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Director's Message



Communicating Scientific Findings: The Toothpaste Case Study

A heavyweight contender for "biggest story" making the media and PR rounds in the aloe vera industry over the past few months has likely been the study published in the May/June 2009 issue of *General Dentistry*, the peer-reviewed journal of the Academy of General Dentistry (AGD) titled "Comparative evaluation of the antimicrobial efficacy of aloe vera tooth gel and two popular commercial toothpastes: An in vitro study".

Since its release I've seen a few companies, among other media outlets, that have crafted PR and marketing efforts that are titled anywhere from the tame "Aloe vera good for teeth and gums" to the more outgoing, "Aloe Toothpaste Proven To Fight Cavities".

While on the one hand it's great to see research being done promoting Aloe vera and its many and varied uses, which is obviously something the IASC values, on the other hand it's important to remember that as responsible members of the industry we need to keep to that fine-line that is adequately and accurately interpreting scientific research and making appropriate, FDA compliant, truthful and nonmisleading claims.

For example, a quote from one such recent [article](#):

"Recent study indicated that the aloe vera in tooth gels is also beneficial for teeth. Study proved its capability to fight cavities as effectively as ordinary toothpaste."

First, what's important to note is that the study itself did not test "Aloe vera inner leaf (or gel)" against 2 commercially branded toothpastes in the human mouth, but in fact tested an IASC members' finished product (Forever Living's Forever Bright Stabilizing Aloe Vera Toothgel). The distinction is important, because one of the only claims that can truly be made from this study about the ingredient used is that the actual toothpaste used in the study was effective against pathogens typically found in the human mouth. While this is potentially good news for the manufacturer of the sample used in the study, it doesn't necessarily make extrapolation of the data to apply to all aloe vera inner leaf a positive step.

Further, the study did not actually test the toothpaste samples on actual teeth, but on samples of pathogenic oral microflora in Petri dishes. Though the study does state that "the success of any toothpaste, in part, lies on its ability to eliminate pathogenic oral microflora", doing so in a Petri dish is not necessarily the same as doing so in people's mouths, and even were the raw ingredient itself used in the study rather than a finished product, only statements to the effect that Aloe vera inner leaf may be effective, in vitro, against pathogens known to cause dental caries would be accurate.

A blanket statement, such as the one quoted above, would be taking this data out of context. In the conclusion, the author's themselves suggest additional, long-term clinical trials should be performed to guarantee the results and effectiveness. Perhaps supporting such a clinical trial is something the IASC will be interested in looking into in the future to further the body of scientific evidence on this amazing botanical.

It's also important to keep in mind exactly how the FDA regulates toothpaste. A toothpaste that is for cleansing, breath

freshening, and even whitening or plaque removal, when the whitening and reduction of the plaque is based on the abrasive action of the product during brushing, is considered a cosmetic. On the other hand, a product that claims to be effective for prevention of cavities, treatment or reduction of gum disease, or an antibacterial is regulated as a drug and may only be sold pursuant to an FDA OTC monograph or new drug approval. At present, the only toothpastes that can claim to prevent cavities are those that contain fluoride and comply with the applicable FDA OTC drug regulations.



Devon Powell
Executive Director

YUN-HO LEE AWARDS



IASC Opens Nominations for 2009-2010 Yun-Ho Lee Merit Award

The International Aloe Science Council (IASC) is pleased to announce the opening of nominations for the 2009-2010 Yun-Ho Lee Merit Award.

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

Ho Lee.

Winners of the Yun-Ho Lee Award receive a cash prize of up to \$10,000. The nomination deadline is Oct. 31, 2009, and awards will be announced in February 2010. More information on submission requirements and a description of the review process and criteria is available on the IASC [Web site](#).

"The Yun-Ho Lee Merit Award recognizes the efforts of researchers working to improve our knowledge and understanding of aloe vera across numerous industries and fields of studies," said IASC Executive Director Devon Powell. "It is a privilege to promote and honor the work of scientists worldwide on aloe vera."

GUEST ARTICLE



Literature Review: NIR in Natural Products Analysis

By Steven Dentali, Ph.D., Chief Science Officer, AHPA, & Scientific Advisor, IASC

Near infrared spectroscopy in natural products analysis. Cozzolino D. *Planta Med.* 2009 Jun;75(7):746-56.

The July/August 2009 issues of *Nutraceuticals World* ran an article titled "Nutraceutical Testing: Under a Microscope" on pages 46 and 48 (see <http://www.nutraceuticalsworld.com/articles/2009/07/nutraceutical-testing-under-a-microscope>). Regarding the GMP imperative of conducting identity testing on every lot of every raw material, Darryl Sullivan, associate director, Scientific Affairs & Analytical Services, Covance Laboratories, Madison, WI and Chair of AHPA's Analytical Laboratories was quoted as saying, "I see a lot of people trying to do some sort of 'quick and dirty' identification testing. We need some better validation around those test methods and we probably need to put some more rigor around that."

The article by Cozzolino (available for free download at <http://www.thieme-connect.com/ejournals/pdf/plantamedica/doi/10.1055/s-0028-1112220.pdf>) examines one popular identity test, near infrared

(NIR) spectroscopy and demonstrates the sort of rigor that must be brought to bear on this technology for it to be considered a scientifically valid botanical identification test. The paper is a mini-review that "highlights recent applications of NIR spectroscopy to the qualitative and quantitative analysis of plant natural products."

Infrared radiation is that part of the electromagnetic spectrum past the red end of the visible spectrum up to microwaves. This energy can be absorbed into the chemical lattice of molecular structures and the absorption measured. The "near" IR frequencies provide a molecular global signature that, with computer algorithms and chemometric techniques, have proven specific food applications related to chemical composition. After covering what NIR spectroscopy is in additional depth, the article goes on to a review of available instrumentation.

The next section gets at what all natural products chemists balk at when faced with the prospect of NIR being an appropriate herbal identity tool out of the box, that of the "highly convoluted spectrum" and the resulting difficulty in making sense of the instrumental output. Without highly technical statistical treatments of this information it would be impossible to determine what is being analyzed in any NIR analytical assay. This section of the paper is key in understanding what must be done to make the instrument "work" for specific applications. The steps involved include choosing an appropriate number or components to model, conducting a calibration, and testing the robustness and accuracy of the model.

Examples of alkaloid analysis in coffee (caffeine, theobromine, and theophylline) and other alkaloids (berberine, palmatine, jatrorrhizine and total alkaloids) in *Coptis* extracts compared to HPLC analyses are presented. Other measurements of chemical components in botanical materials are provided in the review such as phenolics in green tea (*Camelia sinensis*) leaves, quercetin content in Ginkgo biloba leaf extracts, kavalactones in dried kava (*Piper methysticum*) powder, and "glucosinolates in different plant materials (e. g., leaves and seeds) from the *Brassica* species." Note that none of these applications are the same as an identity test as all the materials were identified (or should have been) prior to constituent measurement.

Ginsenosides in American ginseng (*Panax quinquefolius*) were also measured though "the main drawback of this technique is the calibration step, which *requires analysis of several samples covering all the expected spectral variability of the sample* and a reliable HPLC method for the determination of ginsenosides as a reference method (emphasis added)." There is the rub for NIR use as a quantitative method of analysis. The author then considers NIR analysis in qualitative tests, such as would be done when applying it as an identity tool. A method developed from 293 tea samples from 3 gardens was developed in order to classify tea samples. It was accurate up to 77% of the time for three types of samples.

Other examples are provided to show how NIR was used to classify closely related licorice samples, as quality control in the differentiation of two essential oils, and in other qualitative applications. In every case extensive work was done for relatively limited applications, with interesting results such as being able to determine which geographical regions certain tea samples came from and the discrimination of different cocoa genetic groups based on the country of origin.

Out of the box identification of botanical ingredients? This is an application that cannot be considered ready for prime time without the examination of sufficient samples "covering all the expected spectral variability" of the samples, and testing of the method to ensure that it does what it is supposed to do. NIR can be an extremely useful tool but it's not a place to hang your hat for botanical identification without first building the hat stand or shelf that your results rest upon.

Every article in the June 2009 *Planta Medica* issue is devoted to plant analysis. I will be reviewing additional articles in AHPA Reports to come. If you want to get a head start on the material, each article in the issue is available for free download at <http://www.thieme-connect.com/ejournals/toc/plantamedica/94429>. Knowing the strengths and limitations of methods of plant analysis and being able to match them up to the task at hand is the heart of developing methods fit for their intended purpose.

Steven Dentali, PhD, is Chief Science Officer at the American Herbal Products Association (AHPA) where his duties include helping to set quality standards for the botanical products industry and providing guidance and advice to AHPA member companies, related organizations, government agencies, scientific publications, and the popular press. He is a United States Pharmacopoeia Convention Delegate and a member of the USP Committee of Experts, Dietary Supplements - General Chapters. He is also Editorial Board Chair of AOAC and Secretary of the AOAC Presidential Task Force on Dietary Supplements, and an advisory board member of the American Botanical Council and the American Herbal Pharmacopoeia. This article was originally published in the August 2009 issue of the AHPA Report and is republished here with permission.



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299 Broadway Suite 1700
New York, NY 10007
212-571-0068 tel. 212-571-9424 fax.
usulaw@usulaw.com

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GUEST ARTICLE

FDA inspection authority broadened under cGMP regulations and serious adverse event reporting legislation

By Anthony L. Young, Esq., Partner, Kleinfeld Kaplan & Becker

FDA's current Good Manufacturing Practice (cGMP) regulations for dietary supplements is now in effect for companies employing 20 or more persons. These regulations include the requirements that various records be created and maintained. And, under these regulations, FDA inspectors have broad authority to inspect and copy those records that are required to be kept under the regulations.

Also in effect now are the requirements of the Dietary Supplement and Nonprescription Drug Consumer Protection Act ("SAER reporting law"). Under this law, reports of adverse events, and records related to such reports, both serious and non-serious, must be made available when requested during FDA inspections.

Together, these new provisions make substantial changes to the authority of FDA inspectors to inspect and copy records in a dietary supplement manufacturer's facility.

How has FDA Inspection Authority Changed?

Under the Federal Food, Drug, and Cosmetic Act (FFDCA), FDA inspectors have the authority to inspect, at reasonable times, within reasonable limits, and in a reasonable manner, any factory, warehouse, or establishment in which dietary supplements are manufactured, processed, packed, or held for introduction into interstate commerce or after such introduction. Reasonable times include any time during regular business hours that the facility is engaged in any operation. No warrant is required, FDA inspectors provide notices through a form Notice of Inspection.

Prior to the promulgation of the dietary supplement cGMPs and the enactment of the SAER law, FDA had little authority to inspect records related to the manufacture of product. Under the Bioterrorism Act, FDA was granted access to records regarding incoming raw materials and product shipments. Other than that, there was a rather long list of items that FDA inspectors had no authority to inspect. Under the cGMP regulations and the SAER reporting law, the following records are now available to inspectors:

- Information concerning personnel
- Reports and records resulting from internal audits, including failure

- Investigations manufacturing and testing records, including product formulas, batch records, log books, and laboratory worksheets
- Records relating to complaint files
- Written operating procedure

As can be seen from the list set out above, records pertaining to the manufacture of products are now essentially available.

FDA inspectors still do not have access to financial data; customer names; sales data other than shipping information (when shipping information is requested by the FDA inspector in writing); cost or pricing data; research data; and portions of the facility not used for the manufacture, processing, packing or holding of foods.

However, it is not uncommon for an FDA inspector to ask to examine and obtain copies of records that are outside the scope of their authority. A company should establish a policy in advance of any actual inspection as to whether it will comply with such requests, or with certain of such requests.

Whether or not a company's policy is to provide access to records that are outside the scope of an FDA inspectors authority, it is usually a good practice to ask that the inspector provide their request to see and copy such records in writing, and to provide in such written requests references to the agency's legal authority to review the records in question, if such authority exists.

For firms that do not generally, as a matter of company policy, allow FDA to examine such records, the inspector should be informed that it is the firm's understanding that FDA is not authorized to examine or copy such records, and that their access to such records will need to be delayed until receipt of a written request from the inspector and advice of counsel can be obtained. Also, a common outcome of asking that such requests be made in writing is that the requests are dropped.

What Must be Made Available?

Under FDA's cGMP and the SAER law, numerous records are required to be made and maintained. These are the records most dietary supplement manufacturers are required to have on and after June 25, and these are the records FDA inspectors can access if you are inspected on or after June 25.

Provided below is a brief look at select subparts of the cGMP regulation (21 USC Part 111) that require recordkeeping. The following is not a complete list of required records:

Subpart B - Personnel

This section pertains to personnel practices that prevent microbial contamination of product by personnel who may be sick or infected and with respect to hygiene generally. Against the background of recent incidents regarding the microbiological contamination of food, these procedures and training documents can be expected to be a high review priority for FDA Inspectors.

§ 111.14 (b) You must make and keep the following records:

- (1) written procedures for fulfilling the requirements of this subpart B: and
- (2) Documentation of training, including the date of the training, the type of training, and the person(s) trained.

Subpart D - Equipment and Utensils

Don't be misled by this title. This section requires procedures for calibrating and maintaining instruments and controls used in manufacturing. In addition, it requires documentation regarding the use and maintenance of all equipment.

§ 111.35 (b) You must make and keep the following records:

- (1) Written procedures for fulfilling the requirements of this subpart, including written procedures for:
 - (i) Calibrating instruments and controls that you use in manufacturing or testing a component or dietary supplement;
 - (ii) Calibrating, inspecting, and checking automated, mechanical, and electronic equipment; and
 - (iii) Maintaining, cleaning, and sanitizing, as necessary, all equipment, utensils, and any other contact surfaces that are used to

manufacture, package, label, or hold components or dietary supplements;

(2) Documentation, in individual equipment logs, of the date of the use, maintenance, cleaning, and sanitizing of equipment, unless such documentation is kept with the batch record;

(3) Documentation of any calibration, each time the calibration is performed, for instruments and controls that you use in manufacturing or testing a component or dietary supplement. In your documentation, you must:

(i) Identify the instrument or control calibrated;

(ii) Provide the date of calibration;

(iii) Identify the reference standard used including the certification of accuracy of the known reference standard and a history of recertification of accuracy;

(iv) Identify the calibration method used, including appropriate limits for accuracy and precision of instruments and controls when calibrating;

(v) Provide the calibration reading or readings found;

(vi) Identify the recalibration method used, and reading or readings found, if accuracy or precision or both accuracy and precision limits for instruments and controls were not met; and

(vii) Include the initials of the person who performed the calibration and any recalibration.

(4) Written records of calibrations, inspections, and checks of automated, mechanical, and electronic equipment;

(5) Backup file(s) of current software programs (and of outdated software that is necessary to retrieve records that you are required to keep in accordance with subpart P of this part, when current software is not able to retrieve such records) and of data entered into computer systems that you use to manufacture, package, label, or hold dietary supplements.

(i) Your backup file (e.g., a hard copy of data you have entered, diskettes, tapes, microfilm, or compact disks) must be an exact and complete record of the data you entered.

(ii) You must keep your backup software programs and data secure from alterations, inadvertent erasures, or loss; and

(6) Documentation of the controls that you use to ensure that equipment functions in accordance with its intended use.

Subpart K - Production and Process Control System: Requirements for Manufacturing Operations

These include requirements for assuring that there is no contamination of product components; that manufacturing operations protect against the potential for microbial contamination; and that equipment is clean and sanitary prior to each use. In addition, this section provides for requirements that apply to rejected supplements.

§ 111.375 (b) You must make and keep records of the written procedures for manufacturing operations.

As previously mentioned, many records are required to be made and maintained under cGMP. The above is not an inclusive list.

You must keep written records required by 21 USC Part 111 for one year past the shelf life date, if shelf life dating is used. If shelf life dating is not used, written records should be kept for two years beyond the date of distribution of the last batch of dietary supplements associated with those records. Records related to any adverse event report received must be maintained for six years and, as noted earlier, must be made available during inspection.

Examination and Copying of Records

FDA's access to records includes the right to request copies of the records. After determining whether the requested records are within the scope of the inspector's authority, the company's inspection coordinator should have an appropriate employee retrieve the record or records that will be allowed to be examined and provide copies of those to the inspector. Do not allow the inspector direct access to the company's files, but only to the specific requested records, and avoid allowing the inspector to handle original records if possible.

If an inspector asks for a copy of any records which the inspection coordinator has determined is within the scope of the inspector's authority or will be allowed to be copied, the inspection coordinator should have an appropriate employee make two copies of such records. One copy should be provided to the inspector and the other should be maintained in the company's files. It is important to assure that you have maintained a complete set of all records copied by or for FDA. Do not allow the inspector direct access to the company's copying machine.

Additionally, records should be stamped CONFIDENTIAL before they are copied, and the FDA Inspector should be advised that the documents provided are confidential commercial information that are not disclosed by the company to third parties. This should

be done to avoid FDA making any records available under the Freedom of Information Act (FOIA) without at least first providing the company an opportunity to object.

Preparation, Preparation, Preparation

Dietary supplement companies should expect inspection under 21 CFR 111, and it is critical that companies understand their rights and obligations when FDA conducts an inspection of a facility. Additionally, certain foods (e.g., infant formulas, acidified foods, low-acid canned foods, and fish and fishery products), drugs or medical devices have additional requirements. Companies that also manufacture, process, pack or hold products such as fish oil supplements, OTC drugs and homeopathics may therefore need to understand regulations in addition to 21 CFR 111. The importance of preparation - having a standard operating procedure, identifying key personnel, conducting mock inspections - cannot be overemphasized as it is absolutely necessary for a successful inspection.

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Anthony L. Young is a partner at Kleinfeld Kaplan & Becker (Washington, D.C.). He has practiced food, drug and environmental law for more than three decades and has served as General Counsel for the American Herbal Products Association since 1998. Mr. Young is a frequent lecturer at industry meetings on the implementation of DSHEA and counsels a number of dietary supplement companies with respect to compliance with the Federal Food, Drug, and Cosmetic Act. This article was originally printed in the May 2009 AHPA Report and is reprinted here with permission.

THE SCIENCE OF ALOE - Recently Published Studies

- [Hypoglycemic and hypolipidemic effects of processed Aloe vera gel in a mouse model of non-insulin-dependent diabetes mellitus.](#)
- [Promotion proliferation effect of a polysaccharide from Aloe barbadensis Miller on human fibroblasts in vitro.](#)
- [Complementary alternative medicine use in children with type 1 diabetes mellitus in Erzurum, Turkey.](#)
- [Antimicrobial, anti-inflammatory and mutagenic investigation of the South African tree aloe \(Aloe barberae\).](#)
- [A new triglucosylated naphthalene glycoside from Aloe vera L.](#)
- [Effect of Aloe barbadensis Miller Juice on oxidative stress biomarkers in aerobic cells using Artemia franciscana as a model.](#)
- [Gold nanoparticles prepared using cape aloe active components.](#)
- [Comparative hepatotoxicity and clastogenicity of sodium arsenite and three petroleum products in experimental Swiss Albino Mice: The modulatory effects of Aloe vera gel.](#)
- [Separation and purification of aloe polysaccharides by a combination of membrane ultrafiltration and aqueous two-phase extraction.](#)
- [\[Importance of local skin treatments during radiotherapy for prevention and treatment of radio-induced epithelitis\]](#)
- [Aloe-emodin-induced DNA fragmentation in the mouse in vivo comet assay.](#)
- [Effect of extraction solvent/technique on the antioxidant activity of selected medicinal plant extracts.](#)

- [Plant-Derived Polysaccharide Supplements Inhibit Dextran Sulfate Sodium-Induced Colitis in the Rat.](#)
- [Antioxidant capacity of 3D human skin EpiDerm model: effects of skin moisturizers.](#)

REGULATORY NEWS: NEW FDA ENFORCEMENT POLICIES

FDA Commissioner Introduces New Enforcement Steps; Reiterates Steroid Products are Not Dietary Supplements

In a speech to the Food and Drug Law Institute (FDLI) last Thursday, Food and Drug Administration (FDA) Commissioner Margaret Hamburg, M.D., stated that the agency's "pathways for enforcement action" can be "too long and arduous when the public's health is in jeopardy," and identified six new enforcement steps that have been initiated under her new leadership. Explaining that these new policies do not require any new authority, Dr. Hamburg identified these steps as:

- New post-inspection deadlines, so that if an inspection identifies a "serious problem," a company will generally have no more than fifteen working days in which to respond before the FDA moves ahead with a warning letter or enforcement action
- Increased speed in the issuance of warning letters by limiting warning letter review by FDA's general counsel to significant legal issues
- Closer cooperation with FDA's regulatory partners, such as local, state, and international officials who have more authority to take action quickly than the FDA, when the public health is at risk
- Prioritization of enforcement follow-up after issuance of warning letters or product recalls to assess whether a company has made required changes in its practices
- Swiftly and aggressively acting to protect the public, so that FDA will no longer issue multiple warning letters to noncompliant companies and will be prepared to act even without a warning letter when confronting significant health concerns or egregious violations
- Development of a formal warning letter "close-out" process, so that companies will receive (and FDA will post on its Web site) a close-out letter from FDA to indicate that the issues identified in certain types of warning letters have been successfully addressed

Dr. Hamburg, who was confirmed as the FDA Commissioner just eight weeks ago, also identified two recent FDA enforcement actions. She noted, for example, that the agency has issued 65 warning letters to Internet sites promoting products that claimed to diagnose, prevent, or treat the H1N1 virus, and reported that new sites have since reduced from ten per day to about two per week. Hamburg also highlighted a recent action against companies selling anabolic steroids "under the guise of dietary supplements," and stated: "These are unproven and unapproved drugs, not dietary supplements."

In commenting on media responses to FDA's strong response to H1N1 virus claims, Hamburg cited expressions of surprise at the agency's tough enforcement. "I hope that in the future, effective FDA enforcement actions will not be surprising or out of the ordinary," she said.

The Commissioner's complete speech can be found at: <http://www.fda.gov/NewsEvents/Speeches/ucm175983.htm>



FDA's Renewed Interest in Economic Adulteration; A Look at Enforcement Actions 2001-2008

"Economic adulteration" of food has been addressed by societies for thousands of years. "There is evidence of regulation and enforcement mechanisms dating back to ancient times," Marsha A. Echols writes in "Food safety and the WTO" (2001, Kluwer Law International). "The Assyrians established weights and measures for grains. As early as 200 BC India punished the economic adulteration of grains and oils. During the same era Chinese officials tried to prevent consumer fraud. Egypt had food labeling rules. The ancient Athenians issued purity

standards for beer and wine, while the Romans instituted a system to control fraud and bad produce." In the 1980s, the International Aloe Science Council (IASC) launched its certification program.

The IASC Certification Seal is an important tool in preventing the sale of economically-adulterated aloe material. IASC continues to vigilantly protect the integrity of its seal, which assures consumers that the company represents truth in labeling; that the company represents the quantity in aloe content; that the company represents the quality of aloe meets with IASC current standards; and that the company represents that the aloe used in the products comes from a certified source.

In May 2009, the U.S. Food and Drug Administration (FDA) held a meeting to address economic adulteration in a globalized 21st century America and gather public input. The agency introduced a new term for the fraud, "economically-motivated adulteration" or "EMA," and proposed the following working definition:

EMA [is] the fraudulent, intentional substitution or addition of a substance in a product for the purpose of increasing the apparent value of the product or reducing the cost of its production, i.e., for economic gain. EMA includes dilution of products with increased quantities of an already-present substance (e.g., increasing inactive ingredients of a drug with a resulting reduction in strength of the finished product, or watering down of juice) to the extent that such dilution poses a known or possible health risk to consumers, as well as the addition or substitution of substances in order to mask dilution.

The definition is very similar to a definition of adulteration in the Federal Food, Drug and Cosmetic Act (FDCA): "A food shall be deemed to be adulterated...if any substance has been added thereto or mixed or packed therewith so as to increase its bulk or weight, or reduce its quality or strength, or make it appear better or of greater value than it is" (see 21 USC § 402(b)(4)). However, perhaps most notably, the EMA definition proposed by FDA for the May 2009 meeting, specifically includes the phrase "to the extent that such dilution poses a known or possible health risk to consumers."

Enforcement Story

Each year, FDA publishes an "Enforcement Story" that highlights and describes by agency center (e.g., Center for Drug Research and Evaluation (CDER); Center for Food Safety and Applied Nutrition (CFSAN)) enforcement actions taken against companies regulated by FDA to offer a "complete picture of the agency's enforcement activities and investigational priorities." The "Enforcement Story" describes convictions by the Office of Criminal Investigations (OCI), as well as warning letters issued by the agency's centers and product recalls undertaken.

Forty-four percent of all food-related convictions reported by OCI in the annual "Enforcement Story" reports from 2001 to 2008 were for adulterated products. Of these, 18 percent were cases of economic adulteration in which an individual and/or company were convicted of fraudulently and intentionally substituting or adding a substance in a product for the purpose of increasing the apparent value of the product or reducing the cost of its production.

The EMA cases primarily involved dairy products: water and salt in milk (2001); fraudulently-marketed "ice cream" (2001); animal-grade cheese in food for humans (2001); and soybean oil substituted for cream in cream cheese (2003). One case, in 2002, involved the promotion of foreign crabmeat as "domestic," and the remaining two cases of EMA between 2001 and 2008 were for the economically-motivated adulteration of dietary supplements (2002 and 2004).

Supplementing Supplement Ingredients

While the eight-year period has only two reported convictions for dietary supplement EMA, dietary supplement EMA accounts for nearly 30% of all food EMA cases from 2001 to 2008. Both of the instances of dietary supplement EMA reported in the "Enforcement Story" reports involve the substitution of ingredients.

In the 2002 case, a company, CAP TAB Nutritional Formulating and Manufacturing, and several of its officers allegedly "conspired and knowingly substituted lower price ingredients in lieu of the ingredients listed on the label of their dietary supplements (encapsulated vegetable powders)." Additionally, further investigation revealed CAP TAB and its officers forged both organic certifications and an insurance certificate.

In 2003 testimony before the Senate Committee on Commerce, Science, and Transportation, then FDA Associate Commissioner for Regulatory Affairs John M. Taylor, reported on the officers' sentences and fines: "Three of the defendants in the case received sentences of one year's probation and were ordered to pay fines of \$500, \$250, and \$5000, respectively. A fourth defendant received a sentence of 180 days' incarceration followed by five years' incarceration on a related state criminal conviction."

In 2004, FDA's "Enforcement Story" OCI describes a case in which former employees of dietary supplement company Shara Laboratories alleged that "dietary supplements were rebottled and relabeled using expired ingredients or less costly ingredients (product substitution)." The "Enforcement Story" description provides as an example that one product was labeled as containing 100 percent "Pur gar, garlic powder" when in fact, it contained another ingredient, "Triarco, garlic powder." Additionally, Shara Laboratories President Arnold Suresky "instructed his employees to destroy and/or alter business records that were responsive to several Grand Jury Subpoenas," the report states.

Suresky was charged with violating 21 USC 331(a) and 333(a)(c), Introduction and delivery of a Misbranded Product into Interstate Commerce, as well as 18 USC 2, Aiding and Abetting. In 2004, he was convicted and fined \$90,000. "Suresky also agreed that he would never hold any position, in any business, regulated by the Federal Food, Drug and Cosmetic Act or the U.S. Public Health Services Act," OCI writes.

Food EMA Conviction Trend

Notably, no convictions for EMA were reported under CFSAN between 2004 and 2008. The number convictions for any type of food adulteration likewise declined from 2001 to 2008, and the number of convictions for smuggling, tampering and other illegal activity increased. This trend, however, is likely to change with the high-profile occurrences of EMA in 2007 and FDA, the media and consumers' renewed attention on the issue.

REGULATORY NEWS: AER GUIDANCE

FDA Issues Final Guidance on SAER Reporting and Recordkeeping

The U.S. Food and Drug Administration (FDA) announced in today's Federal Register that it has released its final "Guidance for Industry: Questions and Answers Regarding Adverse Event Reporting and Recordkeeping for Dietary Supplements as Required by the Dietary Supplement and Nonprescription Drug Consumer Protection Act" (the Act).

Under the Act, a "responsible person" (in the case of a dietary supplement, this is usually the marketer) has been required since December 2007 to submit to FDA within 15 days any serious adverse event report (SAER) it receives in association with its products. The document FDA released today contains guidance on such details as the minimum data elements that should be included in an SAER, as well as the recordkeeping requirements established under the Act. As with all agency-issued guidance, this document "does not create or confer any rights for or on any person and does not operate to bind FDA or the public," and states that the regulated trade "can use an alternative approach if such approach satisfies the requirements of the applicable statute and regulations."

The final guidance differs in several ways from the draft guidance FDA issued on this topic in October 2007. Changes include the

following:

- The Act defines an SAER to include, among other things, "inpatient hospitalization." Concerns were expressed in written comments that the draft's description of inpatient hospitalization could be misinterpreted such that "the act of seeking treatment at a hospital emergency room for a minor adverse event could be erroneously considered to be a serious adverse event." It was also noted that the mandatory MedWatch Form 3500 provides additional information that would prevent any such confusion. The final guidance now provides an appendix which links to the MedWatch instructions, and so states that "emergency room visits that do not result in admission to the hospital should be evaluated for one of the other serious outcomes." This language clarifies that an emergency room visit does not necessarily and in and of itself constitute inpatient hospitalization.
- FDA's expressed position in the draft was that reports received in error for another manufacturer's product "should be promptly forwarded to that other responsible person." It was suggested in written comments that this language be revised both to acknowledge that there is no requirement under the Act to do anything with such a report, and to replace the words "should be promptly forwarded" with "the agency recommends that such reports be promptly forwarded." FDA incorporated these suggestions.
- The agency recommended in the draft that companies responsible for submitting SAERs "use trained health care practitioners to elicit information from reporters," and suggested that this be described as one of several options for obtaining such essential information. In the final guidance, FDA has revised the punctuation and language of this section to clarify that use of practitioners is just one of the means that can be used to achieve this purpose.
- The draft guidance would have exempted all but one responsible person from submitting an SAER to FDA if the report identified suspect products from more than one responsible person. FDA has revised the final guidance to clarify that all such persons have the same reporting requirement under the Act.
- Finally, written comments suggested that the agency, in addressing other information that might be submitted along with a MedWatch form, acknowledge that responsible persons are explicitly allowed to include "additional information" and "a statement ... that denies that the report or the records constitute an admission that the product involved caused or contributed to the adverse event." The final guidance now states that it "does not provide an exhaustive list of all the documents or information that may be submitted with the report at the responsible person's option."

"IASC is pleased to see suggestions from industry adopted by the agency," said Executive Director Devon Powell, "and the final guidance is a useful resource for responsible persons to comply with the SAER law."

The guidance can be accessed at

<http://www.fda.gov/Food/GuidanceComplianceRegulatoryInformation/GuidanceDocuments/DietarySupplements/ucm171383.htm>



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The International Aloe Science Council
8630 Fenton Street, Suite 918
Silver Spring, MD 20910
o. 301-588-2420 | f. 301-588-1174
info@iasc.org | www.iasc.org