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DIRECTOR'S MESSAGE



As I write this I hear Bob Dylan's "The times they are a-changin" in the background, and what could be more appropriate? The weather has turned cold here outside of Washington, D.C. and the leaves are not the only part of the landscape which has changed, with the recent elections returning control of the House of Representatives decisively back to the Republicans (though the Democratic party did manage to eke out continued control of the Senate). One does wonder what the future holds as we near the end of another year...

And speaking of change and the future, the IASC Board of Directors met on October 23, 2010, and had another very productive meeting – covering a broad range of topics of interest and concern to the industry. The Special Report: Board Meeting Recap (found on page 5) provides information on the highlights of the topics covered and actions taken at the meeting, and I hope you will take the time to review it. Likely of most importance is the news that we're likely to see the draft NTP report on the 2-year oral consumption study released in January 2011 and the efforts the organization has been taking, as well is now considering.

Recently, we also requested that all certification program participants who sell certified raw materials or oral-consumption products submit them for analysis for aloin content, specifically to ensure they are below what is currently the IASC standard for aloin of <10ppm at single-strength as calculated by 0.5% solids (see a copy of the communication on page 15). Though we understand and appreciate this is an additional burden and expense to program participants, we hope it's clear that this had to be done in response to the NTP study's purported results - and is not something that would have been imposed otherwise. Science, as the cliché states, is often a cruel mistress – and though sometimes she favors the industry, it's not always the case.

If the choice is between reducing aloin content in aloe vera products to a LOAEL (Low Observable Adverse Effect Limit) and the potential for no aloe vera products – I'm sure everyone agrees that the former is a much better choice. That said, our risk assessment, which is being produced to provide a LOAEL for aloin content in aloe vera, is suggesting at this point that the number may need to be even lower based on a comprehensive review of all of the available scientific literature. As you'll see in the board recap – the association will be hiring another toxicology firm to review the risk assessment to ensure its accuracy.

Finally, you'll likely have by now received your membership dues renewal and we hope that you will continue to support the organization as we move into a new year. The challenges we've been facing this past 2+ years have not been easy – and hopefully 2011 will see us successfully beyond some of the more significant issues.

On a personal note, with the end of the year fast approaching I would like to express my warmest regards to all members and your families and wish you all the best for a fantastic Thanksgiving, holidays, and New Years – and continued prosperity in 2011.

It has been a pleasure serving you and the aloe vera industry in 2010 and I look forward to continuing the excellent work of the organization next year...

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

Devon Powell Executive Director



Ullman, Shapiro & Ullman INSIDE LAW

POLICING YOUR TRADEMARKS A Giant Step in Protecting Your Intellectual Property

Charles Knull, Trademark Counsel to Ullman, Shapiro & Ullman LLP

Making your company's aloe based product different from the competition involves branding. Branding involves the use of trademarks to identify the source of products.

A trademark is a means of consumer protection. Although a business can register a trademark at the U.S. Patent and Trademark Office ("USPTO"), it does not "own" the trademark. What is signified by registration is an assertion by the business that the goods sold under the trademark are of a certain, established quality. Thus, consumers who buy products identified by the mark have assurances that the quality, whether great or good, or even terrible, is what is expected for that product. The quality of the goods sold under the trademark must be maintained. The quality is the trademark's goodwill.

Thus, the trademark "owner" is really protecting its customers from others selling a different quality (infringing) product under the trademark. The first user of a mark is the one who has the claim and the duty to protect it and its goodwill so long as it continues to be used. Under the current federal law, the Lanham Trademark Act, a first user who has registered its mark can enforce that mark in federal court and obtain sanctions including injunctive relief and/or the infringer's profits. If then infringement is willful, or with knowledge of the prior mark, it can also make the infringer pay its legal costs and, perhaps, obtain treble damages.

In the USA, Trademark protection is obtained through use of the trademark on the product. A trademark can be very strong and never ever registered at the USPTO (although a business would be crazy not to take the step of registration.) Use of the trademark must be continuous over time. The longer one uses a trademark, the stronger it gets. Eventually, a trademark can become "famous" and the owner can keep others from using it even on very

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unrelated products. (Thus, one cannot use XEROX[®] or COCA-COLA[®] as a brand name for automobile tires unless one is Xerox or Coca Cola.)

But a trademark will become worthless if the owner does not take the effort to prevent others from using the trademark or terms similar to the trademark. This effort, in legalese, is called "policing the mark." Thus, bringing lawsuits, and all the steps leading up to those lawsuits, such as sending cease and desist letters and making objection to one's trademarks being misused on websites, or as domain names, are a cost of doing business if one has trademarks.

The more one polices a trademark, the more evidence one gathers showing the policing. Eventually, a well-policed trademark becomes nearly impregnable. It becomes strong. Every time a company can submit evidence to a court showing that the mark has been successfully policed, it is for the better. People who engage in knocking off product marks eventually learn about the enforcement strong marks and move on to someone else's trademark. Eventually policing becomes less work.

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.

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IASC members receive a 10% discount

To protect the goodwill behind the trademark, a trademark user has the right to keep others from using or registering confusingly similar trademarks. It also has the right to sue infringers to obtain an injunction against the infringer's uses plus any profits made, and, in outrageous

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situations where the infringement is found to be willful or a counterfeiting, to obtain attorneys fees and treble damages. If the trademark is registered then the trademark user can also present its trademark to U.S. Customs and block entry of infringing goods into the U.S.

There are many ways to police trademarks depending on how the mark is being infringed or harmed. The first step in policing trademarks is identifying who might be infringing or misusing one's marks. A company can use its field sales people and direct distributors to perform some policing by making it clear that if they find potential problems in the marketplace, they should make the problems known to the owner. A company can also have a staff person assigned on a regular monthly basis to surf the internet for potential problems. To have the ultimate information available, a company can hire a "watch service" that will monitor the entire marketplace and report any problems that they find.

Problems that are found will generally fall into the following areas:



Domain Name Misappropriation

A trademark owner cannot let others take out domain names that contain one's trademarks---even if that person is a beloved distributor. Any evidence that a trademark

does not directly point back to the source of the trademark is evidence that the mark has become diluted and is weakened. Thus, any similar domain names that are taken out must be disputed and must be transferred back. Fortunately, there is a relatively inexpensive arbitration procedure called the UDRP by which such domain names can be retrieved if a demand that domain names be turned over does not work. Often, the threat of the UDRP procedure by trademark counsel is enough to force the transfer.



Knock-Offs and/or Bad Product Available Online

On-line shopping sites create problems for trademark owners. Counterfeit or stale product may be offered for sale and

consumers who purchase it can complain about their quality. This harms one's trademark because it harms the quality that the trademark represents. Fortunately, nearly

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all such websites (E-Bay, Amazon stores, Yahoo stores, etc.) have procedures that allow trademark counsel to file objections to potentially damaging offers to sell. Sellers can be forced to show that their goods are legitimate and/ or fresh, or their ability to sell on the websites will be removed.

Web Disparagement

Trademark owners can also be harmed by websites on which disparaging, untrue comments about products that harm goodwill, are written. (If the comments are true, then the trademark owner has a different problem and should be talking with public relations people and planning ways to improve product quality.) Again, there are ways for trademark counsel to get such comments taken down via the webhosts for the websites. (Since the webhosts have no big financial stake in whether a website has or does not have the comments on it, and since the webhosts can be made defendants in any action against a commenter for untrue comments, once notified, the webhosts will most likely remove the entire offending site.)



Trademark Infringement

If a trademark finds a product that is being sold under the same or similar mark to its own trademark, trademark infringement is

probable. Of all the problems that a trademark owner might have, this is the worst, as continued use of a like offending mark will eventually destroy one's trademark. There are numerous actions that can be taken to police one's trademarks short of actually filing a case in court. When problems are found, a company may first contact the problem maker itself and ask that the infringement be stopped. If that does not work, a company might ask its attorney to draft a "nice" letter setting a deadline for infringement to stop along with letters such as are discussed above to websites and webhosts. If those actions have no effect (and taking steps with the websites and webhosts generally does, since the offender loses his or her entire ability to do business), then the follow up would be either a cease and desist letter or the filing of a law suit.

Adequate trademark policing will increase the value of a company because it increases the value of the brands the company sells. There are many horror stories concerning

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trademark owners who have had strong brands but refused to put the time and effort into policing their marks. These brands and their owners are no longer in business.

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"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 (<u>www.usulaw.com</u>).



Special Report: Board Meeting Recap

The IASC Board of Directors met on October 23, 2010 for the second of two, regularly scheduled meetings for the year. Once again, the issues regarding the National Toxicology Program (NTP) study on the ingredient "Aloe vera whole leaf extract (native)," an unfiltered (nondecolorized) aloe vera leaf juice, was a priority topic, though many other actions concerning important details related to the certification program and other aspects of the organization were undertaken. This special edition of the Director's Message will highlight some of the important items discussed and actions taken by the Board of Directors. Members with questions are encouraged to contact me for more details.

FINANCIAL STATUS & SPECIAL ASSESSMENT

The board reviewed and approved the current financial status of the Council for 2010 and passed a balanced budget for 2011. The 2011 budget included several new additions, including funds for the registering of the certification program seal and trademarked language in numerous foreign countries, including China, India, Mexico, and Brazil. "Registering the trademark seal and related language will make enforcement actions against illegal users in these

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countries much easier and our efforts more effective," said IASC general counsel, Marc Ullman. "It also demonstrates the organization's clear commitment to the participants of the program."

Funds were removed from the budget for holding a scientific seminar in 2011, as staff has happily entered into discussions with Virgo Publishing, the hosts of Supply Side West trade show in Las Vegas, which has expressed an interest in holding the event there as a part or one of their educational tracks. Members who have been waiting for an IASC-aloe science event will hopefully see this come to fruition in 2011, and with limited potential for financial burden or detriment to the association. "This will be a huge win-win for the IASC and Virgo. What we need is for every company or person associated with aloe products, scientific research of aloe, or the marketing of aloe to attend this event so we can make it one that is perpetual," said Devon Powell, IASC Executive Director.

During the report on the current financial status of the Council, the board addressed the non-payment of the Special Assessment by many members, which was levied on the membership by action of the board at the March 2009 meeting in response to the NTP study. The assessment funds have been and will continue to be used to complete several tasks associated with concerns raised by the National Toxicology Program study. Many board members expressed disappointment with those IASC members who had not paid the assessment, and though some restrictions were placed on such non-payers in March 2010, including the removal of discounts for the certification program, the remaining funds have not been collected. "It seems as though it's the same companies that come through and are towing the rope financially for the organization," said Tom Brown, IASC Treasurer, "and what we need is for every IASC member company to realize that their support is vital - no matter where they are located. This NTP study could easily become a global concern."

The board encouraged all members with outstanding Special Assessment balances to remit payment and support the Council in its efforts, encouraged and asked non-IASC members to join and support the Council in its endeavor to protect their business interests, and expressed appreciation and thanks to those who had already provided Special Assessment funding in support of the organization.

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A & A Aloe, Inc.	Concentrated Aloe, Inc.	Mexpo International
Agromayal Botanica S.A. de C.V.	Deynique Cosmetics GmbH	Nahrin AG
Aloe Corp	Dynamic Health Laboratories, Inc.	Natural & Organic Farms Mexico S.A. de C.V.
Aloe Jaumave S.A. de C.V.	Erba Vita S.A.	Natural Aloe de Costa Rica
Aloe Laboratories	Farpoint Distribution	Nature's Sunshine Products
Aloe Life International	Florida Food Products	Naturtech
Aloe Vera Group	Forever Living Products International	Perfect Source
Aloe Vera of America	Hain Celestial Group	RBC Life Sciences, Inc.
Aloe Vera of California	Health Natural Solution International, Inc.	Shen Wei
Aloe Vera Scandinavia AB	Herbalife International of America	Taragro Investments
AloeScience Labs	Laboratorios 2000 S.A. de C.V.	Terry Laboratories
Aloevin Corporation	Lexli International	Unigen Pharmaceuticals, Inc.
Alove Bali	Life Force International	United One International Laboratories
C.H. Erbsloh	LifeStream International	William Ransom & Son PLC
Chemolee Lab Corporation	Lily of the Desert Organic Aloeceuticals	WINNING SOLUTIONS
Coats Aloe International	LR Health & Beauty Systems GmbH	Yeturu Biotech Ltd.

NATIONAL TOXICOLOGY PROGRAM STUDY

Though the general public may not be directly affected by the release of the study itself (though this is an unknown), and though the media may pick it up and cause some issues (we saw some pickup on the NCTR/NTP's study of retinyl palmitate (RP) in June 2010 - RP is a common ingredient found in sunscreen and which Senator Charles Shumer (D-NY) made some noise on that was picked up by Reuters, among others), the most major concern is in regards to the potential regulatory backlash that may develop on multiple levels - but most specifically in California and that state's Proposition 65 law. The NTP is considered by the state of California to be an "authoritative body," and the substance aloe vera could and likely would automatically be added to the California Proposition 65 list of substances shown to cause cancer. Prop. 65 is a state law that requires warning labels on products shown to contain levels of a constituent on the Prop. 65 list beyond the "safe harbor limits" and allows "bounty hunters" to essentially bring class action suits against product manufacturers who are analytically shown to have limits beyond those set of certain constituents. The labeling language is, "This product has been shown to cause cancer," and would need to be applied to all products for sale in California.

"The addition of warning language to aloe vera product labels in California would be noticed, not only by consumers but by both national and international regulatory bodies," said Devon Powell. The FDA indicated in the 2009 meeting with the IASC, when the NTP study was first brought to the organization's attention, that should a Proposition 65 issue arise, the agency would be forced to take action. Beyond the NTP study, Proposition 65 issues are already occurring for aloe vera manufacturers due to lead concerns – with at least 4 aloe vera product manufacturers receiving notices in 2010.

What is clear is there is no way to stop the study from being released – but there are options the organization is considering to increase the chances of keeping the ingredient off of the Prop. 65 list, primarily involving influencing NTP regarding how they characterize and describe the ingredient used in the study. The IASC has also been saying all along that the ingredient studied (non-filtered, aloinrich, aloe vera leaf juice) is not what the majority of IASC members markets to consumers. In a letter from Health & Human Services Secretary Kathleen Sebelius, she states that the ingredient used in the study contains between 5,000 – 7,200ppm aloin – which makes our point. However, she goes on to state that such products ARE available to US consumers.

The organization has been diligently collecting samples of such products and sending them off for analysis in order to be as informed as the NTP. We've also initiated the testing of all products for oral consumption/raw materials within the certification program in order to verify the March 2010 imposed standard of <10ppm aloin. In addition, we've been collecting non-IASC certified materials to get a snapshot of the rest of the products in the marketplace. The analysis of all of these products should give the organization data to further make the argument that the majority of products for sale are not what the NTP studied.

"What we are pushing for is to ensure the NTP clearly characterizes the material used in the study so that should consumers or California see the study information – they are not confused and think that the aloe vera juice products they see on their shelves are what was consumed by the mice and rats as part of the NTP research," said Powell.

The organization continues to work on the development of a Risk Assessment on aloe vera, and the monograph is also still in development. Both of these documents will assist in the development of self-regulatory efforts in regards to quality and compliance for raw materials (in the case of the monograph) as well as establish a clear LOAEL (Low Observable Adverse Effect Level) for aloin in aloe vera. Powell noted, "We still have something of a ways to go – but we have some indication that the draft/review version of the NTP study could be released by the end of January – so we're working hard to get this information completed and out to the members."

CERTIFICATION PROGRAM



The board took action on a variety of items regarding the program, including several notable revisions to the program standards and policies, such as the inclusion of a policy on handling Random Sampling Program failures. The entire, now revised document is available for download on

the IASC website at the following link: http://iasc.org/pdfs/10_1023_IASC_Certification Program_SOP_FINAL.pdf

A report on illegal seal usage efforts was also provided to the board, which included actions against over 20 companies thus far in 2010, in most cases with successful results. Since March, staff reported it had taken 12 such actions.

In relation to this report, and in response to the board's direction in March, staff provided a list of priority countries and associated expenses with registering the IASC seal and trademarked language (India, Brazil, China, Mexico, Taiwan & Hong Kong) – which the board budgeted for

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and approved, and staff will complete by the end of 2011.

The board also instructed staff to host a meeting of the Certification Committee in order to discuss the possible removal of malic acid as a parameter of the program, as well as to provide instructions and parameters regarding the reporting of isocitrate by Process-NMR, the lab conducting analysis for the program.

For more information on the certification program, please contact Rosie Ysasi, Program Coordinator (rysasi@iasc.org).

ETHICS & MEMBERSHIP

The board approved taking suggested revisions to the IASC Bylaws to a vote of the membership, as prescribed in the Bylaws (amendments require a 2/3 majority vote). The revisions are in regards to Board of Directors voting procedures and a vote is anticipated by the end of November, in time for the Board of Directors election "Call for Candidates" which occurs in early December and is the formal process for nominating candidates to the board. The changes to the Bylaws will avoid delays in elections, and allow for such activities to run more smoothly.

On the membership side of things, staff presented a new membership development idea to the board that focused on MLM and direct-sales distributors initially, but which the board suggested should be broadened to include retailers, as well as other potential categories. The program would involve the creation of a new category of membership for this group, and any funding provided would be restricted for carrying out scientific studies (under the direction of the IASC Science & Technology Committee) on efficacy, etc. and then the results translated into IASC developed and branded, 3rd party press and marketing campaigns (think "Got Milk?") that would ultimately be created and publicized in order to sell more aloe vera products. The board appreciated this idea and instructed staff to obtain additional feedback from the membership. "Companies manufacturing and marketing products in the US, that are not drug products, cannot make the claims the IASC could make in its 3rd party literature," said Powell. "Thinking about the possibilities, not only could the IASC become a more effective partner to the direct sellers of aloe vera products, but that would also increase aloe vera sales for all channels of membership - from suppliers on up." Powell further noted, "It would also increase the organization's

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legislative power – when you arrive at a congressional office representing 100,000 people vs. 100 companies – elected officials tend to pay more attention to what you want and need." Anyone interested in more details on this program should contact Devon Powell (dpowell@iasc.org).

In addition to this new membership category idea, staff presented a potential revenue-generating scenario where the IASC would act as a resource in providing consultants to assist in setting up new cultivation and processing operations around the globe. Staff reported that it regularly receives requests from entrepreneurs and individuals looking to establish such operations, and the IASC would sign contracts with viable consultants, who upon engaging with any referred business would pay the IASC a "finder's fee." The board also appreciated this idea and requested a formal proposal with input from counsel.

Science & Technology

It was relayed that the FDA had, in several inspections under 21 CFR 111, been noted as saying that NMR was the only appropriate method currently available for conducting identity testing of aloe vera (and that "the IASC said so" - which is absolutely untrue). Those of us who know the GMP understand that not only is this position off base, if accurate, but goes against the very grain of the GMP regulations themselves – which state the method must be "scientifically valid" – not any specific methodology.

Staff has been drafting Guidance for verification of the identity of aloe vera under the dietary supplement GMP, when they began working with Authen Technologies, a provider of DNA analytical method development and a 3rd party lab offering such services to the industry. Working with Ken Jones at Aloecorp, several samples were sent to the lab to test the applicability of DNA for verifying the identity of aloe vera - and the results were incredibly positive. A proposal for the full development of validated DNA methods was obtained, and the board unanimously moved to engage in this activity. "This is in the very spirit of the organization - and knowing that it will be something we can include in our identity guidance and wave in the face of any FDA inspector who says, 'Why aren't you using NMR?' makes it all the better," said Charlie Metcalfe, newly elected Chair of the committee.





REGULATORY AFFAIRS

The IASC's successful submission to the Food Standards Agency (FSA) in England, No. Ireland, Wales and Scotland was among the items the board was informed of and discussed by the Regulatory Affairs Committee. Those 4 countries had issued an announcement in late July requesting comments from industry food manufacturers and other stakeholders on the costs and benefits of enforcement provisions for the new EU regulations on food flavorings (EC/1334/2008) and their enforcement. The new regulation, which was adopted in late 2008 and is due to replace 88/388/EEC as of January 20, 2011, is the regulation that has been used to establish the 0.1ppm limit for aloin in aloe vera products for oral consumption.

The IASC comments were submitted to the FSA in order to affirmatively establish the IASC position that the aloin regulations currently in effect in the EU under 88/388/ EEC (0.1ppm aloin limit) would no longer be applicable, which was applauded by the board, as well as this effort by staff.

REACH Regulations

Continuing on with European Union and regulatory issues, the IASC's development of a formal position paper in regards to aloe vera and the applicability of the REACH regulations was also discussed by the board. A draft position paper had been created by staff and reviewed by an attorney with expertise in international food and drug law, Mark Mansour with Akin Gump in Washington, D.C., prior to submission to the Executive Committee, which approved the document (and which is now posted on the IASC website at the following link: <u>http://iasc.org/pdfs/10_0811_IASC_Position_on_Aloe_vera_and_REACH.pdf</u>).

During the creation of the draft, staff also sent a request for clarification to a UK REACH Helpdesk, who provided a response that was in-line with the position paper, as well as to the ECHA itself (the organization responsible for implementing the regulations), whose most recent response indicates that they believe that, in the case of aloe vera leaf juice, if the ingredient has been treated with cellulase it has been "chemically modified," and is required to be registered (again, depending on other factors – for more information please read the IASC REACH Guidance (http://iasc.org/pdfs/10_0813_Understanding_the_REACH_Regulations_DRAFT_IASC.pdf) – but did not

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voice disagreement that REACH would not be applicable to inner leaf juice.

The board therefore agreed to hire Mr. Mansour to draft further communications to ECHA regarding the applicability of the REACH regulations to aloe vera ingredients treated with an enzyme, to be provided to the Executive Committee for review prior to submission. "Orange juice and apple juice are treated with cellulase – and we don't see them being registered under REACH," said Powell. "We intend to push back on this with the ECHA and will keep the membership informed of our progress."

<u>Verification of Identity of Aloe Vera Under</u> 21 CFR 111 - Guidance

Staff has been developing industry guidance on verifying the identity of aloe vera under 21 CFR 111, the dietary supplement GMP. It has been noted in several places in this report that during an inspection of an aloe vera manufacturer the FDA indicated that NMR was the only valid method for verifying the identity of the ingredient, which is not accurate and certainly not the way the regulations were written. The board was notified that the draft has gone through several iterations and was expected to be completed by the end of 2010 or early 2011. The board requesting staff make this project a priority.

PUBLIC RELATIONS

The final report of the day was that of the Public Relations Committee, which primarily centered around the NTP study and the organization's efforts and potential efforts. The board was provided with a recap of the situation since its inception in 2009, starting with the February meeting with FDA and leading up to the likely release of the draft of the study in January 2011.

In addition to the NTP information and actions taken by the organization and provided above, the board moved to accept the 2009 Yun Ho Lee Award nominee, which was to Dr. Akev for her body of work on aloe vera over a 7-year period. Powell said, "On behalf of the board and staff, we congratulate Dr. Akev for her efforts to build the ongoing library of aloe vera research."

The board was also told of a possible aloe vera science event at SupplySide West in 2011. "I'm very excited about the

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potential to hold an aloe vera event at SupplySide West," said Powell. "We haven't had a science event in what will be 3 years, and if we can get the industry and scientists together to attend and sponsor this – we could see it again become an annual occurrence." Virgo Publishing, the promoters of the SupplySide Show's, has expressed an interest in providing the opportunity, and the board instructed staff to follow up.

Under new business, the board discussed the idea of establishing an aloe vera quality standard, and due to the limited time and potential challenges of coming up with such a standard, staff was instructed to schedule a special meeting of the board within the next 30-days in order to address the issue.

For more information about the meeting or for more details – please contact Devon Powell (<u>dpowell@iasc.org</u> - 301.588.2420 x102).



Current Situation on Health Claims in the EU

The following information has been provided by IADSA in response to a number of its members outside Europe requesting an overview of the current situation on claims in the EU and the actions underway by European groups.

What is the European Health Claims Regulation?

Since the mid 1980's the EU has wanted to harmonize the claims that can be made for foods to both help manufacturers trade more freely and to ensure a common level of consumer protection.

It was only in 2003, however, that serious work started on what is now the Nutrition and Health Claims Regulation that was finally adopted as EU law in 2006. This Regulation covers all food products, including dietary supplements.

Why are European companies concerned?

The Regulation requires that a list of permitted and prohibited claims is developed for the whole of the EU. European trade associations invested huge resources in 2007-8 to build a list of more than 700 established claims that were being used for dietary supplement products. This list and the substantiation of the claims were submitted to

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the European authorities and eventually to the European Food Safety Authority (EFSA) for review.

However, it looks as though this investment was wasted. On the basis of the EFSA evaluations so far, it is expected that virtually no claims apart from those for vitamins and minerals will be approved. Even antioxidant claims and claims for probiotics, glucosamine and all botanical claims could disappear from the market.

Why is this happening?

EFSA is requiring an inappropriate level of evidence for the substantiation of claims, at a level which is similar to that required for a drug claim. There are simply very few substances with this type of data.

What is being done about it?

It is clear that EFSA is not going to change its approach. The only hope therefore is to ensure that the national regulatory bodies and the European Commission who will have to make a final decision on EFSA's opinions fully understand and recognize the severe impact this will have for both the supplement and food businesses. Almost all energy is now focused on political action.

The European lobby is being led by the European level manufacturers' Federation, EHPM, and a new group composed of senior managers from food and supplement companies, called the European Health Claims Alliance. In addition, the European Responsible Nutrition Alliance is leading work on a new approach to claims evaluation. The intensive activity is focused on the governments of the 27 EU Member States and the European Commission and European Parliament. In addition, work is continuing across the scientific community to engage them in action for a change of approach.

What are the main targets at this point?

The Member States had been aiming for a vote on the first batch of established claims primarily relating to vitamins and minerals on 11 October, but in September, a further delay was announced, likely until the end of 2011. While the industry associations have few objections to the claims for vitamins and minerals that are likely to be proposed, any vote would set a precedent for the future. Whenever the vote occurs, it may make it more difficult to prevent the

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second and third batches of claims containing all the other ingredients being voted in the future.

What is the alternative?

There must be a political recognition that the EFSA process is inappropriate for the majority of the claims currently made on the market. Claims which have been made for many years without challenge should be permitted to be sold if they have reasonable substantiation – not the druglike substantiation required by EFSA. Consumers need these claims and so do manufacturers. If this political understanding is achieved, a long hard look will need to be taken at the Regulation to find ways to permit these claims onto the market.

In addition, the European Federation of Associations of Health Product Manufacturers (EHPM) has recently issued a complaint to the European Ombudsman regarding the EU health claims Regulation. The European Ombudsman looks at cases of maladministration of issues handled by European institutions such as the Commission and EFSA. Its role is to act as a mediator within the EU, aiming to achieve agreement between parties outside courts.

The EHPM's complaint calls upon the European Ombudsman to issue a formal recommendation that the Commission should wait for EFSA to deliver all of its evaluations on the Article 13.1 claims before any further steps are taken towards a formal decision about the Community list of permitted Article 13.1 claims, on the grounds that the current batch-wise approach is maladministration.

And if there is no success?

With the exception of claims for vitamins and minerals, almost all claims will be illegal in the 27 Member States of the EU. Once a claim is prohibited, a manufacturer will have 6 months to withdraw it from the market. Since EU law is so widely followed in other parts of the world, it can be expected that this will impact marketing worldwide. Inevitably this will encourage many companies to go into illegal marketing practices to get their messages across, lowering the credibility of the sector and bringing further problems for the industry with the regulators.

Members are urged to:

Sign up to the letter asking for a time-out on the legislation (www.healthclaimsletter.org).

FDA Sends Warning Letter to Aloe Vera Product Marketer

September 28, 2010, The Food & Drug Administration sent a letter to Enriching Gifts for a myriad of violations after reviewing information available on the company's web sites in July 2010 (www.enrichinggifts.com, which also linked directly to www.enzymesfordigestion.com).

The FDA Warning Letter notes that the search went beyond the available web pages, going into information contained within PDF's regarding specific products. The Warning Letter further noted claims were supplemented by the use of metatags (key words) used to bring consumers to the <u>www.enzymesfordigestion.com</u> website through Internet searches. These metatags include terms such as "Pro-Biotics kill parasitic bacteria just like antibiotics", "ANTIBACTERIAL", and "Anti-viral".

"This is a clear sign that the FDA is continuing to actively review and look for products that are not in compliance with applicable regulations. The 'low hanging fruit' that is companies marketing their products actively via the web or corporate controlled websites is an invitation for FDA action."

The Warning Letter also states that the products referenced within are not generally recognized as safe and effective for the referenced uses and are "new drugs" under section 201(p) of the Act [21 U.S.C. § 321(p)]. A mention of the improper usage of testimonials is also made.

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- Devon Powell

The Warning Letter specifically mentions the following concerns in regards to the product "Aloe Ace Max", including:

...are promoted for conditions that cause the products to be drugs under section 201(g)(1)(B) of the Federal Food, Drug, and Cosmetic Act (the Act) [21 U.S.C. § 321(g)(1)(B)]. The therapeutic claims on these web sites 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.

From the PDF file accessed by clicking on "about aloe acemax" on the web page entitled "enriching gifts international's core product is its exclusive plant enzyme formula":

"ALOE ACE-MAX[™] ... • Reduces inflammation - involved in ulcerative colitis, arthritis, and gastric reflux. ... • Helps with the reduction of blood sugar with both Type I and Type II diabetes. ... • Important in preventing and treating arteriosclerosis, heart disease, and Parkinson's disease ... • Direct anti-bacterial and anti-viral effect. ... • Powerful healing effect on AIDS, cancer ... • Causes the body to produce a natural chemical (tumor necrosis factor) that functions to shut off the blood supply to tumors"

• "Cancer Research ... • All of the immune modulating effects from Aloe [ingredient in product] contribute greatly to the prevention and healing of malignant cells. (Ian Tizard, Ph.D. and Maurice Kemp, Ph.D., Texas A&M)"

• "Benefits Lung Cancer ... • Aloe [ingredient in product] was the only of the plant foods that was protective against cancer. "The results of plant epidemiology suggest that aloe prevents human pulmonary carciogenesis (lung cancer)", and aloe is "widely preventive or suppressive against various human cancers." (Japanese Journal of Cancer Research)"

"AIDS Research ... • In many of the studies [of the ingredient aloe] there was an average of 70% improvement in symptoms and laboratory criteria within 3 to 4 months. (Terry Pulse, M.D., Reg McDaniel, MD., Terry Watson, D.O., Dr. Clumeck). ... • Many patients stated that opportunistic infections had stopped and they were able to return to normal activity.... • Lab studies showed that helper lymphocytes rose to three times the pre-treatment level. HIV-1 virus could no longer be cultures. P-24 antigen levels

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for the virus dropped or became negative.... • Researchers discovered that Aloe mucilaginous polysaccharides alter synthesis and thus the structure of the AIDS virus envelope necessary for infecting lymphocytes. (Vanderbilt Medical Center. Nashville, Tennessee)"

• "Eases Intestinal Problems ... • Aloe [ingredient in the product] can be effective for treating inflammatory bowel disease. (Journal of Alternative Medicine) ... • Other studies have shown that aloe helps ... relieve constipation and gastric ulcers." • "Reduces Blood Sugar in Diabetes ...• Aloe [ingredient in the product] reduced the blood sugar levels in diabetes. (Hormone Research) "

• "Aloe Vera[ingredient in the product] ... has been proven for thousands of years to be one [sic] the most effective healing agents available for wounds and also when ingested into the body for healing."

• "Aloe Vera [ingredient in product] Benefits: Anesthetic-Relieves itching, swelling and pain ... Anti-Allergenic ... Antibiotic Action ... Anti-Fungal Activity ... Anti-Inflammatory ... Arthritis-Helps reduce Arthritis symptoms by reducing inflammation in joints already afflicted by arthritis Bowel - Detoxifies bowel - Effective for treating inflammatory bowel disease Diabetes-Reduces Blood Sugar level in Diabetics ... Digestive Stimulant-Neutralizes stomach acidity, Relieves constipation and gastric ulcers ... Healing Action-Heals burns, Decreases surgical recovery time, Speeds wound healing ... "

"This is a clear sign that the FDA is continuing to actively review and look for products that are not in compliance with applicable regulations. The 'low hanging fruit' that is companies marketing their products actively via the web or corporate controlled websites is an invitation for FDA action", said Devon Powell, Executive Director of the IASC. "I would encourage anyone in the industry to purchase and review the IASC/AHPA seminar '<u>Allowable</u> <u>Claims and Claims Substantiation: How to Comply with</u> <u>the Law & Maximize your Marketing</u>', which featured representatives from FDA, FTC and legal counsel, in order to better understand the regulations and what can lawfully be said in regards to the marketing of aloe vera products."

The full warning letter can be found by clicking <u>HERE</u>.

IASC Opens Submission Cycle for 2010-2011 Yun-Ho Lee Merit Award

The International Aloe Science Council (IASC) is pleased to announce the opening of nominations for the 2010-2011 Yun-Ho Lee Merit Award.

IASC's annual Yun-Ho Lee Merit Award recognizes scientific research done to promote the global awareness, innovation, and use of aloe vera in the fields of agriculture, manufacturing, pharmacology, chemistry and biology. The award was established by Mr. Bill Lee, President and Chairman of the Board of the NamYang Aloe Co., Ltd., in honor of a true pioneer of the aloe industry, his father, Chairman Yun-Ho Lee.

Winners of the Yun-Ho Lee Award receive a cash prize of up to \$10,000. The deadline for submissions is December 1, 2010, and awards will be announced in 2011. More information on submission requirements and a description of the review process and other applicable criteria is available on the <u>IASC Web site</u>.

"The Yun-Ho Lee Merit Award affords us an opportunity to recognize the efforts of researchers around the globe that are working to improve our knowledge and understanding of Aloe vera from clinical studies to chemical analysis to agriculture," said IASC Executive Director Devon Powell. "It continues to be a privilege to promote and honor the global, scientific work that these pioneers produce."



AHPA Releases Primer on Products Liability Insurance

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

A new publication developed by AHPA provides information businesses need to both understand and confidently purchase products liability insurance.

AHPA's "Primer on Products Liability Insurance for the Dietary Supplement Industry" is an overview of the structure of the excess and special (E&S) risk lines insurance market and answers specific questions commonly asked, such as:

- What insurance coverage is included in a basic products liability insurance policy, and what are the limits of coverage?
- What is the minimum premium cost for products liability insurance for a small company?
- Are product labels required to be submitted to obtain products liability insurance?
- Can insurance be obtained for products that contain excluded ingredients?

AHPA has maintained an active role for over a decade in directing its members to qualified experts in the insurance industry and has established the AHPA Program in cooperation with Grifcon Enterprises, Inc., the program manager, and RT Specialty of Illinois, LLC (RTS), an E&S insurance wholesale broker. The AHPA Program is specifically designed to allow participants to maintain their current insurance agent or broker relationship while gaining access to the expertise and experience represented by these program partners.



AHPA is paid a royalty calculated from the premiums of any insurance sold under the AHPA Program. By purchasing products liability insurance through the AHPA Program, member companies provide direct financial support to AHPA. AHPA's royalty is paid from the normal commissions received by Grifcon and RTS, so there is no increased cost to offset this royalty.

To participate in this program, request that your policy – regardless of the broker or agent you use and the specific insurer that provides the policy – be placed through RT Specialty of Illinois Insurance Services. An application to provide to your broker or agent can be found here: <u>http://www.dickgriffin.com/application.html</u>.

For information about this insurance program, or with other insurance questions, contact Dick Griffin of Grifcon Enterprises at 916-434-8874 or at <u>dick@dickgriffin.com</u>.

AHPA's Insurance Primer can be downloaded <u>HERE</u>.



Consumer Reports Gets It Wrong Again(Even with AHPA's Help)

By Michael McGuffin, AHPA President Originally published in the September 2010 AHPA Report. Reprinted by permission of AHPA.

Consumer Reports (CR) first identified its "Dirty Dozen" dietary supplement ingredients in 2004, and the media became very excited and reported broadly on this "news" and its catchy moniker. But there were a lot of problems with the list, and AHPA's Steven Dentali, Ph.D. submitted a letter to the editor to provide some clarity:

- ♦ FDA had already forbidden the sale of herbs that contain aristolochic acid in the U.S. But aristolochic acid was included on CR's 2004 list, as the only "definitely hazardous" material.
- It was wrong to say that skullcap (Scutellaria lateriflora) damages the liver, when it had been well established that case reports suggesting such effects should be attributed to adulteration with germander (Teucrium chamaedrys), which was

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not meaningfully present in the marketplace. Both skullcap and germander were on the 2004 list.

- The issue with pennyroyal (*Hedeoma pulegioides*) is related to internal use of the essential oil, not the herb itself. And while it was the oil that CR included in its "dozen," only products made from the herb were identified.
- Federal regulators had acted as early as 2001 to remove comfrey (*Symphytum officinale*) from the market when offered for sale for internal use.

Although the editor never acknowledged receipt of Dentali's letter, it appears as if someone may have read it. The September issue of the magazine has revised and reprised the list. It still includes comfrey, but the other four (including germander) have now been removed, as have two non-herbal ingredients.

But apparently the tag line was too good to give up, so this year's "Dirty Dozen" has been repopulated with six other ingredients that again betray a lack of expertise. The four new herbs on the list are aconite (*Aconitum* spp.), coltsfoot (*Tussilago farfara*), country mallow (*Sida cordifolia*) and greater celandine (*Chelidonium majus*).

As Matt Lauer said on the Today Show while interviewing Nancy Metcalf, CR's Senior Program Editor on August 3: "I haven't heard of most of these things." But even though these herbs might not be on the tip of everyone's tongue or be key marketplace ingredients (Mark Brush at *Nutrition Business Journal* issued "A Response to Consumer Reports' Scary Supplements" and provided figures that estimate the cumulative sales of these 12 ingredients as ~0.2 percent of the annual supplement market), AHPA offers the following thoughts:

- ♦ Aconite: In the U.S., aconite is primarily available as a homeopathic medicine, which has not been associated with any of the potentially toxic constituents in the plant itself. AHPA recommends that aconite root be excluded as an ingredient from dietary supplements available for retail sale.
- Coltsfoot: AHPA has recommended since 1996 against the oral use of any herb that contains toxic



pyrrolizidine alkaloids – including coltsfoot and also comfrey, which was retained by CR from its 2004 list. The Food and Drug Administration declared in 2001 that it considers any product for oral use that contains toxic pyrrolizidine alkaloids to be adulterated, and the Federal Trade Commission has also acted against the sale of such products.

- Sida cordifolia: CR has identified a concern about "country mallow" based on "possible dangers linked with its ephedrine alkaloids." If there is any ephedrine in Sida cordifolia, however (recent research suggests that there is not), it is present only at a very low level, less that 0.1 percent. And if this herb was, in fact, providing ephedrine, it would not be legal to use in a dietary supplement.
- Several of the other herbs that were identified in both 2004 and CR's current list are labeled to inform consumers of safety issues material to their use. For example, AHPA maintains a labeling policy for kava (*Piper methysticum*) that provides information that is consistent with FDA's 2002 Consumer Advisory on this herb. And chaparral (*Larrea tridentata*), lobelia (*Lobelia inflata*), and yohimbe (*Pausinystalia johimbe*) are all classified by AHPA's *Botanical Safety Handbook* in categories that identify specific cautions.

Consumers Union, the publisher of *Consumer Reports*, describes itself as an organization that was founded in part because consumers "lacked a reliable source of information they could depend on to help them distinguish hype from fact." Unfortunately, the article

that accompanies their new list (Anon. September 2010. Dangerous supplements. What you don't know about these 12 supplements could hurt you. *Consumer Reports*) strays into sensationalism.

Much of this article is focused on individuals who suffered significant adverse events when taking products labeled as dietary supplements. These include one unfortunate man who took a product found to be laced with a synthetic steroid, and another who suffered

from a product found to contain 200 times as much

selenium as was stated on its label. But the first of these products was an illegal drug, and not a dietary supplement, and the second failed to comply with good manufacturing practice, and so was adulterated.

The recent *Consumer Reports* article, similar to that from 2004, attempted to draw broad conclusions about the regulation of dietary supplements based on anecdotes related to products that do not represent the mainstream. This tone is unfortunate and misses an

opportunity to express support for the efforts of responsible industry players to improve enforcement of the good laws already in place.



Certification Program: Aloin Testing

The notice shown below was provided to IASC Certification Program participants who supply raw materials or manufactured/market finished products for oral consumption. As has been stated in other reports and within the document, this new testing requirement has come about due to the National Toxicology



Program (NTP) study of the ingredient "Aloe vera whole leaf extract (native)," an unfiltered aloe vera leaf juice powder, and what we've been told is the high likelihood of the results of the study showing carcinogenicity in mice and rats.

The crux of the organization's argument is that the ingredient studied by the NTP in their 2 year oral consumption study is not what is primarily sold in products in the marketplace – and in order to make that argument, we have to analytically demonstrate this as fact. So, though this is indeed an additional burden on industry and program participants, and one that we would rather not have had to impose, such self-regulatory actions will hopefully alleviate the need for potentially even more restrictive regulatory controls.

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Members or program participants are welcome to contact Devon Powell for more details at <u>dpowell@iasc.org</u>.



NMR as Botanical Identity and Quality Measurement Tool

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

Some of the talks and posters presented at the 51st meeting of the American Society of Pharmacognosy (ASP) dealt with the general topic of NMR as a botanical identity and quality measurement tool. NMR continues to show utility regarding botanical identification because it is able to provide detailed structural information of individual constituents in botanical materials beyond that afforded by the use of other spectroscopic techniques. As should be well known to IASC members by now, proper NMR analysis of aloe materials provides specific information regarding the presence of particular compounds without having to chromatographically separate them. For example, NMR is able to confirm the presence of signals for acemannan while simultaneously detecting the presence of maltodextrin (a common adulterant), preservatives, and compounds indicative of degradation. In order for data from other spectroscopic analytical tools, NIR for example, to be scientifically valid for botanical identification purposes a significant amount of up front work must be done to determine the applicability of it for identification purposes. This is covered in the review if the next entry below.

The first ASP talk on NMR was titled "Validation of an NMR Method for Quality Control and Identification of Botanical Extracts" and given by Kimberly Colson, Ph.D. of Bruker BioSpin (a supplier of NMR instrumentation). The presentation demonstrated the ability of Nuclear Magnetic Resonance, or NMR (a technology you may know as MRI) to analyze complex mixtures. Dr. Colson followed a scientific path to demonstrating the utility





of NMR in identifying and analyzing crude botanical extracts. Working with plants from the *Vaccinium, Panax, Scutellaria, Teucrium, Vitis, Pinus, Smilax, Gaylussacia, Piper, Ginkgo, Origanum, Silybum,* and *Rhodiola* genera Dr. Colson and her team analyzed extracts with different NMR instruments under different conditions in order to determine the critical conditions that will enable reproducible testing.

Dr. Colson's sensible approach is to demonstrate that NMR is a scientifically valid technology for botanical identification and analysis. She is employing it to determine natural variation between botanical extracts of the same species, to identity specific compounds in those crude extracts, and to quantify those same compounds. NMR is already used by the International Aloe Science Council as a tool to help assure the identity of aloe vera material in consumer extracts and we can expect to see its use growing in our field as the necessary foundation is established to justify its use and utility.

To date Dr. Colson has conducted a single laboratory validation (SLV) of her method and will be engaging in a multi-facility reproducibility test. NMR work on botanical materials by her group was the subject of four posters. In one several populations of each of eight *Vaccinium* spp., including blueberry, cranberry, bilberry, and evergreen huckleberry, were collected from Europe and Canada, prepared as ethanol extracts, and analyzed. The results obtained by principal component analysis (PCA) allowed differentiation of the species. It was also possible to quantify key compounds in the crude extracts.

Another poster demonstrated the ability of NMR to identify grape seed extract down to a 1% concentration adulterant in pine bark extract. Both materials are rich sources of oligomeric proanthocyanidins (OPCs), catechin and epicatechin derivatives, and other flavonoids. Differentiating them without first chromatographically separating their constituents demonstrates the potential of scientifically valid spectroscopic methods for routine use in the botanical industry. A third poster, this one on kava, compared NMR and HPLC (high performance liquid chromatography) analyses of crude extracts of *Piper methysticum* looking at consistency over several lots, and the identification and quantification of kavain in them.

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NMR does this by direct analysis of the crude extract while HPLC first separates it from other constituents and then measures it.

The last poster on display by this group presented an evaluation of crude cranberry extract with regard to the identity and amount of individual cranberry leaf constituents such as flavonol glycosides, phenolic acid derivatives, and proanthocyanidins. This work illustrates the potential of NMR to separate cranberry cultivars based on their NMR "fingerprints" and the potential to "provide detailed information such as the geographic origin, speciation, plant part, relative or absolute quantity of key components present in the crude extract, and information on possible adulterants."

Additional work in NMR analysis of botanicals was provided by Tanja Gödecke, Ph.D. a postdoctoral research associate with Guido Pauli, Ph.D., leader of the Standardization of Botanical Dietary Supplements project at the University of Illinois at Chicago/National Institutes of Health (UIC/NIH) Center for Dietary Supplement Research directed by Norman Farnsworth, Ph.D. Dr. Pauli has been a pioneer in the quantitation of botanical constituents by NMR. Dr. Gödecke's talk, titled "NMR-Based Quality Control of *Angelica sinensis* (dong quai) Botanicals" presented information regarding active principles of this botanical widely used for women's health.

Analysis of dong quai extracts and extract fractions for bioactivity indicate that ligustilide is at least associated with the active principle. Plants similar to *A. sinensis*, such as *A. dahurica* (fragrant angelica), *Levisticum officinale (lovage)*, *Ligusticum wallichii* (syn. *L. chuanxiong)*, and *L. porteri* (osha) also contain large amounts of ligustilide. This compound has stability issues that create a demand for its measurement without relying on a primary reference standard for instrument/method calibration. Qualitative NMR analysis of 75% ethanol extracts of these plants allowed unambiguous identification of ligustilide and verification of plant species. Ligustilide quantitation was also achieved by NMR analysis. Specificity, accuracy, and precision of the method were discussed.



Aloecorp's Qmatrix[®] Aloe Now Has GRAS Status!



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







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Spectroscopic and Chromatographic Analyses for Botanical Identification

Davrieux F, Allal F, Piombo G, Kelly B, Okulo JB, Thiam M, Diallo OB, Bouvet JM. Near infrared spectroscopy for high-throughput characterization of Shea tree *(Vitellaria paradoxa)* nut fat profiles. *J Agric Food Chem.* 2010 Jul 14;58(13):7811-9.

Frédérich M, Wauters JN, Tits M, Jason C, de Tullio P, Van der Heyden Y, Fan G, Angenot L. Quality Assessment of *Polygonum cuspidatum* and *Polygonum multiflorum* by 1H NMR Metabolite Fingerprinting and Profiling Analysis. Planta Med. 2010 Jul 19. [Epub ahead of print. Abstract available at doi:10.1055/s-0030-1250132.]

Scopel M, Mentz LA, Henriques AT. Comparative analysis of *Sambucus nigra* and *Sambucus australis* flowers: development and validation of an HPLC method for raw material quantification and preliminary stability study. *Planta Med.* 2010 Jul;76(10):1026-31. Originally published in the September 2010 AHPA Report. Reprinted by permission of AHPA.

I'm all for the use of spectroscopic analyses for botanical identification if such uses are scientifically valid. These two citations illustrate the sort of work necessary to know how well a method performs for its intended use. The first employed NIR (near infra-red) spectroscopy to differentiate samples of shea tree (*Vitellaria paradoxa*) nut butters from East and West African sources. It is quite easily done provided that a sufficiently large number of samples are obtained, proper calibrations are developed and employed, and proper Principle Component Analysis (PCA) is done. Data from over 600 samples were evaluated for this study. The successful use of NIR for botanical identification is more involved than simply collecting spectra over time to form a reference library. A review of this paper indicates at least as much.

The second citation here demonstrates the ability of NMR to discriminate between samples of Japanese knotweed (*Polygonum cuspidatum*) and fo-ti (*Polygonum multiflorum*) based on their stilbene constituent profile without having to separate the compounds as would be done by HPLC. One marketplace sample was found to be clearly mislabeled indicating that there may be some confusion between these two Chinese medicinal plants from time to time. Almost 30 samples of each species were employed for this study.

The third citation demonstrates the differentiation of European elder *(Sambucus nigra)* and southern elder *(Sambucus australis)* flowers by the more traditional techniques of compound separation and comparison of chromatograms obtainable by HPLC analysis. The report demonstrates the detail involved in making sure the method is fit for its intended quality control uses as well as the stability study conducted and reported on.



Heavy Metals and Other Elements in Herbs and Supplements

By Avula B, Wang YH, Smillie TJ, Duzgoren-Aydin NS, Khan IA. Quantitative determination of multiple elements in botanicals and dietary supplements using ICP-MS. *J Agric Food Chem. 2010 Aug* 25;58(16):8887–8894.

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Information on heavy metals may be of interest for IASC members should they wish to establish specifications regarding them or if customers require such information. Generally speaking this information isn't required unless specific materials or products are likely or certain to be contaminated by them. This article is offered for general information. AHPA has general guidance information avaiable at <u>http://www.ahpa.org/Default.aspx?tabid=223</u>. Also USP has proposed heavy metal limits for dietary supplements that are available for review and comment at <u>http://www.usp.org/hottopics/metals.html</u>.

The botanical research team at the University of Mississippi, in Oxford headed up by Ikhlas Khan, Ph.D., this year's winner of AHPA's *Herbal Insight* award, reported the development and validation of an ICP-MS method for the simultaneous quantification of 15 elements in 11 botanicals and 21 supplement products showing it to be simple, fast, and reliable for its intended purpose. This may be applicable for routine heavy metal testing of botanical ingredients or products when warranted.

No serious issues were uncovered for the "big four" heavy metals arsenic, cadmium, lead and mercury though a dose of 8.89 μ g/day cadmium would be consumed by a *Centella asiatica* (gotu kola) product if taken at the highest

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labeled dose. This value is over the AHPA guidance on the maximum quantitative limit for this element but below the minimum risk level of 14 μ g/day referenced in the study.

The brown seaweed products tested had arsenic levels above the inorganic arsenic AHPA guidance level, and further testing will likely show that the arsenic found in these materials is predominately in organic forms that are of limited safety concern. Only one sea vegetable, hijiki, has been shown to contain inorganic arsenic at levels that may raise concern from routine consumption. See the May 2007 *AHPA Report*, Volume 22, Number 5, p. 5 and the study by Nakamura Y, Narukawa T, Yoshinaga J. (Cancer risk to Japanese population from the consumption of inorganic arsenic in cooked hijiki. *J Agric Food Chem.* 2008 Apr 9;56(7):2536-40) for further information.

IASC AND ALOE IN THE NEWS

FDA Warning Letter to manufacturer of products claiming to contain aloe vera http://www.fda.gov/ICECI/EnforcementActions/ WarningLetters/ucm227646.htm

You Had Me At Aloe... Cocktails

http://blogcritics.org/tastes/article/you-had-me-ataloe-cocktails/

LEGAL & LEGISLATIVE NEWS

Food Safety Legislation May Advance in U.S. Senate

By Pete Evich, Van Scoyoc Associates, Federal Affairs Consultant for AHPA.

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

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The idea of amending the Federal Food, Drug & Cosmetic Act to create better assurance that foods are safe has long been discussed in the halls of the U.S. Congress. The current (111th) Congress, with its significant Democratic majorities, has been viewed as providing one of the best opportunities for legislative change in many years. H.R. 2749, the Food Safety Enhancement Act, was passed in the House of Representatives over a year ago. In the Senate, the FDA Food Safety Modernization Act, or S. 510, was approved by the HELP Committee (Health, Education, Labor and Pensions) in November but has not yet been scheduled for full Senate action. Both bills would impose new requirements on food producers and also provide the Food and Drug Administration (FDA) with greater authority. (For a detailed review of these bills, see the AHPA Report, December 2009, pages 5-8.)

"For far too long, the headlines have told the story of why this measure is so urgently needed: foodborne illness outbreaks, product recalls and Americans sickened over the food they eat. This 100-year-old plus food safety structure needed to be modernized."

Several emerging issues now provide indications that the Senate may be nearing a decision to consider S. 510. On August 12, the HELP Committee released its manager's amendment to the bill. The committee's chair, Senator Tom Harkin (D-IA) commented at that time, "For far too long, the headlines have told the story of why this measure is so urgently needed: foodborne illness outbreaks, product recalls and Americans sickened over the food they eat. This 100-year-old plus food safety structure needed to be modernized."

That was before over one-half billion eggs were recalled due to contamination with salmonella. Just one day after Harkin's statement, Wright County Egg Production – ironically in Galt, Iowa – initiated the first wave of a recall that has expanded several times since and now also includes another Iowa egg producer, Hillandale Farms. The FDA reports that hundreds of people have been sickened due to this health risk.



A further irony is that new rules to reduce salmonella contamination of eggs (the Egg Safety Rule) went into place in July for farms like Wright County Egg and Hillandale Farms. When this rule was introduced in 2009, the FDA estimated that its implementation would prevent more than 79,000 salmonella-related illnesses and 30 deaths each year. The agency has not clearly explained what went wrong with this rule to lead to what is reportedly the largest egg recall in history and the most widespread salmonella outbreak since records have been kept, but it has stated that "once it is fully implemented ... [it] will reduce these types of [salmonella] outbreaks.

In spite of the agency's expressed confidence in the Egg Safety Rule, FDA Commissioner Margaret Hamburg has presented the egg recall as the impetus for Congress to complete passage of S. 510. In a joint FDA/CDC (Centers for Disease Control and Prevention) media briefing on the recall on August 23, Dr. Hamburg noted that the pending legislation would "give us [recall] authority and other critical tools such as enhanced authorities to trace back products to the source, to require firms to implement preventive controls, and to provide FDA access to important records. ... So we do hope to see that legislation passed in a timely way."

Although there are differences between this bill and the House legislation, companies in the dietary supplement and ingredients business can expect at least the following changes in federal law:

- FDA would have new authority to initiate mandatory recalls when safety concerns are identified. The AHPA board has expressed support for this change.
- Facility registrations would change from a nocharge one-time requirement to a biennial renewal system, possibly with fees.
- Ingredient manufacturers (but possibly not supplement companies) would need to initiate HACCP (hazard analysis critical control point) plans in their facilities.

Pending "Green Guides" and Others: Will These Affect Your Business?

By Michael McGuffin, President, American Herbal Products Association. Originally published in the November 2010 AHPA Report. Reprinted by permission of AHPA.

The Federal Trade Commission proposed revisions to its "Green Guides" on October 15. These FTC documents, originally issued in 1992 and revised twice since, provide guidance on how companies can make truthful and substantiated environmental marketing claims for products they sell. The Guides include information on how consumers are likely to interpret such claims, as well as how to substantiate them and qualify them if needed.

The National Organic Program (NOP) has also requested comments on draft guidance, in this case to five separate guidance documents. In its October 13 notice, NOP stated that these documents are intended for use by accredited certifying agents and certified operations.

And finally, USDA's Animal and Plant Health Inspection Service (APHIS) on October 29 reopened the comment period for a proposed rule that will establish definitions for the terms "common cultivar" and "common food crop" as those terms are used in APHIS regulations that implement amendments to the Lacey Act, a law that governs certain trade in some plant species. Common cultivars and common food crops are categorically exempted from the Act, but the terms are not defined. USDA and the Department of the Interior have authority to define these by regulation.



What the Warning Letters and an Enforcement Action Teach

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

Two recent FDA Warning Letters demonstrate continued interest in the unlawful inclusion of drug ingredients or

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their analogs in products labeled as dietary supplements and not approved as drugs.

Note that FDA took samples of Natural Wellness product on May 5 and June 30, but sent the <u>Warning Letter to</u> <u>that company</u> only on October 5. FDA had first issued a safety alert on some of these products on March 30 and then updated that alert on August 25. Spiked products are FDA's number one priority and will continue to be for some time.

A joint FTC and FDA <u>Warning Letter to Telledant LLC</u> teaches that claims for herpes, epilepsy, diabetes, and STDs (sexually transmitted diseases) are disease claims that cause products to be drugs and unlawful drugs. It is stunning that companies continue to make claims like these on websites or otherwise.

Is FDA cracking down? Well, sure it is. In fact, it announced on October 27 that it had seized multiple adulterated and unapproved drugs at Tri-Med Labs in Somerset, New Jersey. Here is what FDA said:

"The FDA is taking this action because Tri-Med has refused to take these unapproved products off the market after it receive warning letters and regulatory meetings," said Dara Corrigan, the FDA's associate commissioner for regulatory affairs. "This action shows FDA's commitment to protecting the public health from the dangers of unapproved or adulterated drug products."

FDA inspections of Tri-Med since 1997 revealed Tri-Med continued to manufacture and distribute unapproved, misbranded and adulterated drugs with significant cGMP violations.

This press release in fact sends the WRONG message. What it says is that FDA has allowed this company to manufacture and distribute unapproved or adulterated drugs for thirteen years. The third <u>Warning Letter</u> to this company went out in February of this year.

Please say it isn't so. If this is the message, the level regulatory playing field that most competitors seek is misshapen, filled with potholes and needs to be rehabilitated. 1997 to 2010 is a long time to be given to manufacture drug products that are adulterated or misbranded.

FTC Explains "New" FTC Order Provisions

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

At a Food and Drug Law Institute presentation October 29, FTC Associate Director for Advertising Practices Mary Engle described "The FTC's Recent Food and Dietary Supplement Advertising Orders." (<u>Click here</u> for presentation slides.)

Ms. Engle explained that the requirements in recent Iovate and Nestle Consent Orders reflect how the FTC has viewed claim substantiation requirements in past cases and currently. Those cases included a requirement for two adequate and well-controlled clinical trials for specific claims and a requirement of compliance with FDA drug approval or monograph requirements for drug claims.

She describes three types of FTC Consent Order provisions: those for specified disease claims, those for other specified health related claims, and the residual "fencing-in" provision for other health related claims. Her presentation is instructive regarding the question asked by many in the industry: Do the Iovate and Nestle orders mean that two adequate and well-controlled clinical trials are required for all claims? And, is FDA drug approval required for any disease claims in dietary supplement advertising? She notes that future orders will not contain all three. AHPA will be presenting a webinar in the near future on this evolving area of FTC advertising law.

THE SCIENCE OF ALOE Recently Published Studies

Effects of oral aloe vera on electrocardiographic and blood pressure measurements. http://www.ncbi.nlm.nih.gov/pubmed/21048211

Abstract

Purpose: The effects of oral aloe vera on electrocardiographic and

blood pressure measurements were evaluated. Methods: In this double-blind, placebo-controlled, crossover study, healthy volunteers over age 18 years received either 1200 mg of oral aloe vera powder or matching placebo on day 1 of the study and the treatment not received during the first phase on day 8. In each phase, electrocardiographic variables, systolic blood pressure, and diastolic blood pressure were evaluated at baseline and one, three, five, and eight hours after treatment. The primary endpoint was the maximum posttreatment Q-Tc interval over eight hours in both groups. Results: Sixteen participants were enrolled in the study, with a mean \pm S.D. age of 25 \pm 5 years. No significant differences in electrocardiographic or blood pressure measurements were observed. The maximum Q-Tc interval was 419 ± 17 milliseconds in the placebo group and 422 ± 17 milliseconds in the aloe-treated group. The maximum P-R intervals in the placebo- and aloetreated groups were 166 ± 22 and 169 ± 25 milliseconds, respectively. The maximum QRS complex duration did not significantly differ between the placebo- and aloetreated groups (89.4 ± 9 and 89.3 ± 9 milliseconds, respectively). The maximum systolic blood pressures in the placebo- and aloe-treated groups were 120 ± 16 and 120 ± 14 milliseconds, respectively. The maximum diastolic blood pressures in the placebo- and aloetreated groups were 74 ± 10 and 75 ± 9 milliseconds, respectively. Conclusion: A single dose of oral aloe vera had no effect on electrocardiographic or blood pressure measurements in young healthy volunteers.

Photocarcinogenesis Study of Aloe Vera [CAS NO. 481-72-1(Aloe-emodin)] in SKH-1 Mice (Simulated Solar Light and Topical Application Study).

http://www.ncbi.nlm.nih.gov/pubmed/21031007

Abstract

The popular recognition of the Aloe barbadensis Miller (Aloe vera) plant as a therapeutic dermatologic agent has led to the widespread incorporation of Aloe vera leaf extracts in skincare products. Studies have suggested that Aloe vera in skincare preparations may enhance the induction of skin cancer by ultraviolet radiation. A 1-year study was conducted in mice to determine whether the topical application of creams containing Aloe vera plant extracts (aloe gel, whole

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leaf, or decolorized whole leaf) or creams containing aloe-emodin would enhance the photocarcinogenicity of simulated solar light (SSL). 1-YEAR STUDY: Groups of 36 male and 36 female Crl:SKH-1 (hr -/ hr -) hairless mice received topical applications of control cream or creams containing 3% or 6% (w/w) aloe gel, whole leaf, or decolorized whole leaf or 7.46 or 74.6 µg/g aloe-emodin to the dorsal skin region each weekday morning. The mice were irradiated with SSL emitted from filtered 6 kW xenon arc lamps each weekday afternoon. The topical applications of creams and irradiance exposures were conducted 5 days per week for a period of 40 weeks. A 12-week recovery/ observation period followed the 40-week treatment/ exposure period. Additional groups of 36 male and 36 female mice received no cream and were exposed to 0.00, 6.85, 13.70, or 20.55 mJ · CIE/cm2 SSL per day. Mice that received no cream treatment and were exposed to increasing levels of SSL showed significant SSL exposure-dependent decreases in survival and significant increases in the in-life observations of skin lesion onset, incidence, and multiplicity, and significant SSL exposure-dependent increases in the incidences and multiplicities of histopathologydetermined squamous cell nonneoplastic skin lesions (squamous hyperplasia and focal atypical hyperplasia) and squamous cell neoplasms (papilloma, carcinoma in situ, and/or carcinoma). Squamous cell neoplasms were not detected in mice that received no SSL exposure. The topical treatment with the control cream of mice that were exposed to SSL did not impart a measurable effect when compared with comparable measurements in mice that received no cream treatment and were exposed to the same level of SSL, suggesting that the control cream used in these studies did not alter the efficiency of the SSL delivered to mice or the tolerability of mice to SSL. The application of aloe gel creams to mice had no effect on body weights, survival, or the in-life observations of skin lesion onset, incidence, or multiplicity. The administration of aloe gel creams to male mice had no effect on the incidences or multiplicities of histopathology-determined squamous cell nonneoplastic skin lesions or neoplasms. Female mice treated with aloe gel creams (3% and 6%) had significantly increased multiplicities of squamous cell neoplasms. There were no treatment-related effects on body weights, survival, or the in-life observations of skin

lesion onset, incidence, or multiplicity in mice treated with the whole leaf creams. In male mice exposed to SSL and treated with the 6% whole leaf cream, a significant increase was observed in the multiplicity of squamous cell neoplasms. Female mice exposed to SSL and treated with the 3% whole leaf creams had significantly decreased multiplicity of squamous cell nonneoplastic lesions and significantly increased multiplicity of squamous cell neoplasms. Female mice exposed to SSL and treated with the 6% whole leaf cream had significantly decreased multiplicity of squamous cell nonneoplastic lesions. The application of decolorized whole leaf creams to mice had no effect on body weights, survival, or the in-life observations of skin lesion onset, incidence, or multiplicity. Male mice administered the 3% decolorized whole leaf cream had significantly increased multiplicity of squamous cell neoplasms. Female mice administered the 3% decolorized whole leaf cream had significantly decreased multiplicity of squamous cell nonneoplastic skin lesions and significantly increased multiplicity of squamous cell neoplasms. In female mice that received the 6% decolorized whole leaf cream, there was a significant increase in the multiplicity of squamous cell neoplasms. As with the Aloe vera plant extracts, the application of aloe-emodin creams to mice had no measurable effect on body weights, survival, or the in-life observations of skin lesion onset, incidence, or multiplicity. The administration of aloe-emodin creams to male mice had no effect on the incidence or multiplicity of histopathology-determined nonneoplastic skin lesions or squamous cell neoplasms. Female mice treated with the 74.6 µg/g aloe-emodin cream had significantly decreased multiplicity of histopathologydetermined squamous cell nonneoplastic skin lesions and significantly increased multiplicity of squamous cell neoplasms. CONCLUSIONS: These experiments investigated the potential of topical application of creams containing extracts of Aloe barbadensis Miller plant (aloe gel, whole leaf, or decolorized whole leaf) or aloe-emodin to alter the photocarcinogenic activity of filtered xenon arc simulated solar light (SSL) in male and female SKH-1 hairless mice. Data on skin lesions were collected both on digital images during the in-life phase and by histopathologic evaluation at necropsy. No effects of creams upon SSL-induced skin lesions were identified from data collected during the in-life

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phase. Aloe Gel or Aloe-emodin: Under the conditions of these studies, there was a weak enhancing effect of aloe gel or aloe-emodin on the photocarcinogenic activity of SSL in female but not in male SKH-1 mice based on an increase in the multiplicity of histopathologically-determined squamous cell neoplasms. Aloe Whole Leaf or Decolorized Whole Leaf Under the conditions of these studies, there was a weak enhancing effect of aloe whole leaf or decolorized whole leaf on the photocarcinogenic activity of SSL in both male and female SKH-1 mice based on an increase in the multiplicity of histopathologically-determined squamous cell neoplasms.

Anti-tumor activity of Aloe vera against DMBA/croton oil-induced skin papillomagenesis in Swiss albino mice. http://www.ncbi.nlm.nih.gov/pubmed/20932247

Abstract

Human populations are increasingly exposed to various carcinogens such as chemicals, radiation, and viruses in the environment. Chemopreventive drugs of plant origin are a promising strategy for cancer control because they are generally nontoxic or less toxic than synthetic chemopreventive agents, and can be effective at different stages of carcinogenesis. The present investigation was undertaken to explore the antitumor activity of topical treatment with aloe vera (Aloe vera) gel, oral treatment with aloe vera extract, and topical and oral treatment with both gel and extract in stage-2 skin carcinogenesis in Swiss albino mice induced by 7,12-dim ethylbenz(a) anthracene (DMBA) and promoted croton (Croton tiglium) oil. The animals were randomly divided into 4 groups and treated as follows: Group I, DMBA + croton oil only (controls); Group II, DMBA + croton oil + topical aloe vera gel; Group III, DMBA + croton oil + oral aloe vera extract; Group I V, DMBA + croton oil + topical aloe vera gel + oral aloe vera extract. Results showed that body weight was significantly increased from 78.6% in the control group (Group I) to 92.5%, 87.5%, and 90.0% in Groups II, III, and IV, respectively. A 100% incidence of tumor development was noted in Group I, which was decreased to 50%, 60%, and 40% in Groups II, III, and I V, respectively. Also in Groups II, III, and IV, the cumulative number of papillomas was reduced significantly from 36 to 12,

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15, and 11; tumor yield from 3.6 to 1.2, 1.5, and 1.1; and tumor burden from 3.6 to 2.4, 2.50, and 2.75, respectively, after treatment with aloe vera. Conversely, the average latent period increased significantly from 4.9 (Group I) to 5.23, 5.0, and 6.01 weeks in Groups II, III, and I V, respectively. We conclude that aloe vera protects mice against DMBA/croton oil-induced skin papillomagenesis, likely due to the chemopreventive activity of high concentrations of antioxidants such as vitamins A, C, and E; glutathione peroxidase; several isozymes of superoxide dismutase; the minerals selenium and zinc; and polysaccharides in aloe vera.

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

http://www.ncbi.nlm.nih.gov/pubmed/20923446

Abstract

BACKGROUND:

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

METHODS:

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

RESULTS:

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

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CONCLUSION:

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

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

http://www.ncbi.nlm.nih.gov/pubmed/20888359

Abstract

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

Plantlet Regeneration from Callus Cultures of Selected Genotype of Aloe vera L.-An Ancient Plant for Modern Herbal Industries. http://www.ncbi.nlm.nih.gov/pubmed/20857229

Abstract

Aloe vera L., a member of Liliaceae, is a medicinal plant and has a number of curative properties. We describe here the development of tissue culture method for high-frequency plantlet regeneration from inflorescence axis-derived callus cultures of sweet aloe genotype. Competent callus cultures were established on 0.8% agar-gelled Murashige and Skoog's (MS) basal medium supplemented with 6.0 mg l(-1) of 2,4-dichlorophenoxyacetic acid (2,4-D) and 100.0 mg l(-1) of activated charcoal and additives (100 mg l(-1) of ascorbic acid, 50.0 mg l(-1) each of citric acid and polyvinylpyrrolidone, and 25.0 mg l(-1) each of L: -arginine and adenine sulfate). The callus cultures were cultured on MS medium containing 1.5 mg l(-1) of 2,4-D, 0.25 mg l(-1) of Kinetin (Kin), and additives

with 4% carbohydrate source for multiplication and long-term maintenance of regenerative callus cultures. Callus cultures organized, differentiated, and produced globular embryogenic structures on MS medium with 1.0 mg l(-1) of 2,4-D, 0.25 mg l(-1) of Kin, and additives (50.0 mg l(-1) of ascorbic acid and 25.0 mg l(-1) each of citric acid, L: -arginine, and adenine sulfate). These globular structures subsequently produced shoot buds and then complete plantlets on MS medium containing 1.0 mg l(-1) of 6-benzylaminopurine and additives. A hundred percent regenerated plantlets were hardened in the greenhouse and stored under an agro-net house/nursery. The regeneration system defined could be a useful tool not only for mass-scale propagation of selected genotype of A. vera, but also for genetic improvement of plant species through genetic transformation.

Oral administration of Aloe vera and honey reduces walker tumour growth by decreasing cell proliferation and increasing apoptosis in tumour tissue.

http://www.ncbi.nlm.nih.gov/pubmed/20839215

Abstract

Cancer is diagnosed in approximately 11 million people and is responsible for almost 8 million deaths worldwide every year. Research in cancer control has shown the importance of co-adjuvant therapies. Aloe vera may reduce tumour mass and metastasis rates, while honey may inhibit tumour growth. This study verified the influence of Aloe vera and honey on tumour growth and in the apoptosis process by assessing tumour size, the cell proliferation rate (Ki67-LI) and Bax/Bcl-2 expression at 7, 14 and 20 days after Walker 256 carcinoma implant in Wistar rats distributed into two groups: the WA group tumour-bearing rats that received a gavage with a $670\,\mu\text{L}/$ kg dose of Aloe vera and honey solution daily, and the CW group - tumour-bearing rats which received only a 0.9% NaCl solution. The effect of Aloe vera and honey against tumour growth was observed through a decrease in relative weight (%) and Ki67-LI in tumours from the WA group compared with those from the CW group. The Bax/Bcl-2 ratio increased in tumours from the WA group at all tested timepoints. These data suggest Aloe vera and honey can modulate tumour growth by reducing cell proliferation and increasing apoptosis susceptibility

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Molecular biology, phytochemistry and bioactivity of three endemic Aloe species from Mauritius and Réunion Islands.

http://www.ncbi.nlm.nih.gov/pubmed/20821810

Abstract

Introduction - Aloe tormentorii, A. purpurea and A. macra are used as multipurpose folk medicines in Réunion and Mauritius Islands and are mistaken for the introduced Aloe vera. Objective - To compare the phytochemical, antimicrobial and DNA profiles of Aloe endemic to Mauritius and Réunion with the profiles of A. vera. Methodology - Leaf extracts of these Aloe species were analysed using standard phytochemical screening techniques, TLC and by HPLC. These extracts were also assayed for antimicrobial activity using microdilution techniques. Genetic diversity was studied using RAPD markers. Results - Phytochemical and antimicrobial assays and RAPD analysis showed that Mascarene Aloe species were very different from A. vera. Conclusion - This study is the first report highlighting the differences between Aloe sp.p from Mascarene and Aloe vera at the metabolic and genomic level.

Analysis of Aloe-based phytotherapeutic products by using nano-LC-MS.

http://www.ncbi.nlm.nih.gov/pubmed/20806241

Abstract

This article proposes a chromatographic method for the analysis of extracts of Aloe plants. The method was developed with a laboratory assembled nano-LC system coupled with a UV detector, followed by an IT-mass spectrometer. With a step gradient mode of ACN/H(2) O mixtures and employing a capillary column packed with C(18) (100 μ m id), a complete separation of the following anthrones was achieved: aloin (in its two isomeric forms A and B), 5-hydroxyaloin and 7-hydroxyaloin (in its two isomeric forms A and B). The optimized nano-LC-MS method was validated for the quantification of aloin, the main component of Aloe with known pharmacological activities. RSD values obtained for retention time and peak areas were 1.3 and 12.1%, respectively. LOD and LOQ values of

0.4 and 1.5 µg/mL were obtained for each aloin isomer. The method was applied to the analysis of Aloe vera and A. ferox extracts in order to acquire a fingerprint, characteristic for each plant. Several phenolic compounds were detected by UV and identified by MS. A. vera and A. ferox showed different profiles and it was possible to discriminate them. Several commercial formulations, declared to contain Aloe extracts, were analyzed. Comparing their chromatograms with those obtained from A. vera and A. ferox, it was possible to recognize the Aloe species and to determine aloin.

Comparative study of the topical application of Aloe vera gel, therapeutic ultrasound and phonophoresis on the tissue repair in collagenase-induced rat tendinitis. http://www.ncbi.nlm.nih.gov/pubmed/20800944

Abstract

The aim of our study was to compare topical use of Aloe vera gel, pulsed mode ultrasound (US) and Aloe vera phonophoresis on rat paw with collagenase-induced tendinitis. Edema size, tensile tendon strength, tendon elasticity, number of inflammatory cells and tissue histology were studied at 7 and 14 days after tendinitis induction. Pulse mode US parameters were: 1 MHz frequency, 100 Hz repetition rate, 10% duty cycle, and 0.5 W/cm(2) intensity, applied for 2 min each session. A 0.5 mL of Aloe vera gel at 2% concentration was applied for 2 min per session, topically and by phonophoresis. Topical application of Aloe vera gel did not show any statistically significant improvement in the inflammatory process, whereas phonophoresis enhanced the gel action reducing edema and number of inflammatory cells, promoting the rearrangement of collagen fibers and promoting also the recovery of the tensile strength and elasticity of the inflamed tendon to recover their normal pre-injury status. Results seem to indicate that Aloe vera phonophoresis is a promising technique for tendinitis treatment, without the adverse effect provoked by systemic anti-inflammatory drugs.

The effect of aloe vera plant (aloe barbadensis) extracts on sickle cell blood (hbss). http://www.interesjournals.org/AJFST/

Abstracts/2010%20abstract/September%202010/ Nwaoguikpe%20%20et%20al.htm

Abstract

The phytochemical and antisickling properties of the leaf and gel extracts of the Aloe vera plant were studied. A large quantity of the plant was collected from the Herbarium of the Department of Pharmacognosy, Faculty of Pharmacy, University of Nigeria, Nsukka and authenticated by a taxonomist at the Department of Crop Science and Technology of the Federal University of Technology, Owerri as being of good quality. The phytochemical composition of the gel and leaf extracts revealed the presence of alkaloids, flavonoids, saponins, tannins and phenols at different concentrations . The determination of the antisickling effects of these extracts was directed towards the inhibition of sickle cell polymerization and the improvement of the Fe2+/ Fe3+ ratio of HbSS in the presence of the extracts. Most of the antisickling amino acids identified in the extracts included: phenylalanine, arginine, tyrosine, aspartic acid, histidine and others, all at high concentrations. The relative percent inhibition of sickle hemoglobin polymerization by the extracts ranged from 77.93% for the CAE of the gel to 80.86% for that of the leaf. The Ascorbic acid concentrations of the extracts were remarkable ranging from 2.028±0.1 mg/ml for the gel to 3.631±0.1 mg/ml for the leaf. The CAE fraction of both gel and leaf improved the Fe2+/Fe3+ ratio from 46.98% for the gel to 78.0% for the leaf extracts respectively .The total vitamin C concentration of the samples expressed in mg/100g sample are : 202.8±0.1 for the gel and 199.7±0.1 for the leaf. There is no significant difference in the concentrations of the CAE fractions of the leaf and gel. Aloe vera plant extracts with the preponderance of nutrients, phytochemicals, amino acids and other compounds can be very beneficial in the management of sickle cell disease.

Oral aloe vera for treatment of diabetes mellitus and dyslipidemia.

http://www.ncbi.nlm.nih.gov/pubmed/20966143



Warning Letters

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

Two FDA warning letters in August teach the importance of checking out the lawfulness of claims before they are made and the importance that FDA is placing on adherence to mandated current good manufacturing practices (cGMPs) in domestic and international inspections.

The first letter was to a food product manufacturer and distributor and the second to an over-the-counter (OTC) topical drug manufacturer. While neither is to dietary supplement manufacturers, there is much to be learned from them.

"The lessons here are many. Obvious and high profile drug/disease claims on websites are easily found by FDA, the Federal Trade Commission (FTC) and by competitors. Making changes to violative websites is relatively easy, but if those claims are included on labels, the costs of fixing the problem are more substantial."

Florida Bottling, Inc.

This company maintains a <u>website</u> in which they promote their various bottled juice products, including Fresh Pressed Blueberry Blend, Pure Aloe, Pure Pomegranate (organic), and Tart Cherry juice. It is FDA's position that websites are labeling for products and that what is said on a website are product claims that must be in compliance with the law. On its website, Florida Bottling made various claims for products that are drug/disease claims, including "reduces infections," "fights artherosclerosis [sic]," "helps inhibit the growth of cancer cells," "reduces swelling in joints," "heals bums and wounds," "aids in the healing of ... ulcers" and "reduces the pain of arthritis, gout," and others.

In addition to identifying these drug claims, FDA's letter noted that other claims made for products on product labels or the company website were unapproved health claims for these foods. These included "Heart Healthy," "Reduction of risk factors related to Cancer, Heart Disease, Stroke & Alzheimer's," and "Reduce the Risk Factors Related to Heart Disease." Finally, FDA noted the product labels made unauthorized nutrient content claims and that their labels and Nutrition Facts panels did not meet regulatory requirements.

The lessons here are many. Obvious and high profile drug/disease claims on websites are easily found by FDA, the Federal Trade Commission (FTC) and by competitors. Making changes to violative websites is relatively easy, but if those claims are included on labels, the costs of fixing the problem are more substantial. And is it necessary to the successful marketing of juice products that drug disease claims be made on websites? Do customers for these products look at and shop on websites? Here, claims like these may be like a tree falling in the forest that no one is around to hear, but FDA, FTC and competitors can easily find these claims and complain. And the final lesson is to know what is going on in your own industry.

Those in the juice business should know that <u>FDA got</u> <u>very serious</u> with the cherry juice industry in Michigan in February 2008 when it announced that Brownwood Acres Foods Inc., Cherry Capital Services Inc. (doing business as Flavonoid Sciences) and two of its top executives were required to sign a consent decree of permanent injunction that prohibit the companies and their executives from manufacturing and distributing any products with claims in the label or labeling to cure, treat, mitigate or prevent diseases.



Singapore OTC Topical Drug Manufacturer Warning Letter re Pharmaceutical cGMPs

Ordinarily, a cGMP-related letter to an OTC topical drug manufacturer would not attract attention in the herbal products industry. But one of the products here is Tiger Balm, a leading and well respected product in the natural products industry, a product of Singapore's Haw Par Healthcare Limited.

This warning letter is instructive because it highlights the same kinds of issues that the dietary supplement industry expects FDA to be focusing on in dietary supplement inspections. Some specific examples from this FDA communication:

- Your firm has not established scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to assure that drug products conform to appropriate standards of identity, strength, quality, and purity.
- Your firm fails to thoroughly investigate unexplained discrepancies or the failure of a batch or any of its components to meet any of its specifications, whether or not the batch has already been distributed.

- Representative samples are not taken of each shipment of each lot of components for testing or examination.
- There is no assurance that your firm establishes the reliability of the supplier's analyses through appropriate validation of the supplier's test results at appropriate intervals.
- Your firm does not follow written production and process control procedures in the execution of various production and process control functions, or record and justify deviations from the written procedures.
- Your employees engaged in the manufacture, processing, packing, holding of a drug product lack the training required to perform their assigned functions.
- Your laboratory records are deficient in that they do not include complete data derived from all tests necessary to assure compliance with established specifications and standards, including examinations and assays.

It is interesting that this warning letter was not dated until nine months after the FDA's inspection of Haw Par.



The company responded in detail to FDA's Form 483 within a month and FDA addressed that response in the Warning Letter.

OTC drug manufacturing quality issues are presently in the news as Johnson & Johnson has undertaken massive recalls of various Tylenol children's and other products and is the subject of an ongoing congressional investigation. In addition, FDA has announced that there is a criminal investigation with respect to these recalls.

The Haw Par warning letter shows that FDA is doing "hard look" inspections outside of the United States, even for OTC topical products that do not have the same hazard profiles as ingested products.

More foreign inspections of this nature can be expected in the food, drug and dietary supplement industry, especially as FDA moves aggressively with respect to such inspections domestically. The domestic industry and Congress will be pushing FDA to assure that the same high standards are applied internationally.



AHPA Completes Analysis of FDA cGMP Inspection Trends

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AHPA President Michael McGuffin presented a detailed analysis of inspections conducted by the Food and Drug Administration (FDA) for compliance of dietary supplement manufacturing facilities with current good manufacturing practice (cGMP). The cGMP rule for supplements is codified in Title 21, Code of Federal Regulations, Part 111 (21 CFR 111), and has been implemented over the past three years. As of June 25, 2010 all supplement operations are subject to this rule.

AHPA analyzed cGMP inspection reports for the period July 1, 2007 through March 30, 2010, obtained by AHPA through Freedom of Information Act (FOIA) requests. FDA provided records of 38 such inspections in which the agency's inspectors recorded an aggregate of almost 200 observations, FDA's term for objectionable "This is the first time anyone has provided an analysis to identify the key areas of attention for FDA in their inspections under the dietary supplement cGMP."

- Michael McGuffin

conditions observed during an inspection Key results include the following:

- "There are no surprises." Every observation made in an inspection can be tied back to one or another part of the regulation.
- "Inspectors are interested in everything." They record observations across the complete spectrum of the rule.
- "Production and process controls and quality control are areas of key focus." These are the areas related to sub-parts E and F of 21 CFR 111.

"This is the first time anyone has provided an analysis to identify the key areas of attention for FDA in their inspections under the dietary supplement cGMP," said McGuffin. "I am pleased that AHPA is able to bring the results of this analysis to dietary supplement professionals, especially those with quality control responsibilities."

McGuffin's presentation was included in a symposium held in Anaheim, California and entitled "New Solutions to Food and Dietary Supplement Analytical Challenges." The symposium was sponsored by Covance, a major laboratory providing testing services worldwide.



FTC Issues Administrative Complaint against POM Wonderful LLC

By Anne V. Maher and Anthony L. Young, Kleinfeld, Kaplan & Becker Originally published in the October 2010 AHPA Report.

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Four years ago, the National Advertising Division of the Better Business Bureau in a 48 page decision reviewed advertising for **POM Wonderful® Pomegranate Juice** and found that certain of the claims being made for the product required qualification or more direct substantiation. At the time, POM agreed to take into account NAD's findings in the inquiry with respect to its future advertising by discontinuing or modifying certain claims.

On September 13, 2010, POM filed suit against the Federal Trade Commission in Federal Court in Washington, DC. In its complaint, POM claimed that the FTC has created a new standard for advertising substantiation that encroaches on the authority of FDA, violates POM's 1st and 5th Amendment rights of free speech and due process, and violates the FTC's own rulemaking procedures.

The new substantiation standards which POM sought to challenge first appeared in two July 2010 FTC consent orders entered into with Nestle Healthcare Nutrition, Inc. and Lovate Health Sciences, Inc. At issue in those proceedings were unsubstantiated immunity claims for Nestlé's *BOOST* Kid Essentials probiotic drink, and weight-loss and other claims for several Lovate supplements. In those orders, for the first time, FTC inserted a provision that requires prior FDA approval for any future claims that a product could prevent, treat or mitigate a disease. In addition, the Lovate order requires the company to have two adequate and well-controlled studies for certain non-disease claims (in that case for weight loss).

In statements accompanying the release of these settlements, the Commission acknowledged that FDA preapproval is generally not required to comply with the FTC Act, but noted that in these cases, the requirement was necessary to provide clearer guidance to facilitate the defendants' compliance with the order and to make





the order easier to enforce. As both of these provisions expanded on the FTC's traditional standard of "competent and reliable evidence," they consequently received considerable attention in the food and supplement industries. Even before the FTC formally announced Nestlé's and Lovate settlements, FTC staff began discussing the new order provisions publicly: at its annual spring meeting at Supply Side West, AHPA's General Counsel previewed the FTC position by presenting an FTC PowerPoint presentation that was simultaneously delivered by FTC's Rich Cleland at a Food and Drug Law Institute webinar.

During this past summer, news reports in the legal trade press revealed that the FTC was investigating POM's advertising claims. Apparently, during its investigation, the FTC took the position that POM should consent to similar substantiation requirements and POM responded by filing suit.

The FTC has not, as POM asserts, promulgated new industry-wide rules, as they are usually understood, modifying the standards for ad substantiation that have been developed over the last thirty years in FTC and court decisions. Instead, the Commission has imposed these "fencing-in" requirements in consent decrees entered into with companies who have allegedly violated the law. The companies chose to agree to and abide by these new standards to settle deceptive advertising charges in lieu of litigation. The FTC has not signaled any intention to apply these standards beyond its case-by-case law enforcement actions or on an industry-wide basis through any form of notice and comment rulemaking.

On September 27, the FTC, by a 5 – 0 vote of the Commissioners, issued an administrative complaint charging the makers of POM Wonderful 100% Pomegranate Juice and POMx supplements with making false and unsubstantiated claims that their products will prevent or treat heart disease, prostate cancer, and erectile dysfunction. The ads appeared in national publications such as *Parade, Fitness, The New York Times*, and *Prevention* magazines; on Internet sites such as pomtruth.com, pomwonderful.com, and pompills.com; on bus stops and billboards; in newsletters to customers, and on tags attached to the product.

The FTC's David Vladeck said that "contrary to POM Wonderful's advertising, the available scientific information does not prove that POM Juice or POMx effectively treats or prevents these illnesses." The challenged claims include:

- Clinical studies prove that POM Juice and POMx prevent, reduce the risk of, and treat heart disease, including by decreasing arterial plaque, lowering blood pressure, and improving blood flow to the heart;
- Clinical studies prove that POM Juice and POMx prevent, reduce the risk of, and treat prostate cancer, including by prolonging prostate-specific antigen doubling time;
- Clinical studies prove that POM Juice prevents, reduces the risk of, and treats, erectile dysfunction.

The FTC complaint alleges that POM Wonderful's heart disease claims are false and unsubstantiated because many of the scientific studies conducted by POM Wonderful did not show heart disease benefit from use of its products. It alleges that the prostate cancer claims are false and unsubstantiated because, among other reasons, the study POM Wonderful relied on was neither "blinded" nor controlled. Finally, it alleges that the erectile dysfunction claims are false and unsubstantiated because the study on which the company relied did not show that POM Juice was any more effective than a placebo.

The complaint sets forth a proposed order containing the language challenged by POM in its Federal District Court lawsuit.

In a related case, Mark Dreher, POM Wonderful's former head of scientific and regulatory affairs and expert endorser, agreed to a settlement that bars him from making any disease treatment or prevention claims in advertising for a POM Wonderful product unless the claim is not misleading and comports with FDA requirements for the claim. The settlement also prohibits Dreher from making other health claims for a food, drug, or dietary supplement for human use without competent and reliable scientific evidence to support the claim. The settlement contains a cooperation clause and reporting provisions to assist the FTC in monitoring compliance with the order.

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All of this may be found at: <u>http://www.ftc.gov/opa/2010/09/pom.shtm</u>

POM has been an aggressive defender of its right to provide scientific information about its products. It appears that there has been substantial interplay between POM and the FTC over at least the past year. POM has thus far refused to settle the charges and instead has sought to challenge FTC's authority to obtain the requested relief and the FTC has filed an administrative complaint. This is a complaint that will be heard by an FTC Administrative Law Judge. This promises to be a long proceeding. The last fully litigated case before the FTC, Daniel Chapter One, began with a complaint filed in September 2008 and was decided December 24 of last year and is presently on review in the United Stated Court of Appeals for the District of Columbia Circuit.



FDA Warns Large and Small Companies on Claims

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

A complaint that is often heard in the dietary supplement industry is that the big companies can get away with claims and that small companies bear the brunt of FDA enforcement. That has not been the case for some time, and September brought a number of actions that show the paradigm is changing.

We all know that you cannot make disease claims for dietary supplements and the same applies to foods. And you cannot do so under the guise of reporting research. FDA made these points clear in a <u>Warning Letter</u> earlier this year to POM Wonderful with respect to claims for atherosclerosis, hypertension, prostate cancer, erectile dysfunction.

In September, FDA <u>made the same point</u> to multinational food company Unilever with respect to claims being made for Lipton Green Tea 100% Decaffeinated. "*The therapeutic claims on your website establish that the product is a drug because it is intended for use in the cure, mitigation, treatment, or prevention of disease.*" Those claims evolved

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from descriptions of heart health research on the Lipton Tea and Health website –

"[F]our recent studies in people at risk for coronary disease have shown a significant cholesterol lowering effect from tea or tea flavonoids ... One of these studies, on post-menopausal women, found that total cholesterol was lowered by 8% after drinking 8 cups of green tea daily for 12 weeks"

In these letters, and in a letter to another beverage giant, Dr. Pepper Snapple Group, FDA also made clear that nutrient content claims are limited to those RDI nutrients recognized in FDA regulations. The challenged label claims were antioxidant claims for Canada Dry Sparkling Green Tea Ginger Ale, "ENHANCED WITH 200 mg OF ANTIOXIDANTS FROM GREEN TEA & VITAMIN C," and for Lipton Green Tea Decaffeinated, "packed with protective FLAVONOID ANTIOXIDANTS." With respect to antioxidants from Green Tea, FDA noted to both companies that Green Tea is not a nutrient that is recognized as a source of antioxidants in the antioxidant nutrient content claim regulation 21 CFR 101.54(g). Antioxidant nutrient content claims are limited to RDI





nutrients with recognized antioxidant activity, e.g., Vitamins A, C, and E.

What does this mean? It means that FDA is saying in these Warning Letters that the term "antioxidant" is reserved for RDI nutrients with recognized antioxidant activity pursuant to the nutrient content claim regulation. This means that FDA would view the antioxidant claims that are made for botanicals other than Green Tea or tea in the same way they are viewed here, as not permitted by the regulations. And there is a second point made here that is important for all to understand. Claims that a product is "high in," a "good source of," or "packed with" are nutrient content claims and may only be made for RDI nutrients or other recognized nutrients. These regulations apply both to labels and labeling.

And there may be another message here. When the FDA takes on a company like POM Wonderful with a Warning Letter, it should expect to learn about any other beverage company making similar type claims and it should expect to be asked to take similar action with respect to those companies.

A Warning Letter in June to CTI Science, Lexington, Kentucky, warned the company that its dietary supplement OSR also contained an ingredient that FDA determined was not a dietary ingredient. Another letter alleging that a dietary supplement is unlawful because it does not contain a dietary ingredient was posted by FDA in September to Unlimited Nutrition for their products containing the ingredient Primacetan. In this letter FDA, noted that six years ago, in 2003, FDA had received a New Dietary Ingredient notification for this ingredient announcing that Unlimited Nutrition would be marketing a product containing the ingredient. FDA noted that it had advised the company submitting the notification that the ingredient did not meet the definition of dietary ingredient. What this Warning Letter teaches is that FDA is looking at dietary supplements to ascertain if their ingredients are really dietary supplement ingredients, and it shows that FDA has not done much of a job on following up after reviewing NDI notifications for ingredients that do not meet the statutory definition.

The last Warning Letter to be issued in September was to <u>Enriching Gifts International</u> in Miles City, Montana.

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This company was found to be making disease claims – arthritis, phlebitis, heart attacks, cancer, and to help diabetics. The letter is quite long because this company was making plenty of claims for its plant enzyme, aloe and other products. No big lessons here except that reporting of research results on ingredients is viewed by FDA as making claims for the products being offered with those ingredients.

