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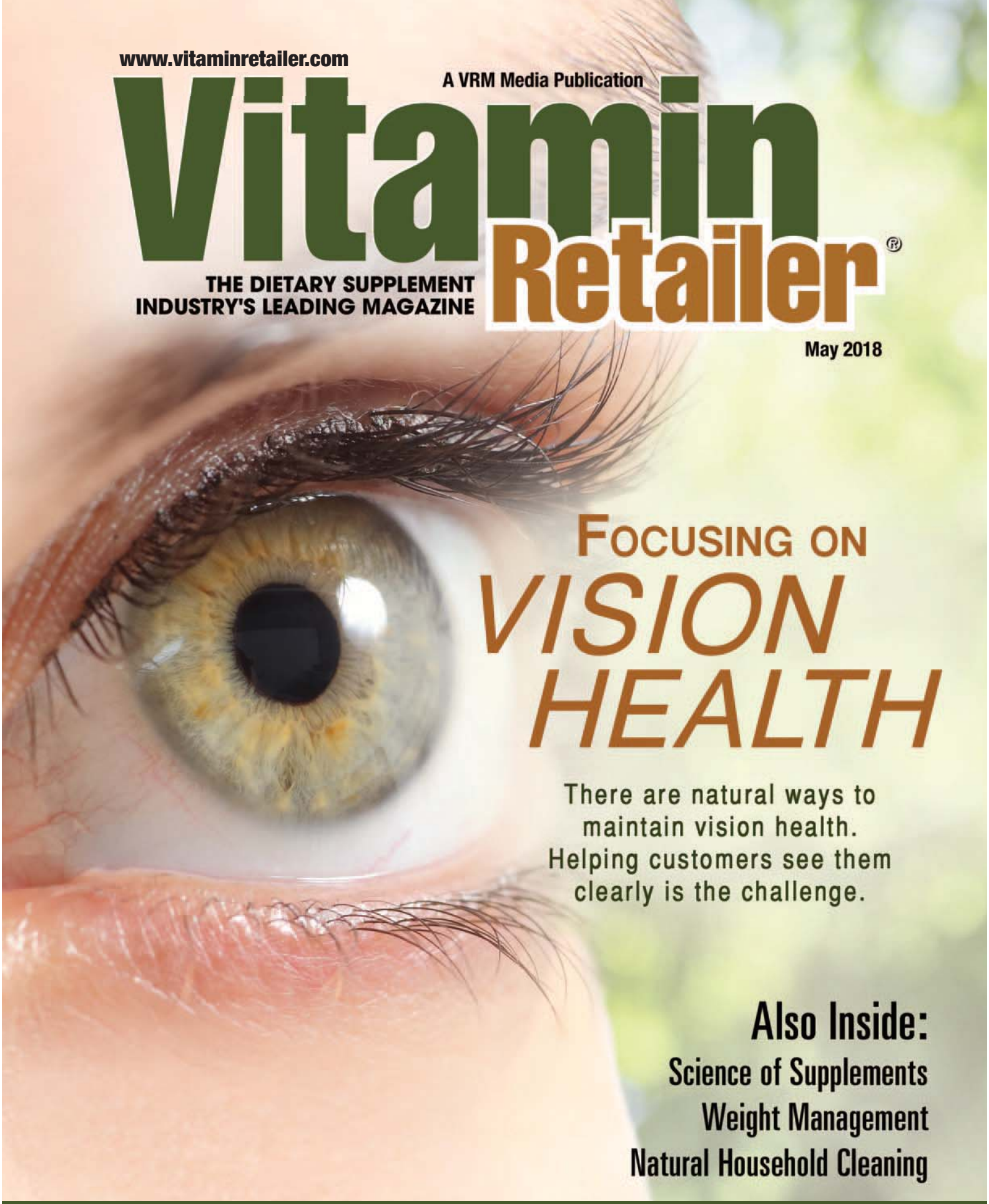

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There are natural ways to maintain vision health. Helping customers see them clearly is the challenge.

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KRATOM: FDA Has a Problem

By Steven Shapiro and Marc Ullman

Despite support from a rabid following of consumers who believe that it is safe and effective for a wide variety of uses, kratom (*Mitragyna speciosa* Korth) has a serious U.S. Food and Drug Administration (FDA) problem.

Kratom is commonly found growing in Thailand, Malaysia, Indonesia and Papua New Guinea, where laborers have traditionally used the fresh or dried leaves, either chewing them or preparing juices or teas, to combat fatigue and improve their work productivity. Kratom also purportedly has a number of other significant health benefits. A search of the internet for "kratom benefits" reveals websites touting the plant's ability to "relieve pain, boost metabolism, increase sexual energy, improve the immune system and prevent diabetes. They ease anxiety, help with addiction, eliminate stress and induce healthy sleep."[1]

Clearly, its most controversial use involves claims that kratom is beneficial in the treatment of opioid addiction.[2] Both FDA[3] and DEA (Drug Enforcement Administration)[4] have stated that kratom compounds have "opioid properties" or "opioid-like activity." It is the herb's opioid properties that make it useful as a treatment.

FDA's History With Kratom

FDA has been building its case against the legal marketing of kratom as a dietary supplement for quite some time. The ingredient first came to our attention because of a presentation at the May 2013 SupplySide trade show by Daniel Fabricant, PhD, then, director of FDA's Division of Dietary Supplements. Fabricant informed industry that the ingredient was being abused in Thailand, where the government has banned the growing of plants since 1943 (Kratom Act 2486) and has, since 1979, classified it as a narcotic. He further stated that FDA had serious concerns of its legitimacy as a dietary ingredient, in terms of its safety, and that FDA was detaining and refusing entry of kratom shipments into the country.

FDA's first action concerning kratom was in 2012, when it was added it to Import Alert 66-41, which is a general import alert identifying specific products known to be entering the country as "unapproved new drugs." This action was specific to only certain kratom products that were making claims to treat or cure disease.

In February 2014, FDA issued a second Import Alert, 54-15, specific to the agency's concern regarding a lack of appropriate safety data for kratom. In it, FDA explained that while kratom is a botanical that qualifies as a dietary ingredient under section 201(ff)(1) of the Federal Food, Drug and Cosmetic Act (the Act), when marketed as such, it is a "new dietary ingredient" under section 413(d) of the Act because, "to

the best of the agency's knowledge, there is no information demonstrating that this substance was marketed as a dietary ingredient in the United States before October 15, 1994."[5]

FDA also asserted that based on its own review of the publicly available information, "there does not appear to be a history of use or other evidence of safety establishing that kratom will reasonably be expected to be safe as a dietary ingredient." According to FDA, "consumption of kratom can lead to a number of health impacts, including respiratory depression, nervousness, agitation, aggression, sleeplessness, hallucinations, delusions, tremors, loss of libido, constipation, skin hyperpigmentation, nausea, vomiting and severe withdrawal signs and symptoms."

It was, therefore, FDA's conclusion that kratom-containing dietary supplements are adulterated under section 402(f)(1)(B) of the Act [21 U.S.C. 342(f)(1)(B)], because they contain a new dietary ingredient for which there is inadequate information to provide reasonable assurance that such ingredient does not present a significant or unreasonable risk of illness or injury.

Since the issuance of the second import alert, U.S. Marshalls, acting at the request of FDA, have conducted at least three seizures of kratom:

- In September 2014, more than 25,000 pounds of raw kratom from Rosefield Management, Inc. in Van Nuys, CA.[6]
- In January 2016, almost 90,000 bottles of kratom dietary supplements, from Dordoniz Natural Products LLC, in South Beloit, IL, marketed as "RelaKzpro."[7]
- In August 2016 more than 100 cases of products distributed by Nature Therapeutics LLC (d/b/a Kratom Therapy) is located in Grover Beach, CA marketed as "Kratom Therapy."[8]

FDA Commissioner Scott Gottlieb, MD, has also been quite vocal about the alleged dangers of consuming kratom having issued several public statements on the ingredient. On February 6, 2018, the commissioner issued a statement on the agency's scientific evidence concerning the presence of opioid compounds in kratom and underscoring its potential for abuse. This follows a November 2017 public health advisory from Gottlieb "about deadly risks associated with kratom."[9]

In this presentation, FDA provided additional information on adverse events alleged to have occurred from kratom consumption. This is reminiscent of how FDA built its case to ban ephedra as a dietary ingredient approximately 15 years ago by releasing information on mounting numbers of AERs (adverse event reports) alleged to be attributable to that ingredient. In the earlier case of ephedra, and now with kratom as well, it is difficult to determine a causal connection, as many AERs document various medical conditions and consumption of a wide variety of substances including both legal and illegal drugs. Yet, FDA claims to have identified 44 reported deaths as of February 6, 2018.[10,11]

On February 21, 2018, FDA announced[12] the voluntary destruction and recall of what it called, "a large volume" of kratom-containing dietary supplements that had been distributed under the brand names "Botany Bay," "Enhance Your Life" and "Divinity" by Divinity Products Distribution of Grain Valley, MO. In cooperation with the agency, the company also agreed to stop marketing all kratom-containing products.

As stated by FDA, based on the scientific evidence of the serious risks associated with the use of kratom, in the interest of public health, the FDA encourages all companies currently involved in the sale of products containing kratom intended for human consumption to take similar steps to take their products off the market and submit any necessary evidence, as appropriate, to the FDA to evaluate them based on the applicable regulatory pathway.

FDA further reported that its in-house review of the scientific data has provided "conclusive evidence that compounds contained in kratom are opioids and are expected to have similar addictive effects as well as, risks of abuse, overdose and, in some cases, death." FDA has therefore publicly announced that it will "continue to affirm the risks associated with kratom, warn consumers against its use and take aggressive enforcement action against kratom-containing products." On February 28, 2018, FDA issued another statement objecting to a kratom compound intended for use as an alternative to prescription opioids and promoted with unproven claims to treat addiction.[13]

Kratom and Salmonella

A new issue arose with kratom in early February when FDA learned of a multistate outbreak of salmonellosis from a rare strain of salmonella. An FDA release followed on March 2, 2018 concerning an FDA and U.S. Centers for Disease Control and Prevention (CDC) monitoring of an active nationwide outbreak across 20 states of a rare type of salmonella apparently associated with kratom products. The outbreak is associated with kratom-containing capsules, teas and powders, and according to FDA, "underscores the risk that harmful bacteria may contaminate these products when not subjected to manufacturing controls to eliminate that risk, in addition to the overall safety concerns for kratom itself."[14]

FDA issued a further announcement on March 15 stating that as of March 14, 2018, the CDC reports that 87 people infected with outbreak strains of Salmonella I 4,[5],12:b:- (50), Salmonella Javiana (5), Salmonella Okatie (16), or Salmonella Thompson (16) have been reported from 35 states. Twenty-seven people have been hospitalized. Twenty-five products have been tested and reported positive for salmonella. Three match one or more of the outbreak strains and an additional 22 have tested positive for salmonella, and either do not match or are pending further characterization.

FDA has concluded that "it is likely

that multiple brands and retailers are supplying contaminated product to the public. The positive results also indicate possible concerns with the manufacturing practices used in production and/or handling of these products." Certainly, one may assume that FDA's import alerts and other enforcement actions are causing manufacturers and marketers to "cut corners" with their GMPs (good manufacturing practices) in order to continue to get product to market resulting in the present outbreak.

Supplement Industry's Best Response

So, considering all the aforementioned FDA actions, and what appears to be an agency game plan with a complete ban of kratom as the end result, what can industry do, if anything?

When intended for use as, or in, a dietary supplement, FDA has made it known that it considers kratom to be a new dietary ingredient. At this point, FDA has also made it known that it is not aware of any evidence of safety establishing that consumption of kratom as a dietary supplement does not present a significant or unreasonable risk of illness or injury under conditions of use recommended or suggested in labeling, or under ordinary conditions of use, which is the required safety standard pursuant to the Dietary Supplement Health and Education Act (DSHEA).

Additionally, if one intends to attempt to legally market kratom, they should not market it to be used to treat any medical conditions, nor should it be marketed for use as an alternative to prescription opioids or to treat opioid addiction. Such intended use would make the product a drug under the act and there are currently no FDA-approved therapeutic uses of kratom. Before kratom can be legally marketed for therapeutic uses in the U.S., kratom's risks and benefits would need to be the subject of a new drug approval submitted to FDA.

To date, it appears that FDA has issued letters in response to three separate new dietary ingredient notifications concerning kratom.

In response to a NDI (new dietary ingredient) notification filed on August 10, 2015 by Luke Dodd to market a kratom extract called "Atomic K" with a maximum daily level of 800 mg, FDA issued a letter on September 22, 2015, finding, among other things, that the notification included "a minimal amount of history of use information and none of that information could be used as a basis to conclude that your dietary supplement containing such a new dietary ingredient would have a reasonable expectation of safety."

One must wonder how "serious" this notification was, as there were numerous deficiencies in the notification and the agency commented that the notifier was clearly suggesting that the product was intended to be used as a drug—"Atomic K ... behaves as a mu-opioid receptor agonist like morphine and is used in the management of chronic pain." 21 CFR 190.6, which sets forth the type of information that FDA requires for an NDI notification, does include the claims that will be made for the ingredient. Providing such information is not required, although if provided, one must seriously question why a notifier would inform the agency of an intent to market an NDI for uses that would fall within the category of an unapproved new drug claim.

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The second notification was filed on September 6, 2016 with additional submissions over various days on behalf of INI Botanicals for a "dietary supplement made from greater than 99 percent purity extract of Mitragynine" to be marketed under the tradename "Mitrasafe." FDA responded to this notification twice on December 20, 2016 and then again on February 26, 2018. FDA rejected the notification for failure to establish the identity of the new dietary ingredient, including failure to provide adequate information on manufacturing.

As to safety data, FDA determined that historical use of the source plant leaves as traditionally ingested, "chewing, smoking, brewing into a tea," could not be compared to the NDI, which was "99 percent pure mitragynine extracted from *Mitragyna speciose*." Further, the notifier did not include studies on the specific product that it intended to market and the toxicity study, among other things, concluded that, "in rats, mitragynine caused withdrawal signs and changed hematological parameters at all dose levels in both males and females, as well as liver, kidney, and brain toxicities." Thus, "adverse effects were observed at all dose levels."

American Botanicals Corporation filed the third notification on February 16, 2017 for a standardized extract as a liquid dietary supplement. FDA responded to this notification on April 28, 2017. According to the FDA letter, the proposed serving size was 40 mL/day, equivalent to 20 mg/day mitragynine. Here too, FDA found insufficient information to establish the identity of the NDI or to fully explain the manufacturing process. In addition, historical use, as with the notification discussed above, was based on consumption of the leaves and not a purified extract, and the toxicity data was claimed by FDA to have the same purported shot comings as discussed above.

These NDI notifications reveal the same obvious shortcomings and problems that any proposed marketer of kratom will face. First, as to traditional use, there has been no evidence submitted demonstrating that kratom in extract form have ever been present in the food supply as an article used for food. All the traditional use submitted so far is specific to chewing or "brewing" the actual leaves.

Could an NDI notification for a product that was based on traditional dried leaf powder present FDA with sufficient evidence that its consumption will reasonably be expected to be safe? This remains to be seen, if a marketer is willing to attempt such a submission. Unfortunately, existing scientific data

questions the safety of even the dried leaf, and FDA has stated that data submitted to date observed adverse effects "at all levels." If there exists safety data on the leaf, it would behoove the trade to have it published in a peer reviewed/reputable toxicological journal as soon as possible. It would seem essential that if this ingredient is to "survive" in any form, that the trade work on "saving the leaf" as every extract is bound to be different.

For the time being, kratom remains available online and at some retailers, although some of the states have enacted bans on the sale of the ingredient or its alkaloids.[15] But, we have seen this before in the example of ephedra, where FDA took its time collecting data and letting adverse events pile-up, which may or may not present causal evidence related to kratom, until the industry was unable to mount any defense to FDA action to remove the ingredient from the market. **VR**

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14 www.fda.gov/food/recallsoutbreaksemergencies/outbreaks/ucm597265.htm#Fast.

15 The American Kratom Association reports that as of March 2018, seven states and the District of Columbia states have banned the sale of kratom or alkaloids contained in kratom and a number of other states have or are considering similar bans. www.americankratom.org/aka-in-your-state.

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