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Probiotics have had a tough media run in recent months. Why are probiotics in the crosshairs, and why now?

Among the negative news: 1) in June, a study in *Clinical and Translational Gastroenterology* (Rao et al.) linking probiotic use with "brain fogliness" as well as abdominal bloating, pain, and gas, 2) in August, an *Annals of Internal Medicine* review (Bafeta et al.) concluding that researchers are not doing a good enough job of harms reporting during probiotics studies and are limiting safety data that might be useful to other researchers, 3) in September, two studies published in *Cell* (Zmora et al.) questioning the efficacy of probiotics because a large portion of the probiotics supplemented in the study passed through the subjects' digestive tracts.

Wading into the fray in September, Harvard Medical School assistant professor Pieter Cohen, MD, a longtime critic of the dietary supplement industry, wrote a *JAMA Internal Medicine* byline titled "Probiotic Safety—No Guarantees," stating that "widespread use [of probiotics], particularly among people who are healthy, has greatly outpaced the science."

I spoke to one of our editorial advisory board members, Duffy MacKay, ND, senior vice president, scientific and regulatory affairs for the Council for Responsible Nutrition (CRN; Washington, DC), about what he thinks about the Cohen piece as well as this wave of negative attention.

According to MacKay, Cohen's piece shouldn't be taken at face value or as an indication that the probiotics industry is the Wild West. For instance, Cohen states that FDA should require probiotic companies to state on their labels the specific bacterial strains in their products; however, MacKay points out, this is already a best practice that industry leaders have been pushing manufacturers to follow for years and that many responsible probiotic manufacturers already heed.

Cohen also states that better care must be taken "to ensure that mobile resistant genes"—antibiotic-resistant genes—"are not contained in the probiotics consumed by millions of people in the United States." Again, this is something the probiotic industry would agree with, not argue against, MacKay says. He points out that many of the bacterial strains heavily used in the probiotics industry, like *Lactobacillus acidophilus*, have been present in the dairy industry for decades and have demonstrated no antibiotic resistance. Secondly, he says, FDA regulations rightly require that if companies are using new bacterial strains that have not been present in the food supply demonstrating safety and whose link to antibiotic resistance has not been fully examined, companies would and should file a new dietary ingredient (NDI) notification by law. "We need to protect public health, and we need to evaluate the safety of these strains before they're introduced to the food supply," MacKay says.

And in response to Cohen's allegations that the success of the industry is largely powered by "hundreds of small studies whose results are spun as favorable...?" MacKay says: "I would disagree with Pieter wholeheartedly," adding that "there is a very large evidence base for particular strains."

Of course, the probiotics industry—like all industries—isn't perfect, and there are some who act irresponsibly. MacKay says, "I have witnessed some overstating over preliminary evidence in some areas." To that end, he says, "We need better enforcement both from the FTC and the FDA to catch companies making unsubstantiated claims.

Why has there been so much probiotic criticism lately? It may just be part of a normal cycle, he says. Probiotics' own market success and some major positive studies may now be triggering critics to pay more attention to the category. For instance, positive studies include a large-scale Cochrane Review in 2015 concluding that probiotic strains *Lactobacillus rhamnosus* and *Saccharomyces boulardii* help prevent antibiotic-associated diarrhea in children. Also, as more doctors prescribe the use of probiotics, "the medical community has been inundated with this non-drug product," he says, which also will activate a subset of industry critics.

"I don't think there's a big, bad conspiracy out there driving this," MacKay says. "When something becomes successful, then people start to research it more, and when there are contrarian findings, they get everyone's attention and become press-worthy."

Such is the situation that probiotic makers may find themselves in now. Negative attention should spur manufacturers to be even more cautious in how they produce and sell their products. "This is a callout to the probiotics industry," he says. "If we want to keep this category growing, we have to button up our science and be willing to use the right strains and make the right claims."

While industry may not have control over negative headlines, Neal Mercado, vice president of marketing and innovation for Designs for Health, maker of ProbioMed dietary supplements for healthcare professionals, says what industry can control is its ability to make these products responsibly and transparently.

"It is very difficult to draw any meaningful conclusions from the most recent trials that have been the subject of negative headlines, other than reiterating the importance of strain specificity, viability, and CFU quantities on efficacy," he says. "Too often, researchers have used generic strains or have not properly reported strain IDs, and we know that different strains of the same species can have very different effects. We also know that the probiotic needs to be alive, viable, and of sufficient quantity to have an effect. That's why Designs for Health believes that transparency is paramount to any quality probiotic formulation."

And lest you worry, there has definitely been a lot of positive news about probiotics as well. Turn to pages 14 and 40 in this issue to read some of the latest developments strengthening this category.

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Herbal dietary supplements saw their strongest sales growth in more than 15 years in 2017, according to new figures out from the HerbalGram Herb Market Report published annually by the American Botanical Council (Austin, TX). This growth was driven by rising interest in Ayurvedic herbs and in herbs and botanicals as a whole, the report’s authors say.

Total consumer spending on herbal dietary supplements in the United States reached an estimated $8.085 billion in 2017—the first time total U.S. retail sales of herbal supplements surpassed $8 billion. This sales figure represents an 8.5% increase in total sales from 2016, the strongest growth in U.S. herbal supplements sales in over 15 years.

The report is based on retail sales data provided by Chicago-based market research firms SPINS and IRI, as well as Nutrition Business Journal (NBJ), published by New Hope Network (Boulder, CO). The information only covers retail sales of herbal supplements and does not reflect the sales of most herbal teas, botanicals in cosmetics, or herbal drug ingredients in over-the-counter medicines.

In a breakdown of market channels, NBJ estimates also showed that retail sales increased across channels in 2017. The strongest growth was in direct sales, totaling $4.012 billion, an 11.2% increase from the previous year. Significantly, this is the first time since 2012 that direct sales growth has outpaced sales growth in the mass market and natural channels. Mass market sales grew to $1.449 billion in 2017, an 8.4% increase, and sales in natural and health food stores increased by 4.7% to a total of $2.624 billion. Figures for sales by channel from SPINS differed substantially because of differences in how NBJ and SPINS define retail channels and which retailers they include in their data.

**Mainstream Channel**

*HerbalGram* also gave a breakdown of the best-selling herbs by channel. The bestseller for 2017—for the fifth consecutive year—in the mainstream/mass market channel was horehound (*Marrubium vulgare*, Lamiaceae). Sales in 2017 totaled $140,832,190, a 12.3% increase from 2016.

Turmeric (*Curcuma longa*, Zingiberaceae) experienced the strongest sales growth with a 46.7% increase in the mainstream channel, with 2017 sales totaling $32,456,933. Four other herbs also experienced a more than 30% growth in the mainstream channel: wheatgrass/barley grass (44.2%), elderberry (34.7%), fenugreek (33.5%), and ivy leaf (30.2%).

On the flip side, three products in the mainstream channel experienced a more than 30% decline from 2016: coconut oil (–34.9%), green coffee (–38.2%), and green tea (–30.4%). According to the *HerbalGram* report, the decline in green tea and green coffee could be due to an overall skepticism of weight-management supplements from consumers, though green tea still has a spot in the top-10 bestsellers. The decline in coconut oil, which in 2013 experienced a 4,000% increase in sales, is most likely due to the highly publicized 2017 Presidential Advisory from the American Heart Association stating that coconut oil is not healthier than beef fat in terms of cardiovascular effects, the report authors note.

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

1. Horehound (*Marrubium vulgare*, Lamiaceae)
2. Echinacea (*Echinacea* spp.)
3. Cranberry (*Vaccinium macrocarpon*)
4. Ivy leaf (*Hedera helix*)
5. Turmeric (*Curcuma longa*, Zingiberaceae)
6. Black cohosh (*Actaea racemosa*)
7. Garcinia (*Garcinia cambogia*)
8. Green tea (*Camellia sinensis*)
9. Ginger (*Zingiber officinale*)
10. Fenugreek (*Trigonella foenum-graecum*)

**The Natural Channel**

The natural channel has seen huge growth in emerging supplements and consistent sales for products that are just now breaking into the mainstream channel. For example, while turmeric did reach the top five in the mainstream channel in 2017, it is the bestselling herbal supplement for the fifth consecutive year in the natural channel, totaling $50,346,121—a 12.2% increase from 2016.
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The natural channel appears to be more stable, with less volatile growth and decline compared to the mainstream channel, which is more susceptible to shifting trends. Rather, the natural channel is a launching pad for many trends that eventually make their way mainstream.

In the natural channel, certain herbs showed enormous growth in 2017. Quite significantly, cannabidiol (CBD) ranked for the first time among the top-40 bestselling herbal supplements of 2017 in the natural channel, hitting the number 12 spot with total sales of $7,583,483, a 303% increase from the previous year. While CBD is controversial from a regulatory and legal standpoint, it’s clear from this report that demand for hemp-derived CBD is only growing.

Nigella (Nigella sativa, Ranunculaceae), also known as black seed or black cumin, is another product experiencing huge growth in the natural channel, with sales up 202.5% compared to 2016. Moringa (Moringa oleifera, Moringaceae) is the only other ingredient in the natural channel to grow more than 30%, with sales growth of 32.9% and making its debut on the list of top-40 bestselling products in the natural channel.

The authors note that these emerging products offer consumers alternative supplement formats like liquids, oils, and powders, a welcome respite for consumers dealing with pill fatigue.

The top-10 bestselling herbal ingredients in the natural channel were:

1. Turmeric (Curcuma longa, Zingiberaceae)
2. Wheatgrass/barley grass (Triticum aestivum/Hordeum vulgare)
3. Flax seed/flax oil (Linum usitatissimum)
4. Aloe (Aloe vera)
5. Elderberry (Sambucus nigra)
6. Ashwagandha (Withania somnifera)
7. Milk thistle (Silybum marianum)
8. Maca (Lepidium meyenii)
9. Echinacea (Echinacea spp.)
10. Oregano (Origanum vulgare)

Authors of the report conclude that the significant increase in sales is the result of a heightened consumer interest and awareness of botanicals and traditional medicine such as Ayurveda.

*New Hope Network and Nutritional Outlook are both owned by parent company Informa.

New FDA Probiotic Draft Guidance Accepts CFUs as Unit of Measure

One of the most significant discussions in the probiotics industry is how manufacturers should label probiotic products and which unit of measurement they should use to list probiotic content. There has been a push to move away from listing probiotic content in metric weight (usually milligrams) and instead to use colony-forming units (CFU), which is a measure of the number of viable, live, active bacteria in a product. FDA regulations require that dietary supplement
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products list ingredients by weight, but in September, FDA released new draft guidance for probiotics indicating the agency will accept CFUs as a unit of measurement.

FDA’s labeling regulations for dietary supplements—specifically, 21 CFR 101.4(a)—have long required that ingredients be listed “in descending order of predominance by weight.” But when it comes to probiotics, a weight-based measurement is not an accurate reflection of how much of the live microorganism is viable at the time the supplement is consumed.

FDA released its draft guidance after the International Probiotics Association (IPA) filed a citizen’s petition in 2016 asking FDA to change dietary supplement regulations to require probiotic content to be listed as the number of CFUs present per serving at the end of a product’s shelf life, instead of by weight. IPA pointed out that, unlike with probiotics, milligram measurements are adequate for most vitamins, minerals, and botanical ingredients. Listing those ingredients by weight usually provides “consumers the information they need to evaluate how much ‘effective’ ingredient is in the product.” In its citizen’s petition, IPA used ginseng to illustrate this point: “For example, a consumer who wants to supplement their diet with ginseng can examine the labels of various products to compare how many milligrams of ginseng each provides, and knows that each milligram contributes to the efficacy of the product and/or is something he/she wants to consume.” In the case of probiotics, however, a weight-based measurement doesn’t provide information about how much of the organism in a probiotic product is live and active—and only live, active organisms will confer a probiotic benefit on the host. In addition, the number of milligrams present does not necessarily uniformly correspond with the number of CFUs in a product; simply put, the number of milligrams in a product cannot be relied on to indicate how many CFUs are in the product. As IPA explained in its petition, “Due to various cell concentrations of the probiotics, the same number of milligrams could represent very different CFU counts. Hence, declaring probiotic ingredients by weight does not provide consumers with relevant information on the amount of effective ingredient they are consuming in a dietary supplement.”

While groups like IPA have said they would like to see FDA actually change its dietary supplement regulations to allow probiotics to sidestep the weight-measurement rule, changing regulations is a significant and lengthy process requiring a proposed rule, a comment period, and many years in between. In its draft guidance, FDA said it would not change the regulations at this time to require labeling in CFUs. (The agency did, however, say, “We recognize that manufacturers are using a number of different units of measure for probiotics, enzymes, and other dietary ingredients...Because of the complexity of these labeling concerns, we plan to issue information related to this subject at a later date.”)

FDA declined to change its regulations, but in the draft guidance, the agency made clear that companies can in fact label their probiotic products in CFUs. While draft guidance is nonbinding and is only meant to represent to the public what FDA’s thoughts are on the topic, the draft guidance indicates that FDA will not consider including CFUs on a probiotic’s Supplement Facts panel a violation of supplement labeling rules. It is important that the agency made its position known, since technically, according to official FDA labeling regulations, CFUs are not an official measurement allowed to appear on the Supplement Facts panel; only weight measurements are allowed by law.

In fact, in the draft guidance, FDA points out the benefits of labeling probiotic products per CFUs and the drawbacks of using weight measurements. “The weight of microbial dietary ingredient in a product represents the product’s total cellular mass, consisting of both live and dead microorganisms, and therefore does not necessarily correlate with the number of viable microorganisms in that product,” the agency wrote. Later, it wrote, “For the reasons articulated in this document, we have determined that consumers would benefit from permitting the label of dietary supplement products to accurately represent the quantity of live microbial dietary ingredients in the Supplement Facts label in terms of CFUs.”

Industry leaders welcomed the draft guidance’s acknowledgement of CFU labeling, which two associations, the IPA and the Council for Responsible Nutrition (CRN; Washington, DC), encouraged as a best practice in a joint probiotic-labeling guideline they released last year. However, many say they still wish FDA would remove probiotics from the requirement to label content by weight. But while labeling by weight remains a supplement-labeling rule, it’s likely that companies will end up listing probiotic content in both CFUs and milligrams. As Duffy MacKay, ND, senior vice president, scientific and regulatory affairs for CRN, explains, because the number of milligrams present does not consistently correspond with the number of CFUs in a product, including both measurements on a label is a problem. As MacKay points out, due to the way bacteria behave, even if companies standardize the number of CFUs in their product, the weight of those products can vary with each batch. “So by requiring both [CFU and milligram measurements], you’re introducing a technical snag for manufacturers because if you keep your CFUs consistent every time, your weight is going to vary just slightly,” he says. The preference would be that labeling include only CFUs, and not milligrams, he says.

Still, he, like others, says he is pleased to see FDA acknowledging the benefits of CFU labeling. MacKay says CRN plans to submit comments to the agency pushing to remove weight-based labeling for probiotics altogether, but he acknowledges that this drastic step might not be a high priority for FDA at this point. “We’re going to push FDA...and see where they go,” he says.

And even if the regulations don’t change, he says, “We got halfway there. Consumers will still have the information they need” with CFU counts listed. He says issuing draft guidance was FDA’s expedient way of permitting CFU labeling even as the labeling regulations stay the same.

“I don’t think we’re going to die on our sword over this issue, but we want to continue to make it clear that this would be the best for consumers,” he adds.
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Supplements and oral care are key children’s health markets.

BY INNOVA MARKET INSIGHTS

Children are still a niche audience within the food and drink market. Innova Market Insights data indicate that just 2.5% of U.S. food and drink launches in the 12 months ending April 2018 targeted children. Many products widely consumed by children are instead marketed with a more general family-friendly positioning.

Sectors with the most developed children’s markets include impulse-type purchases such as chocolate and confectionery, savory snacks, ice cream, and soft drinks, as well as a wide range of products mainly bought as planned purchases during the regular family shopping trip, including fresh dairy products, cereal and fruit snacks, and bakery products.

While children do buy some products for themselves, the majority are still bought by parents for children, although with input from the younger generation regarding the choice of products and brands. Both generations need to be satisfied to achieve repeat purchasing and ongoing market development.

While children’s preferences tend to focus on flavors, colors, character-driven marketing, and what their friends are consuming, most parents’ overriding interest is healthfulness, with clean label, “free from,” and “low” and “light” (particularly sugar reduction) key areas.

Outside of food and drinks, we are also seeing activity in children’s products in areas such as dietary supplements and oral care, where kid-focused products continue to be of key interest to parents.

Dietary Supplements

U.S. consumers are probably the most likely to use supplements to fill perceived gaps in their own diets and their family’s diets. This has ensured a strong role for supplementation in children’s diets, with a particular focus on general health, immunity, closing potential dietary/nutritional gaps, and boosting cognitive development.

The U.S. has traditionally had a strong level of interest in using dietary supplements and has the largest and most developed market in the world. Dietary supplement launches specifically targeting children make up just under 5% of total U.S. supplement launches. There has been a focus in recent years on improving methods of delivery and making products more appealing to children, although the final purchasing decision still generally remains with the parent.

Products for children are increasingly focusing on drinkable, chewable, and gummy options, enhanced with child-friendly flavors, colors, and bright packaging graphics and character marketing, including media-licensed characters. Parental appeal tends to focus on the range of vitamins/minerals and other ingredients included in a product, the health claims used, and added benefits such as sugar-free and GMO-free.

The recent launch of Nutrilife Brainiums DHA dietary supplements illustrates many of these features. The supplements come in the form of gummies, in strawberry and fruit punch flavors, and feature a bee character and are marketed as natural and non-GMO omega-3 supplements to support brain health.
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The use of indulgent flavors is illustrated by Good Day Chocolate supplements for children, which include such versions as Multivitamin (vitamin A, B6, B12, C, D, E, folate, and biotin), Probiotic (with Sabinsa Corp’s (East Windsor, NJ) LactoSpore Bacillus coagulans; MTCC 5856, probiotic strain for digestive health), Sleep (with melatonin), and Calm (with chamomile and theanine). All products are made with fair trade chocolate and are free of GMOs, artificial flavors, and high-fructose corn syrup.

Meanwhile, Church & Dwight’s Lil’ Critters, claimed to be the leading U.S. gummy vitamin brand, relaunched its Gummy Vites product with a new package and twice the level of vitamin D and lutein of the previous version. Other additions to the range include Probiotic with prebiotics for digestive health, a “Despicable Me”/“Minions” branded complete multivitamin, and Immune C + Zinc and Echinacea for immune support.

**Oral Care**

Children are also a key target market in oral care, with more products being launched in this increasingly competitive space. According to Innova Market Insights data, the percentage of children-centric launches (for ages 5-12 years) in oral care rose from 8% of global oral care launches in the second half of 2016 to 12% of global oral care launches in the second half of 2017.

Children’s oral care products tend to feature flavors such as fruity, strawberry, and bubble gum. These were three of the top five flavors used for global launches in the second half of 2017. They also tend to feature bright graphics and characters, often ones licensed from TV and film releases. Parent buy-in, meanwhile, is achieved through the use of natural, sugar free, and tooth friendly claims, with products often featuring alternative sweeteners such as xylitol.

Recent launches include Act Kids Anticavity Fluoride Toothpaste with a fruit punch flavor and a tube featuring Batman, as well as Orajel Anticavity Fluoride Toothpaste in a Bubble Berry flavor featuring Disney Princesses and in a Berry Divine flavor featuring Nickelodeon’s “Shimmer & Shine” characters.

It’s not just toothpaste products, either. Children are also increasingly seeing mouthwash targeted at them, featuring flavors such as bubble gum and tutti frutti, and licensed characters such as Disney Princesses and The Secret Life of Pets.
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In the annals of “What’s Old Is New Again,” you would be hard-pressed to find a better case study than herbal and botanical ingredients. For despite the fact that these plant parts and preparations thereof have been...er, rooted in traditional medical systems for millennia, the convergence of contemporary science and a passion for all things “natural” has shot herbal and botanical dietary supplements onto center stage not only with consumers, but with brands and health professionals, too.

Consider that while SPINS (Chicago) measured 4.2% growth in overall U.S. vitamin and supplement sales for the 52 weeks ending July 15, 2018—$14.6 billion, total—a zoom-in on herbal formulas and singles reveals even greater growth of 21.5% and 8.8%, respectively. Combined, herbal formulas and singles brought in $1.7 billion in sales during the tracking period, per SPINS.

And fresh off the press in September came the annual HerbalGram Herb Market Report published by the American Botanical Council (Austin, TX), stating that back in 2017, U.S. retail sales of herbal supplements grew 8.5% to over $8 billion. This represents “the strongest U.S. sales growth for herbal supplements in more than 15 years” and the first time sales eclipsed $8 billion. Turn to page 12 for more on this report, which combines data from SPINS, market researcher IRI, and Nutrition Business Journal.

This success comes as no surprise to category watchers. “The trend today is toward simple, basic, pure, and natural,” says Bruce Brown, MPH, MA, president, Natreon Inc. (New Brunswick, NJ). “While many trendy ingredient fads come and go, consumers increasingly put their trust in well-established botanicals that remain solidly steeped in rich traditions.”

But consumers’ trust is by no means inviolable, and the herbal/botanical sector has weathered its share of controversy even recently. Thus, says Brown, “To be successful in the market today, botanical ingredients must meet extremely high standards for quality, safety, and purity.” And they’ll need a track record of scientific substantiation to prove it.
A Debt to the Past

The modern nutrition industry undeniably owes a debt to health practitioners of the past. As Brien Quirk, director of R&D, Draco Natural Products (San Jose, CA), points out, the same herbal and botanical ingredients gaining adherents today “existed in Ayurvedic and Traditional Chinese Medicine for thousands of years, where they painstakingly came up with these formulas to address every conceivable health condition.”

That multiplicity of uses helps explain herbs’ and botanicals’ popularity today. So, too, does their DIY ethos. “The human body has a remarkable ability to overcome illness and disease when given the right nourishment and support,” Quirk points out. “Natural products, especially herbs, are thought to encourage the body to heal itself, with fewer side effects than drugs.”

In an era of widespread “life hacking,” this speaks to our desire to take our health into our own hands. And considering that pharmaceuticals can entail side effects more vexing than the ailments they aim to treat, it makes sense that “more health conditions are being addressed with herbal medicine and functional formulas,” Quirk says.

Add to all this the high cost of healthcare, the prevalence of chronic diseases, and the popularity of plant-based products and you have a recipe for herbal and botanical success. But the real clincher, says Ramon Luna of Ecuadorian Rainforest LLC (Clifton, NJ), is the simple fact that we know so much more about herbal and botanical ingredients than we used to. “I believe consumer knowledge is the key proponent of the trend,” he declares. “There are more people now taking an interest in their overall health, and they’re doing research into herbal products as a result.”

Building on Tradition

As are scientists. And their work more than anything else helps legitimate the global herbal and botanical sector, and nudge it toward the $111-billion valuation that Market Research Future predicts it’ll attain by the end of 2023.

After all, says Brown, “Consumers need more than just the knowledge that certain herbs and botanicals have been used effectively for thousands of years. They need hard-hitting scientific evidence to support specific health claims and modes of action.” Building on the ingredients’ longstanding reputation, he says, “Ongoing research continues to validate the evidence for herbal and botanical safety and effectiveness.”

As it does so, it’s building excitement over several marquee ingredients. Principle among them is turmeric (Curcuma longa) and its key active, curcumin. Literally thousands of studies support its antioxidant and anti-inflammatory effects, notes Mariko Hill, product developer, Gencor (Irvine, CA), and that “gives it multiple applications in, for example, nootropic and muscle-recovery formulas.”

The simple fact is that we know so much more about herbal and botanical ingredients than we used to, says Ramon Luna of Ecuadorian Rainforest.

Indeed, “Turmeric spans a notable number of herbal segments, and marketing and research efforts align with this growth,” says Kimberly Kawa, retail reporting analyst at SPINS. Two areas of particular dynamism are cleansing and organ support (up 88.2% over the past 52 weeks, per SPINS data) and brain and circulation (up 525.8%—that’s right: 525.8%). But “the lion’s share of turmeric sales,” Kawa says, still come from pain and inflammation supplements, which captured $35.5 million at a 5.2% rate of growth.

“Considering the research connecting health degeneration and chronic inflammation,” Kawa says, “turmeric, or curcumin, makes sense as a functional ingredient targeting the underlying issues that precede a multitude of syndromes of sickness.” And its prospects look even brighter considering its suitability to delivery not only via supplements, but via teas, tisanes, functional beverages, snacks and more.

And it’s gone mainstream. According to the HerbalGram report, U.S. turmeric sales grew 46.7% in the mainstream channel in 2017 to over $32 million, now ranking number five on the list of the year’s top-selling herbal supplements in that channel. In the U.S. natural channel, turmeric retained its number-one ranking in 2017, growing 12.2% to over $50 million, according to the HerbalGram report.

Another botanical with “great growth potential in the context of aging,” says Hill, is fenugreek (Trigonella foenum-graecum). “Fenugreek and its seeds have anabolic and androgenic properties, and numerous clinical studies have shown its ability to displace and use bound testosterone, resulting in muscle growth, strength, and increased sex drive.”

Gencor’s branded fenugreek extract, Testofen, has shown a capacity in studies to increase lean muscle mass and decrease body fat while also promoting a longer health span and lifespan. “This allows fenugreek to be applied to multiple need states,” Hill continues, “whether in sports nutrition, men’s and women’s health, or healthy aging.” According to the new HerbalGram report, in the mainstream channel, U.S. fenugreek sales increased 33.5% in 2017 over 2016 to $28.8 million. In the natural channel, growth was more modest, at 2.7%, to $3.9 million.

For his part, Brown calls attention to the class of compounds known as adaptogens—“herbs and botanicals that exert a normalizing effect upon bodily processes and have restorative properties that help the body adapt to stress,” as he puts it. SPINS placed adaptogens atop its list of Top 10 Trend Predictions for 2018, and Brown is particularly bullish on ashwagandha (Withania somnifera).

With origins in Ayurveda, ashwagandha, he says, “has been used since ancient times for a wide variety of conditions and helps support the body in dealing with stressors both internal and external.” It’s especially appropriate in sports nutrition, energy, sleep, heart health, and cognitive health formulas, he adds, because recent human studies—the gold standard in supplement research—substantiate its role in everything from alleviating stress and fatigue to boosting energy and improving concentration.
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U.S. sales of ashwagandha in the natural channel grew more than 25% in 2017, hitting $10.6 million according to the HerbalGram report—even though the ingredient did not rank on the mainstream channel’s top-40 list. Innova Market Insights registered an 18% annual growth from 2013 to 2017 in global new product launches featuring ashwagandha. So: watch this space, if you aren’t already.

Finally, as a primary functional ingredient in both herbal formulas and singles, elderberry (genus *Sambucus*) is “a growth driver, up 59.5% and 91.5%, respectively,” Kawa says. A “superfruit” native to temperate regions of North America and Europe, elderberry is “heavily researched,” she adds, and appears to help the immune system fight viruses. As a result, SPINS research found it among the top ingredients in cold and flu formulas.

*HerbalGram* reports U.S. elderberry herbal supplement sales as growing 34.7% in the mainstream channel in 2017, to just over $19 million. In the U.S. natural channel during that time, elderberry supplement sales grew 20.6% to $12.5 million. Like turmeric, elderberry’s roster of viable applications—not just supplements but teas and tisanes, syrups, broths, and soups—adds to its desirability with consumers and versatility for formulators.

**Learning from the Past**

All of the above ingredients—and others still—boast a growing body of research supporting their efficacy. And as Quirk points out, “It almost goes without saying that an herbal ingredient needs strong scientific evidence behind it, especially from human clinical studies.” However, he continues, “A strong track record of safety is also paramount.” Yet even in today’s supplement space, such a record hasn’t always been available.

Within the past decade, sensational stories of unscrupulous manufacturers marketing unsafe or ineffective herbal and botanical products took a toll on the sector and the industry as a whole. But, says Quirk, “with increased regulation implemented through the GMP law, 21 CFR 111, the level of consumer confidence in the quality, safety, and purity of herbas has progressed to a much better place.”

Of course, FDA has its work cut out for it given the mismatch between its surveillance duties and resources for discharging them. But Quirk calls the intra-industry trend toward self-compliance with GMP standards and the voluntary pursuit of certifications from organizations like NSF International and USP “a great development.” (It’s an enlightened one, too, as the appearance of such certifications on a label “do a lot to restore consumer confidence after so many years of negative press,” Quirk says.)

**The Real Thing**

Also crucial to the category’s future will be the ability to demonstrate unequivocally that the herbal and botanical ingredients in a functional formula are, in fact, what the label says they are. “Unfortunately,” laments Deanne Dolnick, science director, TR Nutrionals (Alpharetta, GA), “wherever we see huge growth in higher-cost botanicals, adulteration pops up.”

Adulteration has been a persistent issue with *Ginkgo biloba* extract, and now it appears to threaten turmeric, she warns. And yet adulteration is almost an inevitability of an ingredient’s success—the more the market will pay for an ingredient, the more corners some will cut to supply it. And “with botanicals,” Dolnick maintains, “you get what you pay for.”

The upshot is that honest suppliers “who only sell ingredients they can guarantee are free from adulterants” face an uphill battle. “I’ve had countless customers tell me that they’re paying $50 less per kilo for turmeric extract 95% than what we’re offering,” Dolnick says. “Shouldn’t that be a red flag? I would hope so.”

Quirk also believes that identity verification “is still a challenge.” One cause, he postulates, is that testing labs don’t always have access to the specific cultivar that a botanical extract was made from. Further, FDA only requires that the broader genus-species identity—not the cultivar—be established.

“However,” Quirk goes on, “a good number of herbs, fruits, and vegetables have considerable phytochemical variation depending on the cultivar and its source. Because of this, products will often not pass high-performance thin-layer chromatography (HPTLC) identity testing.” Only after testing is complete do labs realize that the cultivar they used as a reference standard didn’t match the cultivar used to make the extract.

One solution Quirk offers would be to set up a system whereby manufacturers provide voucher samples of raw botanical materials—“though this would have to be coordinated with the lab,” he concedes. “We don’t often know when one of our customers submits a sample for testing, and it can be a challenge to obtain the raw voucher from overseas quickly. Properly preserving and importing the sample can also take time. This is a challenge that can only be solved by all of us working together to figure out a workable strategy.”

**Tell a Story**

Words to live by. But until such a system emerges, don’t discount the power of an origin story to set an herbal or botanical ingredient on a path forward. “Consumers want to know what’s in their supplements, foods, beverages, and personal care products,” Brown says. “They want to know the story behind the ingredients—where they came from, how they’re produced, and even the impact they have on the planet.”

Luna agrees. “Many of the botanicals that I’ve seen grow in popularity have some sort of colorful story behind them,” he says. *Sacha inchi* (*Plukenetia volubilis*) is exhibit A. Much of its recent growth owes to studies elucidating the specifics of its nutritional content and bioactivity, Luna says. But marketers “ran with the idea” of sacha inchi, promoting not just its health benefits and applications, but its history in South American culture. “This combination made sacha inchi a well-known ingredient around the world and will likely help drive its growth in the market,” he says.

The lesson: Proven health benefits and assurances of identity and safety are all well and good. But “a rich history for marketers to use in campaigns is one of the telltale signs of future success for a botanical ingredient.” Luna insists.
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Mood-boosting supplements are increasingly popular as modern lifestyles become more demanding and stressful. This growth is giving rise to copious amounts of new research and innovative products.

Sam Kwon, president of Vesta Pharmaceuticals (Indianapolis, IN), says that current sales trends in the mood and anxiety supplement space are moving the market toward sustainable, clean-label, natural ingredients that consumers—Millennials, in particular—prefer over pharmaceuticals.

“People are more stressed than ever,” Kwon says, “and consumers are looking for a supplement to help them relax, decrease stress, and reduce depressive symptoms.”

Consumers also prefer more convenient product formats that can be consumed quickly. “That’s why functional foods…and performance drinks are emerging as popular product formats,” Kwon adds. “Consumers still prefer something easy that they can take at the start or end of the day without an unpleasant taste or cumbersome wrapper.”

The global brain health market is expected to be worth USD $11.6 billion in 2024, expanding at a compound annual growth rate of 19.6%, according to Research and Markets.1 While the mood and anxiety niche is only one piece of the overall brain health market, these emotional health and wellness supplements are also expected to see significant growth as research continues to prove the value of mood-boosting supplements. As the mood supplement space continues to grow, expect these six ingredients to become top performers.

### Ashwagandha

A staple of Ayurvedic medicine, ashwagandha (*Withania somnifera*) is quickly gaining popularity in the United States as a mood enhancer and stress-reduction supplement thanks to its adaptogenic properties. In September, the American Botanical Council (Austin, TX) published its HerbalGram Herb Market Report on 2017 U.S. retail sales of herbal supplements, reporting that ashwagandha sales in the natural retail channel grew 25.6% in 2017 to $10.6 million.

George Polson, PhD, is the vice president of technology for Innophos (Cranbury, NJ). Polson says that ashwagandha’s growth in the West is being driven by Americans’ need for stress-reduction and mood-support supplements. “Adaptogens like ashwagandha help to protect the body against emotional and physical stressors,” Polson says. “Clinical trial research is demonstrating that ashwagandha’s health benefits are now based on science-backed testing, not just traditional use.”

One randomized, double-blind, placebo-controlled clinical trial followed 98 men and women between the ages of 18 and 60 for 60 days.2 Participants were evaluated on a modified Hamilton anxiety scale (mHAM-A) prior to the trial and were admitted to the trial if they scored between 24 and 42, which indicates moderate stress or anxiety.
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Participants were then randomly assigned to one of four dosage groups and were given varying dosages of ashwagandha extract. The ashwagandha extract used in the study, Sensoril (also called Essentra), is proprietary to Natreon Inc. (New Brunswick, NJ) and distributed by NutraGenesis LLC (Brattleboro, VT). (Innophos acquired NutraGenesis last year.) Group A (n=30) received a once-daily 125-mg dose, Group B (n=35) received the same 125-mg dose twice per day, Group C (n=35) received a 250-mg dose twice per day, and Group D (n=30) received a placebo. Participants were assessed for mHAM-A scores at days 0, 30, and 60, and for serum cortisol, dehydroepiandrosterone sulfate (DHEAS), C-reactive protein, fasting blood glucose, serum total cholesterol, serum triglycerides, serum low-density lipoprotein cholesterol (LDL-C), serum very-low-density lipoprotein cholesterol (VLDL-C), and serum high-density lipoprotein cholesterol (HDL-C) at days 0 and 60.

All experimental groups reported a statistically significant increase in subjective feelings of well-being at day 30 and day 60. All experimental groups also showed significant decreases in mHAM-A scores relative to the placebo group, with higher doses of *Withania somnifera* associated with greater score reductions. Group A exhibited a 62.2% reduction in mHAM-A scores (P<0.001) after 60 days, while the placebo group did not exhibit a statistically significant change.

Natreon funded this study. Polson says this study showcased Sensoril ashwagandha’s stress-reducing properties. “For both doses, consumption of Sensoril extract resulted in significant reductions in serum levels of the stress hormone, cortisol, as well as improvements in self-reported levels of stress and anxiety. Generally, higher doses provided greater benefits, but both doses had statistically significant effects compared to the placebo group.”

Benny Antony, PhD, is the joint managing director for Arjuna Natural Ltd. (Kerala, India). Antony says that *Withania somnifera* has demonstrated itself effective in alleviating anxiety through multiple pathways. “*W. somnifera* has traditionally been used as a tranquilizer,” Antony says. “Animal and human studies have demonstrated its anti-stress, anti-anxiety, monoamine-modulating, and cortisol-lowering properties. Ashwagandha extracts show promise as a potential adjunctive treatment for cognitive impairments as well as mood exacerbations.”

Shaheen Majeed, worldwide president of Sabinsa (East Windsor, NJ), says that ashwagandha is thought to act through the hypothalamic-pituitary-adrenal axis to alleviate stress-induced insomnia and fatigue. In one animal study, ashwagandha was found to induce differential activation of multiple types of GABA receptors, which the study authors say could explain ashwagandha’s adaptogenic properties.  

Majeed says he expects the mood and anxiety supplement market to continue growing due to the inherent complexity of the human condition. “Hectic lifestyles, confusing current events, and the normal ups and downs of life...
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all contribute to increased incidence of anxiety and mood disruptions. This has increased the demand for anti-anxiety products, especially natural alternatives. The World Health Organization has projected that depression will be the second leading cause of disability worldwide, and given the growing preference for natural alternatives, the specialized sector of herbal brain health supplements has a significant role to play in improving human life.

Probiotics

Probiotics are a recent entry to the mood supplement category, but their entry is supported by science. Research demonstrating the gut-brain connection and an increase in consumer awareness around probiotics are paving the way for probiotic mood supplements.

Tom Bayne, DC, is a chiropractic physician and scientific advisor for Probiogen (Scottsdale, AZ). Bayne says that the gut-brain connection is more powerful than was previously known, which is why probiotics are ideal for the mood supplement market. “Research has shown that gut bacteria can produce their own neurotransmitters and essentially hijack the brain,” Bayne says. “This can trigger food cravings, feelings of anxiety, feelings of depression, and other mood imbalances.”

Bérénègre Feuz, marketing director for Lallemand Health Services (Montreal, QC, Canada), notes that probiotics are gaining popularity as mood supplements due to their efficacy as well as their tolerability. She cites the results of a double-blind, placebo-controlled, randomized clinical trial on 110 patients with major depressive disorder that found an eight-week course of probiotic supplementation improved Beck Depression Inventory (BDI) scores relative to a placebo.

Eighty-one subjects completed the trial. This trial separated participants into probiotic (n=27), probiotic (n=28), and placebo (n=26) groups. Participants were administered either 1) 5 g of a probiotic supplement containing Lactobacillus helveticus and Bifidobacterium longum probiotic strains, 2) 5 g of a probiotic supplement containing galactooligosaccharide, or 3) a matching placebo, once daily for eight weeks. Participants were assessed for serum tryptophan and branched-chain amino acids (BCAAs). Researchers recorded participants’ dietary intake and physical activity at baseline. Relative to a placebo, probiotic supplementation resulted in a statistically significant decrease in BDI score (p=0.042), while probiotic supplementation failed to produce a statistically significant effect.

Saffron Extract

Saffron extract (Crocus sativus) is quickly gaining popularity as a mood supplement thanks to its strong performance in clinical trials. Sebastien Merchet, nutrition business development manager, North America, for Seppic (Fairfield, NJ), says that saffron extract’s mood-boosting and anxiolytic properties have been demonstrated in more than 10 clinical trials.

Says Merchet: “Studies have even shown that saffron extract may provide similar effectiveness to well-known pharmaceutical mood stabilizers, such as fluoxetine and imipramine, without the side effects. These clinical studies showed that the mood-stabilizing effects were linked to multiple native actives from saffron, including safranal, crocin, crocetin, picrocrocin, and other derivatives present in sargol, the richest part of saffron.”

A 2014 research review of six randomized, double-blind, placebo-controlled clinical trials found that “saffron had large treatment effects and, when compared with antidepressant medications, had similar antidepressant efficacy.”

Seppic is the exclusive distributor of Activ’Inside products for North America. Merchet says that Activ’Inside’s branded saffron extract, Saf’Inside, contains 10 times more safranal than generic saffron extracts when measured by HPLC, and has standardized concentrations of 25 native active compounds associated with saffron’s mood-stabilizing properties that Activ’Inside has dubbed “Safromotivines.”

Merchet says the mood and anxiety supplement market is diversifying its product formats, with powdered drinks quickly becoming popular. “Chewables, gummies, and other formats are also trending, but powders are quite popular. Consumers want to be able to prepare their own drink, yogurt, or shake—and making your own recipe might be relaxing in and of itself.”

Last year, another saffron supplier, Pharmactive Biotech Products (Madrid, Spain), a partner of Gencor (Irvine, CA), funded a first-of-its-kind clinical study on the effects of the company’s proprietary, patented Affron ingredient in an adolescent population. Researchers found that Affron may help reduce depression and anxiety symptoms in teenage...
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Why Fermentation?
Throughout history, fermentation has been an important way to preserve food and beverages, helping them last longer. It gained even greater relevance when researchers discovered the significance of good bacteria in the gut that help with basic functions such as digestion, absorption, and assimilation of nutrients. It was found that fermented food products help improve these functions, as well as helping boost general health.

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Fermented botanical extracts offer synergistic benefits with the bacteria already present in the digestive tract. During fermentation, new bioactive compounds are formed, including phenolics and flavonoids, that have improved water solubility and easier absorption. The new extracts contain prebiotics in easier-to-use water soluble form, which can boost probiotic growth.

The fermentation process also increases levels of nutrients such as B vitamins and Vitamin K; as well as short chain fatty acids and healthy probiotic flora. The fatty acids, which are essential for healthy gut, help colonize healthy probiotic flora, and break down plant fiber and large polysaccharides, making them easier to metabolize.

Draco Fermentation Process
With Draco’s unique process, the addition of probiotic bacteria, yeast, or fungus to a liquid extract at optimal conditions for a precise growth period creates an enhanced full spectrum of nutrients and bioactives with improved bioavailability, all by virtue of the life cycle of the probiotic bacteria.

Plants are known to naturally contain polysaccharide prebiotics, which can stimulate the growth of the added probiotic bacteria. They feed the added probiotic, and along with short chain fatty acids and metabolites, also provide the microbes in the gut with a ready-to-use nutrient source.

Improved Digestion
Fermentation helps break apart tough, fibrous plant cell wall components, releasing bioactives. Phytocompounds are predigested into more water-soluble compounds by breaking the glycosidic bonds. Difficult to digest long-chain molecules like proteins are broken down into more bioavailable amino acids and peptides. Polysaccharides like beta glucans are broken down into simple sugars and easy-to-utilize lower weight sugar chains. The body’s digestive system alone performs this work, but more slowly and inefficiently. Fermented botanicals improve this process.

Unique new metabolites are formed during the fermentation process, such as phenolics, flavonoids, organic acids, oligosaccharides, sugars, vitamins, and more bioavailable minerals. Some of these new metabolites have their own bioactive effects. The probiotic that is chosen may also add its own compounds to the mix. Brewer’s yeast, for example, adds B vitamins and bioactive GTF chromium.

Safety
Microbiological safety and shelf life of botanicals are improved after fermentation. The growth of pathogenic bacteria is inhibited, while the added probiotics are preserved. Bacteriocins present in the prebiotic also help suppress growth of harmful bacteria.
How is a fermented extract made at Draco?

1. Full Spectrum Extraction
The first step is to perform our proprietary Full Spectrum extraction on specific herbs, fruits, or vegetables, either alone or combined as a formula.

2. Bacterial Inoculation
The extract in liquid form is then inoculated with a pure form of the probiotic bacteria, yeast, or fungus to initially grow a seed culture, which is then added to the larger batch of extract.

3. Fermentation
The inoculated batch of extract is held at an optimal fermentation condition for up to 7 days. Since the probiotic organisms are pure and not contaminated with pathogens, the mixture does not need to be pasteurized.

Herbs, fruits, and vegetables generally contain more than enough prebiotic constituents that are food for the probiotics, such as inulin (fructo-oligosaccharides), pectin, and other polysaccharides to help promote probiotic bacteria/yeast growth in the fermentation process once it gets started. Near the end of fermentation, a safe low heat (50-55° C) is applied to cause probiotic cell lysis, helping release the compounds contained in the probiotic cell.

4. Spray Drying
The fermented extract is spray dried into a fine powder. This operation is very quick, which helps preserve heat sensitive compounds, like B vitamins and antioxidants, and helps ensure that adequate levels of live probiotic bacteria will be present in the final powdered form.

5. Quality, Safety & Purity
Extraction takes place in our state-of-the-art processing facility, which is Certified Organic to both USDA:NOP and European EEC/834 2007 guidelines. Our facilities are also ISO 9001:2015 Certified, GFSI Certified, cGMP Compliant, FSMA Compliant, HACCP Certified, Kosher and Halal Certified.

As always, our extracts undergo rigorous analytical testing for constituent assay (HPLC, HPTLC, UV), moisture, bulk density, heavy metals (USP methods), pesticides, and microbiological plate counts. Micro safety is actually improved in fermented products as bacterocins (natural antibiotics) are generated. We never irradiate or fumigate either our plants or finished extracts. All products are fully traceable.
Applications

Using Draco Fermented Botanical Extracts

Food Products with Enhanced Flavor Profiles
Fermented extracts may be used as nutritional, flavor enhancing food ingredients. The increase in free amino acids, nucleic acids, and peptides creates unique flavor profiles, some that have “umami” characteristics that can both promote appetite and improve assimilation of nutrients. New compounds may include cysteine, aspartic acid, guanylic acid, inosine, and glutamic acid.

Examples of existing fermented foods with enhanced taste include kimchi, miso, red yeast rice, sauerkraut, aged cheeses, aged garlic, wine, beer, seaweeds, and pickled beets. Fermented liquid or powered yeast, mushroom extracts, and soy sauce are also widely used to enhance flavor.

Cosmetics and Personal Care Applications
Along with nutritional applications, fermented extracts are also capable of providing topical benefits for improved skin health. Research has found that the metabolites generated by probiotic activity can produce an antibiotic effect to help repel or suppress the growth of harmful skin bacteria and fungi. With the added inhibitory bacteriocins from fermentation, the reinforced extracts can also help strengthen the skin's immune defenses, reducing skin sensitivity and improving moisture retention.

Draco uses fermentation technology to develop clean, natural ingredients for cosmetic and personal care products – for example, a certified organic glycerin from organic corn using a living cell derived process. Lipoteichoic acid, a metabolite from *L. plantarum*, has anti-photoaging effects by regulating MMP-1 (collagenase). The extract of *Bifido longum* improves sensitive skin and increases skin resistance against physical and chemical aggression. Metabolites from *Lactobacillus johnsonii* relieve inflammatory skin problems such as atopic dermatitis. Other skin care applications of high bioavailability actives are use of those with anti-aging, skin whitening, anti-inflammation, moisturizing, and UV-blocking effects.

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**MOOD SUPPLEMENTATION MAY BE UNCONVENTIONAL SOLUTION TO SOCIETAL PROBLEMS**

Depression and anxiety are only two aspects of mood regulation, and new research into omega-3 fatty acids is opening up potential new avenues of addressing other aspects of mood dysfunction. A recent randomized, double-blind, placebo-controlled, stratified, parallel-group clinical trial on 200 children between 6 and 16 years of age, and 139 adult caregivers, examined the effects of omega-3 supplementation on aggressive behavior in the children and intimate partner violence in the adults.15

All participants received a 200-ml dose of a liquid omega-3 supplement. The experimental group (n=100) also received an additional 1 g of omega-3 fatty acids, while the control group (n=100) received a matching placebo. Participant aggression was measured using the physical assault and psychological aggression subscales of the Conflict Tactics Scales, and omega-3 concentration was assessed through blood analysis.

The study authors found that omega-3 supplementation resulted in long-term statistically significant reductions in psychological aggression and psychopathic tendencies in adult caregivers as measured via the Conflict Tactics Scales. While the study authors note several limitations to the trial and claim their current findings require replication, they also highlight several strengths of the study. The trial had a longer duration, a lower attrition rate, and better compliance relative to prior studies.

**Hemp CBD is becoming competitive as a mood supplement ingredient due to the fact that it induces the same calming effects as marijuana, but without the psychoactive tetrahydrocannabinol (THC).**

children and improved feelings of separation anxiety, social phobia, and depression in young people. The company says Affron is the first saffron extract standardized by HPLC to Lepticrosalides, the trademarked bioactive compounds said to help to improve mood disorders.

The randomized, double-blind, placebo-controlled study included 68 young people between the ages of 12-16 with mild-to-moderate anxiety or depressive symptoms. According to data from the World Health Organization, the study authors write, psychiatric disorders including anxiety and depression are among the leading causes of disability in young people, with as much as 15%-20% of the youth population experiencing an anxiety or depressive disorder before the age of 18. Saffron, they add, has been shown to be effective in reducing feelings of depression and anxiety in adults with mild-to-moderate depression; however, saffron for depression and anxiety had not yet been studied in a youth population prior to publication of the current study, they said.

The researchers divided participants into two groups. One group received 14 mg Affron, while another group received the same dosage of a placebo. Both group were instructed to take one tablet of either Affron or the placebo twice daily for a total of eight weeks. In order to determine what effects supplementation with Affron had on parameters of anxiety and depression, participants completed a 47-item questionnaire called the Revised Child Anxiety and Depression Scale (RCADS). RCADS includes subscales on separation anxiety, social phobia, general anxiety, panic, obsessions and compulsions, and depression. Subjects’ parents also completed the parent-report version of RCADS; those results served as the secondary outcome measure.

The group supplemented with Affron reported improvements in overall internalizing symptoms, separation anxiety, social phobia, and depression, compared with the placebo group. Parental reports of improvement in the subjects’ mental health were inconsistent. The researchers thus concluded that “administration of a standardized saffron extract (Affron) for eight weeks improved anxiety and depressive symptoms in youth with mild-to-moderate symptoms, at least from the perspective of the adolescent.” Affron was also found to be safe and well-tolerated.

The study authors write that while the results are encouraging, the self-reporting nature of this study represents a limitation. The limited study duration, single treatment dose, and non-clinical sample used in this study likewise limit the overall generalizability of the results, warranting the need for further investigation. Pharmactive Biotech Products funded the study.

Imke Marks, commercial director of Pharmactive Biotech Products, says that combination saffron products, such as with curcumin, are also gaining in popularity due to their increased efficacy relative to single-ingredient products.

**SAMe and 5-MTHF**

Lorena Carboni, product support specialist for Gnosis Sp.A. (Desio, Italy), says that SAMe (S-adenosyl-L-methionine) and L-methylfolate
(5-MTHF) are continuing to enjoy privileged positions as top sellers in the mood and anxiety supplement market due to the critical roles they play in the methylation process of monoamines.

“In particular,” Carboni says, “SAMe may improve depressed mood through enhanced methylation of catecholamines and increased serotonin turnover, reuptake inhibition of norepinephrine, enhanced dopaminergic activity, decreased prolactin secretion, and increased phosphatidylcholine conversion.”

Carboni points to a 2016 literature review and meta-analysis that shows SAMe and 5-MTHF are effective adjuncts to antidepressant medications in reducing the occurrence of depressive symptoms. Folate deficiency is common among people with depressed mood, Carboni says; however, not just any folate supplement will be effective in supporting emotional health. Carboni explains that according to studies like one published in the *Journal of Psychopharmacology* 10, not all consumers will benefit from the same kind of folate supplement.

“Up to 70% of patients with depression test positive for a polymorphism of the MTHFR enzyme,” Carboni says, “which means they cannot convert folic acid into L-methylfolate. For that reason, the active form of folate (5-MTHF) is the right approach to raise folate levels, instead of folic acid that is biologically non-active.”

Carboni sees the mood and anxiety supplement market moving toward more natural ingredients in the future, and expects that consumers will first pursue naturally sourced supplements before attempting pharmaceuticals.

**CBD**

Bayne notes that hemp cannabidiol (CBD) from *Cannabis sativa* is becoming competitive as a mood supplement ingredient due to the fact that it induces the same calming effects as marijuana, but without the psychoactive tetrahydrocannabinol (THC). Stuart Tomc, vice president of human nutrition for CV Sciences Inc. (Las Vegas, NV), says that hemp extracts have become a go-to product in the mood and anxiety supplement market.

Says Tomc: “Consumers are actively seeking natural alternatives to pharmaceuticals that induce rapid, sustained effects with better safety profiles. Hemp extracts are trending for these applications because they are natural, safe, and effective.”

While Tomc says CBD oil softgels are currently an industry favorite, the cannabinoid industry is quickly launching new product formats that are expected to greatly disrupt existing offerings as research continues to prove out the mood-boosting benefits of CBD. In September, CV Sciences made a milestone announcement, stating it secured the industry’s first Generally Recognized as Safe (GRAS) self-affirmation for a hemp extract, for its PlusCBD Gold Formula.

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sought-after designation, recognizing an ingredient as presumably safe among experts under the conditions of its intended use, the company said in a press release. At the same time, the company announced that its PlusCBD Oil launched what the company says is the industry’s first CBD gummy in the natural products space.

Tomc speaks to CBD research findings. “A landmark paper published in June 2018 presented data supporting CBD as a new fast-acting option,” Tomc explains. “The rapid antidepressant effect was accompanied by an increase in brain-derived neurotrophic factor levels as well as markers of synaptic plasticity. CBD potentiated nerve growth factors and new neuron-to-neuron connections, making it one of the most promising tools in our natural mental health toolbox.”

The study that Tomc references is an animal experiment on male Swiss mice and Wistar rats. The animal study involved administering injections of CBD at concentrations of 7, 10, and 30 mg/kg, or an inert vehicle at 10 ml/kg, to groups of mice or rats. Group size varied from n=6 to n=13. The mice and rats were then subjected to the forced swim test and the learned helplessness paradigm, and were assessed for changes in postsynaptic density protein 95 (PSD95) and brain-derived neurotrophic factor (BDNF) levels.

The experiment found that administration of CBD increased BDNF levels and markers of synaptic plasticity, while also reducing immobility time during the forced swim test. The study authors concluded that CBD induces a rapid and long-lasting antidepressant effect.

Tomc says that CBD products are already becoming category leaders, with retailers reporting that they are receiving weekly pitches from new hemp startups. Tomc explains this “green rush” signals the successful evolution of hemp into a mainstream health and wellness product.

“Any health food store that sells hemp CBD products will tell you that hemp CBD extract is the best-selling and most effective product to hit store shelves, ever,” Tomc says. “We’re seeing tremendous competition among cannabinoid-based products, and we expect massive disruption for pre-existing offerings.”

Market statistics confirm Tomc’s claims. Market research firm Technavio (London, UK) predicts that global annual sales of CBD oil products will reach $2.7 billion USD by 2022, growing at a compound annual rate of 31%. And in September, the nonprofit group Vote Hemp (Washington, DC) released predictions from a new Hemp Business Journal report that total U.S. retail sales of hemp-derived CBD products will surpass $646 million by 2022.

Positive Space
The mood and depression supplement category is expected to see significant growth in the coming years, making it an ideal market segment for new innovations and new products. Manufacturers and brands need to invest in quality science and effective marketing. Many opportunities lie ahead for brands that can meet this challenge.

Mike Strauss is a freelance writer living in Kelowna, Canada. He has written for publications including Canadian Chiropractor Magazine, Massage Therapy Canada, and Iconic Concierge Vancouver.

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Probiotics have been such a supplement success story that it’s hard to believe they were downright esoteric not long ago—familiar mainly to researchers, health professionals, culture ingredient suppliers, and the occasional “nutrition nerd.”

What a difference a few years makes. Thanks to praiseworthy press, mounting scientific support, and consumers’ embrace of healthy living, probiotic supplementation is now a regular part of even average Americans’ wellness routines—as de rigueur as juicing or joining a gym.

To put that normalization into numbers, consider that market research firm Euro-monitor International (Chicago) tracked the retail value of the domestic probiotic supplement market as shooting from $950.2 million in 2012 to $2.263 billion in 2017, with a total value of $3.511 billion looking likely by 2022; meanwhile, U.S. probiotic yogurt sales went from $3.301 billion to $4.354 billion during the same period, and could hit $4.870 billion in 2022.

But despite this rising profile, probiotics have yet to reach their full potential with Americans, whether as supplements, functional-food ingredients, or scientifically substantiated tools for improving their own health. In other words, there’s room to grow.

Or, as John Quilter, vice president and general manager, Wellmune and GanedenBC30, Kerry Functional Ingredients and Actives (Mayfield Heights, OH), puts it, “The U.S. adoption of probiotics occurred somewhat later than other regions”—namely, with Asia, which remains the world’s largest market for probiotic food and beverages, and Europe, which comes in second.

But judging from the results of an online survey that Chr. Hansen (Milwaukee) recently conducted with a representative sample of 2,246 U.S. consumers, the domestic market appears to be making up for lost time.

To wit, nine out of 10 U.S. consumers surveyed are familiar with probiotics, with 41% consuming them daily, or at least often. Consumption is higher among women, parents, urban consumers, Millennials, and Gen Xers and—crucially—consumers who pay attention to health and carefully monitor what they eat. And 42% of the probiotic consumers...
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Probiotics

Consumers turn to probiotics to address a spectrum of health concerns—and not solely gut health.

surveyed purchase more than one probiotic product weekly or more often, choosing everything from capsules and powders to dairy beverages, nondairy beverages, yogurts, and other fermented products.

Beyond the Gut

Among those who consume probiotics daily or often, the survey found, digestive health/bowel function, overall wellbeing, immune function, and a healthier microbiome were the top-four factors for selecting probiotic supplements or foods.

And the fact that consumers turn to probiotics to address such a spectrum of health concerns—and not solely gut health—illustrates how far these beneficial bacteria have come, both in consumers’ minds and with the scientific community.

As Elodie Ruffin, probiotics marketing manager, Lesaffre Human Care (Marcq en Baroeul, France), says, while consumers approach probiotic supplementation for their own unique reasons, their approaches in general are “starting to shift as they begin to understand how daily probiotic supplementation can enhance their overall wellness, or specific problem areas.”

The evidence supporting that notion is increasingly solid. “Digestive and immune health are still the main drivers of today’s probiotic market,” Ruffin notes, “however, skin health, obesity management, cardiovascular health, stress management, and cognitive health as well as female health are definitely among the wellness conditions beyond the gut that probiotic supplementation can improve, according to ongoing research.”

For example, one area the possibilities of which excite Ruffin and her colleagues is women’s health—a “market that seems to be gaining interest,” she says. Managing vaginal infections with probiotics would represent a breakthrough because current pharmacological therapies, though efficient, “aren’t designed to prevent recurrences and can cause undesirable side effects as well as antifungal resistance,” Ruffin says. Her company’s *Saccharomyces cerevisiae*-based Florigyn Biotic ingredient has undergone several studies investigating its role in the day-to-day management of vaginal infections and “provides a safe and natural solution that can help protect the vaginal flora against pathogenic yeasts and bacteria and prevent recurrences in the long term,” she says.

Bérengère Feuz, marketing director, Lallemand Health Solutions (Montreal), notes that probiotic supplementation has also demonstrated “promising outcomes” with respect to mood, citing two recent studies
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that examine the effect of her company’s proprietary *Lactobacillus helveticus* Rosell-52 and *Bifidobacterium longum* Rosell-175 probiotics on mood and anxiety as mediated by brain-gut and microbiota communication. In one—a double-blind human clinical trial involving 110 patients with major depressive disorder—researchers determined that relative to either placebo or a prebiotic, eight weeks of probiotic supplementation improved scores on the Beck Depression Inventory of depression severity. And in a pilot study results of which were presented at Probiota Americas in June, researchers from Queen’s University, Canada, evaluated the efficacy, safety, and tolerability of the same probiotic formula on depression symptoms in treatment-naïve patients. “Such studies,” Feuz says, “are positive and reinforce the scientific backing of a probiotic formulation already proven to alleviate both physiological and psychological symptoms of chronic stress in the general population.”

John Deaton, vice president, science and technology, Deerland Probiotics & Enzymes (Kennesaw, GA), points out that some probiotics have shown a capacity to maintain a healthy mouth and throat, “which is linked to many health benefits,” he says. “For example, specific strains of *Streptococcus salivarius* BLIS K12 and BLIS M18 are supported by more than 40 clinical trials in the areas of strep sore throat and tonsillitis, otitis media—inner ear infection—halitosis, periodontal disease, and dental health.”

And a study published in 2016 found a relationship between Ganeden’s BC30 *Bacillus coagulans* GBI-30, 6086, product and the body’s more efficient use of protein. Specifically, consumption of 1 billion CFU of the probiotic with one serving of protein helped reduce muscle soreness and enhance recovery post-exercise—making the ingredient, Quilter says, “great for high-protein meal-replacement and sports-nutrition products.”

Similarly, weight management is a focal point for probiotic inquiry, and Johann Maukonen, global health and nutrition science leader, DuPont Nutrition & Health (Madison, WI), notes that her company published results of a weight-management trial showing that 10 billion CFU of its Howarul Shape probiotic (*Bifidobacterium animalis* subsp. *lactis* B420) administered either alone or in symbiotic combination with 12 g of their probiotic Litesse Ultra polydextrose fiber controlled body fat mass, core fat mass, waist circumference, and energy intake in overweight and obese adults. “Moreover,” Maukonen continues, “the unique results were obtained with no changes to diet or exercise habits, and there were no stimulants added, so participants felt like themselves while controlling body fat mass and improving body composition.”

**Long Road Ahead**

The researchers postulate that mechanisms of action likely involve improvements in intestinal integrity, anti-inflammatory effects, and, potentially, beneficial changes in the composition of gut microbiota. “And what’s especially intriguing with the human study,” Maukonen notes, “is that we also assessed the microbiota composition before and after the trial and found that supplementation with the symbiotic product was associated with an increase in the relative abundance of *Akkermansia, Christensenellaceae*, and *Methanobrevibacter*—bacteria well-represented in lean individuals—while relative abundance of *Paraprevotella* spp.—which can be opportunistic pathogens—was reduced in fecal samples. Moreover, B420 alone was shown to increase the relative abundance of beneficial microbes *Lactobacillus* spp. and *Akkermansia* spp. in overweight and obese subjects, with the changes in microbiota composition correlating with benefits shown in obesity-related clinical outcomes.”

That’s heady news for those excited to reap dividends from research not only into probiotics, but into their relationship with the human microbiome. And indeed, says Mirjana Curic-Bawden PhD, principal scientific, application manager, fermented milk and probiotics, Chr. Hansen, “There’s more evidence showing the gut microbiome’s effect on cognition, stress reduction, anxiety, obesity, diabetes, inflammation, chronic fatigue, IBS, and more. Ongoing research is aimed at elucidating details on the mechanism of action, as well as how probiotics react with the rest of the gut microflora.”

We have a ways to go before those dividends start landing in R&D bank accounts as newly developed products. And, adds Feuz, while “the development of novel strains and even new bacterial species with different characteristics and modes of actions allows us to explore new health applications for probiotics and contributes to the credibility of the category,” probiotic watchers would be wise to practice patience as they wait for those advances to translate into on-the-shelf products.

“Isolation of new strains is just the beginning,” Curic-Bawden cautions. “Actual documentation of the health effects is a lengthy and complex process. And some of the new beneficial species or strains targeting balance of the gut microbiome might not be appropriate or feasible to use in fermented milk or food, and will be available only as supplements.”

**Special Delivery**

But because consumers have shown an affinity for eating or drinking their probiotics, brands would do better to focus on applying the strains we’ve already commercialized to a wider sample of the products most consumers eat, or drink.

“Traditionally,” Curic-Bawden notes, “probiotics have been relegated to fermented dairy as well as nondairy products. And from a global perspective, fermented products are, by far, the most popular category for probiotic delivery.” After all, they already harbor live bacteria, so the presence of additional beneficial species “makes sense to consumers.”

But the development of probiotic strains that not only thrive outside fermented dairy but actually survive the otherwise-lethal extremes of the gastrointestinal tract, harsh manufacturing, and long-term storage has opened up whole new environments for fortification, including breakfast cereals, baking mixes and baked goods, instant hot and iced coffee, fruit and vegetable juices and smoothies, enhanced waters, trail mixes, savory snacks and puffs, nut butters, infant formulas, chocolate, and cereal bars—even hot tea and soup.

The strains that make this possible tend to be spore formers. Quilter describes Ganeden’s BC30 *B. coagulans* probiotic as “a hardy strain of bacteria equipped with a natural protective shell” that leaves it more resistant than vegetative cells to the extremes of pH, heat, cold, shear, and pressure common to food and beverage production processes like
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Probiotics

“Research suggests that chocolate and probiotics really do go well together,” says Deerland’s Scott Ravech.

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Deerland’s *Bacillus subtilis* DE111 probiotic forms spores that protect it from the digestive tract’s harsh conditions and suit it to challenging applications like pasteurized beverages, hot tea, and baked goods, says Scott Ravech, Deerland’s CEO. What’s more, the company’s DE111 HS allows for formulation in applications that require solubility. It “mixes easily with liquid and still maintains a high count of colony-forming units in the finished product,” Ravech says. And it opens doors for inclusion in “high-growth natural product markets” like hot beverages, functional drinks, and nutritional supplement gummies.

Speaking of which, Sarah Hansen, scientist, probiotics R&D, DuPont Nutrition & Health, is fielding more requests for gummies and chewable tablets. “Interest in nondairy milks and fermented beverages has increased dramatically over the last year, too,” she continues. “Other delivery systems include food in general—for the ease of use and ability to feed it to people who can’t swallow a pill—and chocolate is a perfect system for this and can deliver a higher dose.”

Ravech agrees. “Research suggests that chocolate and probiotics really do go well together,” he says. “This is because the beneficial bacteria that live toward the end of the digestive tract ferment both the antioxidants and the fiber in cocoa, creating anti-inflammatory compounds. Combining certain probiotics with chocolate multiplies its health benefits because the probiotics work best at the end of the digestive tract, where they set up shop and kick out bad or irrelevant bacteria. More friendly bacteria aid the cocoa fermentation process.”

Trust but Verify

Ravech believes that “continuing to introduce probiotic supplements in fun and innovative delivery systems like this will increase the products’ ‘stickiness’ or brand loyalty as consumers search for more enjoyable ways to consume their supplements.”

But also enhancing their stickiness will be the continued pursuit of reliable, legitimate probiotic science. As Quilter cautions, “Trust is hard won and easily lost.” The straightest path he sees to maintaining it is “to investigate the quality of the scientific substantiation supporting a probiotic strain’s efficacy and benefits. Without good-quality clinical evidence, a probiotic strain can’t be relied on to deliver on its promises. And safety data is certainly important, as well.”

Ruffin notes that most testing methods for probiotic counts are highly specific and sometimes even species-dependent. Because not every lab can perform these analyses, she advises manufacturers “to discuss analytical methods and testing with their supplier and learn more about their level of expertise, which can be an indication of the quality of the documentation received.”

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mass—the number of CFUs is the “scientifically sound way to measure their potency,” Ravech adds. Thus, in September, FDA released new draft guidance in which the agency acknowledged the advantages of labeling probiotic content in CFUs. (Turn to page 14 to read more on this.)

And because today’s consumers expect full transparency, “It’s important to label the probiotic strain’s identity and scientific name, as well as cell count,” Curic-Bawden says. “It allows consumers to do their own research and make educated decisions.”

In the end, “The main rule still stands,” she believes: “A documented dose should be delivered in one serving, and the cell count should be present at the end of shelf life. And it goes without saying that the strain has to be backed up by clinical documentation.”

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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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The human body plays host to a greater number of bacteria and other microbes than the number of human cells. Estimates suggest that there are over 10 trillion bacteria living on or in the body, with the vast majority residing in the colon. The gut is also where the majority of the immune system lies. Obviously, this interface of microbes with the immune system has a tremendous influence on health. Probiotic supplementation has traditionally been considered one means of influencing the gut microbiota, and by connection the human immune system, to achieve both local and systemic effects. However, current research points to prebiotics as another potent tool for favorably influencing the human microbial flora and supporting health.

Recently, the International Scientific Association for Prebiotics and Probiotics (ISAPP) defined a prebiotic as “a substrate that is selectively utilized by host microorganisms conferring a health benefit.” Generally, prebiotic effects have been associated with various plant-based fibers; however, research is showing that there are other substances that also confer prebiotic benefits.

Studies are further highlighting several beneficial clinical outcomes associated with prebiotic intake, not only for digestive health but for other purposes, including supporting metabolic, brain, and heart health. Some of the latest research is reviewed here.

**Yeast Metabolites for Healthy Gut Function**

A unique, immune-enhancing fermentation product from the yeast *Saccharomyces cerevisiae* known as EpiCor (Embria Health Sciences; Ankeny, IA) has shown prebiotic properties in preliminary studies. With a recent double-blind, placebo-controlled pilot study, researchers led by Iris Pinheiro of ProDigest (Ghent, Belgium) aimed to investigate the prebiotic effects of EpiCor in 80 human subjects with gastrointestinal discomfort and reduced bowel movements.

Participants were classified into two groups based on symptom severity: severe and moderate. EpiCor or placebo was administered at a daily dose of 500 mg for 6 weeks after a two-week run-in period. Fecal samples were collected at baseline, 3, and 6 weeks, and subjective measures of constipation-associated quality of life and general perceived stress were also assessed.

In the moderate-symptom subgroup, EpiCor led to a significant reduction in general digestive symptoms, bloating, and feelings of fullness. Stool consistency significantly improved in the total population after two weeks of EpiCor supplementation. Constipation-related quality-of-life and general perceived-stress scores also improved in those taking EpiCor.

Bowel movement frequency showed improvement, nearly reaching statistical significance in the total group. Beneficial changes to the bacterial composition of the microbiome were noted on stool analysis, including an increase in members of the *Bacteroidaceae* and *Prevotellaceae* groups in the severe-symptom subgroup, bacteria which are known to be deficient in constipated individuals. These findings suggest that a relatively low dose of EpiCor (500 mg/day) can confer prebiotic benefits and improve symptoms of digestive health.

**Appetite Regulation in Children**

Inulins are a class of plant-based polysaccharides that are traditionally associated with metabolic health, heart health, and more.
with prebiotic activity. A recent study aimed to explore the potential benefits of inulin in overweight and obese children related to its ability to improve appetite control.

In the randomized, double-blind, placebo-controlled trial, 42 children aged 7 to 12 supplemented with 8 g of oligofructose-enriched inulin per day or a placebo for 16 weeks. Appetite control was assessed using food records, energy intake, and fasting satiety hormone concentrations. Ratings on a visual analog scale were also taken from the children following a buffet breakfast. Caregivers completed Eating Behavior Questionnaires for the children.

Compared to the placebo group, those supplementing with prebiotics had significantly higher feelings of fullness and lower prospective food consumption after 16 weeks. Prebiotics also significantly reduced caloric intake at the week-16 breakfast in 11- to 12-year-olds compared to placebo, though this finding was not significant for 7- to 10-year-olds. Fasting levels of the satiety hormones ghrelin and adiponectin also increased significantly after 16 weeks in the prebiotic group compared to placebo, indicating that prebiotic supplementation with oligofructose-enriched inulin can help with appetite regulation in overweight children.

**Asthma and Airway Inflammation**

As prebiotics influence the makeup of the gut microbiome, which interacts with our immune system, they have the potential to impact areas of the body outside of the digestive tract. A recent pilot study led by a group of UK researchers including Neil Williams from Trent University (Nottingham, UK) aimed to assess the effect of prebiotic supplementation on exercise-induced asthma, a condition associated with airway inflammation.

In the study, 10 adults with asthma and exercise-induced bronchoconstriction and 8 healthy controls were randomized to supplement with 5.5 g of milk-derived galacto-oligosaccharides or placebo daily for three weeks. Participants underwent eucapnic voluntary hyperpnoea (EVH; considered an optimal test for diagnosing exercise-induced asthma that entails breathing in of dry air) at baseline and at the end of the study. In the group with exercise-induced asthma, the post-EVH fall in forced expiratory volume in 1 second (FEV1; a measure of lung function) was reduced by 40% as a result of supplementation with the prebiotic fiber but was unchanged in those taking placebo. Additionally, markers of airway inflammation, including TNF-α and CRP, were reduced in those with exercise-induced asthma symptoms, indicating potential beneficial effects of galacto-oligosaccharide supplementation for airway inflammation.

**Gut-Based Endothelial Support**

Preliminary research in animals is beginning to highlight the link between certain prebiotics and cardiovascular health. Given that
the microbiota influences so many aspects of systemic health, this is not surprising. In a recent study, European researchers created a mouse model that linked fatty liver and endothelial dysfunction by feeding the mice a diet deficient in omega-3 fatty acids for 12 weeks.

For the last 15 days of the study, the researchers separated the mice into two groups and added inulin-derived fructo-oligosaccharides (FOS) to the diet of one group. They found that the mice fed the FOS prebiotics showed a complete reversal of endothelial dysfunction in gut mesentery and carotid arteries. The researchers found this benefit to be nitric oxide–mediated, as the prebiotic fiber induced favorable changes in the microbiota of the mice leading to an increase in the number of nitric oxide–producing bacteria and an accompanying decrease in bacteria involved in bile acid synthesis.

Furthermore, changes in gene expression in the gut and liver also occurred, which favored the preservation of endothelial function. If this holds true in human studies, supplementing with FOS may be a novel approach to preserving endothelial health and could lead to greater benefits for metabolic and cardiovascular health.

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Omega-3 fatty acids from fish, specifically the crucial fatty acids DHA and EPA, suffered negative news headlines this summer as the Cochrane Collaboration published its latest meta-analysis looking at the effects of omega-3 DHA and EPA on reducing the risk of heart disease, stroke, and death. The authors of the review concluded that omega-3 supplements had little or no effect on these parameters.

The review assessed 79 randomized trials involving more than 112,000 people. While the review acknowledged benefits of omega-3 supplements for reducing some blood fats and triglycerides, the authors suggest that omega-3 supplements’ net benefits are negligible for the reduction of heart risk.

However, researchers in the field of omega-3 science have roundly criticized the findings of this review as being highly flawed. Bill Harris, PhD, the founder of OmegaQuant (Sioux Falls, SD) and a researcher who has studied omega-3s for decades, outlines several basic criticisms of the Cochrane review for Nutritional Outlook readers. (Turn to page 66 of this issue to read Harris’s article.) According to Harris, the Cochrane reviewers ignored a large body of evidence showing beneficial effects of omega-3 intake on cardiovascular risk by eliminating some of the larger studies conducted to date. Additionally, Harris states that the Cochrane review essentially rehashes the same old studies that have been included in earlier unfavorable reviews and presents nothing new. Harris also adds that, while such negative reviews are quick to be publicized in the mainstream press, other favorable omega-3 meta-analyses that have been published have not generated the same level of media interest.

Several studies on the benefits of omega-3s for heart risk are underway and should add to our understanding of how significant the effects of these fatty acids ultimately are.

It is well known that EPA and DHA support cardiovascular and metabolic health through several mechanisms. While their ability to impact blood lipids, and specifically triglycerides, are documented, a recent review looking at evidence from human and animal studies highlights several potential areas in which omega-3 fatty acids act to influence metabolic function. These include: influencing the plasma concentrations of adiponectin and leptin, resulting in increased thermogenesis; altering the expression of genes that regulate fat metabolism by up-regulating fatty acid oxidation and down-regulating lipogenesis in fat tissue; reducing inflammatory processes by impairing the activation of a key inflammatory regulator, NF-κB; and improving endothelial health and circulation.

Moreover, several current clinical trials reviewed here have found that omega-3 fatty acids favorably impact metabolic health...
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Several studies on the benefits of omega-3s for heart risk are underway and should add to our understanding of how significant the effects of these fatty acids ultimately are.

in diabetics, while others indicate that omega-3s, when administered to those on statin therapy, provide additional cardiovascular benefits.

As the prevalence of diabetes and metabolic syndrome in the U.S. exceeds 100 million individuals, and the number of those using statin drugs approaches 40 million and continues to grow, adding omega-3s in both of these groups may be well-indicated.

Omega-3s for Diabetes and Metabolic Health

Omega-3 fatty acids have been demonstrated to have beneficial effects on metabolic health and in those with diabetes. Due to their broad mechanism of action, these benefits extend to several different metabolic pathways.

A recent study led by Mohammad Golzari from Tehran University of Medical Sciences (Tehran, Iran) investigated the effects of supplementation with the omega-3 fatty acid EPA (from Mino Pharmaceutical Co.; Iran) on the activity of the enzyme paraoxonase-1 (PON1) in type 2 diabetics. PON1 is an enzyme involved in antioxidant and anti-inflammatory processes in the body, including in supporting the detoxification of free radicals and drug metabolites, while also showing the ability to inhibit the production of Monocyte Chemoattractant Peptide 1 (MCP-1) in endothelial cells incubated with oxidized LDL, an important step in atherogenesis associated with atherosclerosis. PON1 further has been found to support the integrity of HDL cholesterol molecules by displaying antioxidant effects.

In the double-blind, randomized, placebo-controlled study, 36 individuals with type 2 diabetes were asked to supplement with 2 g of EPA daily, or a placebo, for eight weeks. PON1 activity as well as blood lipids were monitored over the course of the study. At the end of the study, researchers found that EPA supplementation led to significant increases versus placebo in PON1 serum levels and activity, as well as an increase in the serum ratio of PON1 to HDL cholesterol. Furthermore, significant increases in HDL cholesterol levels were also noted versus...
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*Health & Wellness 2015 Report, The Hartman Group
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placebo. These results indicate that EPA supplementation may confer some protection against atherogenesis in individuals with type 2 diabetes.

A second trial in type 2 diabetics sought to look at the ability of omega-3 supplements to enhance metabolic health and reduce inflammatory biomarkers. Led by M. Gorety Jacobo-Cejudo of Universidad Autónoma del Estado de México (Toluca, Mexico), the placebo-controlled pilot study included 54 Mexican individuals on metformin who were asked to supplement with fish oil containing daily amounts of 320 mg EPA and 200 mg DHA (from General Nutrition Centers), or a placebo, for six months. The investigators aimed to assess the effects of supplementation on the metabolic markers adiponectin, resistin, and leptin, as well as lipid profiles. They also looked at the effects on blood glucose markers and anthropometric measures.

While no significant changes in body weight, BMI, or body fat were evident in either group, the fish oil group had significant reductions in waist circumference following supplementation. In addition, fish oil decreased fasting blood glucose levels. Decreases in both groups were seen in glycated hemoglobin and leptin, while adiponectin levels did not show significant changes. Interestingly, both groups showed a significant increase in HOMA-IR, a measure of insulin resistance, which the authors attribute to the lack of weight loss seen in the study. It is also likely that concomitant use of metformin impacted the results seen in both groups. However, fish oil supplementation significantly decreased triglyceride levels and the atherogenic index whereas the placebo group showed significant increases in total and non-HDL cholesterol levels as well as in the atherogenic index.

While the results of this pilot study are preliminary in nature, it is likely that fish oil supplementation in type 2 diabetics on metformin leads to several beneficial metabolic effects. Further studies on similar individuals across different ethnic groups are needed to tease out any differences due to genetics, dietary, and cultural factors.

Metabolic abnormalities are also evident in women with gestational diabetes, a common complication of pregnancy, which is further associated with development of diabetes, insulin resistance, and poorly regulated blood lipids after delivery. A study led by Mehr Jamilian from Arak University of Medical Sciences (Arak, Iran) aimed to determine whether fish oil supplementation could benefit gene expression to favorably alter insulin action, inflammatory response, and blood lipids in women with gestational diabetes.

In the double-blind, placebo-controlled study, 40 women aged 18-40 were supplemented with fish oil containing 180 mg EPA and 120 mg DHA (from Barij Essence Pharmaceutical Company; Kashan, Iran) twice daily, or a placebo, for six weeks. Gene expression was assessed using peripheral blood samples. The results indicated that fish oil supplementation led to significant increases in the expression of genes related to insulin action and inflammatory response, as well as decreases in blood lipids.
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mononuclear cells (PBMCs) at baseline and after six weeks. Blood measures for fasting blood sugar, C-reactive protein (CRP; a marker of inflammation), and blood lipids were also evaluated in both groups.

Omega-3 supplementation led to a significant reduction of fasting blood sugar and serum triglycerides, as well as a significant reduction in CRP levels. HDL cholesterol levels increased, while LDL levels also increased in the fish oil group compared to placebo (an effect seen in other studies with fish oil as well). Gene expression was significantly upregulated for peroxisome proliferator-activated receptor gamma (PPAR-γ) and downregulated for the LDL receptor in the fish oil group versus placebo. PPAR-γ is thought to be intimately involved in the regulation of glucose, insulin, and lipid metabolism. Furthermore, omega-3 supplementation led to significant downregulation of gene expression markers of inflammation, including IL-1 and tumor necrosis factor alpha (TNF-α). These results suggest that fish oil may beneficially impact several important parameters of metabolic health in women with gestational diabetes.

**Omega-3s as Statin Companions**

Several recent studies have investigated the effects of adding fish oil therapy in individuals on statin drugs to confer potential additive or additional benefits for reducing cardiovascular risk.

Abdulhamied Alfaddagh and colleagues from Beth Israel Deaconess Medical Center (Boston, MA) conducted a randomized trial in which 285 subjects aged 63 years old on average with stable coronary artery disease already taking statins were given a pharmaceutical product containing 1.86 g of EPA and 1.5 g of DHA as ethyl esters daily (as Lovaza; GlaxoSmithKline; Research Triangle Park, NC) for 30 months or were maintained on statin therapy alone (control group). The researchers assessed coronary plaque volume via computed tomographic angiography.

While non-calcified plaque volume was not significantly different between groups, when researchers stratified the results by age, they found that younger individuals in the omega-3 group had significantly slower progression to non-calcified plaque, indicating a preventive effect of omega-3s in this demographic. Furthermore, fibrous, calcified, and total plaque were all lower in this group.

Looking at plaque subtypes in the overall study group, those in the control group had significant progression to fibrous plaque whereas those in the omega-3 group showed no progression over the study period. When looking at differences between statin dose in the groups at baseline, omega-3s led to significant reductions in progression to fibrous plaque in those on lower-dose statin therapy compared to control subjects. No significant changes were evident in those taking higher doses of statins. These findings suggest significant additive benefits of omega-3s for preventing the progression of coronary plaque in younger individuals on statin therapy as well as those taking lower doses of statins.

A second trial led by Tetsu Watanabe and colleagues from Yamagata University School of Medicine (Yamagata, Japan) looked at whether the addition of EPA to high-dose pitavastatin therapy enhanced its benefits for coronary arterial plaque stabilization. In the study, 193 coronary heart disease patients were randomly assigned to pitavastatin (4 mg/day) or pitavastatin plus EPA (4 mg/day) for eight weeks. Ultrasound analysis of coronary plaque volume and composition was performed.

The results of the study indicated that the group consuming EPA had a greater reduction in total atheroma volume compared to the group on the statin alone, with significant reductions in coronary plaque lipid volume in the fish oil group. The study suggests that adding EPA omega-3 fatty acid supplementation to intensive statin therapy is a promising option to further reduce aspects of cardiovascular risk in patients with coronary heart disease.

A more recent study led by Chee Hae Kim from Seoul National University Hospital Cardiovascular Centre (Seoul, Korea) sought to assess the additive triglyceride-lowering potential of omega-3 fish oil administration in those individuals with elevated triglycerides despite being on rosuvastatin therapy.

In the randomized, double-blind trial, 201 individuals with an average age of 58 on statin therapy underwent a four-week run-in period prior to being randomized to rosuvastatin alone (20 mg/day) or a combination of rosuvastatin and omega-3 fatty acids (20 mg/day rosuvastatin plus 4 g/day omega-3 fatty acids) for eight weeks.

The investigators found that triglycerides decreased significantly more in the fish oil/statin combination group than with the statin alone. Average reductions in triglycerides in the combination group were 26.3%, while they were only 11.4% with the statin alone. Furthermore, non-HDL cholesterol was also reduced to a greater extent in the combination group (-10.7%) than with the statin alone (-2.2%). Thus, the addition of omega-3s to statin therapy resulted in significant additional benefits for the reduction of blood lipid levels than singular therapy with rosuvastatin.

**Omega-3: Building Positive Evidence**

A plethora of research has shown that omega-3 fatty acids have several important benefits for cardiovascular and metabolic health. However, perhaps the jury is still out on whether these benefits translate into preventive effects above and beyond those seen with drug therapy in more chronic conditions.

It is clear that omega-3s from fish have a strong scientific basis for being a healthy nutritional option that is likely to lead to significant heart health support. With recent studies indicating positive effects in two growing groups of individuals—those with diabetes and those on statin drugs—the inclusion of
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omega-3s in an overall health regimen may be a key consideration for cardiometabolic support. 

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

References
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In July 2018, the Cochrane Collaboration produced a 730-page report on the efficacy of omega-3 fatty acids EPA and DHA in cardiovascular disease. The review, titled “Omega-3 fatty acids for the primary and secondary prevention of cardiovascular disease,” claims to be the “most extensive systematic assessment of the effects of omega-3 fats on cardiovascular health to date.” At the end of their paper, the review authors concluded that “moderate- and high-quality evidence suggests that increasing EPA and DHA has little or no effect on mortality or cardiovascular health...”

This report set in motion a series of negative headlines in the mainstream press for long-chain omega-3s EPA and DHA, including “Buy More Vegetables Instead of Omega-3 Supplements to Improve Heart Health, Report Says,”2 “Do Omega-3 Supplements Really Benefit the Heart?”3 and “Omega-3 Supplements Don’t Protect against Heart Disease.”4

Do these headlines signal the nail in the coffin for omega-3s for heart health? Or is there more to the story? The only way to make sense of any of this is to take a deep dive behind these headlines.

Three Takeaways from the Cochrane Review
The Cochrane review’s key findings were as follows, based on evidence cited by review authors.

1. Increasing EPA and DHA intake has little or no effect on preventing all-cause deaths and cardiovascular events (high-quality evidence) and probably makes little or no difference to coronary death, coronary deaths or events, stroke, or heart irregularities (moderate-quality evidence). (Coronary events are illnesses of the arteries.) Additionally, EPA and DHA slightly reduce serum triglycerides and raise HDL (high-quality evidence).

2. Eating more ALA (for example, by increasing intake of walnuts or enriched margarine) probably makes little or no difference to all-cause or cardiovascular deaths or coronary events but probably slightly reduces cardiovascular events, coronary mortality, and heart irregularities (moderate-/low-quality evidence). Effects of ALA on stroke are unclear, as the evidence was of very low quality.

3. There is evidence that taking omega-3 capsules does not reduce heart disease, stroke, or death. There is little evidence of effects of eating fish. Although EPA and DHA reduce triglycerides, supplementary omega-3 fats are probably not useful for preventing or treating heart and circulatory diseases. However, increasing plant-based ALA may be slightly protective for some heart and circulatory diseases.

Biased Conclusions?
At OmegaQuant, we believe that this Cochrane report is biased because it ignores a large body of evidence showing favorable effects of EPA and DHA on cardiovascular risk. In our opinion, the review authors’ conclusions go far beyond the data that they review. Below are some thoughts and considerations regarding this report.

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ers publishing reviews on the links between omega-3s and any benefits for cardiovascular disease continue to conduct reviews based on the same studies, over and over again, generating negative headlines over and over again? This Cochrane review, for instance, presents no new information that other review authors haven’t stated before.

We’ve seen several of these high-profile “no effect” omega-3 meta-analyses published over the years that are based on the same old studies (e.g., Aung et al.5, Balk et al.6, and Rizos et al.7). For this reason, headlines that proclaim “new studies show omega-3 are ineffective…” are often highly misleading because no new studies were involved. Meanwhile, there have been other meta-analyses (e.g., Maki et al.8, Alexander et al.9, and Maki et al.10) based on new data that reported overall benefits for EPA and DHA, but these reviews have not been reported on as broadly as the aforementioned negative headlines.

The Cochrane meta-analysis is just a rehash of old data and certainly does not provide the final answer on the omega-3 question. New data are needed and will be forthcoming with the anticipated publishing of some large trials, including the STRENGTH study11 being sponsored by pharmaceutical firm AstraZeneca.

Editor’s note: In September, researchers from the REDUCE-IT trial12 sponsored by pharmaceutical firm Amarin Pharma on the company’s Vascepa high-concentrate EPA-only omega-3 drug for heart health announced positive results showing a statistically significant relative risk reduction of 25% in the first occurrence of major adverse cardiovascular events in individuals who took the 4 g/day of Vascepa, compared to placebo. The randomized, double-blind, placebo-controlled trial included 8,179 statin-treated adults with elevated cardiovascular risk—specifically, LDL-C levels between 41-100 mg/dL, persistent elevated triglycerides between 150-499 mg/dL, and either established cardiovascular disease or diabetes mellitus and at least one other cardiovascular risk factor. The global study began in 2011 and included subjects from 11 countries across 450 clinical sites. Although the REDUCE-IT trial results focus on the efficacy of a drug, not a supplement, the positive results are a good thing, says Ellen Schutt, executive director of the Global Organization for EPA and DHA Omega-3 (Salt Lake City, UT). “We were pleased to see the results of REDUCE-IT because it supports the body of evidence about the benefits of omega-3s and cardiovascular health,” she told Nutritional Outlook.

What Were These Studies Testing?

Back to the Cochrane meta-analysis: We need to understand what the studies included in the meta-analysis were testing, how they were designed, and who they enrolled. Typically, the people in these studies were older, already had some chronic cardiometabolic disease, and were taking several other medications. What’s more, low doses of omega-3s were typically given, and the studies typically ran for only two to three years on average.

We agree that, in this scenario, omega-3s may not “work,” but that is not the relevant question. The more appropriate question is...
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nutritional, not pharmaceutical: “Do higher intakes of EPA and DHA in the diet over decades reduce risk for disease?” These studies cannot answer that question, and therefore their conclusion that “omega-3s don’t improve heart health” is far too broad.

The Interpretations Don’t Match the Reported Findings
The Cochrane authors’ interpretations do not match their reported findings. For example, there was no statistically significant effect of ALA for coronary heart disease events or angina among the studies, and yet the review authors said there was a “probable benefit.” On the other hand, there was strong statistical significance for EPA and DHA in reducing risk for coronary heart disease events; yet, the review authors said there was “probably no benefit.” Why? Why hold EPA and DHA to different standards than ALA?

This disconnect between the data and the conclusions is troubling, and it clearly reveals a strong bias in favor of ALA and against long-chain omega-3s EPA and DHA.

More specifically, in the “Main Results” section of the Cochrane report, the authors dismiss the highly statistically significant benefit shown for long-chain omega-3s in coronary heart disease events (relative risk (RR) 0.93; 95% confidence interval (CI) 0.88-0.97; 84,301 participants; 5469 people experienced CHD events in 28 randomized controlled trials (RCTs)). Instead, the authors concluded that “Long-chain omega-3 (LCn3) probably makes little or no difference to [coronary heart disease] event risk.” This dismissal, according to the authors, was based on the fact that the observed effect “was not maintained in sensitivity analyses.”

What were these sensitivity analyses? They were sub-analyses that eliminated studies that the authors felt were at “moderate or high risk for bias,” including the following trials: the GISSI-Prevenzione13, JELIS14, and GISSI Heart Failure15 trials, three of the largest and most favorable studies in the long-chain omega-3 field. It’s no wonder that the authors, by omitting these trials, found “no effect.” Granted, the former two trials were controlled, just not placebo-controlled, but the latter trial was eliminated because the investigators said its researchers failed to report that they confirmed that capsule blinding was effective. Really?

In more breathtakingly evidence of bias, the review authors concluded that ALA “may slightly reduce risk of cardiovascular events” based on a non-significant relative risk estimate of 0.95 (95% CI 0.83-1.07*) observed in 19,227 participants with 84 cardiovascular disease events. Evidence was gathered from only five RCTs providing what the review authors describe as “low-quality evidence.” Worse still, they concluded that ALA “probably reduces risk of [coronary heart disease] mortality (RR 0.95; 95% CI 0.72-1.26*; 18,353 participants; 193 coronary heart disease deaths; 3 RCTs), and arrhythmia (RR 0.79; 95% CI 0.57-1.10; 4,837 participants; 141 events, 1 RCT).” The relative risk estimates were not statistically significant for either of these latter two endpoints (coronary heart disease mortality and arrhythmia), and the results were based on data from just three RCTs with coronary heart disease mortality as the endpoint and just one study with arrhythmia as the endpoint.

“If the 95% CI does not include the value of 1.0, the relationship is statistically significant. If 1.0 is included in the confidence interval, then it is not significant. "Non-significant" does not mean "no effect." It means we cannot conclude with the standard level of confidence that the effect observed, which is almost always favorable for omega-3, is real. But that does not mean the effect was not real.

The Doses in These Studies Were Too Low
The doses of EPA and DHA typically used in these studies is unlikely to produce a cardioprotective level of omega-3 in the blood. A cardioprotective level of omega-3 in the blood would be 8% based on the Omega-3 Index (an index for measuring the level of omega-3 in the blood)."** Most likely, the people in these studies included in the Cochrane analysis reached an Omega-3 Index level of about 6%, which is still 2 percentage points away from the level needed to significantly reduce your risk of coronary heart disease.

In a 2017, I co-authored a meta-analysis16 that included 10 prospective cohort studies in which low-versus-high blood omega-3 levels (i.e., an Omega-3 Index of 4% vs. 8%) were compared. In that study we found a significant 35% reduction in risk for cardiac death in the highest versus the lowest Omega-3 Index groups.

Last, but not least, the failure of the investigators in these aforementioned negative trials to screen their patient populations for a low Omega-3 Index at baseline is problematic. This is because you would not expect to see an effect of supplementation in people who already have healthy blood levels of omega-3s. Because background diets nowadays contain more and more omega-3s, the difference in EPA and DHA intakes between the “active” and the “placebo” groups has lessened, making the benefits of additional omega-3 supplementation more difficult to detect between the two groups.

Where Do We Go from Here?
RCTs and prospective population observation studies—especially those that use a biomarker of intake instead of a diet estimate of intake—should carry equal weight in the decision of whether or not a low nutrient intake “causes” disease. It’s very difficult—however not impossible—to replicate the long-term effects of chronic exposure with a short-term (and especially a low-dose) treatment.

In the omega-3 space, we have firm observational data supporting the benefits of supplementation, but we should not necessarily expect to see an effect of omega-3 in the typical RCT trial designs for all the usual reasons: low doses, short-term treatment, concurrent use of powerful heart medications, enrolling people regardless of their baseline omega-3 levels, etc. The takeaway is that we still do see a positive effect of omega-3 supplementation, especially on cardiac death, which is remarkable.

**Editor’s note: The author is the co-creator of the Omega-3 Index test.

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 outsourced from a spike in the number of foodborne illnesses in the early 2000s, the Food Safety Modernization Act (FSMA) was developed to take a more proactive rather than reactive approach when it comes to food contaminants. Though signed into law in January 2011, implementation continues through 2019 as FDA and food manufacturers alike remodel how they approach food safety practices. While the new rules don’t directly impact dietary supplements—“those areas are already addressed within GMP [Good Manufacturing Practices] requirements,” says Steve Holtby, president and CEO of Soft Gel Technologies Inc. (Los Angeles, CA)—they completely change the landscape of expectations when it comes to dietary ingredients, sending a ripple effect across the entire industry.

Among other regulations, dietary ingredient manufacturers must be sure to use approved suppliers, verify them (and figure out how to do so), ensure that preventative controls are implemented and effective, and document all of it. Plus, the FDA now has recall authority—the ability to mandate that companies recall products deemed unsafe—as well as the ability to conduct inspections to ensure compliance. Finally, and perhaps most notably, FSMA brings with it much tougher standards when it comes to imports, requiring importers to ensure that their foreign suppliers have compliant controls in place. At minimum, FSMA demands on-site audits; without them, FDA can block entry.

The good news is that everyone knew this was coming and had ample time to prepare. Still, the question remains: is the industry ready? According to Gisele Atkinson, vice president of quality and technical affairs at the Council for Responsible Nutrition (CRN; Washington, DC), approximately 60% of GMP inspections on dietary supplement companies in 2017 resulted in the FDA issuing a Form 483. “And this compliance report is in relation to a regulation that became mandatory 10 years ago,” she says. “FSMA regulations started rolling out seven years ago, with some compliance dates still a few years ahead; and these regulations are much more far reaching than dietary supplement GMPs alone. So we have yet to see the results of FSMA inspections.”

Still, if you ask Atkinson, FSMA is a good step for the dietary supplement and ingredients industry because a rising tide lifts all boats: holding the industry to a higher standard at every step of the supply chain can only increase consumer confidence as bad actors are eliminated from the market. Responsible companies with a strong track record of quality and compliance will likely go beyond what’s required, she says, and will be prepared for the changes. “The industry has been highly anticipating the passage of FSMA, since it now holds the entire business supply chain accountable to higher standards.”
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for food safety and prevention,” agrees Holtby. “This is important because the food industry governs our raw material manufacturers and distributors, and now they are held accountable to food safety regulations.”

However, as Atkinson points out, there remain a lot of mid-size and smaller companies with less experience that will “continue to struggle with what is required,” she says. “And, unfortunately, there are still some outliers that ignore the law altogether.” Overall, CRN supports FDA enforcement actions against companies that are non-compliant, says Atkinson, since “FDA needs to get these bad actors to come into compliance or face consequences.”

That doesn’t mean, though, that new challenges in the wake of FSMA passage are limited to the bad actors alone. Even well-meaning and well-prepared companies that prioritize transparency and quality will face a few growing pains as FSMA compliance hits its stride.

Challenges Abound

When it comes to outsourcing, the impacts of FSMA are widespread and, regardless of size, companies are bound to run into some challenges.

First, there is a huge amount of responsibility placed on the shoulders of ingredient manufacturers to verify and document their raw materials and ingredients, which didn’t exist in the past. Ingredient suppliers must evaluate hazards, develop written analysis, create and validate (and monitor) preventative controls, and take corrective action if any missteps are discovered. This evaluation needs to happen at every step of the supply chain, from receiving raw materials through processing, packaging, and storing. And it applies to suppliers worldwide. “The Foreign Supplier Verification rule stipulates that the same preventative safety standards apply to food and supplements consumed in the U.S. regardless of where they are produced,” explains Robin C. Koon, executive vice president at Best Formulations (City of Industry, CA). This complicates matters for contract manufacturers who source ingredients from overseas, especially since “the majority of raw materials in the dietary supplement industry come from overseas,” he says. As a result, Koon expects “more possible delays and potential price increases in receiving material shipments from overseas, due to suppliers needing to be compliant with FSMA.”

Indeed, Soft Gel Technologies, a softgel contract manufacturer, has seen both raw material costs and lead times increase, which impacts productivity and profitability. “We’ve also discovered that it is too risky to do business with smaller companies who offer unique ingredients and reasonable minimum order quantities,” adds Holtby, since they’re often unable to comply with the new regulations. As a result, the quality assurance and regulatory department at Soft Gel Technologies has requested that the purchasing and product development groups eliminate several previously approved suppliers “to help prevent delays with securing certain raw materials in a timely manner,” says Holtby.

When it comes to compliance, rising costs will also come into play for suppliers who don’t do in-house testing, says Frank Cantone, president of ABH Pharma Inc. (Brentwood, NY), since the new regulations require stringent documentation. Hiring third-party labs, of course, adds another line item to the budget. Plus, additional challenges exist for manufacturers who source from suppliers that don’t provide sources for the raw materials they sell. “This lack of transparency is problematic, as it creates a compliance issue for the receiving facility who must establish and implement a written supplier verification program,” says Holtby. This is not a problem at Soft Gel Technologies, he notes, as the company must know the origin of all raw materials used and have supporting documentation from the manufacturers and distributors demonstrating compliance.

Another challenge plaguing the industry overall as this transition enters its final stages is that dietary supplement brands aren’t as educated on the nuances of FSMA since it doesn’t impact them directly, says Atkinson. But this isn’t entirely true. “Supplement manufacturers are exempt from some parts of FSMA but there are significant sections like the Foreign Supplier Verification Program and the International Adulteration Rule that fully apply as new requirements,” she adds.

Brand awareness is a challenge that Koon has also faced. “They need to ensure their supply chain is compliant, so as to not cause an interruption of products,” she says. “Currently, most brands are not really aware of FSMA and its potential effects.”

The good news is that, as Cantone explains, the industry is generally “very prepared from a compliance standpoint.” Not ready? Never fear, says Atkinson, as the FDA has stated it will educate as it regulates. “If companies are showing effort toward compliance, FDA is willing to help educate to help get you all the way there,” she says. “But, if you are ignoring the new FSMA regulations, FDA will be sure to give warning letters.”

In the end, Atkinson thinks the investment and challenges will be worth it, as “there will be overall savings as the food industry shifts to a proactive food safety system and not a reactive one.” The result will be increased confidence in the supplement industry as better-quality products are verified and documented at every step in the supply chain. Is there a more worthy effort? 

Melissa Kvidahl is a freelance journalist and copywriter specializing in the health and wellness industry.

When it comes to outsourcing, the impacts of FSMA are widespread and, regardless of size, companies are bound to run into some challenges.
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Functional drinks are on the rise, with data provided to *Nutritional Outlook* by Innova Market Insights showing an 8% compound annual growth rate in global functional beverage launches from 2012 to 2017. The functional water market in particular is diversifying in unexpected ways, with products like CBD-infused spring water and amino acid–enriched water gaining ground in foreign markets.

Domestically, functional waters are quickly becoming popular. Jill Failla of SPINS (Chicago, IL) says that in the U.S., the enhanced-waters segment is now worth $1.9 billion, up 11% from 2017. “All product types that SPINS codes for are showing growth, including alkaline, electrolyte, nutrient, oxygenated, and energy. Natural products are leading the growth among nutrient- and alkaline-enhanced waters, and they dominate the oxygenated water market.”

Here are just a few of the most popular new products that are changing the water market.

**Caffeinated Water Gives Office Workers Extra Pep**

Specialty products dominate the energy water market, Failla says. SPINS data show that within the shelf-stable water category, domestic sales of functional energy beverages grew 300% from May 2017 to May 2018. One of the rapidly growing specialty products within this category is caffeinated water. As caffeine intake increases among professionals, office workers are seeking a means of achieving their caffeine fix while staying hydrated, a need that Limitless Coffee & Tea (Chicago, IL) and others are stepping up to meet.

Limitless company co-founder Matt Matros says the company expanded into functional waters with a line of lightly caffeinated sparkling water products launched in May 2018. “We’re targeting the diet cola drinkers with our product line, but we focus more on refreshment. With a lightly caffeinated sparkling water, consumers can get their kick while staying hydrated.”

Matros says the brand chose to use 12-oz aluminum cans as packaging rather than slender cans in an effort to make consumer adoption simpler. “We’re asking people to give up their cola, which is why we want to mimic the cola experience as much as possible.”

Matros says the functional water market is trending toward a “water-plus” format. “We’re doing water-plus-caffeine. But there’s also water-plus-fiber, water-plus-fats, and even water-plus-hydrogen. There’s lots of fun stuff happening in functional water, which is very exciting.”

**Immune Health Water Gives the Gut a Natural Boost**

As research continues to demonstrate the connection between gut health and immune health, brands are searching out new means of providing a gut health boost. Pervida (Blacksburg, VA) is accomplishing this task with a series of all-natural canned sparkling waters that employ pomegranate seed oil as a primary ingredient.

Pervida founder Josep Bassaganya-Riera, PhD, is an immunologist and the director of the Nutritional Immunology and Molecular Medicine Laboratory at the Biocomplexity Institute.
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Institute of Virginia Tech (Blacksburg, VA). Bassaganya-Riera says that Pervida’s pomegranate seed oil ingredient is very similar to conjugated linoleic acid, which he investigated in the 1990s. However, Bassaganya-Riera says, “We believe our ingredient is more effective,” adding that the company is releasing a product called Pervida Control, “which will use ingredients found in fruits and vegetables to increase extraction of glucose transporters for energy use.”

Bassaganya-Riera says he chose to make Pervida’s beverages carbonated because light carbonation promotes absorption of the beverage’s functional ingredients: vitamin D and conjugated linoleic acid.

Bassaganya-Riera says he believes functional water consumers are looking for education, and that consumers want to understand the science behind the beverages they consume. “The consumers who show interest in Pervida are the kinds of consumers who are willing to pay a premium for validated science and higher-quality ingredients. I see the whole functional water industry trending in that direction.”

Brands Race for the Best Biodegradable Packaging

A 2018 report carried out by Mintel (London, UK) notes that “innovation in packaging coupled with sustainability has been a focus in the bottled water category in recent years,” with brands continually evolving their packaging methods in order to stand out in a competitive niche. But developing sustainable packaging methods involves more than just changing the packaging; it also means changing consumers’ minds.

Mintel’s report notes that while consumers perceive carton water as healthier, more unique, and more natural than bottled water, purchasing intent for carton water is 13 percentage points lower than for bottled water. One brand that aims to generate consumer excitement about boxed water is JUST Water (Glen Falls, NY), which launched its newest line of flavored water in March 2018. JUST Water CEO Ira Laufer says that JUST places a strong emphasis on sustainability. JUST Water is packaged in paper cartons sourced from FSC-certified forests, he says, and JUST’s manufacturing process produces 74% fewer greenhouse gases than plastic bottles due to JUST’s paper- and sugar-cane-based bioplastic construction.

“Our brand’s foundation is built on the ethos of sustainability, and planet-friendly packaging is integral to our mission,” Laufer says. “Using sustainable packaging was non-negotiable for us.”

JUST Water cofounder Jaden Smith, the 20-year-old son of famed film and television actor Will Smith, discovered an early passion for sustainability upon learning of the manner in which disposable plastics are harming the world’s oceans. Smith says he created JUST Water in an effort to reduce plastic waste.

“We believe consumers are looking for a better alternative to traditional plastic bottles,” Laufer says. “Today’s consumer is savvy. Consumers no longer purchase a product because it looks good or tastes good; consumers want to know what the brand behind the product stands for.”

High-Protein Water Gives Athletes a Low-Calorie Shake Alternative

Athletes looking to build muscle have a variety of protein-based beverages available to them; however, traditional protein beverages are a poor option for athletes seeking a low-calorie solution. Andy Horrow, president of Protein2o (Elk Grove Village, IL), says that the company’s founders created Protein2o as a higher-quality protein beverage that contains fewer calories than traditional drinks.

“Most protein beverages either have 100 to 250 calories per bottle, or they use protein sources like collagen that don’t fully contribute to your RDA of protein,” Horrow
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Research over the past two decades has revealed that gut health is critical to overall wellness and immunity, and that an unhealthy gut contributes to a wide range of health challenges. Many researchers believe that supporting digestive health and restoring the integrity of the gut barrier will be one of the most important goals of health professionals in the 21st century.

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Functional Water

notes. "Protein2o contains whey protein isolate, which is great for muscle building and recovery, and our product contains only 60 calories."

Horrow says that three rules govern the functional water market: 1) the product must be a low-calorie drink, 2) the product’s functional benefits must perform as advertised, and 3) the product must taste good. “That’s why our products have a range of sweetness profiles to appeal to everyone. Protein2o is really just water plus protein, so it’s easy to drink without unnecessary additives."

Protein2o’s most recent product launch is a new line of drinks with 10 g of protein per bottle.

Chlorophyll Water Aims to Compete in the Green Food Space

Chlorophyll water is said to have several functional health benefits, with brands making health claims related to inflammation and skin health. It is these kinds of functional benefits that are growing the chlorophyll water space, with consumer and trade publications like Vogue, Whole Foods’ Trend Forecast, and Well+Good naming chlorophyll water as the leading health product trend for 2017.

One brand, Verday (Lafayette, NY), manufactures a chlorophyll-enriched water that it positions as a detoxification aid, skin and blood health product, and dietary supplement. Verday positions its chlorophyll water as a green food alternative for consumers who want the benefits of a wheatgrass shot, but in the form of a bottled water beverage. Last year, Verday expanded its product line to include blueberry-flavored chlorophyll water.

“We have known about the health benefits of chlorophyll for some time,” said Verday founder and CEO Randy Kohana in a press release. “The category should continue to grow as a major trend.”

Functional Waters Expected to See Significant Category Growth

The functional water market’s strong growth is expected to continue. Euromonitor International (London, UK) is forecasting worldwide consumption of functional water products to rise by 3.6% per year, reaching 1.56 billion liters in 2022. Euromonitor predicts the functional water market will be worth $3 billion USD in 2022.

As functional concerns continue to diversify among consumers, it is expected that new opportunities for innovation will allow market entry for a variety of new competitors.

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In 1929, a Danish biochemist by the name of Henrik Dam was studying cholesterol metabolism in chicks when he noticed an unusual incidence of anemia, hemorrhage, and delayed blood clotting among birds fed a fat-deprived diet. He later identified the syndrome’s cause as a deficiency in the fat-soluble vitamin that we now call vitamin K1, after the German koagulationsvitamin.

Dam, along with the American biochemist Edward A. Doisy, received the 1943 Nobel Prize in Medicine for their efforts. Two years later, however, the dentist and nutritional gadfly Weston A. Price received no such nod when he described “a new vitamin-like activator” apparently able to ameliorate everything from tooth decay to heart disease—a compound we now know to be vitamin K2.

And though nobody’s arguing that Price deserved a Nobel for bringing attention to this elusive “Activator X,” as he called it, he at least deserves some kudos. Because vitamin K2, independent of vitamin K1, is an essential factor in an equation linking it, calcium, and vitamin D3 not only to healthy teeth, but to healthy bones and vessels, as well. And though the public has yet fully to appreciate vitamin K2, advocates are working overtime to change that. Our health may depend on it.

One Letter, Many Vitamins

When Dam and Doisy first characterized vitamin K1, they had no idea that the substance they were exploring wasn’t a single vitamin, but rather a member of a vitamin family. That family includes both vitamin K1—or phylloquinone, as it’s formally known—and a group of 10 homologous menaquinone compounds collectively known as vitamin K2.

“It’s been more than 30 years that the research community has been investigating and recognizing differences between vitamins K1 and K2,” says Chris Speed, senior vice president, global sales and marketing, NattoPharma ASA (Oslo, Norway). And among the things they’ve learned is that both K1 phylloquinone and the K2 menaquinones share the structural similarity of a quinone ring.

Where their structures differ is in the side chains attached to it. On K2 menaquinones, those side chains comprise a series of linked isoprene units, with the shortest chain—four units—appearing on menaquinone 4, or MK-4, and the longest, at 13 isoprene units, appearing on MK-13.

Among commercial forms of the vitamin K2 menaquinones, MK-4 and MK-7 are the most common. But thanks to the nature of its side chain, MK-7 has a longer half-life in the body—three-plus days compared to just a few hours for MK-4—granting MK-7 greater access to tissues beyond the liver, Speed says. “So although they have the same molecular mechanism of action, vitamin K2 as MK-7 is more bioavailable than MK-4. And because of MK-4’s short half-life and poor bioavailability, it requires multiple doses per day at milligram levels versus MK-7’s microgram doses for measurable efficacy.”

Calcium Connection

Just what is this molecular mechanism of action? In short, all K vitamins are cofactors for...
the enzyme gamma-glutamyl carboxylase, which carboxylates—and thus activates—a number of K-dependent proteins. Two of these proteins are osteocalcin, produced in the osteoblasts and essential to depositing calcium in bone, and matrix-Gla protein (MGP), which inhibits calcium deposition in soft tissues.

Vitamin K2, and the MK-7 particularly, kicks these proteins into action. In so doing, says Jim Beakey, communications lead, Kappa Bioscience AS (Oslo, Norway), the vitamin forges its link with calcium and vitamin D3.

"Everybody knows that calcium is important for bones," Beakey explains. "And people are starting to understand that vitamin D3 is also important for bones by pulling calcium from the intestines and into the blood, where it can go to work for bone building." But "the missing leg of the stool," as he calls it, is vitamin K2.

Why? Because carboxylated—that is, K2-activated—osteocalcin is necessary both for shuttling calcium into the bone matrix and for binding it there. "So for proper bone health you need calcium, vitamin D3, and vitamin K2," Beakey concludes. "Vitamin K2's primary role, and what it does best, is balancing or regulating calcium transport in the body."

Heart and Bone
And the bones aren't the only site where it does this.

Researchers have long observed a correlation between bone disease and heart disease. And one possible explanation involves vitamin K2. Consider that vitamin K2, primarily as MK-7, helps osteocalcin shunt calcium out of the blood and into the bones. But, as Beakey notes, "any additional calcium in the blood can be absorbed by the soft tissues"—arteries and blood vessels included.

When this happens, arteries and vessels harden. "They absorb the calcium and stiffen even in the absence of any sort of plaques," he says. "But when plaques build up, they can lead to even further stiffening and reduce the diameter of the vessels. Both these forms of calcification lead to heart attacks and strokes."

Where does vitamin K2 come in? It carboxylates, and thus activates, MGP, the vitamin K-dependent protein that binds circulating...
calcium and prevents it from laying down in the vessels. Both Beakey and Speed point to the Rotterdam1 and Prospect studies2,3 as convincingly demonstrating vitamin K2’s cardio-supportive effects. And, Beakey adds, “There’s another great study4 from Knapen”—conducted on NaturoPharma’s MenaQ7 natural vitamin K2 MK-7—“showing that arterial stiffening can even be reversed—people can actually return to a previous state of health, which, in terms of longevity, healthy aging and wellness, is a fantastic finding.”

**Good Luck Eating It**

So by helping to activate osteocalcin and MGP, vitamin K2—again, MK-7 especially—keeps calcium in the bones, where we want it, and out of the vessels, where we don’t. The upshot: We should want plenty of vitamin K2 in our diets. But try though we might, it’s tough to harvest sufficient amounts from the foods most of us regularly eat.

Vitamin K2 is a product of bacterial fermentation, and the single best food source is natto, a Japanese fermented-soybean dish that one might politely describe as an “acquired taste.” Beyond that, certain fermented cheeses, dairy products, liver pate, meat, eggs, and fish also contain vitamin K2. “But for the most part,” Beakey notes, “the K2 is in the less-efficient MK forms and not the high-bioavailability MK-7. So you’d have to eat kilos of cheese and gallons of milk every day just to meet the daily requirement.”

A study5 published recently in Nutrients even examined the vitamin K2 content of cheeses and found that despite their being the best sources of long-chain menaquinones in the Western diet, they vary widely in that content—from 3 to 802 ng/g. Given the researchers’ recommendation to consume 180 to 360 μg of vitamin K2 per day, they conclude, “[Y]ou need to eat at least 225/445 g of French cheese a day (Münster) and at least two times more in case of cheese from Scandinavia” to get your K2 fill.

So how did humans evolve to need a vitamin that’s so challenging to obtain from food? “This is the big conundrum,” Beakey opines. And as a potential explanation, he points to a theory posited by the naturopath and author Kate Rhéaume-Bléue—namely, that industrial changes in food preparation and storage precipitated the current vitamin K2 deficiency.

To wit, refrigeration and chemical preservation made natural food fermentation—vitamin K2’s key generator—both less necessary and less common. The prevalence of grain-fed over grass-fed beef might also play a part. “When livestock is grazed on grasses,” Beakey explains, “their stomachs have a chance to ferment the grasses, which leads to higher levels of MK in the dairy products and meat of those animals. So maybe we used to get enough K2 from our diets, but changes in our environment and our relationship with food are creating a deficiency.”

**Just Can’t Get Enough**

That deficiency is widespread, with some studies showing 97% of the Western population deficient in vitamin K2, based upon food-intake surveys and evaluations of subjects’ circulating levels of activated osteocalcin and MGP. Given vitamin K2’s links to bone health, and its relationship to osteoporosis, osteopenia, and cardiovascular diseases, how serious is vitamin K2 deficiency?

“If you fall and break your hip,” Beakey says, “you may not die immediately. But the osteoporosis that led to that was the first domino to fall. And when you run through the list of cardiovascular diseases, the most lethal among them have a genesis in calcium mediation, calcification of soft tissues, and calcified plaques. Strokes, heart attacks: all come back to calcium. So if you wonder, ‘Well, why aren’t people just dropping dead from vitamin K2 deficiency?’ To some extent, they are.”

**Under the Radar**

Yet you wouldn’t know it from talking to consumers. For unlike probiotics, protein, and other “celebrity” nutrients, vitamin K2 flies surprisingly under their radars—surprising considering its health implications.

Beakey wagers that’s because not long after vitamin K2 emerged in the first half of the twentieth century, “it was essentially forgotten. There was little real study on it.” We had to wait until the early 1990s for glimmers of inquiry to surface in Japan, and by the early 2000s more research was in motion. “But 2007 is probably when it really started to kick in,” he continues. “The real, serious studies—clinical studies and not just epidemiological studies or studies of biomarker activation—started around 2007, and the results are just becoming apparent and publicized for the first time.”

Also stalling vitamin K2’s rise was the near nonexistence of a K2/MK-7 industry to champion its virtues. “The first synthesis of K2 on a commercial scale only happened in 2009,” Beakey says, “and companies didn’t really start rolling into the K2 space until around 2012 or so.”

Fortunately for us all, the convergence of maturing science and a growing community of vitamin K2 suppliers means that “we can finally bring this scientific and
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No RDI exists for vitamin K2.

Rather, current international vitamin K RDIs address solely the amount of vitamin K1 needed for proper blood clotting.

consumer education to the dietary supplements industry,” Beakey says. “And this is all happening as we speak.”

Take a Number

It’s about time it does. Yet a remaining challenge, Beakey continues, “is that K2 is a relatively expensive ingredient.” So if a multivitamin manufacturer were to include it in a formulation that already contains vitamin K1, that manufacturer would probably need some convincing to do so.

And vitamin K2’s bone and vascular arguments are nothing if not convincing. But what would strengthen them further would be an official recommended daily intake (RDI) value specific to vitamin K2. As it stands, no such RDI exists. Rather, current international vitamin K RDIs address solely the amount of vitamin K1 needed for proper blood clotting: 1 μg/kg body weight/day according to the European Food Safety Authority (EFSA), and 90 μg/day for women and 120 μg/day for men according to the U.S. FDA and Health Canada.

Moreover, these recommendations rest on median vitamin K1 intakes estimated from national surveys dating back to 2001. But “with all epidemiological and interventional studies showing that only K2 is cardio-protective or has a beneficial effect on arteries,” Speed says, “it may be time to calculate new requirements that account for the benefits of menaquinones, too.

NattoPharma has embarked on just such a project to establish a much-needed RDI for vitamin K2. As Speed explains, “The program will begin with a team of researchers at Maastricht University, in the Netherlands, which has already led the way to discovering and validating the health benefits of vitamin K2, guided by Dr. Leon Schurgers, professor of biochemistry of vascular calcification at Cardiovascular Research Institute at Maastricht University, or CARIM.”

Joining Schurgers’s team will be the International Science and Health Foundation (ISHF), a research consortium that directs the educational portal VitaminK2.org, and a group of PhD students—sponsored by NattoPharma—who will work to understand the RDI values that FDA, Health Canada, and EFSA have already set. These students will then produce a comprehensive literature review of K2’s bone and cardiovascular benefits to support the argument in favor of updating the RDIs.

The effort could go a long way not only toward advancing vitamin K2 science, but toward improving public health, too. “It’s imperative for global human health that a vitamin K2 RDI be established,” Speed says. “An established RDI will help consumers best select the supplements to meet their health needs, while also giving clear guidance to companies seeking to make the most effective supplements.”

And it’ll put the vitamin on the radar, where it belongs. Then again, for some consumers vitamin K2 may already be on their radar. “In one recent study, half of those we reached out to on a general supplements panel were aware of K2 and were interested in it,” Beakey says. “And studies on product concepts and even actual market data demonstrate that products with K2 for bone health or heart health actually outperform identical products that don’t include K2: purchase intent, uniqueness scores, concepts tests, and actual on-the-ground sales in places where comparisons can be made.”

And this, Beakey concludes, is “the elegant solution and promise of K2. It’s one of those nutrients that could have a fundamental change on populations’ and individuals’ health, wellness, and longevity. It’s such a simple thing. We’re not talking about an exotic root from the jungle. It’s an essential vitamin. And they don’t make those every day.”

K1, that manufacturer would probably need some convincing to do so.

References

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According to the 2017 CRN Consumer Survey on Dietary Supplements, fully 79% of women are supplement users—six points ahead of the men’s team, of whom only 73% profess regular supplement use.

That stat alone should be enough to turn supplement brands’ attention toward this powerful audience. Women are often the custodians of family health, and there are evolving opportunities for reaching female shoppers with a spate of new ingredients, delivery systems, and supplement products.

The numbers are pretty convincing, too. According to SPINS (Chicago), female-positioned supplements grew at a rate of 6%, netting a total of $628.1 million in U.S. sales in the 52 weeks ending July 15, 2018. Meanwhile, though supplements targeting men saw 9% growth, they still attained a market share barely more than half that of women’s at $364.3 million.

But most of all, says Kimberly Kawa, retail reporting analyst for SPINS, “Reviewing some products added to our reporting in the past year, it seems that some of the standout supplements belong to female-centric sets.” So if brands want to stand out from the crowd themselves, they’d be wise to put women’s formulas to work.

Satisfy a Need

So, do women buy more supplements than men? “Yes, for the most part,” says Keena Roberts, senior consumer health analyst, Euromonitor International (Chicago).

“Women tend to be more proactive about preventive health and more likely to incorporate supplements into an established health and wellness regimen,” she notes. “There’s also some evidence to suggest that women more readily incorporate supplements into their daily routines when they’re addressing premenstrual symptoms, and this makes it easier to incorporate other supplements at the same time because they’re just more accustomed to their use.”

And as with their interest in supplements for premenstrual relief, women’s pursuit of supplements across the board is frequently motivated not just by a general desire to be healthy, but by a desire to address specific health issues, as well.

Indeed, says Roberts, “The most popular supplements are positioned around need states. We see the whole vitamin and dietary supplement industry shifting toward products directed at terms like bone health, energy boosting, and digestive health.”
Michael Chernyak, president of CK Nutraceuticals (Oakville, ON, Canada), a supplier of many ingredients to support women's health, says, "Today's female consumer is interested in many areas encompassing health and wellness. It very much depends on a women's specific life stage. Generally speaking, health concerns can revolve around osteoarthritis and osteoporosis, cognition, energy, menopause, digestion, cardiometabolic health, and more. One area where we've focused a great deal of our recent effort is mood balance. Lifestyles are very hectic in today's society, and myriad daily demands are imposed on today's female consumer. Mood support is an area of particular interest for us, as we see healthy mood being a key foundation for optimal wellness and healthy aging."

Rising and Falling

Euromonitor's Roberts has observed growth in immune-boosting formulas that include vitamins C, B6, B12, and E, plus zinc, calcium, magnesium, and iron—all of which are ingredients that women in particular know they need," she says. B vitamins overall appear on an upward trajectory with women, Roberts adds, "because of the perception that they combat fatigue and increase energy."

Like Chernyak, Kawa points to sales of supplements for cognitive health and mood support—up 93% and 50% in the U.S., respectively, among women—as addressing an "emerging health focus in the female gender set." And while such supplements capture a smaller market share than some other formulas, they "do report positive growth rates in the double digits," Kawa says.

So, too, do supplements aimed at digestive health, which, among female customers specifically, brought in $46.7 million in U.S. total sales at a growth rate of 22%. Kawa says, "That's a lot of growth, and mirrors broader interest in digestive health."

And whenever discussing winners in the women's supplement space, products for urinary tract health will come up, which, Kawa says, are "perennially popular with women." To wit, such supplements garnered $22.6 million in U.S. sales among women over SPINS's 52-week reporting period, representing growth of 5%.

But not all lines lead upward with women's supplements. Perhaps surprisingly, SPINS numbers show that though they make up a $38.3 million U.S. market, bone health supplements saw sales to women fall 7%. Sales of energy-support supplements to women were also down 8% for a total U.S. market share of $30.1 million. But the steepest drop of all was for weight-loss products among women, which SPINS data show brought in a trim $8.9 million while seeing their sales totals cut in half.

Take It Easy

Regardless of the supplement category they choose, female consumers "want to feel as if they're taking a product that can help them with a specific prevention plan that works..."
with their overall health and wellness—rather than just ‘taking a vitamin,’ Roberts says.

And yet, SPINS found that good old-fashioned multivitamins topped the list of delivery formats in terms of total U.S. sales, with multivitamins for women earning $395.7 million and seeing 6% growth.

Market data from IRI (Chicago) also found that traditional pills—specifically, tablets and capsules—remain the dominant form in the women’s category, holding onto a 65% share. But liquid and softgels as well as gummies account for a respective 25% and 3% of supplements available, IRI says, and though pills and liquid/softgel products saw dollar gains during the 52 weeks ending August 12, 2018, gummies declined.

Nevertheless, Roberts remains bullish on gummies “because of their ease of use and better absorption potential.” Similarly, supplement powders also show potential “since sachets are light and portable and easily incorporated into the shakes and other drinks women already take,” Roberts says.

Finally, developments in personalized nutrition promise to shape the women’s supplement space. “Consumers are wary of side effects and reluctant to take anything they don’t believe they need,” Roberts says. Consequently, “There’s a lot of interest in this industry about genetic mapping and how increased knowledge of human genetics can help consumers identify their own specific needs, and whether future innovation in this space can help companies develop personalized supplement regimens for individuals based on their genetics.”

While we’ve got a long way to go before such advances start trickling down to supplement shelves, there’s plenty of innovation in the women’s category for us to celebrate now. Ahead are just a handful of female-friendly supplements to keep your eyes on.

**Blessed Events**

According to SPINS, prenatal health is the most popular focus in the women’s supplement category, with total sales of $139.4 million and 4% growth.

As an example, Kawa points to Traditional Medicinals’ line of lozenges and chews, which target pre- and postnatal women with ingredients like raspberry leaf, ginger, fennel, anise, coriander, and fenugreek—galactogogues that promote breastmilk production. “These may be popular for women interested in the convenience of a chew or lozenge from a well-established company in the herbal-botanical space,” she notes.

Rainbow Light also promotes its Vibrance line of products as supporting women from preconception through each trimester and even to the postnatal phase. Key ingredients include active forms of the important vitamins B12 (methylcobalamin) and folate (methyltetrahydrofolate), as well as supportive botanicals for immunity, digestion, nausea, and other pregnancy-related issues, Kawa says.

**Golden Girls**

Among multivitamins for women, those targeting an older demographic brought in $70.1 million in the U.S. for the year ending July 15, 2018, up 10%, per SPINS.

“Natural Factors has a line specific to women with an array of focuses,” Kawa notes, “and their Multi Factors Women’s 50+ Vitamin & Mineral Formula contains botanicals, enzymes, and whole-food antioxidants as well as highly bioavailable forms of vitamins and minerals. The supplement also highlights the delivery method: easy-to-swallow vegetarian capsules.”

**Smells like Teen Spirit**

Kawa calls Rainbow Light’s Teen Girl’s Multivitamin plus Healthy Skin Support product “a top pick” among the female-friendly supplement set that SPINS tracked.

Ginger root extract, spirulina, bioflavonoids, carrot root, and chlorophyll are ingredients that purportedly promote clear and healthy skin. The formula’s iron and bioavailable B vitamins help teen girls maintain energy levels, ease stress, and keep their moods steady. And for improved digestion and gut health, 100 million CFU of probiotics plus prebiotics and plant-sourced digestive enzymes do their best to ease those butterflies that anyone who’s ever been a teen girl will remember.

**Mind the Gap**

Anecdotally, women tend to be more conscientious about eating right—choosing plenty of fruits, vegetables, whole grains, and lean sources of dairy and protein. But frustrating even their best-laid efforts is what’s...
known as the “enzyme gap”—that is, the difference between what a woman eats and what her body’s complement of enzymes can actually help her body digest and absorb.

Apparently, this gap widens as women age, and can lead to a litany of complaints ranging from digestive trouble, fatigue, and a weakened immune system to skin problems, mood swings, joint pain, and more.

So Phoenix-based gastroenterologist Liz Cruz, MD, created Everyday Enzymes, an organic, “all-natural” formulation of amylase, protease, lipase, cellulase, invertase, diastase, lactase, *Lactobacillus acidophilus*, *Bifidobacterium longum*, and cellulose, designed to aid digestion and absorption of all those healthful nutrients that women work so hard to eat.

**Thanks, Mom!**

In December of 2017, biotech firm Biosearch SA signed a license and supply agreement with Nestec SA, a division of the Nestlé group, to market the former’s probiotic strain *Lactobacillus fermentum* LC40, also known as “Hereditum.”

Nestec aims to include the Hereditum strain in a supplement designed to help breastfeeding women maintain healthy lactation—which makes sense, given that Biosearch chose this particular probiotic strain from among the hundreds that occur naturally in breastmilk.

In fact, clinical trials have demonstrated the Hereditum strains ability not only to eliminate the painful symptoms of mastitis—an inflammation of breast tissue—but to allow women to continue breastfeeding, and to continue reaping its benefits for their and their babies’ health.

**Seeking, and Finding, Relief**

Women’s search for products that provide premenstrual relief may never end. But it may have gotten closer to the finish line earlier in 2018 when results of a clinical study1 showed that Lipogen PMS, a natural phospholipid supplement formulation, exhibits positive effects on treating and relieving premenstrual syndrome (PMS) symptoms.

Touted as “a supplement created for women by women,” the Everyday Enzymes supplement was designed by a female gastroenterologist to support digestive health, immune health, metabolism, and overall health, the company says. It can even be taken by expectant mothers.
The randomized, double-blind, placebo-controlled trial involved 40 women aged 18 to 45 with physician-diagnosed PMS. After observing the subjects during an initial baseline menstrual cycle, the researchers administered to the subjects either a daily dose of the supplement complex (400 mg phosphatidylserine and 400 mg phosphatic acid) or a placebo for the following three menstrual cycles.

Results showed that subjects in the Lipogen PMS treatment group saw an ongoing decline in their PMS symptoms, while the placebo group returned to initial PMS-symptom levels.

**Aiding Female Athletes**

Female athletes are a growing—and crucial—subset of the sports nutrition market. There is still great need for more research on the benefits of supplementation in female athletes, as *Nutritional Outlook* discussed in its September 2018 issue. One female-centric company is stepping up to the plate. A prebiotic and probiotic supplement called Regular Girl may help female athletes better absorb iron, according to a new study. The randomized, double-blind, placebo-controlled trial found that the synbiotic supplement combining 5 g of Sunfiber guar fiber from Taiyo International (Minneapolis) and 8 billion CFU of *Bifidobacterium lactis* bacteria, when taken with 140 mg of ferrous sulfate, an iron supplement, significantly improved serum ferritin in female athletes. The trial was conducted by Marywood University, and the results were presented at the American Society for Nutrition’s annual conference in June. According to makers of Regular Girl, an abstract of the study awaits publication in *Current Developments in Nutrition*.

Twenty female athletes with confirmed iron deficiency were eligible to participate, and 19 completed the eight-week trial. Results showed that compared to the placebo group, which received the iron supplement plus placebo, the uptake of ferrous sulfate was significantly improved at four weeks and was sustained over the eight-week trial period in Regular Girl subjects, who were given the iron supplement plus the Regular Girl supplement. After controlling for baseline, regression analysis determined the serum ferritin was improved by 41% in four weeks and by more than 100% at eight weeks for the Regular Girl group, compared to 0% and 10% at four and eight weeks, respectively, for the placebo group.

These results are important because iron deficiency affects about 30% of female athletes, with major consequences to their performance. Poor iron uptake remains a major factor. While the sample size was small, these results show promise for the use of synbiotic supplements in combination with iron supplements to improve iron levels in deficient individuals, the researchers say. The researchers also stated that it’s conceivable that the use of synbiotic supplements may improve the absorption of non-heme iron from plants, which is poorly bioavailable compared to the heme iron obtained by eating meat. This could have positive implications for those who follow a plant-based diet as well as for the larger population because plant sources of iron are more commonly consumed compared to animal products.

**Reference**

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As the saying goes, “If you can measure it, you can manage it.” But whatever “it” is, it’s probably not worth managing if you haven’t measured it accurately. So in the dietary supplement industry, where accurate measurements are prerequisites to effective finished products, it’s no wonder that having access to a broad compendium of quality reference standards and materials is well-nigh indispensable.

After all, says Petra Erlandson, director of sales and marketing, Alkemist Labs (Garden Grove, CA), “Reference materials, along with scientifically valid testing methods, are the bedrock upon which identity, strength, and purity analysis depend.”

But with industry in a continual state of flux, the question arises as to whether reference materials are keeping pace with the changes—and whether the nutrition industry is keeping pace with how best to use them. For as another saying puts it more bluntly, “Garbage in, garbage out.”

GMPs Say...

Erlandson isn’t alone in stressing the role of reference materials in supplement quality control. As John Travis, senior research scientist, NSF International (Ann Arbor, MI), says, “Anywhere measurement science is practiced, reference standards and materials are needed.”

But don’t just take their word for it; it’s written into FDA current Good Manufacturing Practices (cGMPs). Namely, Subpart J—Production and Process Control System: Requirements for Laboratory Operations declares, among other things, that operations “must establish and follow laboratory control processes that are reviewed and approved by quality-control personnel, including the following: (d) Use of criteria for selecting standard reference materials used in performing tests and examinations[.]”

Note that the cGMPs don’t spell out the criteria for selecting those reference standards and materials—a task left to individual labs—nor do they define them. That definition comes from the Bureau International des Poids et Mesures’ (BIPM) International Vocabulary of Metrology (VIM), which describes a reference material as a “material sufficiently homogeneous and stable with reference to specified properties, which has
been established to be fit for its intended use in measurement.” A reference standard, says Travis, “could be a pure chemical that’s been characterized as to its purity, or a solution of said chemical, which is typically used for calibration purposes.”

In any case, the requirements in the cGMPs that dietary supplements use reference standards and materials underscores the “need to evaluate quality in development, production, and trade,” says Gabriel Giancaspro, PhD, vice president, science, dietary supplements and herbal medicines, USP (Rockville, MD). “And anyone interested in evaluating that quality should use a validated analytical procedure together with a reference material for that particular use.”

**Fit for Purpose**

“For that particular use” is no throwaway phrase. That’s because a reference standard or material tells us little in and of itself; rather, says Giancaspro, “it’s what we do with it that tells us something valuable. Once we use it with a validated analytical procedure, then we can tell whether or not we have an accurate measurement of a particular ingredient in a matrix like a dietary supplement. Or that we have an absence of a potential contaminant, or an accurate identification of a particular material.”

What’s more, we don’t use references materials or standards to test the quality of finished products; we use them to test the methods that we use to test those products. Or as Travis puts it, “Reference standards and materials enable laboratories to make accurate measurements to verify specifications of raw materials and finished products,” with standards measuring how much of a substance is present, and materials helping labs determine if that measurement is accurate.

Everyone along the supply chain benefits from the proper use of reference standards and materials. Alas, says Catherine Rimmer PhD, chemical sciences division, National Institute of Standards and Technology (NIST; Gaithersburg, MD), “Based on our sales figures, people aren’t using these as much as we would hope they would be.” For despite their inclusion in the cGMPs, the regulation “leaves their use very open to the manufacturer.”

**The Real Thing**

One use that’s absolutely valid, and growing, is in botanical identity testing and authentication. Consider a potentially adulterated *Ginkgo biloba* extract, Travis suggests. “Standardized extracts of ginkgo generally are specified as containing 24% flavanol glycosides and 6% terpene lactones,” he explains. “Using fit-for-purpose analytical methods and reference standards, analytical chemists can determine if the ginkgo extract has been adulterated with purified flavanols and/or flavanol glycosides from other plant sources.”

Erlandson notes that botanical identity confirmation requires a thorough set of comparisons, including between the formulation sample and a matching reference material of the genus, species, and plant part to be confirmed. When testing for adulteration, the key comparison is between the sample and reference materials of other plant parts from the same botanical, “which would reveal, for example, that the root you thought you were buying and that’s listed on the label isn’t root at all, but is actually leaf,” Erlandson says. “It would also identify if the material is a closely related species, but not the species you think you’re buying and putting on the label. In the same way, reference materials can identify other known adulterants in the supply chain.”

Finally, botanical identity analysis must compare the test sample not only to a reference material from the same genus-species and plant part, but to reference materials from other plant parts, closely related species, and known adulterants. Why? “Essentially, you’re testing for what you think you have, and also what you hope you don’t have but really need to know if you do,” Erlandson says.

**Packing the Pipeline**

Jeff Moore, PhD, senior director, scientific strategy and planning, at USP sees the use of reference materials in authenticity testing as critical to combating economically motivated adulteration and fraud. But, he says, “That becomes a challenge when you don’t know what the next adulterant issue is. There are needs around creating libraries of authentic materials to help define what’s authentic for non-targeted testing, particularly for things like agriculturally derived food ingredients and botanicals where their composition can be highly variable. It’s challenging because it’s a lot of work for any one organization to develop those libraries, and many of those substances aren’t available as reference materials.”

Moreover, while reference standards for “classical dietary supplements”—think vitamins and minerals—are broadly available and well known, as the supplement industry develops new ingredients and delivery systems for them, gaps in the pipeline emerge, Giancaspro observes.

Consider the gummy. “This is an example of a new delivery system,” Giancaspro says.
So, too, are melts and fast-dissolving strips. As such, “industry needs to make sure those systems are delivering the ingredient in the appropriate way,” he continues. Enter reference standards and materials in concert with validated testing methods. “We have dissolution tests at USP to make sure that the dosage forms are able to dissolve and deliver the ingredients,” Giancaspro says. “So while you’re evaluating performance, you’re using reference standards, as well.”

Given that it takes three to five years to create a standard reference material from start to finish, a certain degree of triage among candidates is in order, NIST’s Rimmer says. So when considering whether or not to pursue development of a particular option, “First we triage the marketplace based on where there are safety concerns and how much of the market share a supplement has,” she says. And if a candidate is number 253 on the list of most-used supplements, “there probably isn’t as much need for a standard as there is for a material that’s second on the list.” But if 253 provokes safety concerns, “that’s something we need to look into.”

NIST also works with the National Institutes of Health Office of Dietary Supplements on triage efforts, as well as with trade associations and FDA, to figure out the best sources of the materials from which to develop a needed standard.

Consider the Source

Sourcing is especially critical in developing reference products for botanical ingredients, which can be subject to the whims of weather, environment, and harvest practices. As René de Vaumas PhD, CEO, Extrasynthese (Lyon, France), says, “Knowledge of the sources used to make the standard is critical, as is the control of the manufacturing or purification process. These are the key criteria, before analytical measurement, to assess the identity and non-adulteration of a sample to be qualified as a standard.”

NIST produces some of its botanical references in suites that include both plant and extract materials, “because manufacturers are supposed to test throughout the process and in their finished products,” Rimmer says. They collaborate with farmers, buying significant portions of plant matter from one year’s growth, splitting it into a lot that stays as the original plant, and another that goes through the extraction process, linking the plant and extract, she says.

For its part, Alkemist Labs produces its composite reference botanical products (CRBs) by combining two to three different lots of authenticated, identity-confirmed plant materials of the same genus, species, and part. “We use this composite lot approach to help our clients include some of the normal phytochemical variances that different growing conditions and locations can engender between lots of otherwise identical genus, species, and plant part,” Erlandson says. “Each comprising lot is tested by microscopic analysis as well as HPTLC, and the final combined CRB is retested using the same methods.”

Returning to the importance of reference “libraries,” Erlandson adds that her company’s partnership with Extrasynthese, American Herbal Pharmacopoeia (Scotts Valley, CA), and Botanicert (Grasse, France) brings “a full library of nearly 1,500 phytochemical standards and botanical reference materials to the market through our website shopping cart,” she says. They keep filling the pipeline and have added about 150 new botanical reference materials thus far this year.

Quality Counts

But while libraries of vetted reference standards and materials are essential, not all reference products come with the same seal of approval. And, says Erlandson, “One of the biggest analytical challenges facing the industry is the use of inappropriate reference standards and materials. We often see companies improperly using prior ingredient lots and reagent-grade”—read: low-grade—“chemicals as ‘reference materials’ in willful ignorance or to cut testing costs. If the reference material isn’t fit for purpose for the exact analysis being performed, you’ll have a house of cards built on an unstable foundation.”

Extrasynthese’s De Vaumas agrees. “The challenge is to educate industry as to the value of using QC methods that use standards—and then to educate QC managers to recognize ‘true’ standards versus ‘so-called’ standards,” he says. “Purity determination techniques for fine chemicals such as percent area count by HPLC don’t qualify a sample as a standard.”

So how do we gauge quality in reference standards and materials? “It’s hard,” says NIST’s Rimmer. Reiterating the VIM definition, she qualifies a quality reference as “something that’s well characterized, with its purity established, and coming with a certificate of analysis that tells the user where it’s from and how it’s tested and how the values were generated.” She adds: “A bad one would be not so pure, not so well characterized, and doesn’t come with the same amount of information, where its identity hasn’t been established. And that’s true for either single compounds or a matrix.”

And it’s got to be fit for purpose. “There are some manufacturers that make ID standards that are great if you’re trying to identify your material, but aren’t very good if you want to measure the amount of arsenic in it, because they haven’t measured the arsenic in their own,” Rimmer says.

USP’s Giancaspro considers collaborative testing “a key characteristic of a good-quality reference standard.” His company dedicates “a great amount of resources and time” to test reference standard candidates multiple times in different laboratories “so that we have consistency in the assigned value. And I think that’s a good measure of good-quality reference materials.”

Erlandson also sees the value of testing from all angles. “When an orthogonal approach is used, with multiple complementary analytical techniques whose results are congruent and reinforce each other, the confidence in those results is higher,” she says.

Still, companies must do their due diligence in evaluating suppliers, as they would elsewhere on the supply chain. “Inspect the example certificates of analysis and ask questions: Does the supplier use robust analytical techniques and disclose results of testing ‘a key characteristic of a good-quality reference standard,’” she asks.

“Expertise and transparency are critical to establishing trust.”

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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<td>Mount Franklin Nutritionals LLC</td>
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**Statement of Ownership, Management, and Circulation**

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<th>Extent and Nature of Circulation</th>
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<tr>
<td>Name and Title of Editor, Publisher, Business Manager, or Owner: Christine Shappell, Audience Development Director</td>
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Date: 9/30/2018

I certify that the statements made by me above are correct and complete.

**Nutritional Outlook**

Nutritional Outlook, a monthly publication for foodservice professionals, offers comprehensive information on trends, equipment, and technology. To learn more about our services, visit our website at www.wrightsmedia.com.
So Cool

Refrigerated snacks are hot.

BY SEBASTIAN KRAWIEC, ASSOCIATE EDITOR

Healthy snacking is an important component of the modern diet. Sitting down for a few large meals is not a luxury many with busy work schedules and long commutes can afford. Instead, many of us consume numerous small meals to fill up and maintain energy and focus throughout the day. A snack is no longer just a mindless indulgence, but functions as a meal in its own right.

Fresh snacks, those that require refrigeration, have become an important aspect of this new way of eating because freshness exudes a sense of healthfulness that shelf-stable snacks often do not. According to a report by Mintel (London, UK), titled “The Future of Fresh,” there is also a strong association between “fresh” and no preservatives or additives.

The growing demand for fresh snacks is measurable. According to SPINS (Chicago, IL), in the three years ending April 2018, the $17.5 billion U.S. health and wellness snacking category grew 6% annually. As a subset of this category, fresh snacks, making up $6.8 billion, grew 8% annually, while shelf-stable snacks, a larger portion of the category at $10.7 billion, grew 5%. Compare this to the $40.3 billion conventional snacking category, which declined 2% annually. (Of note, fresh snacks do best in the natural, organic, and specialty-focused channels. In the conventional channel, shelf-stable snacks still reign supreme.)

“Diet tribes and trends around whole-food nutrition (Paleo, Whole30, etc.) are bringing consumers back to the perimeter in search of fresh snacks, and brands are responding,” says Jessica Hochman, natural insights and innovation research manager for SPINS. “We’re watching areas like refrigerated ready-to-eat eggs and refrigerated snacking kits.”

One brand that is really taking advantage of the growth in this space is Organic Valley (La Farge, WI). Products like their two-packs of hard-boiled eggs and recently launched snack kits speak to the desire for snacks as healthy meals. “With the snack kit category, we saw that it was rapidly growing and that it’s an attractive category, but we also identified that there wasn’t anyone else on the market that was doing an organic snack kit option with meat,” says Ellie France, Organic Valley’s brand manager for meat, snacks, and prepared foods. “What was really exciting, too, was knowing that adult-focused snacking options were really driving the growth in the category, and that kind of helped us develop our snack kits through the lens of the adult.”

Snack kits aren’t a particularly novel format, reminiscent of the childhood favorite Lunchables, but here Organic Valley presents an elevated version that feels mature for the adult audience. An adult audience also includes parents, and thus these snack kits are also being served to children. “We’re finding now that there is this secondary market for this new item...especially with young families where moms are focused on the nutrition density of a snack and wanting to give their families the very best,” says France.

Protein is a huge nutrient driving refrigerated snacks. “Protein content is still being highlighted as a primary functional ingredient in multiple snacking segments...Products with some form of protein as a primary functional ingredient are up 9.4% in the U.S. to an annual market of $1.3 billion across channels,” says Kim Kawa, BSc, natural products specialist for SPINS. “This may coincide with the strength of Paleo-positioned products, which report 86.4% growth overall across the same categories.”

In September, Perfect Bar launched Perfect Kids, which the company claims is the first refrigerated kids’ snack bar. “The launch of Perfect Kids comes just after Mintel’s study, ‘The Future of Fresh,’ reported that ‘fresh’ is the number-one purchase driver for Millennials and iGen consumers when shopping for food,” said Leigh Keith, co-founder and president of Perfect Bar LLC, in a press release.

According to Mintel, surveys show that 54% of U.S. consumers believe they need more protein in their diet, and 49% of consumers over the age of 18 who purchased better-for-you snacks in the previous three months cited “good source of protein” as an important factor in their decisions.

This demand is also translating to a transformation of the perimeter in brick-and-mortar retail. With the competition from e-commerce, where shelf-stable foods are purchased in large quantities, fresh snacking presents an opportunity for brick-and-mortar in their refrigerated section, where they have the upper hand.

Mintel reports that the fresh perimeter is growing at 3.8%, much more than any other area, which means that shelf-stable snacks will have to yield space to their fresh counterparts as the perimeter moves inward. Products that are typically shelf stable have even broken into the fresh set—most prominently, refrigerated bars. “One product set driving growth in refrigerated is wellness bars,” says Kawa. “Compared to the growth rate of the shelf-stable wellness bars/gels segment, the refrigerated set is up double digits, up 93.6%, totaling $37.8 million in annual sales.”

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