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The Supplement OWL in Action

It’s been a year since the Council for Responsible Nutrition (CRN; Washington, DC) gave industry insiders a first glimpse of the Supplement OWL (Online Wellness Library) self-regulatory registry for finished dietary supplements.

That initial sneak peek during the association’s 2016 annual conference last October preceded the registry's formal online debut in April 2017. Since the registry went live in April, CRN has devoted significant time, resources, and effort to encouraging supplement manufacturers to add their supplements’ label information to the registry, which itself is designed to provide a more-complete picture for regulators, retailers, and industry of the vast array of finished-product supplements currently in the market.

I spoke to CRN’s president and CEO, Steve Mister, about the registry’s progress over the past year.

“It’s hard to believe that it was only a year ago that this was still pretty much a concept. We were doing screenshots of what we thought it would look like, and I think we were just starting the beta-testing at that point,” Mister says. “So, we’ve come a long way, I think. We’ve got a long way to go, and we really need to up the numbers of participating companies, but we’ve come a long way in one year.”

As of the beginning of this September, there were 68 brands participating in the Supplement OWL and 4,728 product labels already on public view in the registry, with an additional 2,894 in “hidden” view—“hidden,” meaning that those entries were still in private-view mode as companies review them for accuracy before making them live. Combined, there were 7,622 product labels, public and hidden, in the registry as of September.

Mister describes the companies currently participating in the registry as a blend of big and small supplement brands. “It really is a mix,” he says. “Of those 68, 44 of them are CRN members, so that means the other 24 are non-members. Some of those are big companies, like GNC, and some of them are much smaller.”

In addition to the companies participating in Tier 1 of the registry free of charge, Mister confirms that there are also companies already paying to participate in Tier 2, which allows companies to upload additional documents such as certification documentation, etc., and control who sees the information.

Now that the association and the industry have seen the Supplement OWL in action, Mister says CRN has identified some near-term goals and key areas for improvement.

First and foremost is to get more companies to participate in the registry, a promotional effort that CRN has pursued for much of this year. “I think we’re off to a really good start,” Mister says. But, he adds, “We think this needs to grow much bigger. Nobody really knows how many labels are in the industry, but we think it’s at least 40,000 and could be more. So, we’ve still got a ways to go.”

Other goals involve making the registry even easier to use. “We’ve had some companies that have had very smooth processes” uploading labels to the registry, Mister says. “And, quite honestly, we’ve had some companies that have had some hiccups along the way. We’re working with our partner, UL [Underwriters Laboratories], to iron those out, and we think we’re doing a pretty good job as we identify those kinds of issues.”

One of the goals CRN has for improving the user experience is to enhance the registry’s self-service functionality. In the beginning, at least, companies currently must work pretty closely with UL on learning to use the system and uploading labels; however, Mister says, once companies are familiar with the system, they should be able to navigate it more independently. In addition, CRN believes there are opportunities for select third-party vendors to help companies, for a fee, upload their label information to the database so that companies do not have to "commit internal resources to do it themselves,” Mister says. He adds that the association has already identified a few vendor candidates for the job.

The association is also planning to convene an advisory panel for the registry. This panel would identify ways to improve the registry, including better defining the scope of Tier 2 and standardizing what kinds of documents and information should be posted, as well as identifying what types of company information retailers would find most useful.

Finally, Mister says, one of CRN’s biggest goals is to encourage retailers to make participation in the supplement OWL a prerequisite for supplement companies who wish to do business with them.

“Because we really do think that, as retailers use it and start to ask their suppliers, ‘Gee, why aren’t you in this registry?’ that this will create a lot of momentum for the Supplement OWL that will make companies want to get in,” Mister says. “We’re working really hard to make sure that retailers are aware of the potential of this so that they will be our surrogates in asking, ‘Why aren’t you in this?’”

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U.S. Herbal Supplement Sales Up 7.7% in 2016

U.S. sales of herbal supplements continue their impressive growth streak. In 2016, U.S. sales increased by 7.7%, making 2016 the 13th consecutive year of growth for herbal supplements, according to a new HerbalGram report published by the American Botanical Council (ABC; Austin, TX). U.S. consumers spent an estimated $7.452 billion on herbal supplements last year, or roughly $530 million more than in 2015. The report also notes that 2016 marked the first year U.S. sales of herbal supplements exceeded $7 billion. According to the HerbalGram report, growth in 2016 was relatively consistent with the growth rates of years past, if not more impressive. According to the report, 2016’s sales growth is the second highest rate of growth in this category in over a decade. In 2015, the category saw a 7.5% increase in sales, and in 2014, sales of herbal supplements were up 6.8%.

The HerbalGram report is based on retail sales data from the Chicago-based market research firms SPINS and IRI, and from Nutrition Business Journal (NBJ). ABC notes that the report “does not reflect the sales of most herbal teas, botanical ingredients used in cosmetics, or government-approved herbal drug ingredients in over-the-counter medicines.”

Per the report, sales increased for the eighth year running in each of three primary market channels: mainstream channel, which showed an 11% increase over 2015; natural channel, with an increase of 6.4% over 2015; and direct-to-consumer sales, with a 7.3% increase over 2015. Bitter herbs and products marketed for gastrointestinal health were particularly successful categories in 2016, indicating a trend toward “systemic wellness.”

Mark Blumenthal, founder and executive director, ABC, commented on the upward sales trend for the natural supplements category in a press release: “This report documents the consistent growth of consumer demand for natural remedies, as evidenced by the increased sales of herbal dietary supplements. This is indicative of a well-demonstrated, long-term trend toward natural medicine and consumers’ interest in taking responsibility for their own health via the responsible use of herbal medicine as an integral part of self-care.”

Mainstream Channel

Mainstream-channel sales numbers capture data from supermarkets, drugstores, military commissaries, buyer’s clubs, “dollar stores,” and convenience stores, and include data from Walmart and Costco. In the mass-market sector, horehound (Marrubium vulgare), commonly used to relieve upper respiratory symptoms, was once again listed as the top-selling herbal dietary supplement. With sales of $125,468,033 in 2016, up 9.3% from 2015, horehound remained the top seller for a fifth consecutive year. After horehound, cranberry (Vaccinium macrocarpon) was the second highest-selling herbal supplement, with echinacea (Echinacea spp.) rounding out the top three. Other top sellers included green tea (Camellia sinensis), black cohosh (Actaea racemosa), and garcinia (Garcinia gummi-gutta).

For the most part, the top herbal supplement ingredients held steady in 2016; however turmeric (Curcuma longa), fenugreek (Trigonella foenum-graecum), and boswellia (Boswellia serrata) all showed significant growth over the previous year, with an 85.5% increase, a 52.1% increase, and a 118.7% increase, respectively. As Nutritional Outlook reported in last year’s coverage, the sales growth for turmeric and boswellia are indicative of increased consumer interest in anti-inflammatory ingredients—a trend that is showing no sign of slowing. In addition, both turmeric and ivy leaf (Hedera helix) cracked the top 10 mainstream rankings.

The ingredients with the strongest mainstream growth in 2016 were wheatgrass (Triticum aestivum) and barley (Hordeum vulgare) with a 131.9% increase in sales over 2015. As the report notes, SPINS groups the two ingredients together, as they are both members of the grass family. Total mainstream sales for wheatgrass and barley were $5,770,618. Both ingredients are considered “superfoods;” the report says, and their sales success is likely due in part to the green beverage trend that gained traction in 2016. Both ingredients are said to be nutrient dense, with wheatgrass offering a range of purported health benefits, including digestive health support, detoxification, and improved strength, and barley boasting cardiovascular and digestive health benefits, among others.

The top-10 selling herbal ingredients in the mainstream channel were:

1. Horehound (Marrubium vulgare)
2. Cranberry (Vaccinium macrocarpon)
3. Echinacea (Echinacea spp.)
4. Green tea (Camellia sinensis)
5. Black cohosh (Actaea racemosa)

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9. Ivy leaf (Hedera helix)
10. Turmeric (Curcuma longa)

*View the HerbalGram article for a complete list of the top 40 sellers.

Natural Channel

In the natural channel, where sales come from what marketers call “core shoppers,” or consumers who are “committed to a natural lifestyle,” turmeric was the number one ingredient for the fourth consecutive year, posting total sales of $47,654,008, and up 32% from 2015. Though turmeric was the top seller, two other ingredients showed greater sales rates from 2015 to 2016: sales for ashwagandha (Withania somnifera) increased by 55.2% in 2016, while sales for cranberry increased by 36.2%. The report notes that while turmeric has been on the rise for a few years now, 2016 was the year sales for turmeric spiked. Per a search engine query of that time, Google named turmeric the “breakout star” of the functional food movement, and searches for turmeric had increased by 300%.

Broadly, the report indicates that there is a market shift underway toward ingredients that promote overall health and wellness rather than specific health benefits. In last year’s report, ABC called attention to increased consumer interest and awareness of Ayurvedic herbs, which it says contributed to ashwagandha’s increased sales in 2015.

That trend has continued into 2016, but the new HerbalGram report also attributes its success to consumer interest in adaptogenic herbs, or “superherbs,” which it says are “non-toxic substances that promote the normalization of bodily functions and support a healthy response and resistance to ‘noxious factors’ or stressors.” Other ingredients in the report that showed increased sales include mushrooms (up 13.8%), ginseng (Panax spp. Araliaceae, 9.3%), rhodiola (Rhodiola spp. Crassulaceae, up 5.5%), and holy basil (Ocimum tenuiflorum, up 2.8%).

The top-10-selling herbal ingredients in the mainstream channel were:

1. Turmeric (Curcuma longa)
2. Wheatgrass and barley grass (Triticum aestivum and Hordeum vulgare, respectively)
3. Flaxseed (Linum usitatissimum) and/or flax oil
4. Aloe vera
5. Elderberry (Sambucus nigra)
6. Milk thistle (Silybum marianum)
7. Maca (Lepidium meyenii)
8. Ashwagandha (Withania somnifera)
9. Echinacea (Echinacea spp.)
10. Saw palmetto (Serenoa repens)

Finally, U.S. direct-channel sales of herbal supplements increased by 7.3% over 2015, reaching $3.609 billion in 2016. Per the report, the sales data for direct-channel sales is collected from multilevel marketing companies and encompasses mail- and Internet-order sales companies, direct-response TV and radio sales, and sales by health practitioners.

*View the HerbalGram article for a complete list of the top 40 sellers.

Amarin’s Vascepa Omega-3 Drug Aims to Eliminate Dietary Supplement Competition with International Trade Commission Complaint, CRN Says

As new omega-3 drugs enter the heart-health market, the relationship between the drug and dietary supplement industries, where omega-3 has been a star player for decades, grows more complicated. On August 30, drug firm Amarin Pharma filed a complaint with the International Trade Commission alleging that synthetically produced omega-3 dietary supplements that are predominantly composed of EPA in either ethyl ester or re-esterified form are synthetic and therefore not considered “dietary ingredients” under Section 201(ff)(1) of the Federal Food Drug and Cosmetic Act (FD&C Act)—meaning they are not legal dietary supplements at all but unapproved new drugs. Amarin’s own omega-3 Vascepa drug contains EPA omega-3 in ethyl ester form and is synthetically produced.

In its complaint to the ITC, Amarin “respectfully requests that the U.S. International Trade Commission (the ‘ITC’ or ‘Commission’) commence an investigation into the unlawful importation or sale in the United States of synthetically produced omega-3 products that are predominantly comprised of EPA in either ethyl ester (‘EE’) or re-esterified (‘rTG’) form and are falsely labeled, and/or promoted for use as, or in ‘dietary supplements’ (the ‘Synthetically Produced Omega-3 Products’).” The complaint names many of the dietary supplement industry’s leading omega-3 marketers and ingredient suppliers, including DSM, Nordic Naturals, Pharmavite, Carlson Labs, and Nature’s Bounty, among others.

Per the complaint, Amarin alleges that these omega-3 products are falsely labeled as dietary supplements, which it says “constitutes an unfair act and/or unfair method of competition.” Citing the FD&C Act, Amarin says that such supplements are actually unapproved “new drugs.” According to Amarin, the esterified and re-esterified omega-3 ingredients in some supplements undergo manufacturing changes that lead them to be considered synthetic ingredients—and, therefore, according to the FD&C Act, not dietary ingredients. The complaint also specifies that Amarin is not requesting an investigation into “common fish oil” or into “synthetically produced omega-3 products in...
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EE or rTG form that are not predominantly comprised of the omega-3 acid, EPA.*

Amarin takes particular issue with what it deems “false labeling” and unfair promotion of these ethyl ester or re-esterified EPA omega-3 supplement products because, it says, pharmaceutical companies “have invested the necessary resources to bring competing drug products to market.” Ultimately, Amarin states in its complaint, there is no incentive for other drug companies to invest in the development of products containing these forms of omega-3 if supplements manufacturers are able to "avoid the drug approval process and the associated time and investment necessary to conduct clinical trials that show their products are safe and effective for each intended use and to obtain FDA approval for each intended use.”

Nutritional Outlook interviewed Duffy MacKay, ND, senior vice president, scientific and regulatory affairs, Council for Responsible Nutrition (CRN; Washington, DC), on how this ITC complaint could affect the omega-3 dietary supplements industry. MacKay said he is skeptical that Amarin's complaint has legs to stand on. "Amarin is trying to stamp out the competition," MacKay told Nutritional Outlook. "It also seems they're lacking in some specificity. They refer to this ethyl ester form or rTG [that are] predominantly EPA. So, they're really looking at concentrated formulas that are mostly EPA, but that's a big gray [area]. Does that mean 51% EPA, or does that mean 98% EPA? To me, that signifies that they don't really know what they're trying to make a grab for. They're really trying to eliminate a broad section of their competition."

As Nutritional Outlook previously reported, ethyl ester EPA fatty acids are chemically connected to ethanol using processing technology that allows the ethyl ester forms of EPA or DHA to be concentrated—via molecular distillation or other procedures—producing omega-3 "concentrates" that can then be used in dietary supplements. These can also be converted back to the triglyceride form for supplements ("re-esterified" triglycerides). As Nutritional Outlook has also previously reported, demand and innovation around omega-3 high concentrates in the dietary supplements market is growing.

In the ITC complaint, Amarin devotes much discussion to comparing the chemical profile and molecular composition of its ingredient versus omega-3 supplements, noting several molecular forms and mixtures of synthetically produced omega-3 supplements in which ethyl ester or re-esterified EPA is the predominant component. But MacKay said that Amarin is overlooking a major detail in how FDA distinguishes between drugs and dietary supplements.

"I'm a scientist, and I see major gaps and flaws in their technical, regulatory, scientific arguments," MacKay explained. "They're overplaying the synthetic concept. I think their regulatory argument seems spotty because they keep accepting ethyl ester EPA as being a drug, and they never once address a very important distinction, which is that FDA doesn’t regulate and distinguish between supplements and drugs based on the chemistry. They do it based on the intended use.”

On top of that, he said, EPA has long been a mainstay of the supplements industry as a dietary ingredient naturally found in fish oil. Though Amarin’s complaint cites EPA omega-3 research from the 1980s conducted by the National Institutes of Health (NIH), MacKay noted that this doesn't necessarily mean that the research that was done on EPA was exploratory research for drug purposes, or that the research was conducted on Amarin’s specific product. “The bottom line is fish oil was already being sold a dietary supplement at the time, and people were already using ethyl ester at the time,” he said.

Now that one drug company has filed a complaint, will more follow suit? Or will it be possible for supplement and drug companies to coexist moving forward? MacKay pointed out that Lovaza (GlaxoSmithKline) has been able to coexist alongside the omega-3 supplements category for years without trying to erase the competition.

“Amarin is not the first ethyl ester fish oil to become a drug. We already have Lovaza; they’re a drug. They coexisted for over a decade with all the dietary supplement fish oils. Along comes Amarin, and one of their business strategies is obviously to squash the competition by accusing the entire supplements industry of selling an unapproved drug, and going to the International Trade Commission—which is absurd, because this is FDA jurisdiction. FDA should make the decision whether EPA in the ethyl ester form is a drug or not. And it’s not," he said.

The market for omega-3 supplements can operate separately from the market for omega-3 drugs, said MacKay. While 170 million Americans use supplements, there's a large swath of the population who do not engage with supplements; rather, their cardiologist may prescribe an omega-3 drug with a higher omega-3 concentration, for example. Those consumers who would not have gravitated towards a supplement may thus be more receptive to EPA omega-3 in drug form. This, MacKay said, is one of the biggest reasons that omega-3 drug and supplements companies have not yet come to blows. When Lovaza entered the market, MacKay said, "it didn't put a damper on supplement growth in that category."

Finally, while it’s true that omega-3 supplements formulated with higher concentrations of actives are becoming more popular, MacKay said he doesn’t think that such products will take over the omega-3 supplements category anytime soon. For one thing, consumers who take omega-3 supplements likely do so for general health, or for general eye- or heart-health, and not necessarily for the same reasons that patients take omega-3 drugs. And, he said, because highly concentrated omega-3 supplements are generally more expensive than standard omega-3 supplements, the audience for high concentrates remains limited.

For now, said MacKay, the dietary supplements industry is going to have to go on the defensive to ensure that Amarin’s complaint is unsuccessful and unable to set a precedent. "The fight is going to be interesting. Will it be the individual companies named going and fighting one by one against Amarin? Or, will...the entire industry, who sees it as a matter of principle, get together and fight another fight against them?" said MacKay. "Because we don’t want to see precedent set. This is a
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champion ingredient, it’s a safe ingredient, something our industry is very proud of, so they’re going to have the issue of the entire industry, unnamed in the complaint, being very concerned about this.”

According to MacKay, those named in the ITC complaint likely need to rely on a defense based on FDA policy. “They’re trying to skirt things and go to the trade commission, and I think that it needs to be brought back to FDA for determination,” he said. “I think that’s going to be a main strategy.” MacKay emphasized that FDA is, and should continue to be, the appropriate regulatory body with the final word on this complaint.

CRN Submits Filings to ITC

CRN also announced that on September 14, the association submitted two filings to the ITC, urging the ITC to reject Amarin’s complaint.

The first of CRN’s filings argues that Amarin’s complaint runs counter to public interest in that its desired prohibition of the importation or sale of ethyl ester or re-esterified omega-3 supplements would limit consumers’ ability to purchase such supplements without a prescription. If successful, not only would the complaint affect the cost and availability of omega-3 supplements, CRN said, but it would also “further convert a highly competitive market to an Amarin monopoly.”

The filing further states that these omega-3 dietary supplements should not be considered a threat to Amarin’s Vascepa drug because, as MacKay pointed out, consumers who take omega-3 supplements do not necessarily take supplements for the same reason pharmaceutical users take Vascepa (to lower high triglycerides).

In a press release from CRN, Steve Mister, president and CEO, CRN, echoed MacKay’s sentiments. “This appears to be a case of a company seeking a market monopoly that would deprive both legitimate manufacturers of selling legal fish oil supplements and consumers of having access to products that benefit their health and well-being,” he said.

In addition, CRN said, there are substantial legal deficiencies in Amarin’s complaint that should delegitimize the company’s request for an ITC investigation. This is the focus of CRN’s second filing to ITC, which narrows in on Amarin’s claims that “concentrated omega-3 supplements have not been recognized as dietary supplements by the FDA.” CRN’s complaint notes that it is first and foremost the jurisdiction of FDA, not the ITC, to determine whether or not the omega-3 products in question are legal dietary supplements. On this basis, CRN’s complaint says, the ITC should reject Amarin’s complaint and defer to the FDA.

In the CRN press release, Rend Al-Mondhiry, associate general counsel, CRN, stated, “Amarin is inappropriately seeking to bypass the U.S. Food and Drug Administration’s (FDA) rightful authority to make this determination by filing its complaint with the ITC,” she said. “Contrary to Amarin’s assertions, FDA has exclusive authority to make this determination.”

In asking the ITC to make a legal determination on Amarin’s complaint, CRN said, Amarin has crossed a “legal boundary.”

While the complaint is undoubtedly concerning to those in the supplements industry, ultimately MacKay said he isn’t too worried about Amarin’s complaint succeeding. “I don’t think they have a chance,” he said. “But,” he added, “more nonsensical things have happened in DC.”
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Magnesium: Essential but Forgotten?

Many forget how essential magnesium is for good health—and how a deficiency could result in myriad issues.

By Andrea Rosanoff, PhD,
Center for Magnesium Education & Research LLC

One of the first lessons any student of biology learns is that cells are the basic structural, functional, and biological unit of all living organisms. It’s fascinating to think about: humans, plants, and animals all contain these microscopic units of life that provide structure for the body, take in nutrients from food, convert those nutrients into energy, and carry out specialized functions. Cells are called “the building blocks of life” and make us who we are as living things...but what makes a cell?

As a scientist, I know this is not an easy question to answer. We’ve been looking at cells since 1665 when Robert Hooke first noticed the tiny structures through his observation of cork, so it goes without saying that the literature and research on the inner workings of a cell are quite extensive. However, after receiving my PhD in nutrition with a specialty in minerals from the University of California at Berkeley in 1982, I was shocked to realize that a certain element of cell chemistry (no pun intended) was not receiving the recognition it deserved in the academic and medical community. An integral part of a cell’s health and longevity, magnesium had more or less gotten lost in the shuffle of exciting research emerging in the world of nutrition.

Wonderful, impressive research has been conducted on nutritional magnesium, but unintended neglect of this body of work has led many of us to forget how essential magnesium is for good health—and how a deficiency could result in myriad issues. Magnesium is important to so many aspects of the cell—both in structure and function—at the cellular level, the microcellular level, and the protein structure level. Nutritional magnesium is deeply involved in energy production, oxygen uptake, central nervous system function, electrolyte balance, glucose metabolism, and muscle activity—including that of the heart.

The heart is composed of cells, and magnesium contributes to the integral strength of the muscle itself. When magnesium levels begin to drop, basic functions of energy production and cell structure can be affected. The cells begin to malfunction, suffering from a weak membrane system, and calcium and sodium will rush in, resulting in an inability to properly alternate between active and inactive states. This disruption results in a variety of symptoms of heart or cardiovascular disease. Further research has shown that low magnesium levels may cause muscle cramps, migraines, chronic fatigue, and other debilitating conditions.

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blocks, a living thing’s foundation begins to crumble.

So, why now? Why was magnesium research under-taught and under-promoted for so long? What changed since my days at Berkeley that has my colleagues and me so interested in promoting the essential role this mineral plays in health and wellness?

Take a look at the past 70 years, or so. Before the 1950s, reports of magnesium deficiencies were few and far between. Why? Because the average diet in the United States was still heavily plant-based and limited to what was readily available in the garden, cellar, or icebox. Many Americans lived and worked on farms, and the urban sprawl had not yet occurred, so the development of commercial food processing had not yet made its way into our stores and kitchens. Eventually, though, we learned how to make more food in less time.

The rise of industrialization no doubt changed the way the world eats—and, in many ways, for the better. Longer shelf lives, mass production, and an increased access to anything under the sun, in season or not, are innovations we’ve welcomed and embraced as we and our loved ones live longer, more prosperous lives. However, much of this innovation strips our food of essential vitamins and minerals, making it last longer and taste great but not as nutrient-rich. Therefore, we could all use a little fortification.

Magnesium is an oft-striped mineral, and, as illustrated above, that’s a problem. It’s been identified as a shortfall nutrient according to the 2015-2020 Dietary Guidelines for Americans, meaning we’re not getting enough in our diets. The softening of water and wheat processing are just two of the ways magnesium misses the tips of our tongues, so it’s crucial that we do our best to eat magnesium-rich foods—spinach, legumes, nuts, whole grains, bananas—and incorporate supplements containing magnesium into our daily regimens.

As research supporting the life-changing benefits of magnesium makes its way to the forefront of nutrition science, I urge my colleagues, the industry, and other stakeholders to take notice. Modern society continues to innovate, and we must applaud advancements and look ever toward the future, while keeping in mind that, without a solid foundation—those building blocks, those batteries—we’ll be unable to reach our full potential.

Andrea Rosanoff, PhD, is the director of research and science information outreach at the Center for Magnesium Education & Research, a group of independent scholars dedicated to the health of humankind by promoting knowledge of nutritional magnesium and its peer-reviewed science. Visit www.magnesiumeducation.com.
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The number of global sports nutrition product launches has increased significantly, particularly over the past three years or so, according to Innova Market Insights data. This increase is largely driven by expanded use beyond traditional strength and endurance sports by a mainstream audience. Mainstream users, including exercisers and those leading active lifestyles, are interested in “performance” products with recreational- and lifestyle-driven positioning mainly to improve their nutritional intake and/or some aspects of health, well-being, performance, muscle growth, and recovery from exercise. Luckily, these consumers will find a growing array of sports nutrition products in mainstream outlets in all major markets, beyond just in gyms and health clubs.

Consumers’ increased interest in sports and performance drinks was the first signal that sports nutrition was headed mainstream.

The U.S. sports nutrition market is highly developed. In fact, the U.S. market accounted for 39% of global sports nutrition launches recorded by Innova Market Insights in...
May 2016-2017, which is a very large market share for just one country. And, actually, this percentage has fallen from over 50% five years previously. Subsequently, sports nutrition interest has increased in other parts of the world, particularly Europe, which has seen launch numbers more than double and now account for a leading 40% share of the global market.

**Sports Powders**

There are six main sub-categories in sports nutrition. Despite rising demand for more convenient, ready-to-use products in general, sports powders continue to dominate in terms of launch activity, accounting for 49% of global launches in May 2016-2017 (and up to 58% of launches in the U.S.).

Sports powders generally retail in traditional large tubs, although reclosable stand-up pouches have recently become more popular. The most popular flavors for launches are similar to those in the mainstream shake market overall: chocolate, vanilla, and strawberry. Other fruits used singly and in blends in recent launches include orange, lemon, mango, kiwi, passionfruit, and blueberry. Other on-trend flavors in recent months include coconut and coffee, while more complex cookie- and dessert-style flavors are also becoming popular, particularly in the U.S.

**Sports Supplements**

After sports powders, sports supplements have the highest number of product launches in the United States. In the United States, sports supplements accounted for 15% of total U.S. sports nutrition launches—higher than the global average of just under 12%. The interest in sports supplements aligns with the greater popularity of dietary supplements in the United States in general.

Traditional capsules and tablets are increasingly being joined by chew and gummy formats for ease of consumption, as well as some liquid products, both concentrated and ready to drink. Key ingredients used include specific amino acids and amino acid blends, vitamins and minerals, and omega-3 fatty acids.

**Beverages**

The rise of the sports and performance drinks market was probably the first indication of a move mainstream for sports nutrition products. The RTD sports drinks market is long established in the U.S., where it is worth approximately US $6.5 billion a year through multiple retailers alone (IRI data). The RTD market is now dominated by the major soft drink companies, with PepsiCo owning Gatorade and Coca-Cola owning Powerade. These brands have continued to compete and drive the market forward with ongoing new product activity, focusing on developing more targeted products as well as a range of flavors and formats, including the release of limited editions.
Marketing

Despite rising demand for more convenient, ready-to-use products in general, sports powders continue to dominate in terms of launch activity.

Interest in energy drinks took some of the focus away from the more mature sports drinks market in the mid-2000s, but the sports drinks market endured, spurred by the development of more targeted products and the launch of “light” varieties. More recently, the emphasis on performance and the booming interest in protein drinks has regenerated interest in the sector, especially from more casual users looking for products for a healthy lifestyle.

There may be a relative lack of innovation opportunities, however, as the number of RTD sport drinks launches are limited in comparison with some other parts of the sports nutrition market. Ready-to-drink sports drinks accounted for just 6.5% of U.S. sports nutrition launches in May 2016-2017, with the smaller and newer protein sports drinks sub-category responsible for a further 4.7%.

Sports Bars
Sports bars is another sub-category that has benefited from the rising interest in protein, not only in the performance sector but also in the food and drinks industry as a whole. In terms of launch activity in the U.S., sports bars took the number-three spot, accounting for 9% of sports nutrition product launches—behind sports powders and sports supplements. Nearly 88% of sports bar launches in May 2016-2017 were positioned on an “added protein,” “high in protein,” or “source of protein” platform.

Many sports bars take advantage of multiple marketing claims, including clean-label claims about no artificial colors, flavors, or sweeteners; “free from” claims such as gluten-free and non-GMO; and now, with the overall rise in interest in vegan diets, vegan-friendly claims. Examples of recent launches in the U.S. include Powerbar’s Clean Whey Bar and Cytosport’s Muscle Milk Protein Bar, as well as Hammer Nutrition’s Vegan Protein Bar.

Developing, Diversifying
In general, the sports nutrition sector continues to expand and diversify. The range of products is growing, with more mainstream options for everyday activity growing alongside demand for specialized products targeting more specific strength and endurance needs.
A double-blind, placebo-controlled study* showed that after eight weeks of taking Celadrin capsules, average walking ability increased 45%, and participants claimed a 35% decrease in knee discomfort. Results were significantly better than those seen in the placebo group, with no negative side effects.

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*Oral Cetylated Fatty Acids for the Improvement of Functional Ability and Pain in Patients with Knee Osteoarthritis, Jay K. Udani, M.D., et al, Medicus Research LLC, UCLA School of Medicine, Dept. of Medicine. These statements have not been evaluated by the FDA. This product is not intended to diagnose, treat, cure, or prevent any disease.
Protein is so popular these days that it seems nobody can get enough of it. Not getting enough protein can literally be a struggle, however, partly because certain factors impede our ability to fully digest and use the protein we consume. That’s why ingredients that promise to “boost” protein’s power are attracting more and more attention these days. But what do we really know about how these ingredients unlock protein’s potential—and what evidence do we have that they actually do so?

Muscle-Building Bedrock
One thing we do know is that as a trending nutrient, protein maintains its pull. Notes Shawn Baier, MS, MBA, chief operating officer, Metabolic Technologies Inc. (Ames, IA), “We’re most definitely still talking about protein. In sports nutrition, it’s front and center as a key product feature.”

To wit: Fully 90% of the 7+% CAGR that Technavio predicts for the U.S. sports-nutrition market by 2019 will likely come from sales of protein products, says Mallory Junggren, marketing director, Nutrition 21 (Purchase, NY). “This proves that protein products remain the bedrock of the sports-nutrition industry,” she declares.

But protein’s popularity extends beyond sports enthusiasts. Recent years have seen the macronutrient colonize mainstream meal replacement and healthy
snack formulations, says David Keller, vice president of scientific operations, Ganeden (Cleveland). A 2017 Ganeden-sponsored Survey Sampling International (SSI) look at the buying habits of health-conscious consumers found nearly half of all respondents select protein products as “typically purchased items,” Keller notes, “showing that there’s still a large amount of interest in the category.”

What Doesn’t Kill You Makes You Stronger

But for athletes and active types, protein serves a very particular purpose. As Jim Komorowski, chief science officer at Nutrition 21, explains, “During exercise, or just periods of heightened physical activity, muscle fibers are damaged, making them more susceptible to fatigue or injury.” Counterintuitively, it’s this fatigue that signals the body to begin a process called muscle protein synthesis (MPS), “which works to repair and replace damaged muscle fibers through fusing them together into new, strong muscle-protein strands,” Komorowski continues. “As these strands increase in number and thickness, they create muscle growth.”

To feed that growth, the body needs muscle tissue’s basic building blocks: amino acids. And “for those athletes pushing their bodies in training and performance,” says Baier, “dietary protein provides a source of these necessary building blocks to build new and repair existing muscle.” When dietary protein is insufficient, “the body turns to its own muscle tissue to meet the requirement for amino acids,” he says—which kind of defeats the purpose of muscle-building exercise in the first place.

On the Level

Just how much protein athletes and active people need is a moving target, as no two bodies—and no two bodybuilding regimens—are alike. But this we can conclude: “Compared to the RDA, athletes and active people need more protein to ensure they’re meeting the elevated demand for muscle repair and recovery,” Baier says.

A “common approach” he’s observed among athletes is to consume 1 gram of protein per kilogram of body weight “at a minimum,” Baier says, though he’s also seen recommendations for as much as 2 grams per kilogram for some athletes.

Indeed, Ralf Jäger, FISSN, CISSN, MBA, managing member, Incenovo LLC (Milwaukee), notes that intakes of up to 2.3 to 3.1 grams protein per kilogram of body weight per day “may be needed to maximize the retention of lean body weight in resistance-trained subjects during hypocaloric periods.” While emphasizing that optimal intakes for maximizing MPS will vary, he says that 0.25 gram\(^2\) of high-quality protein—that is, protein rich in essential amino acids and especially the branched-chain amino acid (BCAA) leucine—per kilogram of body weight, or an absolute dose of 20 to 40 grams, makes for a wise general recommendation. “These protein doses should ideally be evenly distributed every three to four hours across the day,” Jäger adds.

Barriers to Entry

So, are gym rats and weekend warriors getting their fill? Given the surfeit of protein-packed products in workout bags, it would be puzzling if they weren’t. But either way, as important to athletes as the amount of protein they take in may be how their bodies do with that protein once it’s in there.

As John Deaton, vice president of science and technology, Deerland Enzymes & Probiotics (Kennesaw, GA), says, “Many athletes and active individuals are consuming more protein in one sitting than their bodies can effectively digest and use.” Whey protein, for instance—the gold standard for MPS thanks to its full complement of essential amino acids and the BCAAs leucine, isoleucine, and valine—requires hydrolysis to smaller particles within 90 minutes of consumption to be effective. Yet “it takes approximately 90 minutes for whey to pass from the stomach through the small intestine for digestion, absorption, and assemblage into a bio-usable form for muscle synthesis,” he explains. Undigested portions go right through the body, “rendering them useless to active individuals hoping to improve muscle recovery.”

What’s more, the body’s failure to hydrolyze whey protein into smaller bits leaves larger peptides in the digestive tract, where they produce the bloating, nausea, and cramping that plague many who consume a large amount. “Some may chalk up these discomforts to lactose intolerance, since whey is a dairy protein,” Deaton notes. “However, lactose isn’t present in whey isolates.” The culprit, rather, is the whey itself.

And even if smooth digestion and thorough hydrolysis were a given, there’s another potential barrier to athletes’ ability to pack in enough protein: “Consumers may just get tired of taking their regular high-protein products because they don’t like the flavor,” Baier notes.

No wonder “simply throwing large amounts of protein into the diet doesn’t necessarily accomplish the goals of optimizing recovery or muscle health,” he concludes. “The key lies in shifting protein metabolism ‘in the right direction’—increasing protein synthesis while reducing protein degradation—resulting in a net increase in protein for muscle growth and repair,” he says.

Positive Shift

Protein marketers and sports-nutrition formulators have been looking for ingredients that give protein metabolism just that kind of nudge, as such ingredients promise not only to improve the efficacy of protein products, but to open a new arena of development for sports nutrition and protein products overall.

One such ingredient is β-hydroxy-β-methylbutyrate (HMB). Produced in the body during the metabolism of leucine, it’s “one of the most researched sports-nutrition ingredients,” Baier says, “and has mechanism-of-action data to support its benefit on protein synthesis as well as its minimizing effect on protein breakdown.”

How? It follows a “unique mechanism of action,” says Jäger, “having been shown to increase muscle protein synthesis via the
mTOR pathway”—a signaling sequence that lets cells regulate their lifecycles—"while simultaneously inhibiting muscle protein breakdown via the proteasome pathway."

By "shifting protein metabolism in a positive direction this way," Baier says, HMB lets the body better use protein’s amino acids for muscle growth and repair. What’s more, it may help us better use plant proteins, which have an amino-acid profile and leucine content "considered less optimal for athletes and active persons," Baier notes. "When HMB was combined with a plant-based protein in a recent study," he says, "the plant-based protein performed more like the whey counterpart."

By "shifting protein metabolism in a positive direction this way," Baier says, HMB lets the body better use protein’s amino acids for muscle growth and repair. What’s more, it may help us better use plant proteins, which have an amino-acid profile and leucine content "considered less optimal for athletes and active persons," Baier notes. "When HMB was combined with a plant-based protein in a recent study," he says, "the plant-based protein performed more like the whey counterpart."

Researchers also see potential in the strategic use of digestive enzymes to jumpstart protein hydrolysis and extract more nutrition from "poorer-quality" plant proteins. In a double-blind crossover study published in 2015, protease 6.0, protease 4.5, peptidase, bromelain, and alpha-galactosidase "have been shown to reduce the significant quality differences between animal and plant protein," notes Jäger.

Deaton’s company, Deerland Enzymes & Probiotics, addresses both hydrolysis and digestion with its ProHydrolase enzyme blend. "When consumed with protein," Deaton says, the blend "encourages pre-digestion of the protein, allowing the release of the full content of essential amino acids for building muscle and improving muscle recovery." And because pre-digestion cuts peptides down to size, it "reduces the potential for discomfort often associated with protein consumption," he adds.

One double-blind, placebo-controlled clinical trial—submitted for publication to a peer-reviewed journal but not yet published—examined the enzyme blend’s effect on whey protein in 20 volunteers aged 19 to 35 with normal, healthy BMIs. Each subject took the whey/enzyme blend for nine days followed by an equal interval consuming whey alone. At the study’s end, researchers found that total amino acid concentrations increased significantly more—by 55 mg—after the whey/enzyme protocol than after whey alone. "In other words," Deaton says, "taking whey and ProHydrolase provided 20% more amino acids than whey protein by itself." Moreover, the product appears to be effective not only with whey, but with casein, soy, pea, and hemp proteins, too.

Probiotics Potentiate Protein

Probiotics have earned praise for promoting a range of health benefits in their hosts, and we can add one more entry to their bag of tricks: improving protein use. Specifically, Bacillus coagulans GBI-30, 6086—the patented strain that Ganeden markets as GanedenBC30—has a large body of research validating its ability to act on "a variety of endpoints," Keller says, "including muscle damage and recovery, along with the absorption and use of protein sources."
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**Ingredients that promise to “boost” protein’s power are attracting more and more attention these days.**

Adds Jäger, the probiotic “can withstand the acidic environment of the stomach to reach the intestine where it germinates.” Following germination and activation in the small intestine, the strain seems to aid digestion of carbohydrates and proteins both, and “has been linked to an increased production of digestive enzymes,” he says.

As an added benefit, consumers are already tuned in to probiotics. Keller notes that 52% of the male and 54% of the Millennial respondents to Ganeden’s SSI survey said they were aware that probiotics could enhance protein use. Even better, upwards of 55% of parents and Millennials, respectively—told SSI that they’d willingly pay more for protein-fortified products if probiotics were included. “This shows demand beyond athletes and sports enthusiasts for not only protein products, but ones fortified with probiotics,” Keller says.

### Chromium/Amylopectin Complex

The role of insulin in carbohydrate metabolism is well established, but its effects on muscle-protein metabolism—and the possibility that some substances can increase our cells’ sensitivity to insulin—are still being teased out.

Studies do show that in the presence of sufficient levels of protein and essential amino acids, insulin appears to stimulate MPS while inhibiting muscle protein breakdown when protein and amino acid supplies are inadequate. And it also appears that the mineral chromium may boost insulin sensitivity.

So in a human clinical study published this year in the *Journal of the International Society of Sports Nutrition*, scientists investigated the effects of Velositol, Nutrition 21’s branded chromium/amylopectin complex, on MPS. Using a double-blind, crossover design, the researchers administered either 6 grams of whey protein plus 2 grams of the chromium/amylopectin complex (WPACr) or 6 grams of whey protein (WP) alone to 10 subjects (six men; four women). After receiving their respective supplements, the subjects completed eight sets of bilateral isokinetic leg extensions at 80% of their estimated one-repetition maximum.

Blood test and muscle biopsy results showed that the combination of whey and chromium-amylopectin doubled the MPS rate in subjects by 48% from baseline. “This was compared to a 24% increase from baseline when observing whey protein alone,” Nutrition 21’s Komorowski notes. Researchers concluded that “adding a novel amylopectin/chromium-containing complex to a suboptimal dose of whey protein magnified the increase in MPS from protein intake and resistance exercise.”

### Timing Is Everything?

The subjects in the previous study consumed the chromium/amylopectin complex and whey protein supplement simultaneously, which may or may not have influenced its effectiveness. But the question of timing does emerge when considering how and when to administer a protein-boosting supplement.

For his part, Deaton says that “since protease enzymes work directly on protein to break it down,” his company’s enzyme blend “is most effective when taken with a protein supplement or meal.” Keller, meanwhile, says that while Ganeden’s probiotic strain “has science-backed health benefits even when consumed alone,” the company suggests “taking it when consuming any protein.”

Finally, Metabolic Technologies’ Baier says that HMB’s action emerges whether ingested with protein or without—but he adds that recent research indicates optimal benefits accrue when vitamin D levels are “sufficient.” “Thus, the synergistic combination of HMB and vitamin D is recommended,” he says.

So it appears we still have a lot to learn about this field. Yet it also appears to hold real promise for consumers—athletes or not. As Baier says, “There are many populations that could benefit from improved protein metabolism and improved muscle health.” Perhaps these products can help them.

**References**


**Kimberly J. Decker** writes for the food and nutrition industries from her base in the San Francisco area, where she enjoys eating food as much as she does writing about it.

**OCTOBER 2017 • NUTRITIONAL OUTLOOK**
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According to the Centers for Disease Control and Prevention, an estimated 54.4 million Americans—that’s 22.7% of the adult population—have been told they have some form of arthritis, rheumatoid arthritis, gout, lupus, or fibromyalgia. By 2040, the agency estimates that 26% of adults aged 18 or older will have doctor-diagnosed arthritis.

This, on its own, represents a clear opportunity for supplements, as consumer preferences shift to natural remedies overall. But if you ask Alexis Manfre, global category manager of nutrition and health at Naturex (Avignon, France), even within the joint-health supplement market, trends are shifting from synthetic to natural solutions.

Citing data from SPINS, Manfre explains that traditional category leaders like glucosamine and chondroitin, as well as hyaluronic acid, are experiencing sales declines. On the other hand, SPINS reports that sales of curcumin-based vitamins, dietary supplements, herbal products, and homeopathic products, for instance, are through the roof, growing 45.3% to reach $72 million last year alone.

Why? "Glucosamine, chondroitin, MSM, and various other joint-health products have been around for a long time," says Deanne Dolnick, science director for TR Nutritionals (Alpharetta, GA). "Many consumers have tried these with varying levels of success. For those who are looking for something new, curcumin is a wonderful option. Those consumers who are just purchasing their first joint-health products want the hottest ingredient. Right now, that is curcumin."

Manfre agrees, noting that the most important driver of this trend is that there exists a growing body of research to support curcumin’s benefits for joint health, spurring newfound excitement in this ayurvedic staple.

Curcumin’s joint-health benefits appeal across the board.

**BY MELISSA KVIDAHL**

Just last year, Sabinsa’s (East Windsor, NJ) Curcumin C3 Complex was used in a randomized six-week trial examining the effects of curcumin on reducing systemic oxidative burden in patients suffering from knee osteoarthritis.1 Researchers recruited 40 patients with mild to moderate osteoarthritis, and administered either curcuminoid capsules (1500 mg/day over the course of three doses) or placebo. "The results showed improvement in the osteoarthritic index and also improvement in stiffness, pain, and mobility of the joints," explains Shaheen Majeed, Sabinsa’s worldwide president. "It also showed that in the presence of curcuminoids, the oxidative stress was reduced significantly, with increases in serum levels of superoxide dismutase and glutathione, and concurrently there was a decrease in malondialdehyde concentration." Majeed says this research validates the antioxidant benefits of curcumin for osteoarthritis and its symptoms.

Osteoarthritis of the knee was also the focus of research published last year in research...
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Inflammopharmacology, which examined curcumin’s effect on the condition’s inflammatory and oxidative stress biomarkers. Researchers recruited 160 patients with knee osteoarthritis, randomly assigning them to receive either curcumin or placebo for 120 days. They were assessed on day 0, day 60, and at the conclusion of the study. Each assessment included a visual analog scale (VAS) and Western Ontario and McMaster Universities Osteoarthritis index assessment (WOMAC). Blood samples were collected to assess changes in IL-1 as well as biomarkers of oxidative stress like reactive oxygen species and malondialdehyde.

Overall, significant improvement was observed in the patients taking curcumin, as compared to placebo. The curcumin group’s VAS and WOMAC scores both improved, as did their biomarkers. The researchers concluded that ongoing administration of curcumin could improve both the markers and symptoms of osteoarthritis.

If you ask Yoshihiko Sumi, director of the science group at Tokyo-based Theravantes Corp., studies like these, which highlight the anti-inflammatory benefits of curcumin, have the potential to rebrand the ingredient as not just a joint-health ingredient but also a longevity ingredient. “This enables a better quality of life among the aging society,” he says, citing the vast implications for brain, skin, and other areas. “These are all aging-related impairments, and curcumin will be able to prevent or slow down the progressions of them.”

Hand in hand with joint health is bone health, as the latter is needed to support the former. And perhaps nothing is so closely linked with aging as the loss of bone density. According to the International Osteoporosis Foundation, osteoporosis impacts one out of every 10 women over age 60 and the numbers only increase with age, ultimately impacting two-thirds of women by age 90. Worldwide, one out of every three women over age 50 will experience an osteoporotic fracture, as well one out of every five men over age 50.

New research coming out of Indena (Milan) recently linked curcumin with bone density maintenance. Researchers enrolled 57 healthy subjects with a bone mass condition, and randomized them into two different groups. During the six-month study period, the control group followed a standard management plan, while the supplement group supplemented their standard management plans with 1 g of Meriva, Indena’s proprietary curcumin ingredient. By the end of the study, at week 24, the Meriva group gained 7.1% and 4.8% increases in bone density of the small finger and upper jaw, respectively. No changes, however, were perceived in the control group.

But additional research is showing that curcumin’s benefits aren’t just for the aging; namely, curcumin’s joint-health benefits hold promise for athletes of any age. “New market opportunities within the 30-to-60-year age group are increasing, as these consumers want to maintain their active lifestyle without the associated aches and pains,” says Lynda Doyle, senior vice president of global marketing for OmniActive Health Technologies (Morristown, NJ). “These consumers are also trying to stem the onset of age-related joint conditions.”

To that end, the company’s curcumin ingredient, CurcuWin, is being put to the test with new research examining its ability to support joint health through the reduction of inflammatory pathways, namely lipoxygenase and cyclooxygenase enzymes. This research is awaiting publication, Doyle says. “Our ongoing clinical program continues to support the efficacy of CurcuWin, allowing for the nutritional benefits of turmeric in much smaller doses,” Doyle adds. “CurcuWin provides formulators of sports nutrition products support for a

Those consumers who are just purchasing their first joint-health products want the hottest ingredient. Right now, that is curcumin,” says Deanne Dolnick.
normal, healthy inflammatory response post-exercise, which may result in increased performance and recovery after exercise.”

**Curcumin Delivers**

When an ingredient transforms a category the way curcumin has, it’s only a matter of time until consumers want their supplements via creative deliveries. And if you ask Doyle, it’s undoubtable that delivery formats for curcumin have expanded. “Beverages, gels, powders, and gummies are increasingly popular delivery systems for the joint-health market,” she says. And, as Manfre points out, “we are now seeing turmeric used in a wide variety of applications depending on the targeted benefit, including beverages, shots, capsules, tablets, softgels, instant drinks, and protein bars.”

According to Majeed, one positive trend impacting the curcumin market is the migration of curcumin-based beverages out of Japan—where they’re a part of daily life—to other regions of the world. To meet demand for clear beverages without sediment, Sabinsa has developed uC3 Clear, a clear curcumin ingredient standardized for 10% curcuminoids that makes curcumin both visually appealing and soluble.

At Novel Ingredient Services (East Hanover, NJ), patent-pending Flavor-Balancing Technology allows formulators to incorporate ingredients—including but not limited to the company’s curcumin ingredient, Acumin—into functional foods and beverages without altering test, texture, or mouthfeel. Additionally, its patented Advanced Instantization Technology uses a proprietary particle-distribution technique that allows the incorporation of even the most texture-challenged powders, including Acumin. “Who knows,” muses CEO Rick Antonoff. “Acumin water or Acumin-enhanced Gatorade could be in our future!”

**References**


Melissa Kvidahl is a freelance journalist and copywriter specializing in the health and wellness industry.
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The popularity of methylsulfonylmethane (MSM) as a dietary supplement has grown since the ingredient’s introduction over 25 years ago. As a supplement, MSM is taken for many purposes, most commonly as an anti-inflammatory agent and dietary support for joint health and mobility. Studies have shown that a variety of health-outcome measures improve with MSM supplementation, including inflammation, joint and muscle pain, oxidative stress, immune modulation, and skin appearance.

Over the years, researchers have performed an abundance of studies supporting multiple applications for MSM. Recently, a comprehensive discussion of the collective research was encapsulated in a review paper published in the journal *Nutrients*, titled “Methylsulfonylmethane: Applications and Safety of a Novel Dietary Supplement.”

In the review, the authors explore MSM’s activity in the body and its potential mechanisms of action, including as an anti-inflammatory, an antioxidant, and an immune modulator. The paper also discusses MSM’s specific benefits for reducing joint-associated inflammation, helping to preserve cartilage, reducing oxidative stress, and even reducing muscle soreness associated with exercise. Moreover, the authors discuss MSM’s other notable benefits for skin health, with some evidence suggesting that MSM may improve skin quality and texture by acting as a sulfur donor to keratin. Finally, the authors discuss MSM’s common uses and safety profile, noting that MSM appears to be well-tolerated and safe. Ahead, we take a look at five recent studies done on MSM.

**Joint Health and Mobility**

Osteoarthritis, a common, non-inflammatory, degenerative arthritis, causes moderate to major disability in an increasing number of the elderly population. Analgesic drugs and surgical interventions are commonly used to attenuate the severe pain that often accompanies osteoarthritis; however, complementary and alternative treatments are gaining popularity as a way to help lessen the pain. MSM, either taken alone or with glucosamine and/or chondroitin sulfate, may represent an alternative—and effective—way to control the pain associated with osteoarthritis.

A randomized, placebo-controlled trial on 100 subjects with hip and/or knee osteoarthritis sought to further establish MSM’s potential for joint health and mobility. At the time of this study’s publication, only one randomized, controlled trial on MSM and osteoarthritis existed. Like the new study, the first trial showed significant decrease in osteoarthritis pain. The study subjects were divided into two groups. The first group was given a dosage of 6 g/day (3 g twice daily) of distilled MSM powder, while the second group received the equivalent dosage of a placebo. Over a period of 26 weeks, the study authors recorded subjects’ “study target,” or the particular joint or joints that individual patients informed researchers exhibited the worst pain. In order to assess the osteoarthritis symptoms, the researchers used the Western Ontario and McMaster University Arthritis Index VAS (WOMAC version 3.1). The WOMAC includes subscales on pain, stiffness, physical function, and cumulative total symptoms. WOMAC calculations were recorded at baseline and again at 26 weeks (the end of the study).

At the end of the study period, the study authors noted that subjects given MSM experienced significantly less joint pain and stiffness. Indeed, all WOMAC subscales reflected significant improvements in osteoarthritis symptoms for the MSM group over the placebo group. While the results are promising, additional data is needed to confirm the effects.

**Exercise Performance/Recovery**

Inflammation and oxidative stress are by-products of strenuous exercise, and lead to pain and/or discomfort. This, in turn, can inhibit recovery time. While earlier studies have demonstrated MSM’s antioxidant and anti-inflammatory benefits, a 2013 pilot proof-of-concept study examined the potential relationship between MSM and post-exercise pain, specifically.

In this study, researchers randomly assigned 24 moderately exercise-trained adult men to one of two groups: a group supplemented...
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with 3 mg/day of OptiMSM, a branded MSM ingredient from supplier Bergstrom Nutrition (Vancouver, WA), or a control group given the equivalent dosage of a placebo. The study involved three tests and was conducted over 14 days with a 17-day washout period in between. Each of the three tests involved two visits. In the first visit, participants performed 28 total sets of leg extensions. Two days later, participants completed the second test, which involved 12 total sets of leg extensions. The researchers measured participants’ muscle discomfort or pain using a 10-point VAS scale and measurements of inflammation, blood antioxidant status, and homocysteine, before the exercise as well as at 2 and 48 hours post-exercise. In addition, exercise performance was recorded at 14 days of MSM or placebo supplementation.

The group given MSM exhibited significantly less pain or discomfort than did the group given the placebo. While no substantial differences were recorded for the other biomarkers, the researchers concluded that MSM has the potential to help reduce the discomfort and pain that often follow rigorous exercise.

Skin Health

Antiaging products usually focus on preserving the health of the skin—the largest organ of the body—from an outside-in perspective. But consumers are increasingly interested in beauty products and oral supplements that support healthy skin from within.

A 2015 study1 assessed the efficacy of Bergstrom’s OptiMSM as an oral supplement for overall skin health and wrinkle reduction. Twenty female participants were given either 3 g/day of MSM or the equivalent dose of a placebo for 16 weeks. The researchers evaluated skin health through expert grading, instrumentation, and participants’ self-assessment at baseline, at eight weeks, and at 16 weeks.

The MSM supplement was shown to regulate the genomic expression of key genes responsible for skin health and the prevention of aging. In addition, the group given MSM demonstrated significant improvements in the appearance of wrinkles and skin firmness, compared with the placebo group. The MSM group also had significantly fewer, smaller, and less severe wrinkles and deep lines, compared to the placebo group. The study indicated that MSM supplementation may be beneficial for overall skin health, with particular benefits for reducing fine lines and wrinkles.

Inflammation

The anti-inflammatory properties of MSM have been analyzed in in vitro studies, and it has demonstrated potential to attenuate markers of oxidative stress and muscle damage following short bouts of intense exercise.

A recent study2 sought to evaluate the effects of MSM supplementation on inflammation related to strenuous exercise and whether this in turn prevents cells from responding appropriately to additional stimuli post-exercise. Specifically, the researchers hypothesized that MSM supplementation would reduce inflammatory cytokine production in ex vivo and in vivo testing. In the study, 40 physically active men were supplemented with either 3 g/day of Bergstrom’s OptiMSM or a placebo for a study period of 28 days. Following the supplementation period, subjects were instructed to perform 10 sets of 10 repetitions of eccentric knee extensions with a two-minute rest period between sets. The researchers took blood samples to measure cytokine production once at baseline, then at 24, 48, and 72 hours post-exercise, and once more at the end of the study period.

The subjects’ blood was exposed to lipo-poly saccharide (LPS) ex vivo, thus inducing cytokine release; the cytokine levels for each subject were determined in vivo. The researchers found that MSM inhibited the secretion of the IL-1β cytokine marker in particular, and likely also the IL-6 and TNF-α markers, albeit to a lesser degree. The results indicated that MSM acts as an antioxidant, reducing induction of various cytokine markers.

Overall, supplementation with MSM did reduce resting pro-inflammatory cytokines, while values for these cytokine markers increased in the placebo group. MSM, acting as an antioxidant, may be able to blunt tissue damage and inflammation, as well as diminish muscle soreness, following intense exercise.

Alleviating Oxidative Stress

Given its purported anti-inflammatory and antioxidant properties, MSM has previously been studied for pre- and post-exercise supplementation. But a 2011 study3 sought to determine whether daily supplementation with MSM would affect markers of oxidative stress following acute bouts of exercise in untrained, healthy young men.

Eighteen participants were randomized to receive either 50 mg/kg of MSM in 200 ml of water, or 200 ml water as a placebo. The participants took the supplement or placebo daily for 10 days before running 14 km. The study authors took blood samples immediately following the run, as well as at 30 minutes and at 2, 24, and 48 hours post-exercise.

The researchers found that the acute exercise resulted in elevated levels of serum malondialdehyde, protein carbonyl, and plasma oxidized glutathione, indicating increased oxidative stress. The group supplemented with MSM, however, maintained lower levels of those markers after the run than did the placebo group. In addition, the researchers observed significantly higher plasma levels of plasma-reduced glutathione and a higher ratio of plasma-reduced glutathione to plasma oxidized glutathione compared with placebo, meaning that the subjects given MSM exhibited increased antioxidant capacity.

According to the authors, this study marked the first research on the effects of chronic administration of MSM on exercise-related oxidative stress. The results indicated that daily supplementation with MSM does have some alleviating effects on markers of oxidative stress following intense bouts of exercise, though the researchers noted that further research is needed.

References

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Scientists are just beginning to scratch the surface of this expansive arena. And while the opportunities seem endless, many challenges still need resolution.

BY MELISSA KVIDAHL

If there’s one topic piquing the attention of scientists, nutraceutical formulators, and big pharma alike, it’s the study of the human microbiome. Here lies an area that holds so much promise, from immune- and digestive-health implications to those impacting cognitive health, longevity, and more. But, like all areas of science in the infancy stage, its opportunities are matched only by its challenges.

Research Hurdles

First, researchers face the inherent challenge of the microbiome’s complexity, including its vast community of microbiota. According to one recent study, the body actually contains a 1:1 ratio of bacterial to human cells, rather than the widely cited 10:1 ratio; still, researchers also estimated that gut flora occupies a total mass of about 0.2 kg in the body, including as many as 1,000 different species. “Although some technological advancements in metagenomics methods such as high-throughput sequencing is helping make quicker work,” says Alan Rillorta, director of marketing at AIDP Inc. (City of Industry, CA), “as one can imagine, mapping and documenting the benefits of such a large number of microbiota can still take a lot of time.”

But, as Mervyn de Souza, vice president, health and wellness, new product development, innovation and commercial development, at Tate & Lyle (Hoffman Estates, IL) points out, mapping the microbiome is just the beginning of the challenges facing researchers. Beyond mapping, he says, scientists will need to understand how the microbes interact with each other and with the body, and the consequences of these interactions. “That’s compounded by the fact that we have geographical diversity, lifestyle choices, and disease states,” he adds. “When you factor in all the inherent complexities and try to start to strip away what confounds this field, I think a challenge where we will need to have increasing clarity and alignment is in how we study the microbiome.”

Indeed, the methods by which the microbiome is studied represent a challenge noted by John Deaton, vice president of science and technology at Deerland Enzymes & Probiotics (Kennesaw, GA). “It’s important to understand the limits of the techniques we currently use to analyze the microbiome,” he says, “and how to improve and perfect those techniques.”

Right now, for example, de Souza points out that sampling largely consists of fecal analysis, which is a static data point and not always reflective of the highly dynamic reactions happening within the intestines and colon, and even within specific regions of the colon. Ultimately, the limits of sampling can blur the lines between correlation and causation, he says.

“Because this area of study is new and exciting, there are many people rushing to conclusions based on what are essentially preliminary discoveries,” agrees Deaton.

One way that Tate & Lyle is addressing this issue is by making use of a technology called SHIME (Simulator of the Human Intestinal Microbial Ecosystem), which enables researchers to conduct in vitro studies.
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While Ralf Jäger, scientific advisor at Pharmachem Laboratories (Kearny, NJ), is the first to admit that extensive efforts to characterize the human microbiome, coupled with advances in sequencing technologies, have tremendously increased scientists’ knowledge in this area, it’s a challenge to really take these findings to the next level: “Current challenges include translating all these new findings into safe, clinically validated products with clinically relevant benefits for a healthy population. While the number of well-designed human intervention studies has significantly increased, this seems to currently be the bottleneck to further drive this field.”

Endless Opportunities

Despite the challenges facing this new area of research, the opportunities abound, especially for nutraceutical suppliers and manufacturers.

What’s most exciting about the microbiome is that its composition—healthy or otherwise—seems to have far-reaching effects for the entire body. “In fact, it is starting to become apparent that many diseases or disorders are characterized by a change in microbiome composition, a so-called dysbiosis or dysbiotic state,” says Andrew Morgan, fellow and nutrition and health chief scientist at DuPont Nutrition and Health (Wilmington, DE). Since dysbiosis is often induced by the depletion of a certain microbial species, opportunities exist for nutraceutical brands and manufacturers to tap into these species as next-generation probiotics.

At DuPont, the microbiome modulator of interest is currently human milk oligosaccharides (HMOs), complex glycan structures present in human milk and one of the most important modulators when it comes to infant microbiome formation. According to Morgan, they essentially act as prebiotics in that they support the growth of some microbes, but they also prevent the attachment of pathogenic microbes. In response, DuPont is working on bringing to market its first HMO ingredient (2’-fucosyllactose).

If you ask Jäger, commensal bacteria—bacteria that neither benefits nor provokes any harm to the human body—represent a distinct area of commercial opportunity for nutraceuticals. “For example, Akkermansia muciniphila is commonly found in the human gut, generally at an abundance of 1%-7% of the total bacterial population,” he says. This bacteria, he explains, has been inversely linked with obesity, diabetes, inflammation, and metabolic disorders, and people who are physically active typically have higher amounts than those with sedentary lifestyles. “While the nutritional industry is currently not able to use Akkermansia as a dietary supplement, we can use other nutritional strategies, including probiotic strains, to increase the Akkermansia population,” Jäger says.
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This type of approach opens doors to a new role for nutraceuticals: one in which formulators may be able to pinpoint the impacts of a western lifestyle, from diet and hygiene to antibiotics use, and address them directly with probiotics. “We seem to lose microbes that are key for good functioning of our immune system and other physiological functions in our body,” says Johan van Hylckama Vlieg, vice president of microbiome and human health innovation at Chr. Hansen (Denmark). “Bringing back some of these bacteria can truly impact health, and the probiotic concept is more relevant than ever before.” Addressing specific diet and lifestyle habits can even enable nutraceuticals formulators to solve challenges related to how specific foods and behaviors may influence the personal microbiome.

Essentially, since each person’s microbiome is unique—based on a variety of factors from geographical location to lifestyle choices—the ultimate goal will be to profile the microbial population of a healthy individual and compare it to that of someone with a specific health condition, says Deaton. “Probiotics, prebiotics, and other ingredients that influence the gut microbiota will be key players in formulations for a wide variety of health conditions,” he says.

**What’s Next**
In order to reach its full potential, the study of the microbiome has some ways to go.

Rillorta expects that the future holds potential for probiotics and prebiotics to be marketed towards specific health conditions; however, the specific roles that unique gut probiotic strains play on human health are not yet understood.

“The human gut microbiota comprises approximately 100 trillion microbial cells. An imbalance of the microbiota has a negative effect on many aspects of human physiology, and improving the balance by dietary intervention may be the key to improving overall health,” agrees Jäger. That said, further research is needed to, first, identify the strains that yield specific health benefits, and second, understand how those strains impact the other microbiota at play. “The short-term goal is to have better individual players, better anti-inflammatory strains, better strains to improve immune health, or strains that improve mood or help with food allergies,” he says. “The long-term goal is to have the best team on the field we can find, and [determine] how to put that team together.”

Indeed, Deaton thinks that better genome sequencing techniques are on the horizon, as they become less and less cost prohibitive, which will allow researchers to identify microbiome inhabitants with strain specificity. “I believe that the not-too-distant future holds discoveries on exactly how the microbiome affects many aspects of health such as mood, physique, immunity, and cognition,” he says. “It’s exciting to know that in the coming years, we will begin to see the trees, not just the forest.”

**THE MICROBIOME AND ANTIAGING**
A new study, published in 2017 in *Cell*[^1], found that certain bacterial genes and compounds can slow the progression of tumors and the accumulation of amyloid-beta, a compound associated with Alzheimer’s disease. The study’s researchers posit that, eventually, slowing down the aging process entirely may be possible with supplements derived from gut bacteria.

Researchers turned to the laboratory worm *Caenorhabditis elegans*, since it shares essential characteristics with human biology: throughout the course of its two-to-three-week lifespan, this worm feeds, develops into an adult, reproduces, and then ages, losing strength and health until death. In order to study the effects of individual bacterial genes on the lifespan of the worm, researchers employed a complete gene-deletion library of *E. coli*, with each sample lacking one of close to 4,000 genes. Then, they fed the worms each individual mutant bacteria and looked at its impact on the lifespan. Of the nearly 4,000 bacterial genes tested, 29, when deleted, increased lifespan. Twelve of the mutants protected the worms from tumor growth and amyloid-beta accumulation.

“Altering bacterial genetic composition in the microbiota might be an effective nutraceutical strategy to activate longevity signaling in the host, and this research provides a blueprint for searching for these genetic variants in bacterial species of the human microbiota and for genetically engineering pro-longevity probiotics,” says corresponding author Meng Wang, associate professor of molecular and human genetics and associate professor in the Huffington Center on Aging at the Baylor College of Medicine. “This research demonstrates the possibility that natural compounds purified from pro-longevity bacterial variants can directly exert beneficial effects.”

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**Reference**

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*Melissa Kristahl is a freelance journalist and copywriter specializing in the health and wellness industry.*
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The human body requires a steady and adequate supply of essential nutrients in order to maintain balance—or homeostasis—to continue operating as a finely tuned machine. Of these required nutrients, vitamins and minerals are foundational. They are the sparkplugs that make our metabolic engines run, working as cofactors for enzymes and participating in the process of energy production. One mineral, magnesium, holds a special place within the group of absolutely essential nutrients. As an indispensable mineral that acts as a cofactor for hundreds of enzymes in the body, magnesium is required by every cell in the body. Unfortunately, it’s also a mineral that many of us don’t get enough of. Studies indicate that nearly 50% of the U.S. population consumes an inadequate amount of magnesium from the diet, not meeting the estimated average requirement (EAR) for this mineral. For adults over the age of 30, the EAR for magnesium is 350 mg/day for men and 265 mg/day for women, while the recommended dietary allowance (RDA) is 420 mg/day for men and 320 mg/day for women.

As the incidence of chronic diseases—including cardiovascular disorders, diabetes, and osteoporosis—continues to rise, one can’t help but wonder how much of a contributory factor the population’s insufficient intake of magnesium has played. After all, low levels of magnesium have been linked to all of these aforementioned conditions, and some feel that even the RDA levels of magnesium are not high enough given that certain disease states, stress, and medications often further deplete bodily stores of magnesium. In such cases, they would argue, ensuring an adequate magnesium intake is even more critical.

Research continues to highlight the benefits of this magnificent mineral. Recent studies summarized here indicate magnesium’s growing importance for mental health, arterial flexibility, and metabolic function.

Mental Health
Mood disorders are now highly prevalent globally, with depression alone affecting 350 million people worldwide. One of magnesium’s key benefits seems to be supporting healthy neurological function and mental health. Researchers point to magnesium insufficiency as a potential causative factor in mood disorders, anxiety, and stress-related conditions. Fortunately, recent clinical evidence suggests that magnesium supplementation can be beneficial for these conditions.

A randomized, controlled, crossover clinical trial was conducted by Emily Tarleton and colleagues from the University of Vermont (Burlington, VT) to assess the effect of magnesium supplements in the treatment of depression. The study included 126 adults with an average age of 52 diagnosed with mild to moderate depression. Participants were assigned to six weeks of magnesium chloride supplementation (248 mg of elemental magnesium/day) or control, and the treatments were then crossed over. Assessments of depressive symptoms were performed over the phone every two weeks and improvement was evaluated via Patient Health Questionnaire-9 scores. Anxiety symptoms were also evaluated using Generalized Anxiety Disorders-7 scores.

According to researchers, six weeks of magnesium supplementation led to clinically significant improvements in depression symptoms as well as statistically significant improvements in anxiety. Moreover, the authors noted that improvements became evident within two weeks of the onset of supplementation. The supplements were well tolerated, with no significant adverse events noted.

A second trial led by researchers from Shahid Sadoughi University of Medical Sciences (Yazd, Iran) included 60 adults with diagnosed depression and magnesium deficiency. In the double-blind, placebo-
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controlled, eight-week trial, participants received 500 mg of magnesium oxide or placebo daily. The Beck Depression Inventory-2 assessment was used, and serum magnesium levels were followed from baseline to the end of the study.

Beck scores declined in both groups over the eight-week period, indicating less-severe depression symptoms; however, this decline was significantly greater in the magnesium group. Concurrently, serum magnesium levels also significantly improved over the study period in the magnesium group, with 88.5% of participants reaching normal levels at the end of the study. These results support the positive benefits of magnesium supplementation in depressed individuals.

In fact, a recently published review article authored by Anna Serefko and colleagues from the Medical University of Lublin (Lublin, Poland) highlights clinical studies indicating that magnesium administration helps with major depression as well as depression and anxiety-related symptoms secondary to premenstrual syndrome, chronic fatigue syndrome, epilepsy, and type 2 diabetes.

The authors cite possible mechanisms, including balancing and counteracting elevated levels of calcium and glutamate in the hippocampus, which leads to altered function of synapses in the brain, resulting in mood disorders and depression. A sufficient supply of magnesium would, by contrast, support the normal function of these neuronal synapses. Magnesium is also involved in both the noradrenaline and dopamine systems, which are important neurotransmitters. It further plays significant roles in modulating the stress response by controlling the access of corticosteroids to brain tissue, and it has documented anti-inflammatory activity. Both of these factors otherwise potentially contribute to mood disorders and depression.

Additionally, two recent preliminary studies in mice conducted by researchers in Denmark point to a novel mechanism of magnesium’s impact on depression and anxiety. Comparing mice fed a standard diet or a diet deficient in magnesium for six weeks, researchers noted that magnesium-deficient mice exhibited depressive behavior as well as anxiety symptoms. The investigations revealed that magnesium deficiency impacted the gut microbiota in these animals, leading the researchers to hypothesize that magnesium deficiency possibly contributes to depression and anxiety via an impact on the gut-brain axis and by influencing immune function. While further research is required to investigate the influence of magnesium on the gut microbiota, it is clear that magnesium influences several aspects of healthy neurological function and contributes greatly to the maintenance of mental health.
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Magnesium intake is linked to improved cardiovascular health. For example, a meta-analysis published in 2013 including 16 studies with over 313,000 individuals found that for every 200 mg/day increment in magnesium intake, there was a 22% reduced risk of ischemic heart disease; moreover, higher circulating levels of magnesium were associated with a 30% reduced risk of overall cardiovascular disease.8

Given that dietary magnesium intake has been associated with a significant risk reduction in ischemic heart disease, Peter Joris and colleagues from the Maastricht University Medical Center (Maastricht, The Netherlands) sought to investigate the ability of supplemental magnesium to maintain arterial flexibility.9 In this double-blind, placebo-controlled, 24-week study, 52 healthy obese and overweight adults with an average age of 62 were assigned to either supplement with magnesium (350 mg/day elemental magnesium as magnesium citrate) or placebo. Measurements were taken at baseline, at week 12, and upon study completion, and included serum magnesium concentrations, 24-hour blood pressure readings, as well as carotid-to-femoral pulse wave velocity (PWV) assessments, which is considered the gold-standard measure of arterial stiffness.

While the study results did not show a significant effect of magnesium supplementation on blood pressure (average blood pressure in both groups was already within normal limits at baseline), at the end of the study, the group supplementing with magnesium had a significant change in carotid-to-femoral PWV measurements, showing a reduction of 1.0 meter/second (m/s) and indicating an important reduction in arterial stiffness. Previous epidemiological research has shown that a decrease in carotid-to-femoral PWV of 1.0 m/s is associated with a 14% decrease in risk of cardiovascular events10, highlighting the significance of the findings in the current study and demonstrating the benefits of daily magnesium supplementation.

Onepossible explanation for the ability of magnesium to help support arterial flexibility is that magnesium helps prevent vascular calcification. In a recent review, Anique ter Braake and colleagues from Radboud University Medical Center (Nijmegen, The Netherlands) summarize experimental evidence suggesting that magnesium prevents vascular calcification through multiple mechanisms.11 Magnesium’s effects can be divided into two unique pathways.

The first pathway is passive interference, suggesting that the presence of magnesium in circulation favorably alters the environment to prevent vascular calcification processes. Research points to the fact that dietary magnesium reduces the absorption of inorganic phosphate molecules by binding to them in the intestines. These phosphate molecules would otherwise be necessary to stimulate the calcification process in vascular smooth muscle cells. Additionally, magnesium passively interferes with hydroxyapatite maturation and formation in the blood vessel itself. Hydroxyapatite crystals (containing calcium and phosphorus) are otherwise linked to calcification in blood vessels.

A second pathway by which magnesium prevents vascular calcification is through direct cell-mediated mechanisms.11 Magnesium appears to prevent transcriptional changes in vascular smooth muscle cells that favor calcification, thereby halting this process. Specifically, magnesium prevents the expression of factors associated with matrix mineralization and supports against the loss of calcification inhibitors, which serve to protect smooth muscle cells.

By acting via these two distinct pathways, magnesium plays an essential role in supporting the normal function and morphology of vascular smooth muscle cells and thereby promoting arterial flexibility.

Metabolic Maintenance

Magnesium plays a critical role in supporting numerous facets of health in metabolic conditions, including metabolic syndrome, lipid parameters, and diabetes. For instance, as a cofactor, magnesium is involved in the function of several enzymes related to glucose metabolism, and decreased serum magnesium levels have been identified as a risk factor for the development of prediabetes.12 Furthermore, based on recently published meta-analyses, there is convincing evidence that magnesium levels are lower in individuals with metabolic syndrome than controls.13 Studies also show that individuals with type 2 diabetes are at significant risk of magnesium deficiency and insufficiency.14

Several recently published systematic reviews highlight the benefits of magnesium for parameters related to cardiometabolic health. Luis Simental-Mendia from the Mexican Social Security Institute (Durango, Mexico) led a meta-analysis of randomized controlled trials to evaluate the effect of magnesium supplements on insulin sensitivity and glucose control.15 The analysis found that magnesium supplementation overall had a significant effect on reducing insulin resistance (as assessed by the common measure, HOMA-IR index)—although the review failed to show significant effects on plasma glucose levels, hemoglobin A1c, or fasting insulin.

When the authors performed a subgroup analysis comparing those studies with a duration of less than four months to those studies with a duration of greater than four months of supplementation, they observed a significant
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benefit in favor of the longer-duration studies on fasting glucose levels. These benefits were noted in both diabetic and non-diabetic subjects, suggesting the beneficial effects of magnesium supplements for individuals with metabolic disorders.

A second review of randomized, double-blind trials conducted by the same group out of Durango, Mexico, looked at the effect of magnesium supplementation in metabolic syndrome. Of the 27 trials identified for inclusion in the analysis, 18 showed a benefit of magnesium supplementation on at least one parameter of metabolic syndrome. These included reductions in insulin resistance and fasting glucose, improvements in lipid parameters (including HDL cholesterol and triglyceride levels), and support for blood pressure levels. Daily supplemental doses of magnesium over the spectrum of studies ranged between 300 and 600 mg/day. Of the remaining nine studies showing no benefits on any parameter of metabolic syndrome, seven were conducted in healthy individuals. Overall, the results of the analysis point to significant benefits associated with magnesium supplementation for metabolic syndrome.

Researchers from IKG Punjab Technical University (Kapurthala, India) recently conducted a meta-analysis to assess the effects of magnesium supplementation on type 2 diabetes and associated cardiovascular risk factors. They included randomized controlled trials published before June 30, 2016. On the basis of their analysis, the authors concluded that magnesium supplementation significantly improved fasting blood glucose levels (average decrease of 6.4 mg/dL) in diabetic individuals. Furthermore, magnesium supplements raised HDL cholesterol levels (by an average of 3.2 mg/dL), reduced LDL cholesterol (by an average of -10.7 mg/dL), and reduced triglycerides (by an average of -15.3 mg/dL), while also reducing average systolic blood pressure readings by 3 mm Hg. Thus, magnesium supplementation benefits diabetics and reduces several risk factors for heart disease in this population.

More Magnesium
Magnesium is a nutrient required by all cells and participates in a broad range of physiological processes. Since magnesium levels are often insufficient, ensuring an adequate intake is essential for the body to function as designed. From cardiovascular health and metabolic function to mental health—or any other number benefits magnesium is associated with—magnesium is the spark that makes the body go. Doing without this crucial element is like driving a car that isn’t firing on all cylinders. Without the spark, the fuel is useless.

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Irfan Qureshi, ND, is executive director, research and regulatory affairs, for Healthy Directions.
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Sex and the Supplement

Dietary supplement ingredients for male sexual health

BY ROBBY GARDNER

Dietary supplements for sexual pleasure and procreation—so-called “intimacy products”—make up a big business that brought in an estimated $84.3 million from July 2016 to July 2017, according to the market research firm SPINS. Of those sales, $77.7 million was for products intended for men specifically.

Today’s sex health ingredients for men come from processing and extraction of various components of nature, including barks, roots, and stigmas. Where some of these sexual health ingredients seem to enhance the body in vascular ways, others seem to operate by truly different methods. We explore a few of the top-selling male sexual health ingredients for their science, but also for their recent market challenges.

Pycnogenol and Friends

Though it’s considered a potent antioxidant all on its own, Pycnogenol may be of greater use in the company of other ingredients, at least when it comes to erectile health. Research suggests that pine bark extract can increase the body’s production of eNOS (endothelial nitric oxide synthase), an enzyme that helps to relax blood vessels in, among other parts of the human body, the penis. Proper blood flow is a good indicator of proper erectile health. eNOS doesn’t benefit blood flow on its own, either. It must convert into nitric oxide, a process that requires plentiful stores of L-arginine.

Understandably, interested parties are exploring the potential health benefits of combining Pycnogenol and L-arginine in a single formula. Horphag Research (Geneva), the exclusive global supplier of Pycnogenol, created Prelox, its own blend of Pycnogenol and L-arginine. It’s been associated with self-reported improvements in erectile function.
A patented proprietary composition ZeaLutein is composed of 1% Zeaxanthin, 5% Lutein and 2% Piperine, blended in a ratio optimized to provide maximum benefits in eye health. This blend delivers a perfect 1:5 ratio as occurring in the human eye, and is a highly bioavailable form of Lutein and Zeaxanthin to help support vision health while offering free radical protection. ZeaLutein provides wholesome nutrition to the eye and promotes macular health, naturally.*

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compared to placebo when used over one or more months, with greater perceived improvements over time. A competing product, named Edicare by its manufacturer, shows potential to improve self-reports of erectile function but also to increase sperm concentration in otherwise infertile men. The effect may be due to Pycnogenol’s antioxidant status, which researchers believe could help to reduce sperm damage. Earlier this year, the same product was deemed useful for erectile function but also for managing lower urinary tract infections to an extent greater than saw palmetto—perhaps because of Pycnogenol’s ability to combat oxidative stresses in the bladder. More trials are warranted.

As science continues on Pycnogenol mixes, more options for synergistic benefits are becoming available in this space. L-arginine is impressing in a number of sexual health studies without Pycnogenol. On the other side, Horphag Research just introduced a Prelox formula containing L-citrulline and French oak extract (already deemed beneficial for erectile function and sperm quality and a women’s alternative called Lady Prelox that’s now on the market.

**Maca**

A scattering of unique studies have hinted at maca’s potential use for sex health. Beyond the established idea that the Peruvian root can stimulate male libido, and some limited data to support maca for erectile function, researchers are actively looking at other sexual health parameters. Recent findings from the Czech Republic hint at potential benefits for sperm health (a trend towards increased concentration and motility), and they say they plan to explore maca’s use on men diagnosed with oligozoospermia (low sperm counts). Perhaps more extensively, though, research is mounting on maca for the female libido, with numerous ongoing trials for maca use to ameliorate sexual dysfunction onset by psychiatric medications or menopause. As long as maca remains of interest to consumers, manufacturers should take care in where they source their maca extracts and powders. Convincing data draws differences between nutritional profiles of maca plant from one variety to another. Maca ingredient supplier Naturex (Avignon, France), for example, is committed to batch-to-batch consistencies in identity and content of amino acids, which global category manager Leslie Lannebere says are important for its maca extract’s demonstrated sexual efficacy.

**Fruit Polyphenols**

Again trusting in the nitric oxide effect, growing research supports consumption of polyphenols for improved vascular health and thereby, hopefully, erectile health. Numerous reviews draw a connection between dietary polyphenols and an improved vascular state,
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Sex Health

and research is even targeting populations with erectile function.

Various epidemiological studies link consuming polyphenol-rich foods to improved vascular health\(^{17,18}\), and more recently erectile health\(^{19}\), but few intervention trials exist and precise mechanisms of action are unknown.\(^{20,21}\) Much of the recent interest stems from a two-year study finding improvement in erectile subjects when subjects consumed a Mediterranean diet, especially rich in polyphenols thanks to plant-based foods, such as fruits and herbs.\(^{22}\)

Although few clinical trials are available, Nexira (Rouen, France) aims to narrow the gap with its recently completed clinical trial on men consuming EnoStim, the company’s concentrated extract of apple and grape polyphenols enriched with saffron. The company recently announced the new study results at this September’s SupplySide West trade show.

According to Nexira, the four-week unpublished study conducted on 94 men over the age of 45 found that a 300-mg dose of EnoStim, taken twice daily, helped improve penile erection. Specifically, researchers determined that, after just three weeks of supplementation, 54% of subjects saw their scores improve per the standardized Erection Hardness Score test. In addition, 46% of subjects saw improvements per the International Index of Erectile Function test. By the end of the study, 71% of subjects said they would recommend using EnoStim, 66% said they were satisfied with EnoStim and experienced better erections thanks to EnoStim, and 58% said they felt more confident engaging in intercourse if using EnoStim.

Nexira says EnoStim works by stimulating nitric oxide production and, therefore, blood flow. Part of this effect is due to EnoStim’s antioxidant properties. “Nitric oxide has a short lifespan and is easily degraded by superoxide free radicals,” the company explains in a press release. “As shown in an in vivo study, the antioxidant molecules in Nexira’s proprietary formulation demonstrated the potential to specifically protect nitric oxide by decreasing oxidative stress by 74%.” The company notes that previous studies indicate that the ingredients in EnoStim may be able to increase blood flow by up to 50%.

**Saffron**

In light of positive studies on saffron for erectile health (and there are quite a few), saffron suppliers like to note that a pending European health claim (ID 2427) exists for saffron, seeking claims of “Stimulates the libido” and “Improves erection, contributes to the increase of sperm volume, and relaxes muscles.” Curiously, however, the original application, filed in 2008, hasn’t moved since. Research has continued, and consistent popularity of saffron within the category could benefit from equally impressive research on saffron for the aging brain.

**Fenugreek**

Not just a spice, fenugreek seed (Trigonella foenum-graecum) is popularly sought after for its potential sexual benefits. When consumed in
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extract form, fenugreek may increase human testosterone levels, and the end result is likely to improve libido.

A few studies have honed in on fenugreek supplementation for men with or without andropause, and the results suggest improvement in libido and associated sexual function. Earlier this year, results of a clinical study by fenugreek seed extract supplier Cepham Inc. (Piscataway, NJ) suggested that the company’s ingredient was associated with improved testosterone levels, libido, and sperm count. Seeing the greater potential for increased testosterone, Cepham says it is now working on a study to assess how fenugreek seed consumption can, via testosterone, influence more physical factors, such as grip strength.

A friendly reminder: fenugreek is popularly sold for both male and female sexual health. GE Nutrients Inc. (Gencor; Irvine, CA) promotes its fenugreek extract as a Libifem for women and Testofen for men. The ingredient is backed by much of its own research.

Tongkat Ali

A decent number of studies back the use of tongkat ali (Eurycoma longifolia) for a variety of male sexual health factors. Since the Asian root is associated with increased conversion of pregnenolone to a variety of hormones in the body, including testosterone, it’s no wonder why numerous studies have linked tongkat ali consumption to increased levels of free testosterone in sub-fertile men.

Whether tongkat ali’s testosterone boost can lead to other benefits is less understood. A few studies have looked at this and with some positive results thus far. HP Ingredients (Bradenton, FL) has a few of its own tongkat ali studies to mention, with noted supplementation improvements such as better scores on the erection hardness scale, increased sexual satisfaction, and better libido. The company’s branded extract LJ100 is standardized to guarantee batch-by-batch consistency in select active constituents.

Tribulus

Tribulus (Tribulus terrestris) is another plant product intimately tied to hormones. Its demonstrated potential to improve male and female libido and semen parameters, especially quite recently, are likely due to this plant’s hormonal influence. But further exploration of the plant’s properties and effects, as well as reports of improvements in erectile health, lead some researchers to presume that tribulus may impact male sexual health in other ways, such as via endothelium and nitric oxide–dependent mechanisms.

Yohimbe

Yohimbe (Pausinystalia yohimbe) remains a popular dietary supplement for men’s sexual health. It’s backed by a handful of studies befitting its use for erectile function and fear/anxiety, but its reputation needs improving. Last year, researchers sampled yohimbe dietary supplements from major U.S. retailers and found widespread issues of inadequate dosing, improper labeling, and even signs of potential adulteration. Of the 49 yohimbe bark products sampled, some contained zero traces of yohimbine, the active alkaloid in yohimbe upon which its purported health benefits are based.

The market for yohimbe doesn’t have to remain in this kind of trouble, though. Not long ago, a team of USDA researchers confirmed what they say is an easy and economical laboratory method for detecting and validating yohimbine content in bark extracts using an ultra-HPLC (UHPLC) diode array detector (DAD) in tandem with mass spectrometry.

References

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Reading between the Lines

What Form 483s tell us about FDA action in the Trump era

BY KIMBERLY J. DECKER

With a new administration in office and new leadership guiding FDA, it’s only natural to wonder if the regulatory environment for dietary supplements, as it relates to current good manufacturing practices (GMP) enforcement, will change—and if so, in what direction. After all, Donald J. Trump got elected president in no small part thanks to promises of “smarter”—that is to say, more lenient—regulation.

As the tea-leaf readers try to tease out where FDA may be headed on GMP enforcement, one subject of study is the pace and nature of Form 483 letters documenting concerns observed during supplement facility inspections. Why? Because if White House policy is to regulate with a lighter touch, it stands to reason that inspectors on the ground might be less inclined to dole out Form 483s for what some would argue are nominal violations.

Another consideration: Brutal budget cuts to agencies like FDA might make it harder for officials to do their jobs, regardless of whether they were aiming to do so with vigor or with an eye toward easing the weight of those “burdensome” regulations.

Too Soon to Tell


Marc Ullman, of counsel, Rivkin Radler (Uniondale, NY), agrees, adding that with so many of FDA’s sub-commissioner leadership spots still staffed by holdovers from the pre-Trump era, “Changes in policy or enforcement approach likely wouldn’t be seen until there’s turnover in these positions.”

Thus it looks for now like business as usual—which in the case of FDA means the usual slowness. Indeed, though “there doesn’t seem to be any change in the agency’s tone or level of cGMP enforcement since the Trump administration came in,” Ullman says, “to the
extent that I’ve noticed any change at FDA, I’d say that the pace of any new initiatives by the agency has gone from its usual glacial speed to virtually nonexistent.”

**One In, Two Out**

But while Justin J. Prochnow, shareholder, Greenberg Traurig LLP (Denver, CO), also believes that “the passage of regulations, guidance, and other more overarching action has definitely experienced a slowdown,” he thinks it might be for reasons more complicated than the typical bureaucratic sclerosis.

“Clearly, FDA under the Trump administration has been given orders to slow down any actions initiated under the previous administration,” Prochnow says. This is no surprise, as the White House made clear from the start that it favored a policy of “one in, two out,” meaning that each new law or regulation passed must come at the expense of two existing regulations—a strategy that “has certainly slowed down efforts that had been underway,” Prochnow says.

A case in point is FDA’s request for public comments on the most recent version of the agency’s new dietary ingredient (NDI) draft guidance; changes to the definition of the term healthy under 21 CFR, Part 101.65(d), of the Food, Drug and Cosmetic Act (FD&C Act); and several questions pertaining to the definition of natural, Prochnow continues. “None of those actions is likely to move forward quickly at this time,” he says. What’s more, menu labeling requirements that were set to go into effect on May 5, 2017, and changes to the Nutrition Facts Panel that were set to take effect next July have also been delayed. “Yet companies continue to be inspected by FDA compliance officers, have products inspected at Customs, and otherwise experience day-to-day regulation in substantially the same manner,” he says.

**No Uptick, No Letup**

And what of inspectors’ use of FDA’s Form 483? Known as a “483” for short, the form documents any failure of a manufacturer to meet the minimum requirements listed in 21 CFR 111. Failure to correct problems listed in a 483, or to respond to FDA adequately, may land one in the path of further regulatory action in the form of an “official” FDA warning letter.

Which is unwelcome news for any supplement company. So it might be some relief to hear that, as far as Ullman can tell, “things appear to be fairly steady” with regard to the Trump FDA’s treatment of 483s so far: no massive uptick, and no wished-for letup, either.

Then again, Ullman notes that manufacturers wishing for a regulatory letup might do well to reconsider what they wish for. After all, even if FDA’s conduct of inspections seems to be the same as it ever was, “I think that industry should be grateful for this,” he concludes. “Any noticeable letup would only benefit the scofflaws who are frequently the cause of our headaches in the media and at FDA.”

**GMPs Always Matter**

In other words, be grateful for regulatory blessings in disguise—and don’t get complacent. For despite uncertainty as to FDA’s future moves, one thing we can be sure of is that GMPs still matter—as they should. “Regardless of the enforcement trends, supplement manufacturers need to remain vigilant and committed to ensuring compliance with GMP requirements,” Glyph Lattimore says. And with several new provisions of the Food Safety Modernization Act (FSMA) now going into effect for supplement makers, “we’ll likely see increased enforcement of the FSMA requirements in the coming year,” she adds.
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FDA is even soliciting consumers for help. On July 25 of this year, the agency, through its official blog FDA Voice, called upon the public to report supplement products that don’t work as advertised, produce adverse effects, bear false or overstated claims, or simply aren’t as pure or safe as they claim to be. The lesson: “The industry needs to continue demonstrating its ability to self-regulate,” Glymph Lattimore says, whether it sees a surge in 483s or not.

Here’s a look at some recent FDA warning letters and what they tell us about agency enforcement. (Thanks to Marc Ullman, of counsel, Rivkin Radler, and his FYI Service Newsletter for collecting and sharing the letters.)

Clean Up Your Acts
GMPs are the backbone of safe and successful supplement production. And, not surprisingly, the task of ensuring that companies comply with them occupies much of an FDA inspector’s time when taking the measure of how a plant is operating. But there’s a reason that keeping up with GMPs is so time consuming, both for inspectors and for companies: they’re complicated, lengthy, and surprisingly easy to run afoul of.

That’s what Unique EnCapsulation Technology LLC (Landing, NJ) learned in an FDA warning letter dated January 17, 2017. The letter called out GMP violations ranging from i-dotting and t-crossing matters—failing to include an actual or representative product label in batch production records, for instance—to more serious violations, such as not rejecting a supplement or product component that didn’t meet established specifications, as well as water test results indicating the presence of yeast and mold.

Misbranded It by That Much
If your idea of a misbranded dietary supplement is one that, for instance, promotes itself as being made primarily of ingredient X but actually contains very little X and a whole lot more of Y, you’re not thinking creatively enough. And you’re certainly not thinking like an FDA inspector. Those inspectors will label a supplement as misbranded for a whole lot of reasons, many of which are far more subtle than simply marketing a product that isn’t what it says it is.

For example, Morhaim Pharmalab Inc. (Miami) received an FDA letter dated May 16, 2017, noting a host of misbranding violations related to its Vital Procollagen product. Among the violations: failing to declare all the common or “usual” names of ingredients, not identifying the part of the plant that’s the source of the product’s botanical ingredients, out-of-spec nutrition information, and even failure to include a domestic address or phone number for the company on the label. Oops!

A Drug by Any Other Name…
When is a dietary supplement not a dietary supplement? When it makes claims—either
on pack or online—that FDA deems sufficient to tip the product into drug territory. And that’s not something you want FDA to have to do.

Witness the case of Black Seed Herb Inc. (Liberty, NY), which received a letter from FDA dated July 11, 2017, stating that disease claims for its Diabalance Herbal Blood Sugar Balance Tablets, Quick Slim with pure Hoodia Gordonii Capsules, BHealthy Black Seed Bitter Melon 90 Veggie Capsules, and Black Seed w/ Olive Leaf/ Garlic Capsules “establish that these products are drugs under section 201(g)(1)(B) of the Act [21 U.S.C. § 321(g)(1)(B)] because they are intended for use in the cure, mitigation, treatment, or prevention of disease.”

Some of the disputed claims seem relatively innocuous—“Sweet Sunnah QuickSlim is an all-natural formula that...attacks obesity...” “The main focus of the herbs within Diabalance is blood sugar balancing...”—but as far as FDA is concerned, they qualify the products as “new drugs” prohibited from legal introduction into interstate commerce absent prior FDA approval.

“This is a good example of a typical letter to a dietary supplement company for what I call the trifecta of warning letter bases: disease claims, GMP violations, and labeling violations,” says Justin J. Prochnow, shareholder, Greenberg Traurig LLP. “Such letters are pretty common in that companies receiving such letters generally have deficiencies in all three areas.”

**Brace for the Cure**

When it comes to unauthorized drug claims, FDA may have a particular beef with products promising to cure, treat, mitigate, or otherwise address cancer. According to the agency’s consumer updates page, FDA sent out warning letters in April 2017 to 14 companies advising them to change or remove fraudulent web statements promising to do just that. “If the companies don’t comply,” the page declared, “the FDA may take further legal action to prevent their products from reaching consumers.”

Yet companies continue to play upon consumers’ fear of this complex disease. Exhibit A: Nature’s Health Company LLC (Hoover, AL) presents an “anecdotal history” on its website of an incident in which a tea containing the same four ingredients as are in the company’s Ojibwa Herbal Tea Formula “somehow seemed to cause the different organs in the body to ‘normalize,’ helping the body’s own immune system to fight and correct whatever was wrong” once a cancer-stricken nurse consumed them.

We know: Huh? Fortunately, the claim was enough to raise FDA’s hackles. Further, says Prochnow, “Companies need to understand that any information put out there by the company on any platform may be viewed by the FDA as evidence of the true intent of the company to sell products.”

**Seeking Approval**

There’s nothing willy-nilly about how FDA monitors which ingredients are permitted in dietary supplements. To wit, Section 201(ff) (1) of the FD&C Act defines “dietary ingredients” as “a vitamin; mineral; amino acid; herb or other botanical; dietary substance for use by man to supplement the diet by increasing the total dietary intake; or a concentrate, metabolite, constituent, extract, or combination of any dietary ingredient from the preceding categories.”

So when AndroPharm LLC (Boca Raton, FL) decided to formulate 2,17a-dimethyl-17b-hydroxy-5a-androst-1-en-3-one and 17b-hydroxy-2a, 17b-dimethyl-5a-androstan-3-one-azine into its Sten Z product, and methyl-1-etiocholenol-epiethiocholanolone into a product called M1 Alpha, it was asking for trouble.

Both ingredients are synthetic steroids and do not constitute dietary ingredients as per section 201(ff)(1) of the FD&C Act. So in a letter dated June 5, 2017, FDA pronounced the products not dietary supplements and sternly requested that the company follow up with the appropriate actions. As Prochnow notes, letters like that “reinforce the need for companies to ensure that all ingredients in dietary supplements are permissible dietary ingredients, or if they’re new dietary ingredients that the proper notification is filed with FDA unless the ingredients are exempt.”

**Don’t Pass the Buck**

It’s so tempting to leave all this legal and regulatory rigmarole to the friendly contract manufacturers who help keep our industry humming. But as Nature’s Vision Inc. (Portage, MI) learned in an FDA letter dated May 1, 2017, it’s not so easy to pass the buck.

In the letter, FDA noted that though Nature’s Vision contracts out the production of its supplements to a third-party manufacturer, the former maintained “no documentation of product specifications or certificates of analysis for the product received, and [has] not performed any audit or engaged in any other activity to determine the acceptability of the manufacturer to manufacture [its] dietary supplement products, or to ensure the quality of the dietary supplements received and that the products are packaged and labeled as specified in the master manufacturing record.”

This will not do! FDA says it best: “Although a firm may contract out certain dietary supplement manufacturing, packaging, and/or labeling operations, it cannot contract out its ultimate responsibility to ensure that the dietary supplement it places into commerce (or causes to be placed into commerce) is not adulterated for failure to comply with dietary supplement CGMP requirements.” Let that be a lesson.

**Kimberly J. Decker** writes for the food and nutrition industries from her base in the San Francisco area, where she enjoys eating food as much as she does writing about it.
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Supplement transparency and traceability in action

BY KIMBERLY J. DECKER

These days, you can’t be in the supplement biz without being in the transparency biz. Or the traceability one. Or the supply-chain one, either. That’s because the complexities of a global marketplace have shone a light on our industry’s need to—well, shine a light on how we source and produce supplement products—and to do so before someone else does it for us.

A handful of unfortunate but high-profile quality breaches have converged with consumers’ expanding appetites for and access to information to remind us—as if we needed it—that our business is, in a very real way, the public’s business. And as far as Brent Bauer, marketing, food issues and sustainability leader, Cargill (Minneapolis), is concerned, we should’ve seen it coming.

“As labels become cleaner,” he says, “and as consumers grow more satisfied that the ingredients in the products they buy are what they wish them to be, the conversation will move increasingly toward factors that fall under the umbrella of transparency.” That’s a big umbrella, covering everything from ingredient identity and origin to fair treatment of labor. But it’s an umbrella that supplement brands and suppliers will have to hold high. For, as Bauer says, “We don’t expect consumer demand for transparency to subside; in fact, we think it’ll only grow in intensity and specificity as the years unfold.”

Pulling the Trigger

Ask industry insiders what they think triggered the tilt toward transparency and you’ll hear a variety of theories. But one view all share is this: “We’ve seen the trend building for several years,” says Timothée Olagne, U.S. marketing director for health and nutrition, Naturex (Avignon, France). “This isn’t something that’s completely new.”

A key turning point in the trend’s progression came in 2015, when the office of New York State Attorney General Eric T. Schneiderman revealed the results of an investigation—some would call it a sting operation—into supplement industry practices. DNA barcoding of supplements sold at four major retailers revealed not only that some contained few of the botanicals listed on their labels, but that others actually contained contaminants, as well.

Not surprisingly, the story took off, and the resulting publicity lit a fire under an industry already aware of the reputational risk such a scandal posed. “Although some of us had been talking about transparency for a very long time,” says Shaheen Majeed, marketing director, Sabinsa (East Windsor, NJ), “when the New York attorney general took action against some large supplement retailers and the media headlined the story from coast to coast, the industry woke up and started focusing on the need to do things right—and to talk about it in terms of transparency.”

Further momentum came from pending implementation of FDA’s New Dietary Ingredient (NDI) and Food Safety Modernization Act (FSMA) regulations. And at least in the food sector, Bauer says, another catalyst has been the raft of GMO-labeling referenda on ballots in several localities. “Those provided transparency advocates a high-profile vehicle to express their views within the context of, arguably, one of the most emotive subjects in the agro-food industry,” he says. “That really turned the flywheel, in my opinion.”
Consumers in Control

Of course, any time events call into question—for good reason or not—the safety of what we put in our bodies, it’s bound to stir up emotions. And supplement users are as liable to emotional stirring as anyone else.

That’s why Sandra Gillot, CEO, Benexia (Santiago, Chile), believes industry would be wise “not to underestimate the attention and knowledge of today’s consumers”—the same consumers who, to a great extent, are driving the move toward transparency. “They can and will be very vocal about a product they feel isn’t living up to its label claims,” she says, “and they’ll never trust that brand again.”

Fear is hardly their only motivator for digging into supplements’ backstories. “Consumers are passionate about nutrition and what they eat,” says Olagne. Because it reflects so deeply who we are, he adds, “people really look for information about food and nutrition and want to know more. And now that they have a voice through social media, brands know that they’ll use it.”

Nowhere to Hide

And how. The Internet and social media have “completely revolutionized” consumers’ exposure to transparency developments, says Vincent Tricarico, vice president of contract manufacturing, NutraScience Labs (Farmingdale, NY). “Whether it’s via something like a digital community of likeminded consumers, a brand’s social media accounts, or a local or federal organization’s official website, those who wish to remain informed have more power than ever when it comes to deciding which stories or issues remain in the spotlight.”

That informational access can cut both ways for supplement brands: It leaves them nowhere to hide if they fall short on commitments, but it also gives them a louder megaphone for spreading good news when they do. As Tricarico says, social media and digital technologies “have increased the ways in which a supplement brand can interact with its customers—or prospective customers—tenfold. Whether it’s by means of an on-label QR code or a live-streamed question-and-answer session, companies looking to keep their customers engaged and informed on sourcing and traceability can choose from dozens of options.”

What Consumers Want…to Know

Which raises the question of what consumers want to learn when engaging brands about transparency. Bauer notes that a
Hartmann Group survey of 1,800 consumers found transparency to be “driven by clarity around ingredients, sourcing and production practices, and social criteria,” he says. At a rate of 64%, consumers were most interested in learning about ingredients themselves, while just under half cited factors including how products are manufactured, how companies treat animals along the way, where companies do their sourcing, and how they manage labor practices and environmental impact. “All of these have varying degrees of importance,” Bauer says.

Declarations of organic, non-GMO, and “natural” identity also come into play, with certifying agencies eager to help brands prove their inputs’ bona fides. And today’s consumers demand “purpose-driven products,” adds Steve Holtby, president and CEO, Soft Gel Technologies Inc. (Commerce, CA)—even in the supplement aisle. “That means they want to buy sustainable and eco-conscious products from companies whose values are most like their own.”

But when you get down to it, consumers’ demands for transparency stem from their desire to know that the products they buy for themselves and their families are safe. They don’t need to know all the details, Bauer says, but “they want access to information how, when and where they want it. And they don’t want technical jargon.”

**Tough Row to Hoe**

Alas, there’s no shortage of jargon in the pursuit of transparency—or at least no shortage of arcane words describing complicated practices. That’s because achieving transparency is
PUTTING PRINCIPLES INTO PRACTICE

How supplement suppliers and manufacturers are “doing” transparency

Supplement brands, suppliers, and contract manufacturers all understand that supply “chain” isn’t just a metaphor. Each party really does occupy a link that, only when firmly connected to the others, delivers supplements safely, traceably, and transparently to consumers. So here’s what several of those links are doing to keep that chain locked tight.

Sandra Gillot, CEO, Benexia (Santiago, Chile)
Her company, a vertically integrated source of chia seed powders and oils, demonstrates its commitment to sustainable sourcing with its sustainable-farming certification from GLOBALG.A.P., which guarantees no-till farming, crop rotation, natural soil nutrition, agrochemical control, manual plague and weed control, technological innovation, and “traceability from the field to the plate,” she says. In addition, they analyze each seed batch via internal and external testing for moisture, microbial load, purity, toxins, and agrochemical residue on the entire lot.

Chris Oesterheld, executive vice president, Jiaherb Inc. (Pine Brook, NJ)
Oesterheld claims that his company “was one of the first manufacturers” to use HPTLC testing—high-performance thin-layer chromatography—for botanicals. But just as important is its commitment to on-the-ground sourcing. “We have the ability to be there in the fields or countryside firsthand to confirm macroscopically that we’re starting with the correct species of crude raw material,” he says. “Then, in the lab, we confirm through HPTLC both for the crude raw material and finished extract powder.” While they’ve increased the amount of DNA testing they do, “we still feel strongly about the accuracy HPTLC testing offers.” And sensing the “strong push for clearer and more accurate information” on ingredients, Jiaherb created its HerbaLink program, an “efficient way of presenting all this information in a single document packet showing each link in the supply chain from plant to finished powder or extract,” Oesterheld says.

Guy Woodman, general manager, Euromed (Presto, PA)
Woodman believes his company is “well positioned” to demonstrate transparency with a supplier certification and qualification program applied to all botanical ingredients it purchases. The firm has a full-time staff agronomist “who oversees and establishes the global cultivation of different medicinal plant species,” he adds, and it provides other support like efficacy and stability studies, extract-dissolution test results, and species testing via DNA analysis. Euromed also introduced its Phyto-Proof quality-control process to boost consumer confidence in its products. “Every batch of extract undergoes a minimum 20 laboratory tests beginning with the farm-grown or wildcrafted plant all the way to the finished extract,” Woodman says. And retailers benefit by knowing that the ingredients “are verified for purity, potency, and plant identity.”

Steve Holtby, president and CEO, Soft Gel Technologies Inc. (Commerce, CA)
As a contract manufacturer of softgels, Holtby sees the connection between transparency and a strict adherence to GMPs. That being the case, he says, “Our QA department monitors quality throughout the manufacturing process. We maintain complete, detailed batch records for traceability purposes and ensure that we’re GMP compliant so that we keep our certifications. In fact, some of our customers require us to undergo periodic internal and third-party audits to confirm GMP compliance.” And because “it’s common for distributors of raw ingredients not to perform all necessary testing,” he adds, “in those cases we would perform or arrange for the testing ourselves”—providing not just standard analysis of finished softgels, but also extensive testing on raw materials for identity, potency, and contaminants.

Brent Bauer, marketing, food issues and sustainability leader, Cargill (Minneapolis)
With demand for non-GMO ingredients growing, Cargill launched its Known Origins GMO tracing program in March, 2017, covering non-GMO and corn and soybeans produced in North America and high-oleic canola seeds produced in Australia. The program allows the company to identify each farmer in the non-GMO producer program, and while it’s been a big shift for industry, “in some cases, we’re able to work with our customers to create supply chains that enable not only the ability to draw specific connections back to individual farmers, but also to explore improvements in on-farm practices that address sustainability drivers,” Bauer says. In the end, he believes, “The more that consumers place value in understanding supply-chain dynamics, the more brands and their supply-chain partners will respond and put in place the mechanisms to explain.”
Quality Assurance & Traceability

itself arcane and complicated, as companies are learning in their attempts to trace ingredients from seed to shelf.

Notes Chris Oesterheld, executive vice president, Jiaherb Inc. (Pine Brook, NJ), the fact that most crude raw material going into supplements is wildcrafted from multiple locations rather than farmed on a single plot makes achieving transparency even harder. "For example," he explains, "Rhodiola rosea root grows wild, high in the northern mountains of China. Its harvest involves various self-employed 'pickers' scouring the landscape and filling burlap sacks with Rhodiola rosea roots. Then they go to a local broker who gathers from various pickers, and those brokers ultimately sell to a manufacturer of botanicals. It's easy to trace crude materials that are harvested from a specific farm, but wildcrafted materials present a true challenge."

As do some of the costs associated with ensuring traceability and transparency. Yet, says Majeed, "There's a disconnect between wanting transparency and traceability, and buying by price."

Guy Woodman, general manager, Euromed (Presto, PA), agrees. "Buyers dictate the level of ingredient traceability required and, subsequently, the investments that suppliers will make," he says. But sound agriculture, cultivation, and harvesting practices "require additional financial investments, and brand marketers need to recognize the value of this stewardship in providing botanical ingredient quality to consumers. When companies focus only on price, suppliers have to cut corners somewhere and certainly reduce their investment in quality control."

Fortunately, consumers in the natural and organic channels have demonstrated a willingness to bear the costs of quality, says O Elaine. "The biggest question remains with the mass market," he concludes. "Are consumers in the mass market ready to digest the pill? This we don't yet know. But we do know that mass-market customers are asking questions, as well." 

Need to Know
As well they should. Woodman believes that transparency "is more than just saying you have documentation available; it's actually providing evidence of this." Supplement makers can "cut through the veneer" of traceability, he says, if they "drill down deeper to determine the supplier's level of knowledge about the products they're working with."

This means asking about country of origin for botanicals, the harvest season, the method of species identification, and testing results. Ask to see a spec sheet for both the plant material and the extract, Woodman emphasizes. When customers ask this of his own products, the company provides a "full spec sheet, including minimum chemistry content for the plant material we extract," he says. "This ensures product quality and consistency because the manufacturer can test using the same lab methods as we do and receive our lab test results, as well."

Majeed adds that for branded ingredients, customers should ask to see published research on their efficacy, and make sure that the ingredients don't infringe on anyone else's patents. And Holtby adds that brands should keep shining transparency's light at the contract manufacturing stage, too, performing regular audits "on a timetable that's consistent with their buying habits—i.e. at least annually if not more often," he says. "Look at batch records and raw-material certificates of analysis and, most importantly, make sure they're doing all the testing required by the GMPs. Manufacturers can save a lot of money if they're not doing all the required testing; if a quote looks too good to be true, there's probably a reason."

Team Effort
Supplement brands are better positioned than consumers not only to attain this information, but to interpret it accurately, as well. As Majeed points out, "The difference between consumers and the industry is that we know where the vulnerabilities are. So the question becomes, 'Are companies focused on doing just enough to use transparency claims in their marketing, or are they truly demonstrating best practices?'"

To hear Tricarico tell it, it's the latter. "From what we've seen, some of the most significant turning points in the conversation concerning transparency and traceability in our industry have come as actions that industry players have taken themselves," he says. Pointing to initiatives like the Council for Responsible Nutrition's (CRN; Washington, DC) Supplement OWL—an online wellness library and supplement registry—he applauds the work of industry advocates. "At the same time," he adds, "we're seeing an increase in the number of individual supplement manufacturers, companies, and brands making the effort to take responsibility for the transparency and traceability of their processes, and improve the ease with which consumers can gain access to this information."

Which is a smart idea all around. After all, says Cargill’s Bauer, "We're in this together. If you're listening to your consumer and engaged in understanding what they're looking for, you could argue that the marketplace will reward you for that. And in that situation, it's an ecosystem between the consumer, the brand, and the supply chain because we can't do it without each other."
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Non-GMO is quickly becoming one of the fastest-growing claims in the U.S. food industry. With demand for non-GMO and organic products projected to grow 12% annually through 2018, North American food manufacturers are looking for ways to quickly and confidently introduce new non-GMO products to the marketplace.

Today, nearly 95% of corn and soybeans and 99% of canola grown in the U.S. and Canada are sourced from bio-engineered seeds. This leaves food and beverage manufacturers interested in meeting consumer demand for non-GMO products with a significant challenge: finding a reliable non-GMO ingredient supply chain.

Manufacturers need confidence that they can efficiently source non-GMO ingredients and need to trust that those ingredients meet the rigor and standards consumers and non-GMO certifiers have for products entering the marketplace. While speed to market is critical for the growth of a brand, food manufacturers also require a reliable verification process for their non-GMO products. To be able to more confidently assess the non-GMO status of their products, food manufacturers should partner with suppliers with reliable identity preservation processes. Critical components of these programs include traceability, established co-mingling standards, and third-party verification.

BY TIM BAUER, STARCH PRODUCT LINE MANAGER, CARGILL
Traceability
Traceability is increasingly important to consumers. They want to know where their food came from and what happened to it before it ended up on the shelf and, ultimately, in their grocery cart. To that end, manufacturers need to be able to trace their non-GMO ingredients back to the specific producer, whether that is a corn, soy, or high-oleic canola farmer.

Co-Mingling Standards
Segregation and cleaning procedures can help safeguard non-GMO ingredients from cross-contact with GMO ingredients, ensuring that co-mingling levels are within range of the agreed-to standard. This level of transparency increases consumer trust in non-GMO labels.

Third-Party Verification
Testing can be performed on harvest bin composites, incoming truck deliveries, and finished ingredients to ensure non-GMO ingredient products comply with third-party standards. Since there is not a federal standard for non-GMO products in the U.S., suppliers must work with each customer to identify and then test against the non-GMO standards they wish to meet, including those set by the European Union and third-party groups such as the Non-GMO Project.

Another critical verification point happens at non-GMO production facilities. For example, plants that operate under Good Manufacturing Practices and have been verified by Global Food Safety Initiative certification agencies give manufacturers additional confidence in the integrity of their ingredients.

Customer Preference
Customer preference is driving market demand, for both non-GMO and GMO ingredients. In the last three years, the amount of meals or snacks that include a food item with a non-GMO label has jumped from 1% to 11%, according to the Pew Research Center. To meet that growing demand, food and beverage manufacturers need a reliable supply chain partner that can provide both the rigor needed to verify non-GMO ingredients and the scale to support large production of non-GMO food and beverage products.
Is It Natural?
How carbon-14 analysis can confirm a dietary supplement’s natural content

BY JASMINE GARSIDE, BETA ANALYTIC

The current regulatory landscape is hazy when it comes to criteria for vitamins and dietary supplements labeled as ‘natural.’ Still, this hasn’t stopped many supplement manufacturers from moving toward natural formulas. Synthetic vitamin complexes derived from petrochemicals can suffer from poor consumer perception, and this alone is enough to push many manufacturers developing vitamins to source plant-based materials instead of synthetic ones.

According to projections from Grand View Research Inc., the market for botanical extracts is expected to grow 9.7% annually through 2024 as a result of the rising consumer demand for plant-derived ingredients in supplements. And the total market value for dietary supplements could reach over US $278 billion by 2024, a testament to the growing popularity of nutraceuticals’ approach to health and preventive medicine.1

Data on the comparative market shares of natural and synthetic dietary supplements is scarce, but a Zion Research report2 focused specifically on antioxidants suggests, for instance, that sales of synthetic antioxidants make up approximately 60% of the total category’s revenue. The report compared revenue generated from synthetic ingredients, including butylated hydroxyanisole (BHA) and butylated hydroxytoluene (BHT), with revenue generated by natural antioxidants such as rosemary extract, vitamin C and ascorbic acid, vitamin A and carotenoids, and vitamin E tocopherols and tocotrienols. The success of synthetic antioxidants is primarily attributed to low cost, but growing demand for natural and organic products means the market share for natural antioxidants is expected to expand considerably in the near future.

Impetus for Carbon-14 Testing of Natural Products

Debates on comparative efficacy of natural and synthetic ingredients aside, synthetic analogues can suffer from
increased consumer scrutiny in the "wellness" sector. With the Internet at their disposal and a host of information online, ranging from the scientific to the wildly inaccurate, increasingly inquisitive and health-conscious consumers have the tools available to research products and ingredients more than ever. As a result, companies moving into natural, plant-derived ingredients must ensure that they know how to perform diligent quality assurance when procuring ingredients labeled as natural for their formulas. These companies are now using sophisticated screening methods to vet the purity and origin of their ingredients before product launch. One such tool is carbon-14 analysis, which is used to determine whether ingredients are sourced from petrochemicals or whether they are bio-based (plant, animal, or microbial).

Carbon-14 analysis is a tool that is frequently employed, for example, by stakeholders in the curcumin industry, including for turmeric powder and oleoresin, to screen for synthetic adulterants that can be procured at half the price of the natural variant. The method can be used to identify chemical additives in natural extracts such as amla, acerola, and baobab—products with an increasing market share and a rising price tag that makes them vulnerable to adulteration.

Carbon-14 testing is also used widely in the fragrance and flavor industry for "natural" ingredients that an importer or downstream user suspects may have been mixed with cheaper, fossil-fuel-derived substances—all in order to avert liability issues and erroneous labeling claims. In fact, the test method has been used internationally for over a decade in retail sectors such as cosmetics, personal care, bioplastics, and packaging.

**Scope of Carbon-14 Testing in Nutraceuticals**

Because many ingredients can be manufactured from coal, tar, or other fossil sources, the quality-assurance manager trying to identify such a synthetic analogue in a dietary supplement labeled as natural will undoubtedly resort to carbon-14 testing. Examples of supplements where carbon-14 testing is useful include vitamins A, E, and K; and vitamins B1, B3, B5, B6, and B12, which are frequently synthesized from fossil resources like petroleum and readily available and extremely cheap due to the enduring low cost of this commodity.

Carbon-14 testing does have its limitations. For a plant-derived vitamin C ingredient, for instance, carbon-14 testing will not differentiate between what type of plant source is used, such as acerola cherries, citrus fruit, or rose hips. Neither is it employed to differentiate the natural extract from ascorbic acid, frequently labeled as "vitamin C complex" and sourced from corn or rice starch. However, since the ingredient sources in all these cases are plant-based, when carbon-14 testing is employed, the percent modern carbon (pMC) in a sample should match that of modern-day plants when measured by accelerator mass spectrometry (AMS), the advanced technology used to perform the measurement, and, as a result, these natural sources will register as "biobased."

The analysis is extremely flexible in application, as it can be used on samples in solid, liquid, or gaseous form, at any stage of processing—from raw materials to finished products—and requires a small sample size at the milligram/milliliter scale.

Carbon-14 analysis has long been established as a standardized method by such standardization bodies as The European Committee for Standardization (CEN), the International Organization for Standardization (ISO), and ASTM International as a way to facilitate comparative and reproducible testing between batches and product lines. Results from a supplier or regulator can be corroborated by duplicate analyses performed according to a standardized analytical procedure, which is welcome news to quality-assurance managers resorting to ad hoc analytical techniques or results that depend heavily on the accuracy of a laboratory's internal reference database.

**As Demand for Natural Products Grows, So Will Demand for Carbon Testing**

Market projections promise a bright future for botanical extracts and plant-derived dietary supplements. In this context, tools such as carbon-14 analysis are in high demand because they can help manufacturers determine the veracity of high-value natural ingredients imported from a plethora of suppliers around the world. Such analytical tools are a vital component of quality-assurance work in any nutraceutical company to ensure that claims are substantiated before the brand name and commercial interests are put on the line.

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**References**


5. See ASTM D6866, ISO 16650-2, CEN 16640, CEN 16137
Reporting from the Field

Quality-assurance experts convened at August’s Capsugel Quality Summit. Here’s what they discussed.

BY MISSY LOWERY; CAPSUGEL, A LONZA COMPANY

Quality assurance, compliance, risk management, and best practices were on the minds of 80 quality professionals who convened at the Capsugel Quality Summit in late August. The purpose of the meeting was to highlight shared industry challenges, identify alternative approaches through intercompany discussion, and to feature best practices that could be adopted for world-class programs.

Speakers at the event included Michael Lelah, PhD, chief research scientist for Dr. Mercola; Dave Schoneker, director of global regulatory affairs for Colorcon; Larisa Pavlick, vice president of global regulatory and compliance for the United Natural Products Alliance (UNPA); Aaron Secrist, director of quality and R&D for Now Foods; Tim Murray, senior manager of quality assurance for Gaia Herbs; Andy Roche, continuous improvement expert consultant; Tony Nguyen, senior director, Covance Food Solutions; and John Davidson, director of supply chain and quality engineering services, Capsugel, now a Lonza company.

Risk Management: A Coordinated Approach

Andy Roche, a continuous improvement expert consultant, spoke about how risk management is now part of quality control for both health & nutrition and pharmaceutical manufacturing. Both require formal risk-management programs and risk-based thinking.

Roche challenged the group to think of risk management as a coordinated effort. This paradigm shift, according to Roche, should involve anticipating and looking for negative events, as well as assessing and prioritizing risk (monitoring the probability and impact of both opportunities and negative events). He recommended starting with the highest-risk issues (the top 20%) and evaluating each for pluses and minuses. For instance, he said, quality-assessment tools were used to solve a downtime issue for one company, leading the company to realize that the root cause of the problem was cotton insert sizes in packaging, not machine adjustments. Making the change to the cotton inserts doubled the firm’s output. In addition, he stressed, every...
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Source: AAM Digital Audit, June 2015
audit should involve the entire organization because the solutions are generated by all, not just one department.

**Quality Control in Testing**

Another speaker, Tony Nguyen of Covance Food Solutions, provided an overview of the quality-control challenges in testing. Nguyen pointed out that problems with ingredient samples that are out of specification may actually have more to do with basic business practices. Better supply chain management practices are key to solving common analytical testing problems or objections. Nguyen said. Moreover, he said, fraudulent laboratory practices such as “dry labbing,” where no testing is done but paperwork is still forwarded on, are the result of a supply chain that may have been hijacked by poor purchasing practices. The way to avoid “testing into compliance” is using a stringent vendor-qualification process for ingredients, excipients, and testing laboratories, where the analytical test-method selection would be a part of qualification. Well-crafted supply and quality agreements, as well as an agreement that the analytical test methods should be done in advance and agreed upon by both parties, are key to success.

*If a company engages in good management practices, then good manufacturing practices will result as a matter of fact.*

**FSMA in Action**

FD&A Food Safety Modernization Act (FSMA) with Preventative Controls for Human Food (PCHF) and Foreign Supplier Verification Programs (FSVP) was fully implemented last month for all but the smallest of dietary supplement manufacturers. Larisa Pavlick, vice president of global regulatory and compliance for the United Natural Products Alliance (UNPA), spoke about how these new regulations require Food Safety Plans, in addition to GMPs and other prerequisite programs. Under FSMA, dietary ingredients are now subject to requirements such as hazard analysis and risk-based preventative controls.

The Preventive Controls rules also created a new term: a Preventive Controls Qualified Individual (PCQI), defined as a “qualified individual” who has trained in risk-based preventive controls and who is in charge of developing a facility’s food safety system. All companies are now required to have additional, specific PCQI training for the individual managing the food safety system. Pavlick reported that many companies have instituted training for staff and that UNPA is assisting by offering wide range of public and onsite trainings.

**Good Management Practices**

What does GMP stand for? That is the question that Colorcon’s Dave Schoneker asked attendees. For quality groups proactive about quality management, GMP stands for “good management practices” as much as it stands for “good manufacturing practices.” For, as Schoneker pointed out, if a company engages in good management practices, then good manufacturing practices will result as a matter of fact.

Schoneker also promoted a proactive approach and, much like Andy Roche, suggested approaching the role of regulatory and compliance as an opportunity. He emphasized that product development should not be focused on what we are limited to do based on current regulations but instead on what we want to do that makes good scientific sense. With the risk-based approach of FSMA, regulatory professionals are now required to work to justify a position the company has taken, rather than simply following a prescription. Working with high-quality suppliers that can support that approach is also key to success, he concluded.

**The Cost of Quality**

Speaker Aaron Secrist, director of quality and R&D for NOW Foods, said that by identifying the total cost of ownership, NOW Foods has been able to replace priced-based buying with strategic sourcing. Under a strategic-sourcing approach, quality control and procurement meet in the middle. This approach, he said, also involves suppliers more heavily in the process.

Secrist emphasized that the total cost of quality is not about the price of creating a quality product or service; it’s the cost of not creating the quality product or service.

He outlined the four main factors that impact the total cost of quality: 1) external failure cost (such as consumer-discovered defects), 2) internal failure costs (such as waste), 3) appraisal costs (such as incoming testing), and 4) prevention costs (such as the cost of running a quality system). Secrist concluded that many organizations will have true quality-related costs as high as 15%–20% of sales revenue, with some as high as 40% of total operations; thus these costs must be factored into decisions about vendor selection and management. By demanding accountability and transparency from vendors, companies can achieve stronger, more open communication so that vendors can provide insights and improvements and assist in minimizing risk.

**Quality in Practice: Capsules**

Quality by Design (QbD), a systematic approach to quality control, asserts that quality can be planned. John Davidson, director of supply chain and quality engineering at Capsugel, walked the group through a series of case studies that demonstrated the elements of the QbD process at work.

The QbD cycle involves agreeing on a Quality Target Product Profile, determining the Critical Quality Attributes (CQAs), building the risk assessment (linking material attributes and process parameters to the CQAs), defining the design space, defining the control strategy, and then driving continual improvements. It was this process that enabled Capsugel to move to a Sigma Series quality level and achieve 6.0 Sigma critical defect levels for all printed capsules.

Applying these tenets to the encapsulation process, Davidson recommended using available tools to assess the physical characteristics of a formula, properly sizing the capsule for the product characteristics and intended dosing style, and developing a collaborative relationship with the operations team to maximize opportunities for success. He encouraged pilot programs and periodic reviews. By beginning with the end in mind, Davidson concluded, companies can design success into the formulation.
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Supplementing diets with omega-3 fatty acids docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA), and alpha-linolenic acid (ALA) benefits consumers in numerous ways, including helping to promote normal blood pressure levels and lowering triglyceride levels. In addition, DHA has been shown to promote eye and brain health. These omega-3 oils are predominantly sourced from marine organisms, including fish livers, Antarctic krill, and green lipped mussels. Oils like ALA, which is converted to EPA and DHA in the body, can also be derived from plant sources. Alternative non-animal omega-3 sources also include microalgae, which frequently contain EPA or DHA either as glycolipids or phospholipids. Biotechnological genetic modification techniques are also utilized to produce EPA from yeast.

The source of omega-3s is important to health-conscious consumers, as are products that provide superior quality and quantifiable benefits. Today’s consumers are looking for greater convenience and more enjoyable supplements, and delivery systems for omega-3 supplements are continuing to improve.

Fish oils were traditionally served as liquids, with consumers taking a spoonful a day. Many consumers were put off by the liquids’ fishy taste and odor, as well as their tendency to cause acid reflux and a lingering, unpleasant aftertaste. The cause of this often-described rancid taste is the natural oxidation of the omega-3 oil molecules. With a liquid formulation, this effect was almost unpreventable, given that serving the product on a spoon exposes the contents of the bottle to oxygen as soon as the seal is broken for the first time. The purity of the product could also affect the speed of the product’s deterioration, as the presence of trace metals or enzymes within the oil will accelerate oxidation.

Today, there are numerous alternative dosage forms to overcome these delivery system issues. One of the most successful are softgels. For the consumer, this dose form is more convenient and less messy to handle, and for formulation scientists, encapsulation provides the significant advantage of protecting the oil from the effects of atmospheric oxidation, maintaining the quality of the product. The shelf life of products is also greatly increased.

Oxidation of omega-3 oils is irreversible, and besides the unpleasant physical characteristics, oxidation may also reduce a product’s nutritional quality and adversely affect safety via the formation of by-products, including aldehydes, ketones, acids, and other complex molecules. In addition to oxidation, omega-3 oils are prone to degradation brought about by exposure to heat and light, so careful handling throughout softgel manufacturing is critical.

**Manufacturing the Optimal Omega-3 Softgel**

As with any process, starting with the highest-quality raw material is essential. The next step is to look for a compatible
antioxidant molecule with which to co-formulate the omega-3 oil that may help minimize oxidation. There are a number of options for complementary antioxidants, including tocopherols, which are naturally present in some sources of omega-3 oils, or citric and ascorbic acids and a range of spice extracts. There is no one-size-fits-all solution because of the variations—and various needs—of different types of oils. Often, a blend of antioxidants is preferable to a single source.

Next, it’s crucial to find the right manufacturing process. The modern form-fill-seal process used to manufacture most softgel capsules today was invented over 80 years ago by RP Scherer. This process starts off by creating two flat ribbons of gel, which can be animal-gelatin-based, fish-derived, or vegetarian. In Southeast Asian markets, vegetarian materials are becoming more popular, including ones using the seaweed-derived hydrocolloid carrageenan, in combination with starch.

The manufacturing process brings the ribbons of gel together between two rotating dies with capsule-shaped indentation, forming a capsule which is then filled using a nozzle containing the liquid oil, which has been pre-formulated with any other ingredients such as the antioxidants. The softgel is then sealed. It is at this point that the air-proof environment is formed, protecting the omega-3 oil.

Throughout production, it is important to maintain a closed system for the transfer of materials so that products remain protected by a blanket of inert gas such as nitrogen, including within the storage drums that the raw materials are delivered in.

The softgels will then undergo primary packaging, usually in bottles or filled into blister packs, preferably in an inert atmosphere to maintain integrity and minimize the risks of oxidation.

Innovative Omega-3 Dose Forms

Within the highly competitive nutritional supplements market, there is strong demand for new innovation in the marketing of products. Softgel encapsulation has revolutionized the omega-3 market away from liquid formulations. In addition, technology advancements such as microemulsion fill technology can improve user compliance by further eliminating the fish oil taste and anti-reflux properties, helping address some of the key challenges with today’s omega-3 products. And technologies for controlled release and a modified delivery profile offer significant benefits to consumers. An acid-stable enteric coating, for instance, would allow softgels to pass through the acidic conditions of the stomach and then dissolve in the more alkaline conditions of the small intestine, reducing reflux and minimizing the potential for unpleasant, fishy aftertastes.

By taking advantage of advanced delivery technologies, formulators and manufacturers are ensuring that consumers have access to convenient and high-quality omega-3 supplements. From liquids and softgels to vegetarian softgels and beyond, the ongoing challenge is to ensure that innovations can continue to meet evolving market demands.

In addition to oxidation, omega-3 oils are prone to degradation brought about by exposure to heat and light.

Authors are employed by Catalent Consumer Health. Humera Ahmad is director of product development, APAC; Claudia Valla is product development adviser; and Rosa Bertolami is senior scientist adviser.
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Researchers estimate that the human body could contain as many as 75 trillion cells. Each of those cells is surrounded by a bean-shaped membrane made up of dense rows of fatty acids that require protection from lipid peroxidation. Of the many popular antioxidants that help protect cells (e.g., astaxanthin, lutein, lycopene, CoQ10), vitamin E is the one nature chose to reside within the lipid cell membrane to protect its integrity. Vitamin E comes in the perfect molecular shape to do this job—like a tadpole, with a head and tail, similar to the phospholipids that complement the cell membrane. Vitamin E is distinguished by a chromanol head with a lipid-soluble side chain.

There are two forms of vitamin E: tocotrienols and tocopherols. Not all forms of vitamin E are the same, however. Tocopherols have a longer tail (phytanyl), whereas tocotrienols have a shorter, more flexible tail (farnesyl). This small difference in molecular structure allows tocotrienols to cover a larger surface area of the cell membrane more quickly, hence making them more effective as antioxidants. As this article will discuss, an expanding body of research points to significant benefits supporting the tocotrienol form.

**Tocotrienols vs. Tocopherols**

When vitamin E was discovered in 1922, it was discovered as alpha-tocopherol. Between that time and 1940, scientists delved into tocopherol research, ranging from alpha-tocopherol’s isolation from plants, chemical identification, complete synthesis, and antioxidant activity. In fact, the tocopherol form remained the main focus of vitamin E science for decades, and, as such, research on tocopherols boomed.

Tocotrienols were discovered later, in the mid-1960s. Tocotrienols’ ability to lower lipids was first reported in the early 1980s in the 1990s, tocotrienols were associated with reduction of cardiovascular diseases and inhibition of cancers. Despite the growing research on tocotrienols, they are still often confused with tocopherols and were not even properly listed in the Merck Index, the encyclopedia of chemicals, drugs, and biologicals, until 2001.

 Lingering confusion over the difference between tocotrienols and tocopherols is understandable, considering that both have the same chromanol head. Today, alphatocopherol remains the most common vitamin E source on the market despite some lingering debate around it.

**Debate around Tocopherols**

Commercialization of natural, soy-derived tocopherols began in the 1950s; however, high demand for tocopherols prompted many companies to eventually switch from soy- and corn-derived tocopherols (whose crops typically yielded less than 20% alpha-tocopherol) to 100% alpha-tocopherol. Today, much of the “natural” alpha-tocopherol on the market is in fact semi-synthetic, with soy- and corn-based tocopherols synthesized to (RRR- or d-) alpha-tocopherol via the addition of one methyl group to gamma-tocopherol and two methyl groups to delta-tocopherol.

While synthetic tocopherol ingredients do exist in the market, synthetic tocotrienol ingredients do not. Tocotrienols are still sourced from a wide array of foods, including wheat, barley, and corn. Rice, palm, and annatto are the richest tocotrienol sources. Some research suggests that alpha-tocopherol interferes with the helpful activity of tocotrienols. Following an animal study...
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published in the Journal of Nutrition in 1996\(^\text{14}\), researchers suggested that tocotrienols were more potent hypocholesterolemic agents when administered with the lowest alpha-tocopherol content possible. In the study, chickens were fed either an alpha-tocopherol control diet or alpha-tocopherol administered in combination with gamma-tocotrienol. The group with the largest-supplemented amount of alpha-tocopherol showed increased activity of the rate-limiting enzyme responsible for cholesterol production, 3-hydroxy-3-methyl-glutaryl-CoA reductase (HMGR), and as a result cholesterol levels rose in that group—prompting researchers to conclude that in order for tocotrienols to help lower cholesterol, alpha-tocopherol content should not be more than 15%.

Four years later, another study in guinea pigs reported similar findings in favor of tocotrienols compared to tocopherols.\(^\text{15}\) In this study, researchers found that alpha-tocopherol, when co-administered with tocotrienols, reduced tocotrienols’ inhibitory effect on HMGR. When administered alone, tocotrienols reduced the enzyme’s activity by 48%; however, adding alpha-tocopherol meant that the combination inhibited HMGR by only 13%. Fast-forward through 15 years of clinical studies: tocopherol-tocotrienol mixtures did little or nothing to lower lipids, but when tocopherols were removed from the mixtures, lipids would decrease.\(^\text{16, 17}\)

Additional research suggests that tocopherols may be a monkey-wrench to tocotrienol functions. One small 2009 prospective study indicated that tocopherols may interfere with breast cancer medication\(^\text{18}\), while a 2015 animal study\(^\text{19}\) found that excessive amounts of alpha-tocopherol may worsen stroke-related brain injuries. In 2005, those same researchers found that while orally supplemented alpha-tocotrienol was shown to reach most tissues and vital organs (including the skin, adipose tissue, ovaries, heart, liver, central nervous system, spinal cord, brain, lung, testes, and skeletal muscle), the mechanisms for transporting alpha-tocopherol and alpha-tocotrienol apparently compete, leading the researchers to note that “the transport efficiency of alpha-tocotrienol to tissues may be maximized by eliminating the co-presence of alpha-tocopherol in the oral supplement.”\(^\text{20}\)

The reasoning behind this can be readily understood. Of all eight isomers of vitamin E, only alpha-tocopherol has a known transport protein—a protein chaperone that recognizes alpha-tocopherol alone of all the eight isomers and delivers it to the tissues of interest. Then, by passive diffusion and emulsification with fats in a meal, all other vitamin E isomers get absorbed, like most lipid-soluble nutrients. Thus, co-supplementation with alpha-tocopherol is likely to compromise tissue delivery of alpha-tocotrienol.\(^\text{21}\) Alpha-tocopherol administration has also been
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Growing consumer demands for natural sources of vitamin E, coupled with promising research in several important health categories, should fuel more interest in tocotrienols.

Tocotrienols’ Time to Shine
While alpha-tocopherol research still occurs at a much greater level than tocotrienol research, there has been a downward trend in alpha-tocopherol research alongside an increase in understanding of tocotrienols driven by a growing body of science. Furthermore, FDA’s impending changes to the US. Nutrition Facts label, which include changing the unit of measure for vitamin E from IU to mg, will further underscore the differences between the two forms. Under the new labeling standard, 1 mg of natural vitamin E (RRR-alpha-tocopherol) equals 1 mg of vitamin E, but 2 mg of synthetic vitamin E (all-rac-alpha-tocopherol) equates to only 1 mg of natural vitamin E. The reason? In a nutshell: when synthesizing alpha-tocopherol, the stereochemistry changes that occur result in molecules that are not identical to natural alpha-tocopherol, although they may still be of the same molecular weight.

Growing consumer demands for natural sources of vitamin E, coupled with promising research in several important health categories, should fuel more interest in tocotrienols. Below are just a few study areas of interest showing positive results.

Editor’s note: Asterisks indicate studies performed by the author’s company, American River Nutrition (Hadley, MA), or on the company’s DeltaGold annatto tocotrienol ingredient. Some studies were also funded by American River Nutrition.

Cardiovascular Health
Thirty-one subjects with high cholesterol took escalating doses of tocotrienols—125, 250, 500, and 750 mg/day of American River Nutrition’s DeltaGold annatto tocotrienol— for four weeks each, with a two-week wash-out period between each dose. Researchers concluded that total cholesterol fell by 15%, while LDL cholesterol was reduced by 18%. Other notable outcomes: triglycerides decreased by 14%, and the cytokines associated with cardiovascular disease decreased by as much as 64%.*

Anti-Inflammation
The same parameters were employed to examine DeltaGold annatto tocotrienols’ effect on inflammatory markers, with equally impressive results. (Note: In this study and the one previously profiled, 250 mg/day was identified as an optimal dose of tocotrienols.) Among the promising results: C-reactive protein levels (a predictor of chronic inflammation) were reduced by 40%, and nitric oxide levels, which are aberrant in inflammatory conditions and should be reduced (only in inflammatory conditions), were also lowered by 40% in subjects.**

Two clinical studies indicate that delta-tocotrienol, combined with antioxidant polyphenols, may curb inflammation and help manage dyslipidemia (the elevation of plasma cholesterol), triglycerides, or both, or help to lower high-density lipoprotein levels that contribute to the development of atherosclerosis.*** One placebo-controlled study was conducted in two groups of elderly subjects over six weeks, one with normal lipid levels, the other elevated. The product formulation was composed of DeltaGold delta-tocotrienol from annatto along with a B-vitamin (niacin) and polyphenols. In both groups, supplementation led to a significant drop in C-reactive protein and γ-glutamyltransferase (a predictor of non-fatal myocardial infarction and fatal coronary heart disease), while increasing total antioxidant status. In the hypercholesterolemic group, the following also dropped: LDL cholesterol (by 20%-28%) and triglycerides (by 11%-18%). C-reactive protein dropped in healthy elderly subjects (by 21%-29%) and in the hypercholesterolemic elderly (by 31%-48%). No adverse effects were observed.

Bone Health
In a 2017 in vivo study involving 48 female Sprague-Dawley rats, DeltaGold tocotrienol from annatto—with or without lovastatin—increased bone formation and mineralization in rats. Researchers concluded that supplementation of tocotrienol in statin users can potentially protect them from osteoporosis.****

Our company is also embarking on (and sponsoring) a study of DeltaGold tocotrienols’ effect on the bone health of 89 postmenopausal women on tocopherol-free tocotrienol. This study will hopefully provide welcome clarity on how the nutrient affects human subjects. The study should be published in late 2017. As of this writing, early results look very promising.

Bioavailability
Tocotrienols’ bioavailability has been questioned in the past, resulting in the marketing of bio-enhanced, synthetic emulsions that are said to increase absorption. The solution for increasing tocotrienols’ bioavailability is easy, however, and time-tested: take tocotrienols with a meal.

Two studies on DeltaGold confirmed the bioavailability of tocopherol-free annatto tocotrienol. An open-label randomized trial involved 125, 250, 500, 750, and 1000 mg/day dosage groups. Many pharmacokinetic parameters were studied in healthy subjects to ascertain that delta- and gamma-tocotrienol were absorbed. When taken with a meal, both tocotrienols were absorbed and bioavailable.*

The Future for Tocotrienols
Research clearly shows that not all vitamin E isomers are the same. Tocotrienols...
have well-differentiated functions from tocopherols, with a growing body of evidence supporting its benefits for chronic conditions. Considering that studies show that tocopherol does not augment the function of tocotrienol, but rather antagonizes it, in my professional opinion, in order to fully appreciate the benefits of tocotrienol, manufacturers should formulate with delta- and gamma-tocotrienols, without tocopherol or with the lowest amount of alpha-tocopherol possible.

Barrie Tan, PhD, a foremost vitamin E expert, is credited with identifying the primary sources of plant-based tocotrienols. Today, his research focuses on nutrients that impact aging conditions. Tan is the senior expert, is credited with identifying the primary sources of plant-based tocotrienols. Today, his research focuses on nutrients that impact aging conditions. Tan is the senior editor of Tocotrienols: Vitamin E Beyond Tocopherols (2013), and collaborates with universities worldwide to further tocotrienol research.

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Even nutrition nerds might need to consult their smartphones when pressed to describe what glutathione is—and why it matters. After all, this unassuming tripeptide doesn’t enjoy the same high profile as, say, curcumin, probiotics, pea protein, or any of the other “trending” nutrients jamming Google’s search engines. But that doesn’t mean it’s not important. Nor does it mean that its profile isn’t rising.

For while glutathione has flown under the radar for years, its ineluctable role in human health, not to mention mounting evidence of its benefits, is finally earning it the attention it deserves. According to Elyse Lovett, marketing manager, Kyowa Hakko USA (New York City), glutathione awareness rose from 7% in 2015 to 9% a year later, as measured by the 2016 Gallup Study on Nutrient Knowledge & Consumption. And as for the academy’s role, the number of glutathione-related items found in PubMed’s database rose from a mere 469 in 1976 to 5,826 in 2016.

So why does glutathione deserve attention? Because it really is—as it’s often called—the “mother of all antioxidants.” Comprising the amino acids cysteine, glycine, and glutamine, glutathione, or GSH, is found in every cell of the body, which produces it endogenously. Its location within the cells optimally situates it for protecting cellular structures against oxidation, which it does by siccing its thiol (-SH) groups on free radicals wherever they attack.

But that’s not all that glutathione does. As an antioxidant, glutathione helps maintain active stores of other key free-radical fighters, like vitamins C and E. It participates in the synthesis of DNA, proteins, and prostaglandin hormones. It aids amino acid transport. It’s involved in cell cycling and differentiation. It even helps activate some enzymes.

Linked to everything from cancer and heart disease to dementia, cystic fibrosis, and autism, it’s especially important in immune and detoxification functions.

In fact, says Lovett, “I’ve been seeing many more innovative products on the market for detoxification.” Manufacturers, she says, “are noticing the importance of tying overall health with not only the immune system, but with detoxification, too. Some are even going one step further and tying in the antiaging benefits of antioxidants like glutathione.” No wonder the top-three reasons people turn to glutathione these days are its utility as a

The number of glutathione-related search results in PubMed reached 5,826 in 2016.
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While glutathione has flown under the radar for years, its ineluctable role in human health, not to mention mounting evidence of its benefits, is finally earning it the attention it deserves.

powerful antioxidant, its appeal as an antiaging nutrient, and its reputation as a detoxifier, she says. But if our bodies produce glutathione endogenously, why do we need to supplement it at all? The reason lies within: when glutathione guards our cells against oxidation, it nobly sacrifices itself in the process, becoming oxidized to its glutathione disulfide form.

Under ideal circumstances, glutathione disulfide can be reduced back to active glutathione courtesy of the electron donor nicotinamide adenine dinucleotide phosphate (NADPH). But contemporary circumstances are rarely ideal. We live in an oxidative environment, with assaults from pollution, poor diet, stress, and even the passage of time all attenuating the body’s ability to maintain sufficient stores of active glutathione. And yet a high cellular ratio of oxidized to reduced glutathione is widely acknowledged as an indicator of oxidative stress and a warning sign of future health problems.

So don’t let glutathione go by the wayside. “There are so many antioxidants out there,” Lovett says. With continued research and in combination with other ingredients, she says, “We’re learning more about the benefits of glutathione and all these nutrients.”

Clean Up Your Act
It’s a dirty world out there. And as Lovett says, glutathione “is one of the key ingredients that belongs in the detox supplement space. It’s getting a ton of buzz lately.” As the body’s master antioxidant, it not only “intercepts and neutralizes toxins in the GI tract before they’re even absorbed,” she says; glutathione also helps eliminate the toxins, chemicals, and potential carcinogens that the body’s already absorbed. As a hydrophilic compound, glutathione also mixes with lipophilic toxins and waste products in the liver—a crucial step in the production of bile.

Willing and Able
For a long time, an “old myth that glutathione doesn’t get absorbed well when taken orally” remained stubbornly persistent, Lovett says. And to be fair, proteases found throughout the alimentary canal are known to tear apart at this tripeptide. But a 2014 study published in the European Journal of Nutrition showed for the first time that supplementation with Kyowa Hakko’s Setria glutathione effectively increased the body’s glutathione stores.

“The study measured the effect of glutathione supplementation at 250-mg and 1,000-mg doses over a six-month period in 54 healthy adults,”Lovett says, and “findings showed that Setria glutathione levels increased in the blood after one, three, and six months versus baseline at both doses.” Let that old myth about poor bioavailability go the way of the dodo.

NO Tag Team
Nitric oxide (NO) is a gas, not a supplement. But supplements that allow the body to produce more NO have become wildly popular with bodybuilders and fitness enthusiasts because NO not only increases blood flow to the muscles—feeding them the nutrients they need to grow—but possibly speeds recovery time post-exertion.

A 2015 study published in the Journal of the International Society of Sports Nutrition found that one week of daily oral supplementation with 200 mg of Setria glutathione plus 2 g of L-citrulline enhanced NO levels in 60 healthy, resistance-trained males aged 18 to 30. The study found that the paired glutathione and L-citrulline not only increased levels of NO but kept them elevated for a longer time relative to a placebo “by preventing glutathione’s oxidative reaction when ingested in combination with L-citrulline,” Lovett explains.

Bright Days Ahead
Now that we know about the damage that sunlight wreaks on our delicate skin, tanning seems so passé. These days, it’s skin lighteners that are attracting attention, with a market that’s expected to hit $23 million by 2020, according to market researcher Global Industry Analysts Inc. And even here, glutathione plays a role.

A recent study published in Clinical, Cosmetic, and Investigational Dermatology found that a daily dose of 250 mg of Setria glutathione taken orally may decrease melanin production in subjects with light-brown to brown/olive skin. This is lower than the 500-mg dose that an earlier study found effective in brightening skin tone. Further, the current study showed that the Setria may help reduce wrinkles in middle-aged women by boosting skin hydration and possibly even improving the skin barrier.

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Here Comes Kefir

Fermented beverages like kombucha have surged in popularity in recent years, but here’s why kefir drinks—and their dairy-free iterations—are poised to steal the show.

BY JENNIFER PRINCE, ASSOCIATE EDITOR

Kefir is nothing new—in European countries like Russia and Poland. In fact, it’s been around for centuries. But here in the U.S., kefir’s popularity is still gaining traction. The fermented beverage, which is usually made by adding kefir “grains” to cow or goat milk, boasts myriad health benefits. For starters, kefir is considered to be a more powerful probiotic than yogurt, is said to boost immunity, and may even help to build bone strength. Now, the traditionally milk-based drink is making forays into the non-dairy sector, too. These alternatives, formulated with coconut milk, almond milk, and water, give consumers more options for consuming kefir. So, make no mistake about it: kefir is here to stay.

Last March, Innova Market Insights released a report analyzing just how much of a dent kefir is making in the fermented foods category. According to the report, kefir launches increased more than threefold between 2011 and 2016, compared to more moderate increases for overall yogurt and fermented beverages. In terms of dairy free, however, currently only a few companies, like U.K.-based lactose-free probiotics startup Rhythm Health Ltd., have made forays into the dairy-free kefir sector. But with the kefir market on the rise, odds are good more will follow suit.

Although kefir is still relatively unknown among a majority of consumers, there are a few likely factors contributing to its rise. According to Joana Maricato, market research manager, New Nutrition Business, kefir is a great way to create a “new point of difference” from more traditional fermented fare like yogurt. “Kefir is different from yogurt in terms of taste and texture, but the biggest differences are related to its fermentation and the number of bacteria [present]. Kefir is fermented for a longer period of time than yogurt, resulting in less…lactose in the final product. It also contains different strains and a higher number of bacteria culture,” she says.

Another factor in its favor? A natural alignment with the human microbiome. Brian Owens, founder, Rhythm Health, tells Nutritional Outlook that his coconut-based kefir products feature “real living cultures from a mother culture that have a natural order of bacteria, a synergistic community that survives together—just like our microbiome, in fact.”

Maricato tells Nutritional Outlook that dairy-free kefir can be formulated with just about any non-dairy milk, including coconut milk or almond milk, as well as with water. “However, there will be differences in terms of taste and texture of the final product depending on which milk you use as a basis,” she says. “For example, almond milk kefir might be much more watery than coconut milk kefir.”

Rhythm Health offers an array of lactose-free kefir formulations, including its coconut-based kefir drinks, Make Your Own Kefir Yogurt, and Kefir Life Shots, which the company says contain “a minimum of 50 billion live, synergistic, natural, multi-strain bacteria from lactose-free kefir cultures.” Owens founded the company three years ago with an eye toward a dairy-free kefir future. Coconut, which Owens says is “a special raw material called the tree of life in Sanskrit...for good reason,” offers its own health benefits, like antioxidants and potassium, in addition to being allergen- and lactose-free.

Though kefir products are entering the market in ever greater numbers, there is still plenty of room for growth. And, although Asian and European countries are more familiar with the concept of fermentation, the potential for growth is stronger in the U.S. where, according to Maricato, “the idea of fermentation is still fairly novel.”

Owens adds: “Here in the U.K. and Europe, investigative TV shows...have shined the spotlight on kefir by actually testing [human subjects]...gut microflora” before and after consuming a kefir beverage. Owens says that kefir’s future is bright—particularly as consumers become more educated about functional foods like kefir. “It’s a slow process...when your diet has been compromised by processed junk food, it’s a battle to get the function back. But it’s possible with natural cultures and raw fiber,” he says. “There’s so much world press on diversity being the key to a healthy life that people are making more educated choices [and] looking for that diversity.” Kefir just happens to be a relatively untapped way to meet that demand.
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