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IASC Board of Directors Fall Meeting

The IASC Board of Directors met several weeks ago in Las Vegas just after the SupplySide West tradeshow to discuss many items of interest to the industry and membership. Below is a brief recap of many of those issues and items:

Financial

The board passed the proposed 2012 budget, which included additional funding for seal enforcement. The board expressed appreciation for the continued fiscal responsibility shown by staff in regards to the management of IASC funds.

Special Presentation: AHP Monograph

The board was shown a draft of the American Herbal Pharmacopoeia (AHP) monograph on aloe vera leaf and inner leaf juice during a presentation from AHP Executive Director Roy Upton. This project was initiated by the board several years ago, with funding provided by the membership as part of the 2009 special assessment. The project is nearing completion and will include compliance and quality standards, methods of analysis, and under discussion at the meeting, was the inclusion of a therapeutic compendium, for which there was some interest. Upton indicated that it would likely cost $20,000 to develop that section of the monograph should IASC choose to include it, but that the monograph could be initially released without a therapeutic compendium, which could be inserted at a later date upon completion.

There was also a discussion pertaining to the inclusion of an isocitrate method within the monograph, and a working group was established to discuss this topic further. Anyone interested in serving on this working group is encouraged to do so. Please contact me for details.

Upton requested that anyone with technical expertise on aloe vera and with an interest in acting as a reviewer for the monograph to contact IASC.

Certification Program

The board was provided with a report of seal-enforcement activities since March 2011, where staff had acted against businesses displaying the IASC certification seal on products without authorization. These included actions against the following companies:

- Green Aloe Tech, South Korea
- Puritan Products
- Vitamin World
- Take Herb
- Aloemaxx
- Sonnomacht
- Fruit of the Earth
In addition, the board was provided with a more detailed report on the ongoing actions taken against Fruit of the Earth, in which IASC filed litigation for the unauthorized, continued usage of the seal. Staff also reported on the board’s instruction to file the IASC seal as a trademark in the following countries, which are in process or completed, and further instructed staff to file for trademark in South Korea:

- Brazil
- China
- Hong Kong
- India
- Mexico
- Taiwan

Science & Technology Committee

Concerns with “whole leaf marker” or isocitrate and the current IASC standard (<5%) was discussed at length. Concern that the standard was too low was expressed as a primary issue, and a working group was established to further consider the topic. Anyone interested in serving on the working group is encouraged to do so. Please contact me for details.

The aloin standard/limit was also discussed. It is currently <10ppm. It was noted that in Germany, a non-authoritative body had established an arbitrary limit of <5ppm, which was under review by some jurisdictions in the country.

Public Relations Committee

With FDA and NTP soon to embark on new studies to determine the root cause of results from the 2-year study in rats conducted by NTP using “non-decolorized whole leaf extract” as an ingredient, the board instructed staff to solicit any toxicology data that may exist from members for the purpose of a review by a retained toxicology group, LSRO, to hopefully provide an initial defense. Members with such information, which would include animal/rodent studies, etc., please forward it to staff.

Staff also reminded the board that at the May 10 meeting with FDA, IASC promised to provide market data on what ingredients were most prominent in finished products in the U.S. market. Staff reported that only two companies had, at the time of the board meeting, responded to the survey request, which was sent to the membership on July 15, 2011. It was made clear that FDA, which had expressed a willingness to work with and share information with IASC, would likely not have that same disposition should IASC not be willing or able to provide the data as requested. Manufacturers are asked to request their suppliers provide the survey data to IASC promptly.

The aloe vera juice de-colorization video was presented to the board at the meeting and was approved by the board subject to a title change, which has been completed. The new title is: “Aloe Vera Juice: The Process of De-Colorization.” The board approved the placement of the video on the IASC website as well as on the AllAboutAloe.org website. A working group will be meeting to discuss further disseminating the video.
Ethics Committee

The Ethics Committee noted that the bylaws revision process was still incomplete, with only a few companies submitting the ballot for the revision. The board was informed again that the revision was to ensure that funds were not expended needlessly in regard to an annual membership meeting, which was mandated in the bylaws, even if no members attend. All members are encouraged to submit the ballot immediately.

The board also discussed the creation of a new membership category for MLM distributors. The committee was instructed to meet to discuss this issue further as well as to brainstorm other membership/revenue-development ideas.

In Conclusion

In all, the board continues to take actions on a variety of topics of importance to the industry and the IASC membership and seemed pleased overall with the continued efforts of staff and counsel. If you have questions about any of the above items, please feel free to contact me!

Devon Powell
Executive Director
FDA’s New and Expanded Powers under the Food Safety Modernization Act of 2010

By Marc Ullman and Linda Dougherty

The Food Safety Modernization Act of 2010 (FSMA), which was signed into law in January 2011, greatly expands the Food and Drug Administration’s (FDA) reach and regulatory powers relating to the production, handling, and importation of food. Secretary Kathleen Sebelius of the Department of Health and Human Services has called the FSMA “the most significant food safety law of the last 100 years.” As a dietary supplement or food manufacturer, importer, or handler, it is imperative that your company become familiar with the new requirements. Discussed below are some of the key regulatory provisions that will significantly affect the U.S. food industry.

Hazard Analysis And Preventive Controls

Section 103 of the FSMA implements expanded regulatory requirements for persons in charge of facilities that manufacture, process, pack, or hold food. This section provides that the owner, operator, or agent in charge of such a facility must evaluate the hazards that could affect food, implement preventative controls to “significantly minimize or prevent” such hazards, provide assurances that the food is not adulterated or misbranded, monitor the performance of the preventative controls used, and maintain records. This provision carves out an exception for dietary supplement facilities, but this exception is almost certainly limited to companies that are required to comply with the dietary supplement good manufacturing practices (GMPs); in other words, the exception does not apply to dietary ingredient facilities.

Mandatory Recall Authority

Previously, all food and dietary supplement recalls in the United States were technically “voluntary”; FDA did not have the authority to order a mandatory recall. Under section 206 of the FSMA, FDA now has authority to order a “responsible party” to conduct a recall of any FDA-regulated food that FDA determines is adulterated or misbranded due to the failure to contain an allergen warning, where FDA has determined that consumption of the food will cause “serious adverse health consequences or death to humans or animals.”

FDA is required to give the responsible party the opportunity to conduct a voluntary recall prior to initiating mandatory recall procedures. If the responsible party declines to “voluntarily” recall the product, FDA may issue an order requiring the responsible party to immediately cease distribution of the food.

FDA must offer the responsible party the opportunity to have an “informal” hearing within 48 hours after the order is issued to determine whether “adequate grounds” exist to continue the order to cease distribution. If, following the opportunity for a hearing, FDA determines that removal of the food from the market is necessary, FDA may order a recall or other appropriate action.

Failure to comply with a recall order is a prohibited act, subject to injunction, imposition of a civil fine ($50,000 for individuals and $250,000 for corporations), and/or criminal prosecution.

Administrative Detention

Previously, FDA could order food to be detained only if it possessed “credible evidence or information” that the food posed a “threat of serious adverse health consequences or death to humans or animals.” Under section 207 of the FSMA, FDA may now order an administrative detention whenever it has “reason to believe” that the food is adulterated or misbranded.

While an Interim Final Rule published on May 24, 2011 (with an effective date 180 days after publication) appears to allow detentions for technical misbranding, FDA has indicated that it intends to use this new authority only in cases where there is a risk to human health. (See related story, page 37.)
Registration

Registration is required under section 102 of the FSMA every two years. If FDA determines that there is a reasonable probability that food from a facility could cause serious adverse health consequences, FDA may suspend the registration of the facility that is responsible for producing the food, or the registration of any facility that packed, received, or held the food and knew of, or had reason to know of, the food’s potential to pose a reasonable probability of adverse health consequences.

FDA is required to provide an opportunity for an informal hearing on the corrective action required for reinstatement of a registration within 48 hours of suspension. If the suspension remains necessary, the registrant must submit a corrective action plan within 14 days.

A facility with a suspended registration may not import or introduce into interstate commerce any food. Failure to comply with this prohibition may lead to an injunction and/or criminal prosecution.

Inspections

Section 306 of the FSMA requires FDA to identify “high risk” facilities. Factors for FDA to consider include the nature of the food handled, prior compliance history, effectiveness of hazard analysis, and preventive control plans. High-risk facilities must be inspected by FDA by January 4, 2016, and every three years thereafter. Other facilities must be inspected by January 4, 2018, and at least once every five years thereafter.

In addition, FDA has been directed to inspect 600 foreign facilities by January 4, 2012, and then double the number of inspections each year for 5 years. Food from any foreign facility that refuses to permit an inspection will be denied entry into the United States.

Import Requirements

Effective January 4, 2013, all importers of food into the United States must verify that the food it imports is produced under a suitable hazard analysis and preventive control program, is not adulterated, and is not misbranded. FDA may require that every article of food offered for import is accompanied by a certification that the food complies with all requirements of U.S. law. In addition, importers are required to identify any other country where the food has been denied entry.

Fees

Under Section 107 of the FSMA, FDA may assess fees to cover the re-inspection costs (including fees to cover the investigator’s time, travel, and costs of lab tests) for any facility that was found to have a violation “materially related to food safety” during the initial inspection. In addition, FDA may assess fees following a refusal to comply with a recall order. Fees range from $240 an hour for FDA action performed in the United States to $340 for FDA action performed outside of the United States. (See related story, page 38.)

Conclusion

The issues noted above constitute some, but not all, of the regulatory changes that will affect the food industry. It is advisable for any manufacturer, importer, or handler of food to review the FSMA and consult with legal counsel regarding any questions as to the new requirements.

Marc Ullman is a partner at the law firm of Ullman, Shapiro & Ullman LLP in New York, whose practice concentrates in legal issues affecting the dietary supplement and natural products industry. Linda Dougherty is an associate at the firm.
IASC Produces Video Demonstrating De-Colorization Process

The IASC announced the release of “Aloe Vera Juice: The Process of De-Colorization,” which shows the typical steps taken to manufacture aloe vera leaf and aloe vera inner leaf juice from the field to the final ingredient form. The video, which has been posted on the IASC homepage, should provide users of aloe vera juice products with a much greater understanding of the manufacturing process, and leave viewers with a profound sense of the magnitude of the time, effort and thoughtfulness that goes into the making of these materials.

The video, shot on location in Mexico, follows the entire process of creating aloe vera leaf and aloe vera inner leaf juice raw material ingredients, beginning with leaf harvesting, cleaning, rind/inner leaf separation or grinding, pulp extraction, pasteurization, and aloin reduction, all the way to the final form of a powder or juice. Of particular interest is the de-colorization step, which, as the video shows, involves the adding of diatomaceous earth and activated charcoal to vastly reduce the aloe latex content. The aloe latex contains the powerful laxative constituent, aloin. The video also shows the subsequent qualitative and quantitative analysis employed to verify compliance with the IASC standard of <10ppm.

“The IASC is proud to have been involved in the creation of this video and to share it with the industry and public”, said Devon Powell, IASC executive director. “It is a fascinating journey that visually depicts the myriad of steps involved in the manufacture of this widely used and loved ingredient in order to offer it for use in finished products for human consumption”.

For more information on the video, please contact Devon Powell.

IASC Adds Green Aloe Kr and Nahrin to “Not Certified” List

In its continuing efforts to protect its certification-seal-program trademark, IASC announced on October 18 that it had added Green Aloe Kr to the list of companies that are improperly using the IASC Certification Seal on its products. On Nov. 7, IASC added Nahrin to the list.

The IASC maintains a 3rd-party certification program that verifies the content and purity of aloe vera in products. This program and the certification seal are recognized globally, and consumers can be assured that the products legally displaying the seal contain the required amount of aloe vera in accordance with the IASC program standards. The IASC maintains lists of currently and no longer certified products, as well as a list of manufacturers who have illegally displayed the seal on products/marketing (the “Not Certified” list).

Upon being notified that the Green Aloe Kr was using the seal on its products, IASC staff and legal counsel began taking actions to have the seal removed from Green Aloe Kr products, including utilizing cease and desist letters and obtaining counsel in Korea. The IASC board, at its most recent meeting on October 14, also passed a motion to have the certification seal trademark registered in South Korea, and this project has been undertaken with the assistance of counsel.

Upon being notified that Nahrin was using the seal on its products by a consumer, IASC staff and counsel began taking actions to have the seal removed from Nahrin’s products. Nahrin has also been added to the IASC “Not Certified” list on the website.

“We will continue to take action to protect the seal as it provides clear value to consumers and manufacturers of aloe vera products,” said Devon Powell, executive director of the IASC. “Companies found using the seal without authorization will be dealt with accordingly”.

For questions about the IASC or the Certification Program please contact Devon Powell.
Shelf Life Dating Document Now Available

Shelf Life Dating of Botanical Supplement Ingredients and Products, a 36-page document authored by the American Herbal Products Association (AHPA) Standards Committee and the AHPA Shelf Life Working Group, with Staci Eisner as managing editor, explains the federal regulations regarding the use of shelf life dates for dietary ingredients and dietary supplements sold in the United States, with a particular emphasis on botanical ingredients and products.

In addition, it presents various strategies for meeting those requirements.

This new guidance document is available for free to IASC members courtesy of AHPA.

Although use of shelf life dates is voluntary for dietary ingredients and dietary supplements sold in the United States, there are a number of important reasons—including liability reduction and a reduction in record-keeping regulations related to cGMP compliance—why a manufacturer would choose to include this information on its product labels.

Topics covered in this comprehensive document:

- U.S. Regulations
- Shelf Life Tests and Examinations
- Factors Affecting Shelf Life
- Sources of Shelf Life Data
- Developing Shelf Life Data
- Handling Shelf Life Issues During an FDA Inspection

The Shelf Life Dating of Botanical Supplement Ingredients and Products is free to IASC members; the price for non-members is $250. Download this new document from the AHPA Bookstore.
Proposition 65 Update: Five Additional Settlements Reached

IASC provides members with a number of resources to understand the issues and reduce possible exposure to legal action

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

Since recently reporting an $80,000 settlement (1) borne by Integrity Marketing in its April 18, 2011, judgment with the Environmental Research Center (ERC), five further settlements have been placed in the California attorney general’s record of notices filed by ERC.

These new settlements occurred from mid-July to mid-September for an additional cost to industry of $317,500, with individual settlements ranging from $50,000 to $77,000 each. This brings the total cost to date to industry from ERC settlements to $397,500 and the average settlement amount to $66,250.

However, additional conditions were included in most of the settlements, including:

- Compulsory Proposition 65 warning statements added to product labeling and/or packaging
- Mandatory lead-testing programs on product lines
- Companies required to provide the results of said tests to ERC for periods of up to two years from the settlement date
- Nondiscretionary, 45-day product holds following any successful reformulation reducing tested lead levels below those requiring a Proposition 65 warning prior to product distribution without said warnings.

These six settlements may just be the tip of the iceberg. Record numbers of California Proposition 65 Notices continue to be issued in 2011, with 93 Proposition 65 60-Day Notices submitted through the first half of 2011 (only 172 were submitted during 2010 (2), more than were submitted for dietary supplement products from 1996 to May 2010 combined). These most recent 93 notices regarded 742 distinct products, which were alleged to be in violation of Proposition 65. As of press time, an additional 30 notices are on record, arriving between July and October 26, 2011.

Of these most recent 123 notices submitted in 2011, all but five were filed by this same plaintiff, ERC, and alleged excessive lead exposure from product use. A large variety of products appeared in these 123 notices, although clear patterns were visible. Protein powders and protein bar products as well as powdered green-food and fiber-supplement drink-mix products continued to frequently appear through the first half of 2011 (2).

Purely herbal products also appeared fairly often, however, and did so in large numbers with between 10 and 30 herbal products cited at once about half the time they appeared. The most extensive such notice named more than 160 distinct herbal dietary supplement products simultaneously as allegedly containing lead levels that might require labeling under Proposition 65.

Proposition 65 Resources

International Aloe Science Council (IASC) members that would like a copy of the ERC settlements to date should contact Merle Zimmermann, AHPA Information Analyst, 301.588.1171 x106.
AHPA has several options to help membership further understand and reduce its exposure to potential California Proposition 65 issues. A general overview of Proposition 65 issues, *Background on California Proposition 65: Issues related to heavy metals and herbal products* is available to all IASC members. It is the result of a joint project between AHAP and its Proposition 65 counsel, Trent Norris of Arnold & Porter. For further information and a more complete review of Proposition 65, the educational symposium *Proposition 65: Preventative Measures & Defending Against a 60-Day Notice* is available through the AHPA Bookstore on the association’s website.

In a related matter, AHPA President Michael McGuffin will again be speaking at the Prop 65 Clearinghouse’s Prop 65 Annual Conference, on November 29, at the City Club of San Francisco. He will be representing the industry on a panel focusing on risk-management issues. The conference will also feature sessions on testing laboratories, negotiating settlements, and an overview of 25 years of Prop 65. Breakout sessions on exposure, opt-in settlements, and “naturally occurring” materials wrap up the all-day event. For further information or to register, visit the Prop 65 Clearinghouse website.

Additionally, AHPA has worked with longtime AHPA member Grifcon Enterprises and ThinkRisk, a managing general underwriting agency based in Kansas City, Mo., to develop a comprehensive Proposition 65 risk-coverage product: the *ThinkRisk Vitamin & Supplement Program*, which aside from covering claims brought under Proposition 65 up to a specific sublimit (typically $100,000), also provides coverage for media and intellectual property claims, first- and third-party costs arising out of breaches to data security, as well as false advertising and other similar claims, including labeling claims (3).

Further information on this program and how the coverage can address your needs is available via contacting Dick Griffin, Grifcon Enterprises, 916.434.8874, or by email or the firm’s website. An additional resource, *Primer on Products Liability Insurance for the Dietary Supplement Industry*, is available from AHPA to provide you with a basic reprinted from McGuffin M. August 2010. 52 New Proposition 65 Complaints Filed Against Supplement Companies; Settlements Now Exceed $4 Million. AHPA Report 25(8):10-11.

**Prop 65: A Quick Summary**

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

Lead is listed under Proposition 65 both as a carcinogen and as a reproductive toxin, with a no significant risk level (NSRL, relevant to carcinogens) of 15 mcg/day and a maximum allowable daily level (MADL, for reproductive toxins) of just 0.5 mcg. Most actions against supplement companies have focused just on the MADL, and products that present more than 0.5 mcg of lead at the highest labeled daily consumption level must provide a “clear and reasonable” warning that it “contains a chemical known to the State of California to cause birth defects.”

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

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

The building of value in a small- or medium-size herbal dietary supplement company has the characteristics of a positive, upward spiral. In the process of building value, management learns how to make the business stronger and consequently, it has additional capital available to fund the business through a combination of internally generated cash flow and access to debt- and/or equity-capital. For stockholders, a “valuable” business can result in a strong annual income flow for many years, a financially successful sale of the company, and/or an advantageous merger or joint venture relationship with another company.

Here, we present several recommendations for building stockholder value in small- and medium-size companies, using the experiences of a handful of successful small- and medium size-dietary supplement entities. Management-led initiatives to greatly enhance the business fundamentals of their companies led to either lucrative exit-transaction opportunities or the creation of profitable joint ventures.

<table>
<thead>
<tr>
<th>Firm</th>
<th>Date of ERC Settlement</th>
<th>Amount of Settlement</th>
<th>Products Affected</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Integrity Marketing</td>
<td>4/18/2011</td>
<td>$80,000</td>
<td>One cleansing product</td>
<td>Warning labels required.</td>
</tr>
<tr>
<td>Jeunique</td>
<td>7/19/2011</td>
<td>$67,500</td>
<td>Four herbal tablet products</td>
<td>Warning labels required. Testing program (with testing results to be sent to ERC). 45-day hold on reformulated products tested to meet lead limits.</td>
</tr>
<tr>
<td>Orange Peel Enterprises</td>
<td>7/19/2011</td>
<td>$77,000</td>
<td>Nine green food products</td>
<td>Warning labels required. Testing program (not required to be sent to ERC).</td>
</tr>
<tr>
<td>Tianshi</td>
<td>8/19/2011</td>
<td>$50,000</td>
<td>Six herbal capsule products</td>
<td>Warning labels required. Yearly testing program (with testing results to be sent to ERC).</td>
</tr>
<tr>
<td>NNC (Naturade)</td>
<td>9/1/2011</td>
<td>$52,500</td>
<td>Two soy protein powder products, two herbal/ fiber dietary supplement products</td>
<td>Noted that Naturade has &lt;10 employees. If Naturade exceeds nine employees, warning labels and yearly testing (with results sent to ERC) will be required.</td>
</tr>
<tr>
<td>VitaTech</td>
<td>9/14/2011</td>
<td>$70,500</td>
<td>Three herbal/vitamin supplement products</td>
<td>Warning labels required. Testing program (with testing results to be sent to ERC for at least 2 years). 45-day hold on reformulated products tested to meet lead limits.</td>
</tr>
</tbody>
</table>

understanding of products liability insurance and the processes involved in purchasing it.

***

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References

of a long-term opportunity to generate large annual cash returns to the owners.

The Market Environment and Valuations

Investors and corporate partners attach premium valuation multiples to markets that are growing rapidly. Given the moderate growth prospects for the broad herbal dietary supplement market and the slow growth prospects for the overall economy, however, no rising tide exists to raise the value of all of the boats.

The herbal dietary supplement market has grown at a compound annual growth rate of only 3.3 percent from about $4.3 billion in 2004 to $5.2 billion in 2010. This compares to the go-go days of the 1990s, when the herbal dietary supplement market was growing at double-digit rates for most of the decade.

Given the medium-term annual growth forecast for the nutrition market of 4 - 5 percent (NBJ Summit 2011), the overall herbal market will not be returning to the heady times of the 1990s. The one exception pertains to the Internet retail channel that has grown at double-digit rates over the past five years. This channel has proven lucrative for those companies that have invested wisely in developing channel expertise and a track record of success. Many other companies have not done well in this channel because they refused to make the necessary investment to achieve success.

A note about valuations: Back in the 1990s, acquirers were occasionally paying premium prices for small- and medium-size herbal dietary supplement companies—in some instances more than 2.0 times sales. But that is not the case based on recent examples. The Carlyle Group, for example, acquired NBTY, the largest player in the domestic dietary supplement market, in late 2010, for $3.8 billion. The acquirer valued NBTY’s long-term compound annual growth rate of 11.7 percent at 8.6 times EBITDA (earnings before interest, taxes, depreciation, and amortization) or about 1.4 times revenue—far below the benchmark 2.0 times revenue.

Additionally, acquirers/investors generally value small companies at a discount to large companies due to the view that: a.) smaller companies are riskier investments than larger companies; and b.) small companies have
a hard time maintaining healthy profit margins in the long run since they are not likely to achieve the economies of scale available to larger companies.

That discount can range between 25 - 33 percent for smaller companies that have similar performance measures compared to larger companies. We define a small herbal dietary supplement company as having revenues under $10 million and a medium-size company as having revenues of $10 - $30 million. The decrease in valuations as a result of these discounts has two implications: a.) small companies have a steeply higher cost of capital than larger companies as well as less access to capital; and b.) owners of small companies need to realize that the value of their companies may be significantly lower than what they have calculated, based on either public-company valuation data or market scuttlebutt about the value of recent private transactions involving small and medium and large companies.

Examples of Positive Actions

The following four dietary supplement companies (three of which are not named here) are successful small- and medium-size companies that took strong actions to further enhance their value once they determined that significant changes were necessary. “Change” meant that the founders decided that their companies could be at risk in terms of loss of competitive advantage, stagnating growth, and falling profits. They wanted to deepen their companies’ ability to manage rapid growth, develop customer relationships with Fortune 500 companies, transition their companies from a product-centric view to a market-centric orientation, and/or prepare for an exit transaction. For these entrepreneurs, bringing in outsiders meant letting go of the tight control that they typically had exercised in their respective companies. On the other hand, some of these founders enjoyed relinquishing responsibility for activities that they did not enjoy.

These case studies should be instructive to companies in the herbal products niche since the managements of these companies focused to one degree or another on the following keys to success: a.) establishing high brand recognition in a market niche or sub-niche; b.) devotion to product quality and consistency; c.) exploiting proprietary science; and, d.) ensuring access to growth capital.

An Ingredient Manufacturer. This company was a rapidly growing and profitable manufacturer of ingredients for branded nutrition-product companies where the owner-managers saw huge future opportunities. They decided to bring in an angel investor who had substantial business experience in the conventional health care world. They needed his experience and reputation as much as his capital. In less than three years, company revenue doubled and the value of the company more than tripled when another company acquired it for more than $20 million.

An Internet Brand. The owners of this company were pioneers in selling their branded product line via the Internet. Several years of high growth in sales and profits were followed by a flat period due to intensifying competition. The owners then hired a senior executive who had successful experience in both ecommerce and building her own company. Over a two-year period, the executive re-established the strong growth curve by hiring experienced ecommerce professionals. When the owners began to explore an exit transaction, they received a bona-fide offer that was more than twice as high as the valuation that an outside valuation firm had computed two years previously. The valuation was 1.5 times revenues and 6.0 times EBITDA as a result of the company’s growth in sales and profitability vs. multiples under 1.0 times sales and 4.0 - 4.5 times EBITDA that a company with stagnant growth could expect to receive.

An Ingredient Manufacturer/Brand Marketer. This medium-size company with multiple lines of business had experienced rapid growth on the basis of differentiated products only to experience flat sales during the recent downturn in the economy. Believing that their company’s future opportunity was significant, the entrepreneurial owners hired several managers who revamped the company’s operating systems and implemented a consistent marketing/sales strategy. While these management moves were expensive, this investment has resulted in the restoration of rapid growth that has been managed profitably. Currently, no need for an exit transaction or merger exists on the basis of business fundamentals or access to growth capital.

Sirtris. We disclose this company’s name since the information below comes from publicly available sources. This company performed groundbreaking
research on resveratrol that it turned into valuable intellectual property. The founders funded their substantial research and development expenses with outside capital. On the basis of such promising science, Glaxo Smith Kline paid $720 million to acquire the company. Valuation multiples were irrelevant in this case since Sirtris was essentially a drug-development company with no significant revenue and large operating losses. This situation is an anomaly, although it does demonstrate the extraordinary value of owning strong intellectual property with huge market potential.

**Negative Outcomes**

Bad things actually do happen to brilliant innovators! We all know of entrepreneurs who have developed companies that were initially successful on the basis of a highly efficacious product, effective branding, and/or proprietary formulas and processes. Unfortunately, they can often find themselves not able to materially capitalize on these advantages. While some of these companies may continue to grow handsomely in the medium term because they occupy a protected niche within a niche, other companies can provide formidable competition in a dynamic environment.

Unlike the four companies described above, these otherwise innovative entrepreneurs have not come to grips with the tough business choices facing them: either invest heavily to establish a sustainable position in a market niche or sell/merge with another company. The alternative to taking action now is the risk of a sharp decrease in the value of a business over time as a result of taking insufficient or ineffective action.

**Recommendations**

The herbal dietary supplements market will continue to grow, although its moderate growth prospects will not automatically lift the value of all companies. Increasingly, they will be subject to intense competition, a challenging regulatory environment, pressure from large retailers and consumers to moderate price increases, and other obstacles along the path to growth—and potentially, a successful exit. Even branded-products companies in the high-growth Internet distribution channel will not prosper in the long run unless they invest in the appropriate people and systems.
Based on these circumstances, we make the following recommendations for maintaining or building stockholder value in your business:

- Assess your company’s business fundamentals and prospects with an eye toward determining where value-enhancing improvements need to be made.
- Determine how you will implement these changes and what human and financial resources you need in order to be successful.
- Prepare a roadmap in the form of a business plan or overview that includes detailed financial forecasts that will be necessary to monitor progress in the business and/or to raise capital.
- Decide if you want to be the executive responsible for implementation of these initiatives.
- Either forcefully take the steps needed to properly position the company for a sustainable business future or seek to sell/merge the company.

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Recommended Botanical Reading List

Compiled by Michael McGuffin, AHPA President

The following list can serve as a good “starter” botanical reference library as it includes texts that are both contemporary and historical. IASC members are encouraged to recommend additional entries for the list, which will be posted on the AHPA website. Email Michael McGuffin with your suggestions.

For herbs generally:
- The American Herbal Pharmacopeia monographs

For Western herbs:
- WHO; WHO monographs on selected medicinal plants (4 volumes)
- Health Canada NHPD; Single Ingredient Monographs
- EMEA; Community herbal monographs
- ESCOP; ESCOP Monographs (2nd ed, 2003; plus 2nd edition supplement, 2009)
- Wichtl; Herbal Drugs and Phytopharmaceuticals, 3rd edition
- Blumenthal; Herbal Medicine: Expanded Complete Commission E Monographs
- Various authors; The Dispensatory of the United States, any edition (the 15th edition is here)

For Chinese herbs:
- Bensky; Materia Medica 3rd edition
- Chen & Chen; Chinese Medical Herbology & Pharmacology

For Ayurvedic/Indian herbs:
- India Dept. of Ayush; The Ayurvedic Pharmacopoeia of India; volumes available online: 1, 2, 3, 4 and 5.
- Dymock; Pharmacographia Indica [This is a multi-volume text at least one of which is available on Google Books. See also the “Related Books” on that page – the Nadkarni text is also useful.]

For African herbs:
- Brendler; African Herbal Pharmacopoeia
- Ayensu; Medicinal Plants of West Africa
- Boulos; Medicinal Plants of North Africa

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Aloe Vera Juice Not Likely to Significantly Affect Drug Metabolism


This study evaluated the ability of two aloe vera juice products to inhibit the two major drug-metabolizing enzymes and concluded that the inhibitory values were too low to cause any major interference in drug metabolism. Grapefruit juice is known to be a significant inhibitor of these enzymes and can lead to elevated levels of drugs in the body that would have been otherwise metabolized. The researchers suggested the possibility of a clinically significant effect from aloe vera juice because of their finding of more than one mechanism of drug-enzyme inhibition. However, human trials would be needed to determine if such an effect exists and to what extent.

Attitudes by Pharmacists on Reporting Adverse Event Reactions


This study presents the results of 12 individual interviews with Canadian pharmacists about their attitudes and comfort with Natural Health Products (which are regulated as a class of drugs in Canada) and their responsibility regarding reporting of serious adverse events to Health Canada. Pharmacists that saw their role solely as supporting medical doctors were less inclined to report adverse events than those who assumed responsibility for their patients and the need to contribute to the general store of information on medicines.

Nanoparticle Toxicity in Plants: What Do We Know?


This review covers what little is known about the uptake, movement, and storage of engineered nanomaterials in edible plants. While most studies have revealed positive or no effects of nanoparticles on plants, this is not always the case. It is clear that the study of the toxicity of engineered nanomaterials in plants is just beginning as the new field of nanoeotoxicology emerges.

A New Role for Ethnopharmacology: A Sustainable Future


Based on a keynote lecture given at the 11th Congress of the International Society of Ethnopharmacology last year, this review points out the convergence of interest between the fields of agricultural biodiversity and biodiversity conservation and the importance of crop biodiversity and use of wild species. Taken together, the suggestion is made that the study of indigenous use of medicinal plants can be expanded into a wider role that includes the study of local communities in managing agricultural biodiversity.

A New Protocol for Biodiversity Benefit Sharing


This lecture discusses the progress that has been made in the sharing of benefits gained from research through the Convention on Biological Diversity (CBD). It presents
the significant innovations to the CBD from the Nagoya Protocol that was adopted in November of last year.

This review is from a lecture given at the 58th International Congress and Annual Meeting of the Society for Medicinal Plant and Natural Product Research (GA) last year. All of the talks from that meeting presented in the July issue of *Planta Medica* are available here for free download.

**Natural Product Antimicrobial Synergism**


This review examines the therapeutic value of herbal synergism in light of recent studies on the topic and focuses on antimicrobial synergy. The available literature is discussed and experimental approaches presented. Such research may be important next steps in our understanding of the mechanisms of action of complex herbal preparations.

This review is from a lecture given at the 58th International Congress and Annual Meeting of the Society for Medicinal Plant and Natural Product Research (GA) last year. All of the talks from that meeting presented in the July issue of *Planta Medica* are available here for free download.

**More Than Two-Thirds of Jamaicans Self-Medicate with Herbs**


This study surveyed more than 350 Jamaicans regarding their medicinal herb use, including use with other medications, and reported that about three in four self-medicated with herbs in the previous year. The most common uses were for treating respiratory system and gastro-intestinal tract illnesses as well as using tonics for the maintenance of general health. About one in four herb users also took prescription drugs with such use highest among those 65 and older. Only about one in five physicians were aware of this practice.

**Beyond ORAC, TEAC, TRAP, Etc.**


The use of reliable, cell-based bioassays may both offer an alternative to animal testing and provide more relevant health information than can be obtained from chemical-based assays. Antioxidant chemical-based assays can show how molecules may be protected from oxidation, but are not a good measure for what happens in biological systems. This article reviews the adequacy of cell-based, antioxidant bioassays for determining antioxidant activity, which should be more relevant to the human condition than ORAC or other chemical-based assays. However, the transition from using research-quality, cell-based bioassay models to being able to employ them as routine test models still requires analytical protocols to be optimized, standardized, and validated.

**Look Beyond Flavonoids**


This short commentary evaluated literature reports of anti-inflammatory activity from crude plant extracts based on the results of cell-based assays. The authors noted that ubiquitous flavonoids are often found to be bioactive in these assays and questioned the meaning of an assignment of unique anti-inflammatory activity to a plant due to the presence of common flavonoids. They concluded by encouraging researchers to include some fractionation of plant extracts when studying them in these models.

**Researchers Identify Common Contaminants of Plant Extracts and Essential Oils**

♦ Radulović NS, Blagojević PD. The most frequently encountered volatile contaminants

Researchers occasionally report the presence of artificial, synthetic plasticizers as naturally occurring compounds in plant extracts or essential oils without realizing that they are contaminants from solvent impurities or from contact with plastics. In response, a database of frequently encountered contaminants was created from analyzing the residues of a commercial solvent (ether) used for extraction and a distillate from plastic bags. Attention to this information will help researchers avoid the identification of industrial synthesized compounds, such as phthalates and BHT, as native plant constituents.

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introduced The Dietary Supplement Labeling Act (S. 1310). S. 1310 would place costly and unnecessary regulatory burdens on supplement companies through a complex product registration and warning-labeling scheme. Other key provisions of the Durbin bill seek outcomes that can be achieved through enforcement of existing federal authorities, laws, and regulations by the Food and Drug Administration (FDA). For further details on the provisions of this legislation, I refer you to AHPA's July 2011 AHPA Report, which provides a complete summary of S. 1310. The AHPA Report is available to all IASC members courtesy of AHPA. Contact Devon Powell for more information.

How concerned should AHPA members be about the future prospects of this anti-supplement measure? When the Senate majority whip (Durbin) introduces legislation, it certainly should not be taken lightly. And we know that Durbin was particularly dogged on previous congressional efforts related to imposing greater regulatory burdens on the industry. However, enacting S. 1310 in the 112th Congress would be an uphill sled for Durbin.

Here's why: It is no secret that FDA’s resources are already extremely stretched and as a result, the agency is not able to adequately implement its public health and safety mission or provide the regulatory oversight, which falls within its jurisdiction. Given this reality, adding more regulatory authorities to FDA would be counterproductive. For instance, FDA does not have the necessary funding to implement the provisions of the landmark Food Safety Modernization Act, which Congress passed last year. And with the federal government ready to go on a major diet for the foreseeable future, any effort to provide FDA additional resources will not succeed in this Congress.

And when you add to the equation the anti-regulatory bent of the House of Representatives and the strength of our Senate champions—Sens. Orrin Hatch, R-Utah, and Tom Harkin, D-Iowa—you can start to see the high hurdles that lie in the way of legislative progress for the Durbin bill.

Let us, of course, not forget the most powerful weapon in beating this measure back: the merits behind opposing it! Plain and simple, the provisions of the
bill are flat-out unnecessary. One of the primary drivers behind Durbin’s impetus to introduce S. 1310 was the issue surrounding Lazy Cakes. Lazy Cakes, which the company that makes them now calls Lazy Larry, is a conventional food that is mislabeled as a dietary supplement. Since melatonin—the “active” ingredient in Lazy Cakes—is unlawful for use in food, the company sought to get around this problem by labeling the product a dietary supplement. Such blatant mislabeling is a violation of federal law, and therefore, FDA has the authority to use its enforcement discretion take Lazy Cakes off the shelves.

While it took FDA about two months longer to act than it should have, on July 28—a month after the Durbin bill was introduced—the agency sent a warning letter to the manufacturer of Lazy Cakes informing the company that it was peddling an adulterated product and needed to take corrective actions to comply with federal law or face the consequences. The company took notice and almost immediately, the case was closed on the Lazy Cakes matter.

FDA’s decision to take rightful action against Lazy Cakes not only vindicates the voices advocating on behalf of this industry, including AHPA and the other supplement associations that have stated that the authority already exists within the regulatory framework to rectify this matter and there is no need for another law or layer of regulation, but it also—perhaps more importantly—severely undermines the need for key provisions of the Durbin bill.

Having made the case that the prospect of the Durbin bill passing in this Congress is exceedingly slim, we should not underestimate a seasoned and powerful legislator, like Durbin, who is known to be persistent on issues that drive him. He also has a track record of being creative and knows how to readily identify and take advantage of opportunities that work outside of the regular legislative order (e.g. appropriations bills and other must-pass measures).

Therefore, putting our guard down is never an option.

While FDA’s draft new dietary ingredients guidance (see articles, pgs. 15 and 17) rightfully deserve the preponderance of our attention at this time, we cannot overlook the Durbin bill and the need to effectively advocate against it. Toward this end, AHPA will be soon providing you a draft letter to send to your senators in opposition to the Durbin bill. You will need to tailor the letter to incorporate your company profile, but we intend to make the process easy for you.

S. 1310 opens up an excellent opportunity to engage your senators and convey to them the truth about how dietary supplements are regulated (highly!) and that the overwhelming majority of those who make up of this industry are committed and responsible individuals who are creating jobs and employing workers in their state.

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**THE SCIENCE OF ALOE**

**Recently Published Studies**

**Immunomodulatory effects of Aloe vera and its fractions on response of macrophages against Candida albicans.**

**Abstract**

Natural products are important resources in traditional medicine and have been long used for prevention and treatment of many diseases. Medicinal plants have immunomodulatory properties. Aloe is one of the herbal medicines widely used in natural treatment and alternative therapy for various types of diseases. *Aloe vera* has been shown to modulate the immune response. Macrophages have been shown to play an essential role as the first line of defense against invading pathogen. *Candida albicans* is a communal and opportunistic pathogen in humans. In this study, we investigated the effect of *A. vera* extract and its fractions on infected macrophages with *C. albicans*. Viability of intraperitoneal macrophages was evaluated by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT) test. Cell viability of infected macrophages was increased by the extract and dose of some isolated fractions dependently. The extract as well as R100, R50, R30, and R10 fractions of *A. vera* significantly increased cell viability of macrophages in most doses. R5 and F5 fractions showed no significant...
difference in comparison with control group. Further studies in animal models and human are necessary to clarify the modulatory effects of A. vera on macrophage function. Isolation and purification of A. vera components are also needed to find out the effective molecules.

**Reduction of nectarine decay caused by Rhizopus stolonifer, Botrytis cinerea and Penicillium digitatum with Aloe vera gel alone or with the addition of thymol.**

**Abstract**

Two nectarine cultivars (‘Flavela’ and ‘Flanoba’) were treated with Aloe vera gel alone, or with the addition of thymol, and then inoculated with Rhizopus stolonifer, Botrytis cinerea and Penicillium digitatum. Both treatments were effective in reducing the decay incidence caused by the 3 fungi species, although the addition of thymol did not generally improve the efficacy of Aloe vera gel on reducing the infection damage. The coatings were clearly effective in reducing the postharvest ripening process of both nectarine cultivars manifested by a delay in ethylene production and respiration rate, weight loss and softening. Interestingly, these coatings showed effectiveness on reducing decay development in inoculated fruits and thus Aloe vera could be considered as natural antifungal compound and might serve as alternative of synthetic fungicides.

**Aloe vera or resveratrol supplementation in larval diet delays adult aging in the fruit fly, Drosophila melanogaster.**

**Abstract**

Longevity extension in Drosophila melanogaster by feeding diet supplemented with chemicals throughout adulthood can cause harmful side effects. We tested the effect of larval diet supplementation with five different concentrations of resveratrol and one concentration of Aloe vera extract on the adult longevity of short-lived D melanogaster populations. Resveratrol and A. vera extract supplementation of larval diet extended adult longevity in both the male and female flies without reducing fecundity but by efficient reactive oxygen species scavenging through increased antioxidant enzymes activity and better neuroprotection as indicated by increased locomotor activity in adult males.

**Proangiogenic activity of plant extracts in accelerating wound healing - a new face of old phytomedicines.**

**Abstract**

Angiogenesis, the formation of new capillaries from pre-existing vascular network, plays an important role in physiological and pathological processes such as embryonic development, wound healing, and development of atherosclerosis. Extension of the circulatory network is also considered to be one the most important factors during cancerogenesis. Inhibition of angiogenesis may lead to inhibition of tumor growth whereas stimulation may improve wound healing. Research achievements suggest the use of plants and their extracts as potential therapeutic agents with pro- or antiangiogenic activity. Since the anticancer and antiangiogenic properties of many phytomedicines have been amply reviewed elsewhere this paper will focus on the treatment of vascular insufficiency in wound healing. Globally accepted herbal drugs are thought to be safe and effective, however, there is a need for more evidence-based confirmation in controlled and validated trials. Among the most frequently studied proangiogenic phytochemicals are ginsenosides from Panax ginseng, beta-sitosterol from Aloe vera, calycosin from Radix Astragali, and extracts from Hippophae rhamnoides L. and Angelica sinensis.

**Cloud point extraction of aloe anthraquinones based on non-ionic surfactant aqueous two-phase system.**

**Abstract**

Non-ionic surfactant-based aqueous two-phase system had been investigated to extract aloe anthraquinones. It had the advantage of using a single auxiliary chemical to induce phase separation above cloud point at a low concentration. Non-ionic surfactant Triton X-114 was chosen for its excellent phase-separating ability and low cloud point. The main factors affecting the cloud point extraction were discussed such as equilibrium temperature and time, concentrations of surfactant and inorganic electrolytes, pH, etc. Under the optimised conditions, the highest extraction yield 96.93% was obtained. The reverse extraction of anthraquinones from
injured veterans were randomized to apply *A. vera* olive oil (*n* = 34, completers = 31) or betamethasone 0.1% (*n* = 33, completers = 32) cream twice daily for 6 weeks. Evaluation of pruritus severity was performed using a pruritic score questionnaire and visual analogue scale (VAS).

**RESULTS:** Both treatments were associated with significant reductions in the frequency of pruritus (*p < 0.05*), burning sensation (*p < 0.01* and *p < 0.001* in *A. vera* olive oil and betamethasone group, respectively), scaling (*p < 0.01* and *p < 0.05*) and dry skin (*p < 0.001*) at the end of trial. Fissure and excoriation were only reduced in the *A. vera* group (*p < 0.05*). The change in the frequency of hyper- and hypopigmentation lesions, blisters, erythema and lichenification did not reach statistical significance in any of the groups (*p > 0.05*). Mean pruritus (*p < 0.05*) and VAS scores (*p < 0.01* and *p < 0.05*) were significantly decreased by the end of trial in both groups. The rate of improvement in the pruritus severity [defined as being classified in a less severe...
Abstract
We assess the evidence for health benefits of three commonly consumed plant food supplements (PFS), green tea, isoflavone and aloe vera, based on published systematic reviews of randomised controlled trials (RCTs). Whilst the potential benefits of green tea have been reported in a wide range of health areas, it is only in the area of the metabolic syndrome that the number of RCTs is approaching sufficient to judge such efficacy. Isoflavone supplements are widely used, and RCTs indicate that they affect bone resorption at lower doses in postmenopausal women undergoing estrogen-related bone loss, but this is only translated to attenuation of bone loss at higher doses of isoflavones. A systematic review on RCTs concluded that the effects of isoflavones on hot flashes in postmenopausal women were highly variable and no conclusions could be drawn. Despite the popularity of aloe vera as a PFS, the evaluation of its efficacy as a coadjuvant therapy for certain metabolic or digestive pathologies remains scarce; it constitutes a typical example of a naturally occurring ingredient whose efficacy in topical applications presupposes its efficacy in systemic applications. Nevertheless, its possible toxic effects on oral consumption call for caution in its utility as a PFS. Since 2007, efficacy evaluation of PFS in Europe has been covered by European Union Nutrition and Health Claims legislation. The European Food Safety Authority has adopted an approach relying on RCTs, while medicinal effects are accepted based on traditional use. In general, there are insufficient RCTs for claims to be made, and conclusive results on PFS should be obtained in the future by conducting studies with more homogeneous populations, by using supplements with optimised and measured bioavailability, and by conducting larger RCTs.

Review of the efficacy of green tea, isoflavones and aloe vera supplements based on randomised controlled trials.

Abstract
Aloe vera is one of the most commonly used botanicals for various prophylactic and therapeutic purposes. Recently, NTP/NCTR has demonstrated a dose-dependent increase in large intestinal tumors in F344 rats chronically exposed to Aloe barbadensis Miller (Aloe vera) non-decolorized whole leaf extract (AVNWLE) in drinking water. The morphological and molecular pathways of AVNWLE-induced large intestinal tumors in the F344 rats were compared to human colorectal cancer (hCRC) literature. Defined histological criteria were used to compare AVNWLE-induced large intestinal tumors with hCRC. The commonly mutated genes (Kras, Ctnnb1, and Tp53) and altered signaling pathways (MAPK, WNT, and TGF-β) important in hCRC were evaluated within AVNWLE-induced large intestinal tumors. Histological evaluation of the large intestinal tumors indicated eight of twelve adenomas (Ads) and four of twelve carcinomas (Cas). Mutation analysis of eight Ads and four Cas identified point mutations in exons 1 and 2 of the Kras gene (two of eight Ads, two of four Cas), and in exon 2 of the Ctnnb1 gene (three of eight Ads, one of four Cas). No Tp53 (exons 5-8) mutations were found in Ads or Cas. Molecular pathways important in hCRC such as MAPK, WNT, and TGF-β signaling were also altered in AVNWLE-induced Ads and Cas. In conclusion, the AVNWLE-induced large intestinal tumors in F344 rats share several similarities with hCRC at the morphological and molecular levels.

Evaluation of the Antipsoriatic Activity of Aloe Vera Leaf Extract Using a Mouse Tail Model of Psoriasis.

Abstract
Aloe vera gel is used traditionally for the treatment of skin diseases, including psoriasis. An ethanolic extract of the gel was assessed for antipsoriatic activity using a mouse tail model of psoriasis. The extract produced a significant differentiation in the epidermis, as seen
Assessment of Genetic Stability and Instability of Tissue Culture-Propagated Plantlets of Aloe vera L. by RAPD and ISSR Markers.

Abstract
Efficient plantlet regeneration with and without intermediate callus phase was achieved for a selected genotype of Aloe vera L. which is sweet in test and used as a vegetable and source of food. Random amplified polymorphic DNA (RAPD) and inter simple sequence repeats (ISSR) marker assays were employed to evaluate genetic stability of plantlets and validate the most reliable method for true-to-type propagation of sweet aloe, among two regeneration systems developed so far. Despite phenotypic similarities in plantlets produced through both regeneration systems, the differences in genomic constituents of plantlets produced through intermediate callus phase using soft base of inflorescence have been effectively distinguished by RAPD and ISSR markers. No polymorphism was observed in regenerants produced following direct regeneration of axillary buds, whereas 80% and 73.3% of polymorphism were observed in RAPD and ISSR, respectively, in the regenerants produced indirectly from base of the inflorescence axis via an intermediate callus phase. Overall, 86.6% of variations were observed in the plantlets produced via an intermediate callus phase. The occurrence of genetic polymorphism is associated with choice of explants and method used for plantlet regeneration. This confirms that clonal propagation of sweet aloe using axillary shoot buds can be used for commercial exploitation of the selected genotype where a high degree of fidelity is an essential prerequisite. On the other hand, a high degree of variations were observed in plantlets obtained through indirect regeneration and thus cannot be used for the mass multiplication of the genotype; however, it can be used for crop improvement through induction of somaclonal variations and genetic manipulations.

Common complementary and alternative therapies with potential use in dermatologic surgery: Risks and benefits.

Abstract
BACKGROUND: Ambulatory surgery patients often use complementary and alternative medicine (CAM) therapies. CAM therapies may create beneficial and detrimental perioperative conditions.

OBJECTIVE: We sought to improve knowledge of CAM effects in dermatologic surgery, allowing dermatologists to potentially capitalize on therapeutic actions and to mitigate complications.

METHODS: PubMed literature search of CAM therapies in dermatologic and surgical settings was conducted.
performed. Common CAM therapies with possible effects on dermatologic surgery were selected. Beneficial and detrimental effects were reviewed.

RESULTS: A myriad of products may be used perioperatively by the patient. Therapies appearing to have some evidence for potential benefit include bromelain, honey, propolis, arnica, vitamin C and bioflavonoids, chamomile, aloe vera gel, grape seed extract, zinc, turmeric, calendula, chlorella, lavender oil, and gotu kola. Potential complications vary according to product and include platelet inhibition, contact dermatitis and, in rare cases, systemic toxicity.

LIMITATIONS: This review focuses on CAM having significant published studies evaluating efficacy for wound healing, anti-inflammatory, antipurpuric, or perioperative-related use. Most published studies have been small and often have design flaws. The scope of CAM is large and not all therapies are discussed.

CONCLUSION: Selected CAM therapies have been reported to promote wound healing, reduce edema or purpura, and provide anti-inflammatory effects. Because of high rates of CAM use, surgeons should familiarize themselves with common uses, potential benefits, and complications. Further study of effects in the dermatologic surgery setting may improve the patient-doctor relationship and enhance outcomes.

In this case, the law is a notification provision. Where an NDI notification is required, it must be made 75 days in advance of the marketing of the ingredient. In contrast, notifications of structure/function claims are made within 30 days of the first marketing of a dietary supplement. In enacting DSHEA, Congress took care to assure that both of these provisions are notification provisions—in contrast to the provisions for drugs and devices, which are approval and clearance provisions.

In September 1996, FDA proposed, and in September 1997, FDA made final, the regulations implementing the NDI law. That proposal and final regulation represents FDA’s relatively contemporaneous understanding of the NDI law. In publishing this final regulation, FDA noted that there had been no comments on FDA’s estimated cost per notification of $410 or estimate of zero to 12 notifications per year. FDA then determined that the regulation was neither “significant” as defined by executive order nor a “major rule” for purposes of congressional review. In addition, FDA concluded that the regulation would not have a significant impact on a substantial number of small business entities.

What do the law and the regulation require? FDA stated this succinctly in the description of the paperwork requirements of the regulation:

“FDA is requiring, by regulation, the submission to the agency of information that is the basis on which a manufacturer or distributor of a new dietary ingredient or a dietary supplement containing a new dietary ingredient has concluded that the dietary supplement containing such dietary ingredient will reasonably be expected to be safe. This information must be submitted to the agency at least 75 days prior to the first commercial distribution of a dietary supplement containing a new dietary ingredient. FDA will review the submitted information to determine whether the submission meets the requirements of section 413 of the act. The agency is establishing § 190.6 as the procedural regulation for this program. This regulation provides details of the administrative procedures associated with the submission and identifies the information that must be included in the submission in order to meet the requirements of section 413 of the act and to show the basis on which a manufacturer or distributor of
a new dietary ingredient or a dietary supplement containing a new dietary ingredient has concluded that the dietary supplement containing such dietary ingredient will reasonably be expected to be safe.”

The regulation states succinctly the requirement regarding information supporting the submitter’s conclusion regarding safety. It is to include:

21 CFR 190.6(b)(4). The history of use or other evidence of safety establishing that the dietary ingredient, when used under the conditions recommended or suggested in the labeling of the dietary supplement, will reasonably be expected to be safe, including any citation to published articles or other evidence that is the basis on which the distributor or manufacturer of the dietary supplement that contains the new dietary ingredient has concluded that the new dietary supplement will reasonably be expected to be safe. Any reference to published information offered in support of the notification shall be accompanied by reprints or photostatic copies of such references. If any part of the material submitted is in a foreign language, it shall be accompanied by an accurate and complete English translation.

Once a notification is made, the company making the notification may go to market after the 75th day has past. FDA’s responses to NDI notifications have evolved over the years, and response letters increasingly indicated FDA’s view that on the basis of the information submitted, a dietary supplement containing the NDI “may be adulterated” when used under the conditions of use recommended or suggested in the labeling. The percentage of letters so indicating has stayed at roughly 75 - 80 percent for a number of years now.

It is noteworthy that neither the statute nor the regulation provides for these forms of NDI notification responses from FDA.

In November 2004, FDA held a public meeting on NDI notifications. The American Herbal Products Association presented testimony at that meeting and filed comments. Almost annually thereafter, FDA stated that publishing a draft NDI guidance document was an agency priority. Fast forward to the FDA Food Safety Modernization Act, enacted in January of 2011, in which FDA was directed to publish an NDI guidance within 180 days, which FDA did. Interestingly, the FDA publication citing this does not mention FDA’s November 2004 NDI public meeting, its request for comments, or the comments received.

Yet the 86-page draft NDI guidance for industry, published by FDA on July 5 bears little resemblance to the previously published NDI law or the NDI regulation.

If your business is the dietary supplement business, then you must read the draft guidance. And if you read it, you need to then go back to the NDI law and FDA’s regulations implementing the law.

The NDI law was made a part of DSHEA because Congress determined to declare pre-DSHEA dietary ingredients to be not adulterated until proven otherwise. New dietary ingredients that are not food in a form that have not been chemically altered were designated to require premarket notification. Congress determined this would be a simple process, requiring that the company making the notification share with FDA the basis upon which it has concluded that the dietary supplement containing such dietary ingredient will reasonably be expected to be safe.

Nothing more.

Congress did not mandate animal or human studies or in vitro studies. Congress did not mandate “general recognition of safety” or any manor of expert reviews. All Congress mandated was that companies share with FDA the basis upon which it has concluded that the dietary supplement containing a particular new dietary ingredient will reasonably be expected to be safe.

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The FDA NDI Guidance: Key Issues for Industry
by Michael McGuffin, AHPA President

In a Federal Register notice dated July 5, 2011, the Food and Drug Administration (FDA) announced the availability of a draft Guidance for Industry: New Dietary Ingredient Notifications and Related Issues. There are numerous details in the draft guidance that would create significant new burdens for the dietary supplement industry if the draft becomes a final guidance and if FDA’s enforcement closely adheres to these details.

Of primary concern are the following two points, as these appear to be positions that are contrary to the law (see related story, this page):

- **Notification for all dietary supplements containing an NDI (Questions IV.C.1 and IV.C.2).** The draft guidance purports to require submission of a notification for every dietary supplement that contains a new dietary ingredient (NDI).
- **Old dietary ingredient (ODI) documentation implication (Question IV.A.8).** The draft does not directly state but implies that each individual supplement company has an affirmative obligation to document, with a pre-Dietary Supplement Health and Education Act (DSHEA)-dated record, that each ingredient used in its products is an ODI.

Additional significant concerns with the draft guidance include the following, listed in the same order as found in the guidance:

- **NDI status of pre-DSHEA food ingredients (Question IV.A.3).** The draft guidance identifies ingredients that were marketed in the United States prior to the passage of DSHEA only in foods, but not “in or as a dietary supplement, or for use in dietary supplements” as NDIs.
- **Absence of authoritative ODI records (Question IV.A.10).** The draft takes the position that there are no authoritative lists of “grandfathered” ODIs at the same time that it acknowledges that trade associations submitted lists of ingredients believed to be marketed in the United State pre-DSHEA (the Natural Products Association [as the National Nutritional Foods Association] in 1996; the American Herbal Products Association in 1997; and the Council for Responsible Nutrition in 1998). (See related story, pg. 17)
- **Synthetic botanical constituents (Question IV.D.2).** The draft guidance states that synthetic constituents and extracts of botanicals do not qualify as dietary ingredients under 21 U.S.C. 321 (ff)(1)(F) because these were “never part of the botanical” and were “not actually extracted from the botanical,” respectively.
- **Costs implied (Questions V.B.15-20).** In describing the types of data that an NDI notification might include if the submitting manufacturer or distributor is not relying entirely on history-of-use data, the draft guidance identifies tests that would be prohibitively costly and would be three to four orders of magnitude greater than FDA’s prior estimates of the cost of submitting an NDI notification.
of recognizing the associations’ efforts to be complete. And one association’s admission that there are no “complete” lists was turned against the ODI lists, as well. This response by FDA to the ODI lists represents a return to the old-style, attack-dog FDA the industry knew pre-DSHEA.

Instead of responding to these lists when they were submitted, FDA laid in wait to jump on the lists and to state its view that even “affidavits attesting to recollection of historical events which are unsupported by contemporaneously created written records are not adequate to show that an ingredient was marketed prior to October 15, 1994.”

Why did FDA not voice these issues when the lists were submitted? Why didn’t FDA encourage the industry to substantiate these lists shortly after they were submitted? The answer: to do so would have required that FDA behave transparently, something FDA only now, in 2011, purports to do.

It took the pharmaceutical industry and the food-ingredients industry decades to move FDA from its “Gotcha!” stance as a way of doing business. To move FDA from smug-faced silence, from a “we are not here to help you” stance, from a “spend your research millions, and then we will tell you what we are thinking (and by the way, how many fingers do we have open behind our back?)” approach, took a sea change in attitude—an understanding that when industry and government agencies work together in the public interest, the public benefits.

By putting into the draft NDI guidance what FDA views as sufficient to establish ODI status, FDA misleads companies into believing that the law requires that they have such records and that affidavits and declarations are inadequate.

It’s just another “Gotcha!” in the making.

What FDA fails to disclose is that under the Federal Food, Drug, and Cosmetic Act, FDA bears the burden of proof that a dietary supplement is adulterated or misbranded. If FDA alleges a dietary supplement contains new dietary ingredients for which a pre-market notification was required and not made, FDA bears the burden of proof. FDA must make that case itself. If FDA inspectors ask for ODI information, companies should simply call their counsel.

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AHPA’s NDI Webinar: Many Questions Remain from Review of FDA Draft Guidance

by Frank Lampe, AHPA Director of Communications

On July 19, the American Herbal Products Association (AHPA) held a special webinar for industry members titled, “FDA’s NDI Guidance: What It Means for Your Business.” The two-hour session included experts in the legal and regulatory arena to analyze and discuss the new Food and Drug Administration (FDA) proposed guidelines on New Dietary Ingredients (NDIs) and what it will mean for trade members. The guidelines were issued on July 5th, and the industry has 90 days to respond to FDA’s draft.

Webinar speakers included Michael McGuffin, AHPA president, who addressed the background of the NDIs and the connection to the Dietary Supplement Health and Education Act (DSHEA); Vasilios Frankos, Ph.D., Herbalife International, speaking on FDA’s development of the draft NDI document; Anthony Young, Esq., a partner at Kleinfeld, Kaplan and Becker, LLP, and AHPA general counsel, who discussed specifics of the document; and four attorneys with extensive NDI experience: Jim Prochnow, Esq., of GreenbergTraurig; Paul Rubin, Esq., of Patton Boggs; Ashish Talati, Esq., of Amin Talati; and Alan Feldstein, Esq., of Collins, McDonald & Gann.

NDI Background

Michael McGuffin opened the webinar by explaining that the NDI guidelines are a requirement under the
percent of the notifications [submitted by industry] were being objected to by FDA—mostly based on a lack of understanding on part of industry.”

To help clear up any misunderstanding about the NDI process, FDA held a public meeting in 2004 and issued six key categories of discussion:

A. Status of a Substance as a “New Dietary Ingredient.” This received the most comments and reflected a diversity of opinion.

B. Chemical Identification of the NDI. There was strong support to include the information listed in the notice.

C. Information About the Dietary Supplement. Industry strongly supported the inclusion of the information listed in the notice.

D. Establishing a Reasonable Expectation of Safety. Surprisingly, says Frankos, this category elicited very few substantive comments.

E. The Role of Definitions in Evaluating NDIs. This too stirred very few substantive comments.

F. Is There a Need for Guidance or Amendment of Current Requirements? This category was strongly supported.

Frankos explained that category A received the most comments and the most diverse opinions because it was attempting to define NDIs, but he found it odd that category D received the fewest comments, even though it is the topic that has caused the most controversy in the current draft NDI guidelines.

One of the most important things for industry to understand, Frankos said, is that FDA only implements laws that Congress writes, which means if Congress is not clear on its intentions (and such is the case with Congress’ definition of what constitutes an altered ingredient), then FDA must interpret congressional intent using whatever prior evidence it can find. As for the alteration of a food ingredient, FDA had little empirical evidence to go on as to the intent of Congress, which is why, Frankos said, FDA needed more input from industry, particularly from those who had been involved in congressional discussions at the time. Since that did not occur, FDA decided what constituted a chemically altered ingredient based on the evidence it had—one record on one ingredient.
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“You can see that the final outline of the guidelines is similar to what was discussed in the 2004 request for comment,” Frankos said. While the first section of the guidelines focuses on “what is an NDI?” the rest of the document lays out the process of submitting information to FDA.

**Impact of NDI Guidance on Industry**

In his presentation, Anthony Young went right to the point: “This provision is part of DSHEA—remember the mantra of ’93?” he asked. “It was ‘don’t let them take our supplements away.’ It was a preservation mantra, and not a future mantra.”

Young continued by saying that at the time, DSHEA champions were concerned about allowing new ingredients to come to market and how FDA would observe them as that happened. DSHEA grandfathered all ingredients in supplements, but new ingredients were intended to be the subject of notification to FDA. FDA drafted the NDI guidelines to be broad and to serve as a safety net for FDA, Young said, that is, as a way for FDA to protect itself if an ingredient proved to be unsafe.

“Given the history of ingredients,” Young said, “it is most likely that if we see a safety issue, it will be from something new. FDA is covering itself by assuring it has asked for notification of any change [in ingredients].” But Young said he did not understand industry’s furor over the guidelines in and of themselves and asked, “What part of ‘notification’ has this industry not understood?” Young explained that the NDI provision is a notification provision only and that FDA did not seek and was not given premarket approval authority in DSHEA. FDA files notifications after noting that a product may be adulterated, has inadequate information to provide reasonable assurance, and does not present a significant or unreasonable risk of illness or injury.

“Prudent manufacturers have been assuring through suppliers and prior to formulation that they have a rational defense for using NDIs in their products.” Young said, adding that it is “risk takers,” those bringing out new patented or first-time ingredients, who might have cause to worry.

According to Young, the NDI guidance teaches that: 1.) dietary ingredients must meet the definition – vitamin, mineral, amino acid, botanical, dietary substance; 2.) that a food ingredient in a form not chemically altered can be an NDI without notification; 3.) that an ingredient may be determined to be Generally Recognized as Safe (GRAS) for use in food and used in food and then as an NDI without notification, if not chemically altered; 4.) such an ingredient may qualify as a dietary substance even if not a vitamin, mineral, etc.

“This all came about because someone on the House staff said, ‘if I’m getting x amount of lycopene out of three tomatoes when I eat them, then I’m concerned for my safety if you give me lycopene in a supplement that is equal to two cases of tomatoes,’” Young said. “You can’t get that much lycopene out of tomatoes without chemical alteration.”

Other key points to take away from the guidance include how definitions of dietary supplements are considered. “A synthetic copy of a constituent of a botanical was never part of the botanical and thus cannot be a ‘constituent’ of the botanical,” Young explained. For example, L-theanine is a constituent of tea but synthetic L-theanine has been GRAS Notified to FDA. GRAS synthetic L-theanine has been an ingredient used in food (a dietary substance), and thus while it would be considered an NDI, no notification is required. However, Young said the chemical alteration list does need to be addressed further by industry.

“So, what are FDA’s enforcement priorities?” he asked. “Safety is first.” To that, Young surmised, FDA will first go after the “low-hanging fruit,” meaning those ingredients and products that “stand out” from the crowd, which will likely include sports nutrition ingredients.

“They’re at risk,” Young said of sports nutrition ingredients. “FDA has to make cases the old-fashioned way—through seizure and prosecution—and that is a lot of work.” That’s why Young believes FDA will carefully select the cases it will pursue, looking first at the products that blatantly claim to be “new” or “exotic.” “FDA has the burden of proof to show that a supplement is adulterated or misbranded, but we know that imports of ingredients and products are at greatest risk, because when they stop you at the border, you have to show the product is safe,” Young said. “If you want to play with NDIs, maybe do it within U.S. borders.”

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there was no legal definition for dietary supplements. FDA attempted to regulate them as drugs or foods. In other words, FDA attempted to regulate such products as conventional foods, subject to GRAS/food additive requirements prior to October 15, 1994, which supports the conclusion that marketing of ingredients in conventional foods prior to that date should satisfy the NDI standard.

“Guidance Document Proposes a Legally Suspect ‘New Dietary Ingredient’ Definition

Paul Rubin agreed with Young that FDA established as broad of a policy as possible, but said he was “disappointed” in the draft document. “The agency had 17 years of experience to produce a rigorous, focused policy to address these NDI issues. Instead, the document is inconsistent with congressional intent and goes far beyond what is legally necessary. FDA had a chance to get industry support instead of pushing companies toward being in non-compliance.”

One of the more particularly troubling aspects of the NDI guidance, Rubin said, is that it would improperly categorize ingredients marketed in conventional foods prior to October 15, 1994, as “NDIs.” Prior to 1994, Congress enacted DSHEA in order to secure consumer access and to counter FDA’s creative efforts to enforce against such products, he said. DSHEA created the “dietary supplement” definition, and expressly indicates that dietary supplements are a subcategory of “food” under the Federal Food, Drug, and Cosmetic Act (FFDCA). A “new dietary ingredient” is defined under
DSHEA as a “dietary ingredient not marketed in the United States before October 15, 1994.” The definition incorporates the DSHEA “dietary ingredient” definition, which is based upon the properties of the ingredient, not whether the ingredient was present in dietary supplements or conventional foods. The purpose of the “exclusionary clause” in DSHEA was to distinguish foods from drugs, and this, Rubin says, is a critical point for industry comments to FDA. “Think about what Congress was intending to do,” Rubin says. “I’m confident there was no intent to exclude ingredients in conventional foods as relevant to the NDI definition. In fact, Congress was trying to do that because it didn’t have a dietary supplement definition to work with back then.”

Synthetics: Scope of Clause (E) of § 201 (ff)(1) of the Federal Food Drug and Cosmetic Act

Jim Prochnow agreed with Rubin, saying that the “law we are talking about says what a dietary supplement is and this is important because if something is not a dietary supplement then it cannot be subject to NDI regulation.”

In the draft guidelines, FDA gave little attention to this issue and to Clause (E) of the FFDCA, and this is vital to the NDI issue because if it is not a dietary ingredient, it is ineligible to be an NDI, Prochnow noted. Too, the clause is important because innovation is a key competitive factor in the dietary supplement industry; new scientific techniques and methodology are always in development. And, in Clause E, the word “synthetic” was not used.

But, Prochnow says, first, there isn’t any broad prohibition against the use of a synthetic dietary ingredient in a dietary supplement. Second, a synthetic vitamin, mineral, amino acid, herb, or other botanical is eligible as a dietary ingredient pursuant to Clause (E) if it has been “commonly used as food or drink,” but he noted that FDA did not determine the scope of “commonly used,” which he added, was problematic and not included in DSHEA.

“FDA is wrongly interpreting Clause E,” Prochnow said. He based his statement on these points: 1.) FDA is neither the law nor the source of the statute in focus; 2.) no court has decided this issue; 3.) FDA has not issued any regulation that interprets Clause (E); 4.) FDA has issued Warning Letters that provide some notice of its position as well as a 2003 response to a NDI for conjugated linoleic acids. And 5.) FDA is often accorded a degree of deference when interpreting the FFDCA.

GRAS vs. NDI

Ashish Talati said if there is an area in the guidance document that is positive for industry, it is the section on GRAS and NDI notification exemption. A notification is not needed if the dietary ingredients have been present in the food supply as an article used for food or are in a form in which the food is not chemically altered.

“The key is chemical alteration,” Talati said. “If it is not chemically altered, it is exempt.” While there is no definitive GRAS list, companies can look at the GRAS notifications page. Another route for industry is the “self-affirmed GRAS,” he said. While there are some disadvantages with this, Talati says it is a good option to consider. In this case, the company does not notify FDA at all because it is already selling the ingredients. If changes are made to the dosage, form, or duration of use, however, that could impact its status. One of the disadvantages of this route, Talati said, is for ingredients being brought across the border into the United States, in which case companies will need to show why the ingredient is qualified and is exempt, which could cause delays in production. Still, Talati said, if there is a safety history for an ingredient, consider the self-affirmed GRAS option.

Filing Multiple NDI Notifications for the Same Ingredient: Balanced & Reasonable Approach Needed

Alan Feldstein represents clients in the sports nutrition area and said he was disappointed in the guidance document. “In November 2004, I testified to FDA about the NDI process,” he said. “I stated then that for the process to work, FDA had to stay within congressional intent—I think this document is unreasonable. And we are aware that sports nutrition will be the focus of guidance.”

Feldstein pointed out that it is an impossible burden to take into account every possible interaction of an ingredient or product, particularly when put in the
context of how industry functions—where many products have the same ingredients. This is a burden for both industry and FDA, he said. “There is no logic in requiring each company to submit NDIs with virtually identical information for different products that contain the same ingredients.” The process of what is needed in a submission is “time consuming and expensive,” he added, particularly given the history of safe usage of dietary ingredients in general.

Too, Feldstein said that an ingredient supplier marketing the same ingredient to manufacturers is better suited than manufacturers to be responsible for notification. “Why should FDA have to look at 100 NDI notifications from 100 manufacturers when it could look at one from a supplier?” he asked. “If FDA truly wants to work with industry and have companies comply, then it must take a more balanced and reasonable approach. We cannot begin the slippery slope to pre-market approval.” However, others on the panel were concerned about how proprietary information could be protected in NDI notification and how companies with innovative ingredients and who were first to market could be treated fairly if others could piggyback on their NDIs.

**Probiotics and Nanotechnology**

To the question “Should I notify FDA about a microbial ingredient in my dietary supplement?” Young responded that not all bacterial microorganisms are dietary ingredients, and a microorganism that is not a dietary ingredient cannot be an NDI. New microorganisms would most certainly be considered an NDI, he said.

“For example, pathogenic species of bacteria, such as Salmonella species or E. coli, are not dietary ingredients even though they may have been inadvertently present in foods as contaminants,” he said. “Bacteria that have never been consumed as food are unlikely to be dietary ingredients.”

Noting that FDA has long been concerned about probiotics, Young said that probiotics have been in dietary supplements pre-DSHEA. There is, he said, also the previously mentioned GRAS escape hatch because probiotics are used in food and a number of probiotic GRAS notifications are on FDA’s website, and thus it can be assumed that probiotics are also self-affirmed, as well. “They can be brought over to the dietary supplement category if not chemically altered, and you can use them as NDIs without notification if you don’t change dose, form etc.,” he added.

There might be concerns, however, for those doing clinical trials with probiotics. Companies need to be careful because FDA is concerned about different deliveries of ingredients, and that might require an investigational new drug application.

Speaking of nanotechnology, Young said, “FDA is concerned because, obviously, nano means new or altered form of ingredients because this does not exist in nature,” Young said. “Guidance suggests that NDI notification should be submitted where the ‘application of nanotechnology results in new or altered chemical properties of the ingredient.’”

**Conclusion**

The panelists agreed that NDI guidance is promised as part of DHSEA but that the present form of the FDA draft guidelines require substantial industry input on various sections. But many of the questions posed by industry are complex ones and will require it to think creatively, form consensus, and work through the trade associations to form a cohesive voice. Such issues as how to protect proprietary information contained within NDI notifications, who should bear the cost and labor of NDI notifications, what should require an NDI and what should not, and what constitutes a chemically altered substance are all highly complex issues that need further analysis and discussion.

In closing, the AHPA webinar panelists underscored the importance for industry to understand that a.) guidance is required as part of DSHEA, b.) that the FDA guidelines are a draft proposal only, and c.) that industry is urged to respond, especially through trade associations.

“The law requires filing, but while we have a duty to obey the law, it involves a good-faith determination. Be practical,” Prochnow said. “If you are developing a new ingredient, and your purchasers are insisting on
an NDI or your lawyer says it is not necessary, then you have to decide. You have to have a good defense if the matter comes up. There is no guide in the sky to second guess you.”

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### What Being in a Regulated Dietary Supplement Industry Means

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

At the SupplySide West International Trade Show and Conference, held in Las Vegas in October, AHPA President Michael McGuffin and I gave a presentation on Food and Drug Administration (FDA) current good manufacturing practice (cGMP) inspections and what FDA is focusing on in those inspections. We pointed out that recent inspections have been made of those who distribute own-label products manufactured by contract manufacturers and of contract manufacturers. We emphasized that all in the industry should be reading FDA’s cGMP warning letters and learning from them.

During the presentation, we were asked whether FDA might use cGMPs and their inspections as a way to generate adverse information about the industry to build a case for amending the Dietary Supplement Health and Education Act (DSHEA). Our response was that this was not likely. DSHEA and the cGMPs promulgated under DSHEA cause this industry to be regulated. And when you have an industry that is already regulated, FDA does not need more power or to change the law. All FDA needs to do is to use its present power, and it is doing so.

If you are in the business of dietary supplement manufacturing, packaging, or holding, you are regulated by the cGMPs, 21 CFR Part 111 of the federal Code of Regulations, “Current Good Manufacturing Practice in Manufacturing, Packaging, Labeling or Holding Operations for Dietary Supplements.” These cGMPs require you to have procedures in place for assuring that your operations are in compliance. If you hold dietary supplements for distribution, you need to have procedures in place for handling product returns. If you manufacture dietary supplements for others and affix your customers’ labels to those products, you have to have procedures in place for quality control to approve or release the labels prior to use.

It’s your business! Review FDA’s warning letters as they are published by AHPA and distributed via email as Legal Alerts. Go to FDA’s website and find the warning letters at the lower right corner of the homepage and review those that have been sent regarding dietary supplement cGMPs. There should be no misunderstanding—this is a regulated industry, and if you are in it, you must be in compliance.

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### cGMP Manufacturer Liability for Private-Label Retailers/Distributors?

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

When the dietary supplement good manufacturing practices (cGMPs) were promulgated by the Food and Drug Administration (FDA), there was a general consensus that small manufacturers/marketers would have difficulty meeting the requirements.

The belief was that this would drive such manufacturers/marketers to contract manufacturers. In this fashion, their established markets, trademarks, and goodwill would be preserved while substantial capital costs of cGMP compliance would be avoided.
This would preserve, it was thought, the small businesses that had grown the dietary supplement industry through the 1980s and 1990s while assuring the integrity of their products under the 2007 cGMPs.

Contract manufacturing also accounts for a substantial percentage of the volume of dietary supplement sales through marketing companies that sell under their own labels—Walmart and Costco are examples of this. These mega-retailers use one or more contract manufacturers to produce their dietary supplements. Similarly, practitioners and brick and mortar and Internet retailers sell products under their own labels that are manufactured for them by others.

FDA’s recent application of the cGMPs for manufacturing dietary supplements to a company that uses contract manufacturers may be serious cause for concern for these large and small businesses. In a warning letter sent to Confidence, Inc., FDA said:

“...you informed our investigators that your firm is an own-label dietary supplement distributor that has entered into agreements with contract manufacturers to manufacture your dietary supplement products. You stated that these contract manufacturers are required to meet your firm’s dietary supplement specifications. Further, you stated that your firm is ultimately responsible for marketing and distributing your finished dietary supplement products. As an own-label dietary supplement distributor that contracts with other manufacturers to manufacture dietary supplements that your firm releases for distribution under your firm’s name, FDA considers you to be a manufacturer of such dietary supplements. As such, you have ultimate responsibility for the dietary supplements that you introduce or deliver for introduction into interstate commerce.”

Could not the same be said for Walmart and for the health food store that has own-label products made for it?

FDA then went on to note that it had found “serious” and “significant” violations in that Confidence “failed to establish any specifications for the gelatin capsules used in the manufacture of your dietary supplements,” “did not establish specifications for your dietary supplement labels,” and “did not make and keep written procedures for the responsibility of quality control operations.” These three sections apply to manufacturers of dietary supplements and are not generally understood to apply to those who contract for the manufacture of dietary supplements by others. [The FDA 483 and the Establishment Inspection Report (EIR) for this inspection are not yet publicly available so it is not possible to determine if there were any special circumstances regarding the contract manufacturing involved.]

Contract manufacturers and those who contract for the manufacture of private-label dietary supplements should examine this warning letter carefully and assess its impact.

In this warning letter, FDA repeatedly cites the preamble to the dietary supplement cGMPs. So, if you thought that the cGMPs, which take up 30 pages in the Code of Federal Regulations, were a lot to review and understand—consider that the 208 pages of the Federal Register notice promulgating those regulations must be read and reviewed, as well. Here is where FDA appears to be taking its “authority” to designate those who contract with others for the manufacture of dietary supplements to be manufacturers themselves:

In cases where a distributor contracts with a manufacturer to manufacture a dietary supplement that the distributor then distributes under its own label, the distributor has an obligation to know what and how manufacturing activities are performed so that the distributor can make decisions related to whether the packaged and labeled product conforms to its established specifications and whether to approve and release the product for distribution.


This same generalized mantra is set out in Example 3 on page 12 of FDA’s December 2010 “Guidance for Industry - Current Good Manufacturing Practice in Manufacturing, Packaging, Labeling, or Holding Operations for Dietary Supplements Small Entity Compliance Guide.”

Note: retailers are exempt from the cGMP requirements that apply to “holding” dietary supplements. [21 CFR 111.1(b)]. “The requirements pertaining to holding dietary
FDA is authorized to order administrative detention of a food—including a dietary supplement—from 20 to 30 days. FSMA amended this authority so that FDA is now allowed to order such detention of a food if it has “reason to believe” that the food is “adulterated or misbranded.” The authority was previously limited to instances in which the agency had “credible evidence or information” indicating that a food “presents a threat of serious adverse health consequences or death.”

FDA’s interim rule modifies two sections of Title 21 of the Code of Federal Regulations and specifically § 1.378 (“What criteria does FDA use to order a detention?”) and § 1.393 (“What information must FDA include in the detention order?”), in language that exactly mirrors the language in FSMA.

AHPA’s comments suggest that FDA continue to use its administrative detention authority sparingly (the agency has never used it since it was granted in 2004). AHPA also notes, however, that Congress did not limit administrative detention to food that is in domestic commerce, such that “any detention of food that is made due to FDA’s determination that is has a reason to believe that the food is adulterated or misbranded, including detentions at a point of importation or of domestic possession, should be considered to be an administrative detention.”

If FDA agrees with this analysis, any adulteration—or misbranding-based adulteration—would be subject to certain rules, including that such detention could not exceed 30 days.

AHPA also commented that the agency should be required to provide specific, rather than only general, information on the reasons for any administrative detention, and that better training of FDA field office personnel may reduce incidents of detentions that are later found not to violate any federal provisions.

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FDA Issues Guidance on Fees Under FSMA; Delays Billing Until At Least January

In a Federal Register notice dated October 6, 2011, the Food and Drug Administration (FDA) announced the availability of a guidance for industry titled, “Implementation of the Fee Provisions of Section 107 of the FDA Food Safety Modernization Act” (FSMA). The agency stated that it is issuing this guidance “to provide answers to common questions that might arise about the new fee provisions and FDA’s plans for their implementation in fiscal year FY 2012.”

Section 107 of FSMA granted FDA new authority to charge companies fees in certain circumstances, including, among others, to recover FDA’s re-inspection-related costs when a re-inspection is a follow-up to an inspection “which identified noncompliance materially related to a food safety requirement” of the law, and to recover the costs of food-recall activities undertaken by FDA if a company does not comply with an FDA-issued recall order (1).

In its new guidance, FDA provides several examples of the kinds of noncompliance that it would consider to be “materi­ally related to a food safety requirement,” and lists the following:

- Foodborne pathogens in ready-to-eat products
- Pesticide residues on a food or feed product above tolerance levels
- Failure to declare the presence of a major food allergen (e.g., peanuts, milk) in product labeling
- Lack of adequate hazard controls for seafood or juices

In describing this list of examples, however, FDA’s guidance states that, “Most violations that would support an adulteration charge ... and certain violations that support misbranding charges ... could be noncompliance materially related to a food safety requirement of the FD&C Act.”

“If these fees are too broadly applied, they could add up quickly, especially for a small company,” noted Michael McGuffin, president of the American Herbal Products Association. “FDA will need to make sure that it limits its cost recovery to instances in which there is truly a violation that produces a food safety risk, as the Congress did not intend to unduly burden companies every time FDA revisits a facility where a minor infraction is observed that technically adulterates or misbrands a food,” he added.

The FDA guidance clarifies that FDA will assess re-inspection fees for any re-inspection that follows an initial inspection that begins on or after October 1, 2011, and will assess recall-order fees for any recall order that is issued on or after that same date. The guidance states though that FDA will not submit bills for these assessments prior to January 1, 2012. The guidance also states that the agency is developing a separate guidance document to outline a process whereby small companies may request a reduction of fees and that FDA does not intend to issue invoices for re-inspection or recall-order fees until this other guidance document has been finalized.

Reference

1. In an August 1, 2011, Federal Register notice, FDA stated that its fees in fiscal year 2012 will be billed at a rate of $224 per hour if no foreign travel is required and at a rate of $335 (later corrected to $325) if foreign travel is involved. This fee structure became effective on October 1, 2011. In this notice the agency stated that it recognized that collecting these fees “could impose severe economic hardship” on some small firms, and that the agency “will consider waiving in limited cases some or all of an invoiced fee based on a severe economic hardship, the nature and extent of the underlying violation, and other relevant factors.”