is a compilation of research on species of aloe with regard to potential anticancer activity based primarily on *in vitro* cell and animal studies. Actual substantiation of anticancer activity in humans is apparently lacking. This pie-in-the-sky paper is full of unconvincing evidence that the authors interpret as great unrealized potential. Companies should be cautioned that even if clear evidence for clinically significant anticancer activity were present in this paper, which it is not, making product claims based on such research would render it an unapproved drug.

## Found Food Fraud Database

- ♦ Moore JC, Spink J, Lipp M. [Development and application of a database of food ingredient fraud and economically motivated adulteration from 1980 to 2010](#). *J Food Sci.* 2012 Apr 4. doi: 10.1111/j.1750-3841.2012.02657.x. [Epub ahead of print]

This report describes the development of a food-ingredient fraud database from reports in the scientific literature and the media from 1980 to 2010. The full database of 1,305 records of food ingredient fraud (categorized as replacement, addition, or removal fraud) will be available in tabular format in the eighth edition of the *Food Chemicals Codex* (United States Pharmacopeia, 2012). It is currently available [online](#).

While accounting for only 1 percent of total records, adulteration of (Chinese) star anise (*Illicium verum*) fell within the top 25 ingredients subject to adulteration identified in the scientific literature. The top six ingredients subject to adulteration were olive oil, milk, honey, saffron, orange juice, and coffee. Chemometrics, a data analysis tool, was identified as an emerging



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analytical trend in identifying food fraud, which suggests a potential need for its use in routine quality assurance testing. Indeed, this is the intent of employing near-infrared spectroscopy instrumentation for botanical-ingredient authentication, though appropriate data sets must first be constructed and the applicability of the method proven.

## The Matter of Measurement

- ♦ Schieberle P, Molyneux RJ. [Quantitation of sensory-active and bioactive constituents of food: a Journal of Agricultural and Food Chemistry perspective](#). J Agric Food Chem. 2012 Mar 14;60(10):2404-2408.

This article provides direction on proper procedures for the measurement of amounts of compounds that may be present in a food or other matrices from the perspective of submitting manuscripts to the *Journal of Agricultural and Food Chemistry*. It also explains that *quantitation* is a better term than *quantification* for our uses if we are measuring the quantity of something with high accuracy as opposed to something that may be understood more broadly. This is definitely cocktail discussion subject matter! Specifics of reporting measurements are also covered and may be of interest to botanical supplement analytical experts.

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## IASC AND ALOE IN THE NEWS

- ♦ [Aloe vera juice: The magic potion](#) – The Times of India
- ♦ [New to nature No 66: Aloe welmelensis: An endangered aloe found in Ethiopia has reopened the debate on the ethics of species collection](#) – The Guardian (UK)
- ♦ [Growing aloe in all of its glorious colors](#) – The Los Angeles Times

- ♦ [Aloe Vera: The Succulent with Skin-Soothing, Cell-Protecting Properties](#) – healthy.net
- ♦ [The Many Ways You Can Benefit from Aloe Vera](#) – Article Outlet
- ♦ [Aloe vera is effective when used both internally and externally](#) – Articlesbase

## LEGAL & LEGISLATIVE NEWS

### Capitol Hill Update: Election-year Paralysis; FDA-related Issues Likely to See Movement

*by Peter Evich, Vice President, Van Scoyoc Associates, and AHPA National Legislative Consultant*

#### Congressional Outlook

While both chambers of Congress have been humming with hearings, markups, and floor action this spring, the flurry of activity should not be viewed as an indicator of the amount of legislation that Congress will actually enact prior to the November elections. For the second year in a row, House Republicans have passed a long-term, ambitious budget measure crafted by House Budget Chairman Paul Ryan, R-Wisc. This year's budget iteration would cut government spending as a percent of gross domestic product from 24 percent to 20 percent by 2015. On the other side of the congressional corridor, Senate Democrats are once again taking a pass on moving a budget blueprint. This will be the third straight year that the Senate has balked on producing a budget document. Senate Budget Chairman Kent Conrad, D-N.D., stated recently: "This is the wrong time to vote in committee; this is the wrong time to vote on the floor. I don't think we will be prepared to vote before the election."

The larger congressional budget impasse is not impeding the House and Senate from moving in earnest on their independent versions of the annual appropriations

spending measures for the next fiscal year (FY). These are the bills that fund all of the federal agencies and programs on the discretionary side of the ledger. However, as a result of adopting the Ryan proposal, the House budget pie for discretionary spending is about \$20 billion less than what the Senate plans to allocate for its FY 2013 appropriations bills. Since the House and Senate are not working off of the same numbers, deliberations on the spending measure are assured to go past the official start of FY 2013 (Oct. 1), beyond the election, and into a lame duck session after the elections.

On a wide range of issues, such as energy, taxes, health care, environment, and financial services, we can expect to see a continuation of the theme of the 112th Congress: The Republican-controlled House passes legislation antithetical to the administration and Democrat-controlled Senate and that Senate Majority Leader Harry Reid, D-Nev., doesn't allow to see the light of day. Senate Democrats will also push their own political legislation (e.g., the "Buffet Rule" tax measure), most of which, however, will not get the 60 votes needed to pass in the upper chamber. In short, with the presidential and congressional elections approximately six months away, both parties are producing pieces of legislation that sharpen the differences between them and that match their respective political messages and rhetorics.

Virtually all substantive legislative activity will cease once Congress adjourns for the month-long August recess. The presidential conventions will occur in late August and early September. Congress will go back into session for two to three weeks in September and early October in hopes it can dispense with some bipartisan items and then head back home to campaign for the November elections.

As a result of election-year legislative paralysis, the magnitude of the issues Congress will need to address in the post-election lame duck session is eye-popping. The litany includes expiring Bush-implemented tax rates, budget sequestration, a debt ceiling increase, expiration of the payroll tax cut, extending unemployment benefits, reversing cuts to doctors' Medicare payments, a spike to both the Alternative Minimum Tax and the estate tax, renewal of a series of tax extenders popular with business, and passage of FY 2013 spending measures. I'll provide more on the fiscal cliff that Congress will be facing after

Nov. 6 in my next Legislative Update.

## **FDA User-Fee Reauthorization Measure**

One major piece of legislation that has a very good chance of making it to the finish line of a presidential signature before November is a measure to reauthorize a number of Food and Drug Administration (FDA) user-fee programs. The House and Senate are currently in the throes of moving their own versions of a bill that reauthorizes FDA drug- and device-user fees, which is a central funding element for the agency. User fees from drug and device manufacturers accounted for 36 percent of the 2012 FDA budget and are set to increase to 44 percent in 2013. The current drug user-fee law expires Sept. 30, and there is a serious push by both the House and Senate to get a new user-fee reauthorization measure enacted by that date.

The House and Senate committees of jurisdiction marked up their respective user-fee bills the week of April 23. While some non-user-fee policy language has been incorporated into each chamber's respective bills, there is a concerted effort by the chairmen and ranking members of the House Energy and Commerce Committee and Senate Health, Education, Labor, and Pensions Committee from overburdening the legislation with extraneous provisions. This may prove difficult to do when the measures hit the House and Senate floors, but the odds at this point are strong that this Congress will be able to get the bill to a conference committee and produce a final package by the end of September.

So far, there has not been language added to either chamber's measure that would directly impact the supplement industry. However, we will remain on watch to thwart any potentially harmful provisions that may be considered by our congressional detractors, such as Sen. Richard Durbin, D-Ill., as possible floor amendments to the user-fee legislation.

## **Congressional Letters to FDA on NDI Guidance**

It was widely reported in trade publications when the industry's top Senate champions (Sens. Orrin Hatch, R-Utah, and Tom Harkin, D-Iowa) wrote a strong letter to FDA last December in response to the agency's [Draft Guidance for Industry: Dietary Supplements: New Dietary Ingredient Notifications and Related Issues](#)

document. Over the last couple months, two letters, which were signed by more than 30 members of the House, were sent to FDA expressing grave concerns about the NDI guidance. We are also aware that there have been a few other House letters from members who sent individual correspondence to FDA in regard to the NDI draft guidance.

FDA should be getting the message that Congress is watching it closely on this issue and the draft product the agency issued last July contravenes Congressional intent regarding the Dietary Supplement Health and Education Act's NDI provision.

As of recently, there have been no significant developments from FDA on the NDI draft. Those of us who are following this closely do not believe that we will see any public overtures from FDA for the better part of this year—at least.

### **Sen. Durbin Letter to FDA on Energy Drinks**

As reported in an April 5 *AHPA Legal Alert* ("Sen. Durbin Calls for FDA to Investigate Energy Drinks"), supplement industry critic Durbin issued on April 4

a missive to FDA Commissioner Margaret Hamburg calling on the agency to investigate the safety of some popular energy drinks on the basis of their caffeine contents and other ingredients. Durbin also takes issue with the marketing compliance (i.e., conventional food versus dietary supplement) of some energy drinks.

This is one of a series of actions that the assistant Senate majority leader has taken over the last year in furtherance of his desire to see FDA further regulate dietary supplements. Last summer, Durbin introduced the Dietary Supplement Labeling Act (S 1310). S 1310 would place costly and unnecessary regulatory burdens on supplement companies through a complex product registration and warning-labeling scheme. Other key provisions of the bill seek outcomes that can be achieved through enforcement of existing federal authorities, laws, and regulations by FDA.

The one thing we have learned about Durbin when it comes to his desire to overregulate our class of goods: He has no plans to relent. So we expect to see the good senator take additional steps throughout the course of this year to advance his goals as they relate to dietary

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supplements. Durbin is not the only detractor of the supplement trade in Congress, but his actions (and future actions) are reason to remain vigilant against potential regulatory attacks.

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## THE SCIENCE OF ALOE RECENTLY PUBLISHED STUDIES

### ***Aloe barbadensis* Mill. formulation restores lipid profile to normal in a letrozole-induced polycystic ovarian syndrome rat model.**

#### **Abstract**

**BACKGROUND:** Polycystic ovarian syndrome (PCOS), characterized by ovulatory infertility and hyperandrogenism, is associated with metabolic complications such as dyslipidemia, insulin resistance and endothelial dysfunction. Almost 70% PCOS women have abnormal serum lipid levels (dyslipidemia) and 50% of these women are obese. Several classes of pharmacological agents have been used to manage dyslipidemia. However, studies have shown adverse effects associated with these drugs. In the light of alternate therapy, many medicinal herbs have been reported to show hypoglycemic, anti-hyperlipidemic potential. *Aloe barbadensis* Mill. or *Aloe vera* is reported as one such herb. This study was to evaluate the lipid correcting effect of *Aloe vera* gel (AVG) in a PCOS rat model.

**MATERIALS AND METHODS:** PCOS was induced in Charles Foster female rats by oral administration of non-steroidal aromatase inhibitor letrozole (0.5 mg/kg body weight, 21 days). All rats were hyperglycemic and 90% rats also showed elevated plasma triglycerides, elevated LDL cholesterol levels, and lowered plasma HDL cholesterol levels indicative of a dyslipidemic profile. PCOS positive rats with an aberrant lipid profile were selected for treatment. An AVG formulation (1 ml (10 mg)/day, 30 days) was administered orally.

**RESULTS AND CONCLUSION:** AVG treated PCOS rats exhibited significant reduction in plasma triglyceride

and LDL cholesterol levels, with an increase in HDL cholesterol. The gel treatment also caused reversion of abnormal estrous cyclicity, glucose intolerance, and lipid metabolizing enzyme activities, bringing them to normal. In conclusion, AVG has phyto components with anti-hyperlipidemic effects and it has shown efficacy in management of not only PCOS but also the associated metabolic complication : dyslipidemia.

### **Anticancer potential of aloes: Antioxidant, antiproliferative, and immunostimulatory attributes.**

#### **Abstract**

Aloe is a genus of medicinal plants with a notable history of medical use. Basic research over the past couple of decades has begun to reveal the extent of Aloe's pharmaceutical potential, particularly against neoplastic disease. This review looks at Aloe, both the genus and the folk medicine, often being called informally "aloes", and delineates their chemistry and anticancer pharmacognosy. Structures of key compounds are provided, and their pharmacological activities reviewed. Particular attention is given to their free radical scavenging, antiproliferative, and immunostimulatory properties. This review highlights major research directions on aloes, reflecting the enormous potential of natural sources, and of the genus Aloe in particular, in preventing and treating cancer.

### **On the novel action of melanolysis by a leaf extract of *Aloe vera* and its active ingredient aloin, potent skin depigmenting agents.**

#### **Abstract**

The present study was carried out to investigate the effects of an *Aloe vera* leaf extract, along with its standard active ingredient aloin, on the isolated tail melanophores of *Bufo melanostictus* tadpoles, which are a type of disguised smooth muscle cells offering excellent *in vitro* opportunities for studying the effects of pharmacological and pharmaceutical agents. It was found that the leaf extract of *A. vera* and its active ingredient aloin induced powerful, dose-dependent, physiologically significant melanin aggregating effects in the isolated tail melanophores of *B. melanostictus* similar to those of adrenaline per se. These preliminary

findings clearly demonstrate that the extract of *A. vera* and its active ingredient aloin cause melanin aggregation leading to skin lightening via alpha adrenergic receptor stimulation. The present study opens new vistas for the use of *A. vera* regarding its clinical application as a new nontoxic melanolytic agent for the treatment of hyperpigmentation.

## Augmented humoral immune response and decreased cell-mediated immunity by *Aloe vera* in rats.

### Abstract

**OBJECTIVE:** The present study was performed to explore the effect of aqueous extract of *Aloe vera* on parameters of humoral and cell-mediated immunity.

**MATERIALS AND METHODS:** Delayed-type hypersensitivity was assessed by measuring foot pad thickness following sensitisation by keyhole limpet haemocyanin injection and subsequently challenged by the same. Humoral immunity was assessed by measurement of haemagglutination titre to sheep red blood cells.

**RESULTS:** *Aloe vera* (400 mg/kg, p.o.) produced a significant decrease in foot pad thickness compared with the control group, and also significantly enhanced the secondary humoral immune response.

**CONCLUSION:** Thus, these findings suggest that *A. vera* can modulate immune response by augmenting secondary humoral immunity and decreasing cell-mediated immunity.

## A comparative study of the effects of topical application of *Aloe vera*, thyroid hormone and silver sulfadiazine on skin wounds in Wistar rats.

### Abstract

Many research studies report the healing effects of *Aloe vera*, thyroid hormone cream and silver sulfadiazine. However, the effects of these therapeutic agents are not well understood and have not been compared in one study. This study aimed at investigating the effects of topical application of an *Aloe vera* gel, a thyroid hormone cream and a silver sulfadiazine cream on the healing of skin wounds surgically induced in Wistar rats for determining the treatment of choice. In a

randomized controlled trial, twelve male rats, aged 120 days and with a mean weight of 250 to 300 g, were divided randomly into 5 groups based on drug treatments: *Aloe vera* gel (AV), thyroid hormone cream (TC), silver sulfadiazine 1% (S), vehicle (V) and control. To evaluate the efficacy of each treatment technique, a biomechanical approach was used to assess tensile stress after 14 days of treatment. Tensile stress was significantly improved in the *Aloe vera* gel group as compared with the other four groups ( $P \leq 0.05$ ). While the other treatment options resulted in better healing than the control group, this difference was not significant. We conclude that *Aloe vera* topical application accelerated the healing process more than thyroid hormone, silver sulfadiazine and vehicle in surgically induced incisions in rats.

## Inhibitory activity of *Aloe vera* gel on some clinically isolated cariogenic and periodontopathic bacteria.

### Abstract

*Aloe vera* is a medicinal plant with anti-inflammatory, antimicrobial, antidiabetic and immune-boosting properties. In the present study we investigated the inhibitory activities of *Aloe vera* gel on some cariogenic (*Streptococcus mutans*), periodontopathic (*Aggregatibacter actinomycetemcomitans*, *Porphyromonas gingivalis*) and an opportunistic periodontopathogen (*Bacteroides fragilis*) isolated from patients with dental caries and periodontal diseases. Twenty isolates of each of these bacteria were investigated for their sensitivity to *Aloe vera* gel using the disk diffusion and microdilution methods. *S. mutans* was the species most sensitive to *Aloe vera* gel with a MIC of 12.5 µg/ml, while *A. actinomycetemcomitans*, *P. gingivalis*, and *B. fragilis* were less sensitive, with a MIC of 25-50 µg/ml ( $P < 0.01$ ). Based on our present findings it is concluded that *Aloe vera* gel at optimum concentration could be used as an antiseptic for prevention of dental caries and periodontal diseases.

## *In vitro* drug permeation enhancement potential of aloe gel materials.

### Abstract

*Aloe vera* gel previously showed the ability to increase the bioavailability of vitamins and to enhance the *in vitro* transport of a macromolecular drug across intestinal

epithelial cell monolayers. The purpose of this study is to investigate the potential of other species of aloe to act as drug absorption enhancement agents. The effect of gel materials from three South African aloes; *Aloe ferox*, *A. marlothii* and *A. speciosa* on the transepithelial electrical resistance and permeability of atenolol across excised intestinal tissue of the rat as well as the transport of FITC-dextran across Caco-2 cell monolayers was investigated. The aloe gel materials exhibited the ability to statistically significantly reduce the transepithelial electrical resistance of excised rat intestinal tissue but did not significantly increase the transport of atenolol across this *in vitro* tissue model at the concentrations tested. At least one concentration of each aloe gel material enhanced the transport of FITC-dextran statistically significantly across Caco-2 cell monolayers. The aloe gel materials showed potential to act as drug absorption enhancing agents across intestinal epithelia. The absorption enhancement effect was dependent on the type of *in vitro* model and type of drug was investigated.

***In vitro* anti inflammatory activity of Aloe vera by down regulation of MMP-9 in peripheral blood mononuclear cells.**

## Abstract

**AIM OF THE STUDY:** The anti-inflammatory activity of *Aloe vera* was investigated through MMP inhibition studies. The effect of *Aloe vera* on MMP-9 inhibition was tested on peripheral blood mononuclear cells (PBMC).

**MATERIALS AND METHODS:** Peripheral blood mononuclear cells (PBMC) were isolated from the heparinised venous blood by Ficoll Diatrizoate gradient centrifugation. The cell count and viability was determined using dye exclusion technique. Cytotoxicity was evaluated by MTT assay. Activation of MMP-9 was visualized by gelatin zymography. Inhibition of MMP-9 in the presence of aqueous extract of Aloe vera was detected by gelatin zymography and confirmed by RT-PCR.

**RESULTS:** Peripheral blood mononuclear cells (PBMC) showed significant inhibition in the activity of MMP-9, indicating the *in vitro* inhibitory effect of *Aloe vera* on MMP-9. Zymographic analysis and RT-PCR showed that it caused a significant reduction in the production of MMP-9 in a concentration dependent manner.

**CONCLUSION:** The inhibition of MMP-9 production

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in the cells was detected by gelatin zymography and was confirmed by RT-PCR.

## Effects of the blended fibroin/aloe gel film on wound healing in streptozotocin-induced diabetic rats.

### Abstract

Delayed healing remains a major clinical problem and here we have sought to develop an improved dressing film comprising 1.95% w/v fibroin and 0.05% w/v aloe gel extract. The tensile strength of dry film was  $21.1 \pm 0.5$  MPa and broke at  $1.1 \pm 0.2\%$  elongation; corresponding values for wet film were  $18.3 \pm 1.3$  MPa and  $1.9 \pm 0.1\%$ . The film maintained its shape upon water immersion and the swelling ratio of the dry film was  $0.8 \pm 0.1$  while the water uptake was  $43.7 \pm 2.6\%$ . After 28 days of incubation in phosphate buffered saline (1 M, pH 7.4, 37 °C), the weight of film was reduced by  $6.7 \pm 1.1\%$  and the tensile strength and elongation at breaking point (dry state) were  $15.4 \pm 0.6$  MPa and  $1.5 \pm 0.2\%$ , respectively. Compared to aloe-free fibroin film (2.0% fibroin extract only), the blended film enhanced the attachment and proliferation of skin fibroblasts. The bFGF immunofluorescence of fibroblasts cultured on the blended film appeared greater than those cultured on tissue culture plate or on aloe-free fibroin film while  $\alpha$ -smooth muscle actin was maintained. In streptozotocin-induced diabetic rats, the wounds dressed with the blended film were smaller ( $p < 0.05$ ) by day 7 after wounding, compared to untreated diabetic wounds. Histology of repaired diabetic wounds showed the fibroblast distribution and collagen fiber organization to be similar to wounds in normal rats, and this was matched by enhanced hydroxyproline content. Thus, such accelerated wound healing by the blended fibroin/aloe gel films may find application in treatment of diabetic non-healing skin ulcers.

## Oral ingestion of *Aloe vera* phytosterols alters hepatic gene expression profiles and ameliorates obesity-associated metabolic disorders in Zucker diabetic fatty rats.

### Abstract

We investigated the effects of the oral administration of lophenol (Lo) and cycloartanol (Cy), two kinds of antidiabetic phytosterol isolated from *Aloe vera*, on

glucose and lipid metabolism in Zucker diabetic fatty (ZDF) rats. We demonstrated that the administrations of Lo and Cy suppressed random and fasting glucose levels and reduced visceral fat weights significantly. It was also observed that treatments with Lo and Cy decreased serum and hepatic lipid concentrations (triglyceride, nonesterified fatty acid, and total cholesterol). Additionally, Lo and Cy treatments resulted in a tendency for reduction in serum monocyte chemotactic protein-1 (MCP-1) level and an elevation in serum adiponectin level. Furthermore, the expression levels of hepatic genes encoding gluconeogenic enzymes (G6 Pase, PEPCK), lipogenic enzymes (ACC, FAS), and SREBP-1 were decreased significantly by the administrations of aloe sterols. In contrast, Lo and Cy administration increased mRNA levels of glycolysis enzyme (GK) in the liver. It was also observed that the hepatic  $\beta$ -oxidation enzymes (ACO, CPT1) and PPAR $\alpha$  expressions tended to increase in the livers of the Lo- and Cy-treated rats compared with those in ZDF-control rats. We therefore conclude that orally ingested aloe sterols altered the expressions of genes related to glucose and lipid metabolism, and ameliorated obesity-associated metabolic disorders in ZDF rats. These findings suggest that aloe sterols could be beneficial in preventing and improving metabolic disorders with obesity and diabetes in rats.



## REGULATORY NEWS

## FDA's Strategic Plan and CEO and Retailer Responsibilities

by Anthony L. Young, Kleinfeld, Kaplan & Becker LLC, and AHPA General Counsel

Below are updates on and analysis of three recent issues of interest to those in the botanicals and supplement trade.

### FDA's Strategic Plan: Business as Usual is Good

The Food and Drug Administration (FDA) announced its *Final Strategic Plan for the Foods and Veterinary Medicine Program* on April 23. This plan sets out how

FDA intends to proceed with respect to enforcement and initiatives for the 2012-2016 period.

So, if you are in this business, and your business is important to you, you would be well served to turn to the part of this plan that applies to this industry.

There are seven program goals, and the one related to dietary supplements is Program Goal 5: "Encourage Food Product Reformulation and Safe Production of Dietary Supplements." Food product reformulation has to do with reducing sodium and industrially produced trans fats in the food supply. Those are points one and two of Program Goal 5. The last part of Program Goal 5 is to "Improve the Safety of Dietary Supplement Products and the Supply Chain."

Here is what FDA proposes:

1. *Develop and implement strategic, risk-based, and innovative compliance and regulatory strategies to address dietary supplement safety issues.* There is nothing new here; this is how we understand FDA has been addressing these kinds of issues for the past several years. Safety is a priority, and FDA has used available tools, such as the serious adverse event reporting (SAER) system and the accompanying requirement for companies to keep all adverse events (AERs) in their files, to investigate and address safety issues.
2. *Advance post-market surveillance systems in the regulation of dietary supplements.* New here would be to "advance" the systems that are already in place: SAERs and AERs. Also on this list would be complaints companies receive regarding product quality, which are addressed under current good manufacturing practice. And, finally, there are reports received by Poison Control Centers throughout the United States and reports received by the Centers for Disease Control and Prevention. There's nothing really new here, and again, these proposals are safety related.
3. *Advance pre-market oversight of dietary supplements by finalizing and implementing new dietary ingredient (NDI) guidance.* No surprise here; this subject has been in FDA's strategic plan for years. Of course, the industry firmly believes that the [Draft](#)

## [Guidance for Industry: Dietary Supplements: New Dietary Ingredient Notifications and Related Issues](#)

published last year was a false start that ought to be put back in the box. But note the focus here on pre-market oversight of dietary supplements by implementing NDI Guidance. FDA speaks here with respect to "pre-market oversight." This does not state that FDA plans to go back and examine ingredients that have entered the market since the Dietary Supplement Health and Education Act (DSHEA) became law in 1994. And note the operative word is pre-market "oversight" and not pre-market "approval." That is all that DSHEA requires: pre-market notification to FDA.

So, FDA's strategic plan represents business as usual, and business is now good. There is nothing in this plan that presents new concerns to this industry. The focus is on safe products, and that is always a shared goal among consumers, retailers, manufacturers, and regulators.

## **Personal Liability for the Boss**

The Federal Food, Drug, and Cosmetic Act is a strict criminal-liability statute. The nature of this provision is taught in first-year criminal law classes because the law does not require that a responsible individual had intended to violate the law.

Quoting the government's April 9 [press release](#) announcing the guilty plea by Bodybuilding.com's founder and CEO Ryan DeLuca to five misdemeanor counts of introduction and delivery for introduction of misbranded drugs into interstate commerce: "Under the Food, Drug, and Cosmetic Act, an individual in a business who has responsibility and authority either to prevent or correct a violation of the Food, Drug, and Cosmetic Act is strictly liable for a misdemeanor criminal violation of the Act, regardless of the extent of his knowledge of the violations."

The strict liability provision of the law became controversial in the early 1970s when the CEO of a Baltimore grocery chain was found guilty under this provision. But in that case, there had been warnings regarding filthy conditions in the company's facilities. Have you noticed that when FDA inspectors provide an FDA Form 483 after an inspection that it is addressed to and given to the CEO? Have you noticed that

warning letters are addressed to CEOs? The reason is that FDA wants to be able to establish that in fact the responsible company officer knew of the situation upon which prosecution is based.

In the Bodybuilding.com case, the government press release noted that the CEO “acknowledged at the plea hearing that as Bodybuilding.com’s CEO, he was responsible for Bodybuilding.com’s sales of misbranded products.”

In addition, the plea agreement further states that during 2008 and 2009, the FDA compliance officer at Bodybuilding.com informed Bodybuilding.com’s management, including [the CEO], that some of their products contained ingredients that did not qualify as dietary ingredients.

## Retailer Responsibility

Bodybuilding.com is a retailer. The products it sells are the products of others, unless there are “house brands.” This case is a lesson for retailers. Retailers that sell adulterated or misbranded dietary supplements or unlawful drugs masquerading as dietary supplements can be and have been held liable for selling such products. Be careful out there.

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## cGMPs Loom Large Over Industry

*The time for all supplement companies, large and small, to comply, is clearly upon us*

*by Anthony L. Young, Kleinfeld, Kaplan & Becker LLP, and  
AHPA General Counsel*

When a company gets a Warning Letter about disease claims on its website, compliance is easy: the claims can be dropped, and this can be done rather easily by removing them from the website by its computer gurus. And where disease claims are made on labels and labeling, these can be changed out rather quickly, even

by placing new labels over previously labeled product.

When a company receives a Food and Drug Administration (FDA) Form 483 regarding good manufacturing practice (cGMP) compliance issues and a follow-on Warning Letter, the situation is much different. The cost of compliance can be substantial, and coming into compliance after FDA has inspected a facility can be very capital intensive. The compliance date for the smallest companies under the cGMPs was June 25, 2010. The cGMP regulations now apply to all dietary supplement manufacturers large and small.

FDA is serious about cGMP compliance and is now inspecting large companies and small companies. An example: a small family business, with its website housed and orders taken by one family member from his home business in one state and orders filled and products shipped by a family member from a garage-sized warehouse in another state. A contract manufacturer manufactures the product, but the dietary ingredient is ordered by the business and drop-shipped to the contract manufacturer.

FDA inspectors arrived at company “headquarters” and requested records and asserted various requirements under the cGMPs, many of which did not appear to mesh with the requirements for a business distributing a product made and labeled for it by a contract manufacturer. In addition, FDA directed that the facility from which the product was shipped—in another state in another FDA district—be inspected by that other district, and this was done. FDA issued the company a 483, which was responded to.

All of the items noted in the 483 referred to events that occurred prior to the cGMPs becoming final for this size of company in June 2010. This rather vigorous pursuit of a company marketing one noncontroversial dietary supplement, with no controversial website or other claims, exemplifies FDA’s aggressive attitude toward this industry.

What FDA’s inspection of this small company shows is that all dietary supplement manufacturers could have this happen. And I write about this because the main questions from those attending the American Herbal Products Association’s Feb. 23 cGMP webinar appeared to be directed at whether there was a way to figure out



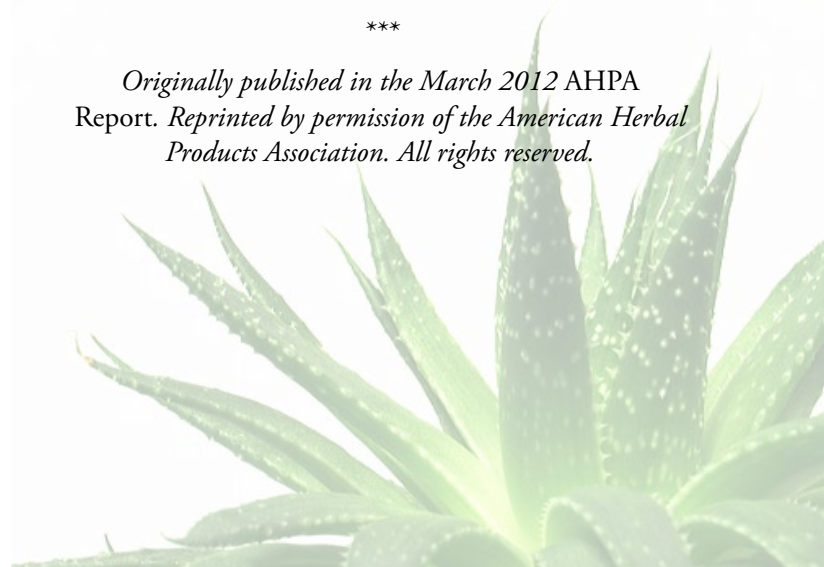
which companies are most likely to be inspected. Where are most inspections occurring? What size companies are being targeted? Are companies making disease claims being inspected more often? Is there an FDA speed trap on the Long Island Expressway, or is it nearly south of the border on I-95? For this industry, the time for compliance with the cGMPs has arrived. Those who have not complied with the requirements should do so. All companies need to understand that FDA may well move from Warning Letters regarding cGMP non-compliance, always deemed “significant violations,” to more substantial enforcement actions, such as seizure of

products or injunctions requiring cGMP compliance, or pushing companies to consider recalls.

And do you sell products to the federal government? FDA often uses that as a hook to force compliance. So, if you are insecure about cGMP compliance, the time to gain confidence is clearly upon us.

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