Holistic Primary Care's

Quality Counts

A Clinician's Guide to Supplement Quality

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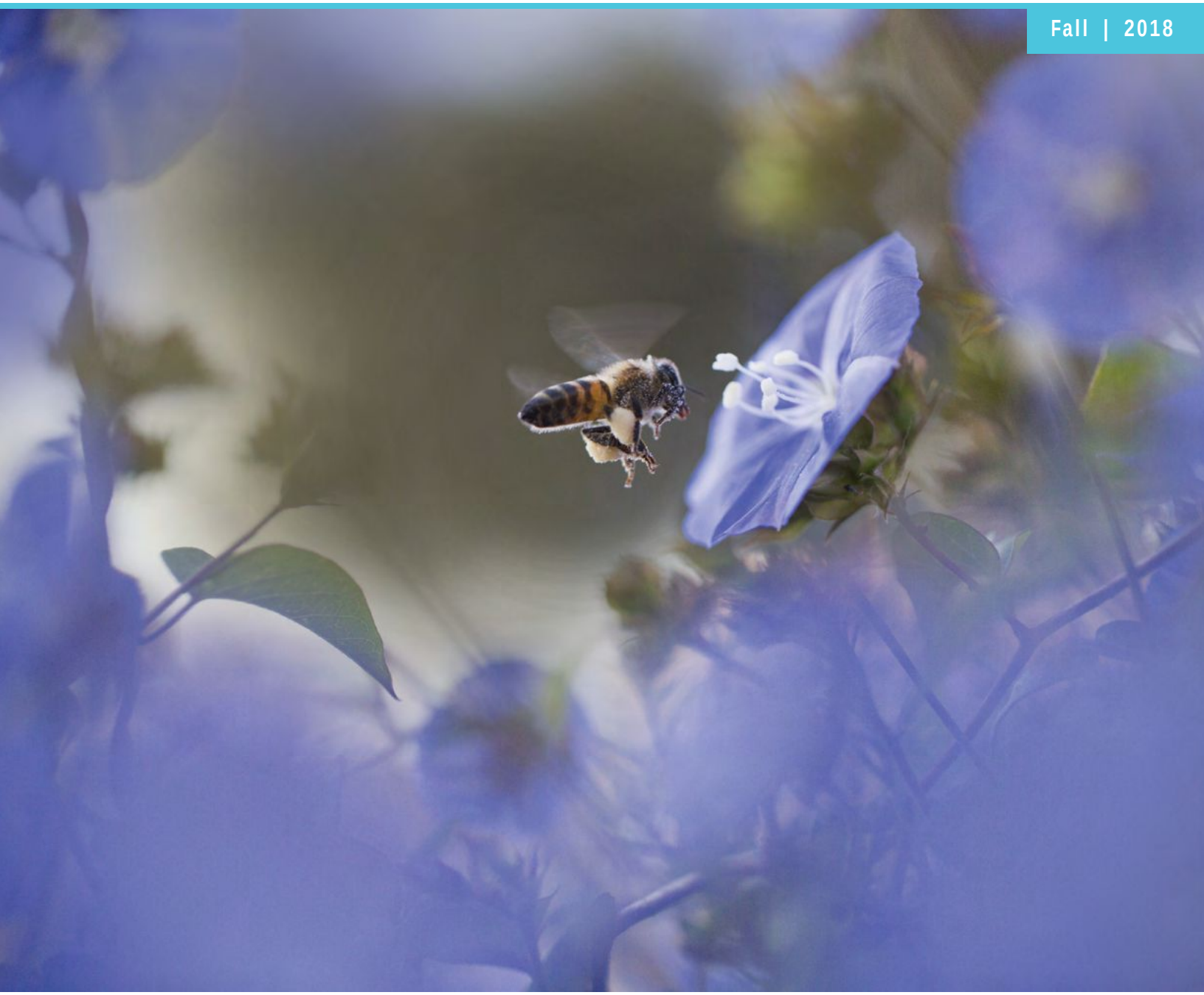

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Transparency, Truthfulness & Trust: The Cornerstones of Quality

Supplements and nutrition are no longer a "fringe" part of medicine.

By Erik Goldman | Editor in Chief

In the 12 months since we published last year's edition of *Quality Counts*, there have been many significant—and largely positive—developments that signal the maturing and mainstreaming of the dietary supplement industry, particularly its practitioner-focused segment.

It is becoming very clear that supplements and nutrition are no longer a "fringe" part of medicine. Though pharmaceutical-based strategies remain the dominant clinical toolset, nutrition-based therapies and other forms of holistic medicine are very definitely moving into the mainstream.

We see signs of this evolution in academia, at major medical centers, in the corporate sector, and in the trenches of community-based primary care.

The supplement companies that serve the holistic and functional medicine sector are also growing rapidly, and committing ever more resources to quality control, clinical research, and practitioner education.

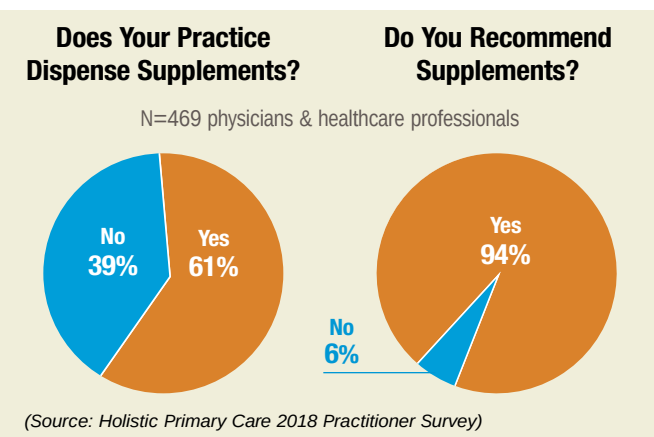
Consider the following:

- **Cleveland Clinic's expansion of its Center for Functional Medicine**: What began in October 2014 as a 2,500 square foot space with one MD, one RD, a health coach and three support staffers, is now a 17,000 square foot custom-built center with 9 MDs, 4 nurse practitioners, 5 dietitians, 3 health coaches, a 27-member support team, a waiting list of over 2,000 patients, and a robust clinical research agenda.
- **Mayo Clinic's nutraceutical research collaboration**: Four years ago, the Mayo Clinic entered into a research partnership with one of the major practitioner channel brands, Thorne Research, for a series of controlled trials on the safety and efficacy of single-ingredient and multi-ingredient nutraceutical and botanical combinations.
- **Nestlé's acquisition of Atrium Innovations**: Last December, the world's largest consumer products conglomerate purchased Atrium, a Canadian company holding several practitioner-only brands (including Pure Encapsulations, Douglas Labs, and Seroyal), as well as one of the best-selling retail brands (Garden of Life). The $2.3 billion deal puts these brands under Nestlé Health Sciences, which currently does business with 4,500 US hospitals and clinics.
- **Klaire Labs' integration of three major pro-only brands**: In a move that will create synergy, eliminate redundancy, and vastly expand global reach, Soho Floridis International (SFI) unified Prothera, Complementary Prescriptions, and Klaire Labs under a single brand. The new company has a strong commitment to product innovation, particularly in probiotics; has built a massive state-of-the-art production facility in Reno, NV, and made significant investments in clinical research.
- **Standard Process opens Nutrition Innovation Center**: The new research and education center, located at the Carolina Research Campus, Kannapolis, NC, features a public-facing "Clinic of the Future;" a center for nutrition-focused trials; a product development facility; and an education & media center. The Carolina campus fosters collaborations between academia, public agencies, and private sector.

These are just a few of the many indicators that supplements, nutrition, and holistic/functional medicine are becoming integral parts of American life—and American healthcare.

Out in the field, we see similar trends. Our 2018 practitioner survey, with responses from 469 *Holistic Primary Care* readers, indicates that 61% of respondents currently dispense supplements in their practices. That's up from around 34% in 2013.

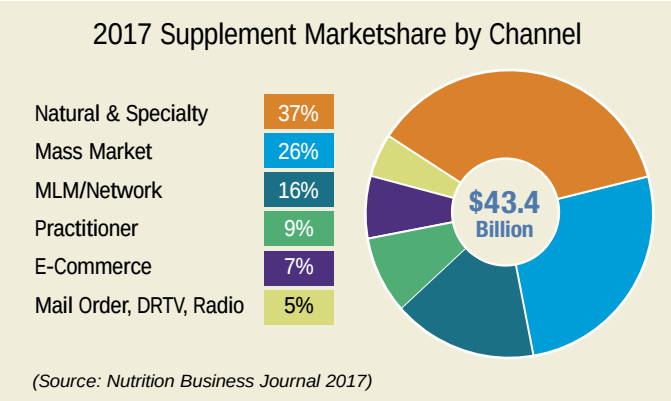
Among those who do not dispense, 94% routinely recommend supplements to their patients.



(Source: Holistic Primary Care 2018 Practitioner Survey)

While we won't posit that these figures are representative of all American physicians, there's no question that the number of doctors who discuss, recommend, or sell supplements has grown, even in conventional settings.

According to the most recent statistics from *Nutrition Business Journal*, supplement sales in clinical settings generated $3.9 billion in revenue in 2017, and currently represent 9% of the entire $43.4 billion US supplement market. Annual growth in practitioner sales outpaces growth of the industry as a whole.



Patients Want Guidance

Despite the perception that people don't listen to their doctors, consumer surveys show repeatedly that people want physician guidance when choosing supplements. The 2017 *Supplements OTC & Rx Database (SORD)* study—a biannual survey of 2,000 representative US consumers—indicates that 63% of people purchasing supplements at retail deem their physicians as a major influence on their purchase choices.

A physician recommendation is one of the strongest factors influencing the initiation of supplement use among prior non-users.

This is all the more reason that healthcare professionals need to understand the regulations governing this industry, and the ways in which ethical, committed companies ensure the quality, safety, and efficacy of their products.

"Supplements are an important part of our therapeutic interventions. We have curated the supplements that we are asking our patients to use—we've vetted the manufacturers, the specific brands and doses," said Patrick Hanaway, MD, Director of Research at the Cleveland Clinic's Center for Functional Medicine.

Dr. Hanaway noted that the Cleveland Clinic utilizes a formulary system called Vitamin Portfolio, that provides most if not all leading practitioner-only brands including Metagenics, Ortho Molecular Products, Vital Nutrients, and Pure Encapsulations.

"We tell patients, "Please don't go on Amazon and buy something that looks the same. "We've had histories of patients getting rancid Omega-3 fats, and other problems, when they try to shop online. We try to educate them."

Our surveys show a big education gap when it comes to clinician understanding of the regulations. In our 2018 survey, 46% of respondents did not recognize DSHEA—the Dietary Supplement Health and Education Act—as the main federal law governing the industry. (See *DSHEA: The Ground Rules for Dietary Supplement Regulation*, p. 6)

HPC readers certainly have quality concerns, though. The survey indicated that when considering supplement products, 75% consider "Free of Heavy Metals" to be a decisive factor, 71% cited "Free of Artificial Sweeteners," 60% cited "GMO-Free" and 56% cited "Allergen-Free" (See, "***How Do Practitioners Define Supplement Quality***" Holistic Primary Care Fall 2018, p. 12)

Ensuring quality and safety of supplements is not an easy task. The leading companies put considerable resources—money, time, and personnel—toward their QC efforts.

In addition to monitoring for the ever-present risk of microbial contaminants, pesticides, environmental toxins, and solvent residues, supplement makers must also contend with intentional, economically motivated adulteration of raw materials (See ***Eliminating Adulteration***, p. 16).

Impact of the Tariff War

Many supplement ingredients are grown or produced in China—some come almost exclusively from China. Even prior to the Trump administration's tariff war, the prices of Chinese ingredients have been increasing over the last year.

That, according to the United Natural Products Alliance (UNPA), an industry trade group, is due in part to price increases mandated by the Chinese government to offset the cost of that nation's desperately needed environmental clean-up.

Practitioner-facing supplement companies contacted by ***Holistic Primary Care*** say they are, indeed, contending with higher raw materials costs. In some cases, they're seeing price increases on up to 70% of the ingredients they use. Most struggle to hold finished product prices stable.

The potential impact of the US-China trade war is a big unknown. Earlier this summer, the Chinese government issued a list of botanicals, minerals, vitamins, and specialty ingredients—such as coenzyme Q10 (for which China is a major producer)—that could be slapped with a 10% tariff.

It's a massive game of geopolitical "chicken." At this point nobody knows how the tariffs will play out—or if they will even be enforced at all. But the threat has created great uncertainty. Manufacturers must decide whether to pre-emptively increase current supply orders at pre-tariff prices, or wait and risk a 10% increase in their fixed costs.

All of this creates a ripe environment for ingredient adulteration. It is also fostering the rapid—and some would say disturbing—rise in the use of synthetic biology to produce ingredients for foods and supplements.

International trade battles are only part of the problem, though. And the challenges are not limited to ingredients from China. As herbal medicine expert, Roy Upton pointed out in last year's ***Quality Counts***, Chinese companies produce some of the finest raw materials in the world, and they also produce some of the worst. It all depends on what manufacturers are willing to buy.

DSHEA gives federal agencies clear and far-reaching authority over supplement makers. But while it provides basic ground rules, DSHEA has many gray areas and contradictions, and enforcement has been spotty. The regulatory framework is far from fail-safe, foolproof, or first-rate.

Addressing Quality Gaps

While many supplement companies—especially those in the practitioner channel—hold themselves to impeccable quality standards, unfortunately, others do not.

A widely cited chemical analysis published last Fall by hepatologist Victor J. Navarro, in collaboration with Ikhlas Khan at the University of Mississippi's National Center for Natural Products Research, showed that 56% of a group of 229 off-the-shelf herbal or nutritional products were in some way mislabeled.

This research team included a number of scientists with strong expertise in botanical medicine and natural products, and they used well-established analytical methods. Some products studied simply did not contain the amounts of ingredients listed on their labels; others contained non-labeled ingredients. Some contained compounds linked to liver injury (Navarro VJ, et al. Hepatology. 2017: 65(1): 363-373.)

These are troubling findings, and they underscore the fact that while there are very definitely federal laws regulating the supplement industry, they are not evenly or thoroughly enforced, and there are a lot of holes through which poor quality products enter the market.

DSHEA gives federal agencies clear and far-reaching authority over supplement makers. But while it provides basic ground rules, DSHEA has many gray areas and contradictions, and enforcement has been spotty. In short, the current regulatory framework is far from fail-safe, foolproof, or first-rate.

Fortunately, industry organizations and federal regulatory agencies are starting to collaborate more closely to remedy the situation. There have been a number of noteworthy initiatives over the last year:

- **The Food Safety Modernization Act (FSMA)**: This federal regulation requires food and supplement manufacturers to be wholly accountable for their entire supply chains. FSMA—the largest change in food regs in 70 years—moves quality assurance "upstream" to the raw materials suppliers. A company importing raw materials from outside the US must ensure these ingredients meet US food safety standards. The Act has strong buy-in from all major supplement trade groups, some of which are training member companies in FSMA compliance. FDA is already conducting FSMA inspections, and that will intensify in the coming years.
- **American Botanical Council's Botanical Adulterants Prevention Program**: One of the big problems in the herbal industry is that even if one company returns a batch of raw materials because of adulteration, the stuff can still end up on the market because the supplier will simply sell it to someone else at a discount. The American Botanical Council, one of the nation's preeminent herbal medicine groups, is spearheading an effort to stop this, by getting herbal companies to insist on contracts with their suppliers that mandate complete destruction of adulterated or irreparably defective materials—at the supplier's cost (see p. 17)
- **American Herbal Products Association's Good Agriculture & Collection Practices initiative**: In the last year, AHPA—the other major herbal medicine trade organization—issued a comprehensive guidance document setting new—and high—standards for all aspects of the cultivation, harvesting, and processing of medicinal herbs and other plant-based ingredients. AHPA has also developed a set of assessment tools to help manufacturers evaluate their suppliers and ensure they are adhering to strict quality standards.
- **NSF International's "DNA Authenticated" Mark for Supplement Ingredients**: Earlier this year, NSF—one of the world's leaders in science-based public health standards—launched a DNA-based raw materials verification program that utilizes next-generation sequencing techniques, and is backed by NSF's extensive genome database of plants, fungi, and probiotic bacteria used in food and supplement products.
- **Clean Label Project's Protein Powder Monitoring Study**: This independent, non-profit consumer group rates multiple product categories using state-of-the-art analytical methods to identify best- and worst-in-class based on product authenticity and labeling transparency. The group's most recent effort tested 134 protein powders from 52 brands, and found that many of them—including some that are "USDA certified organic"—contain heavy metals, bisphenol-A, and other toxins.

- **Council for Responsible Nutrition's Supplement OWL Project Shows Rapid Growth**: In the year since launching it's Online Wellness Library of supplement product labels, CRN has garnered participation from 89 major brands, and has now catalogued nearly 11,000 individual product labels. The goal is to foster quality and transparency by giving responsible companies a registry in which to publish their product labels, certificates of analysis, and supply chain verifications in a database freely accessible to regulators, attorneys, practitioners, and the general public.

As you'll learn in the following pages, many individual companies are going to great lengths and investing tremendous resources to ensure that you and your patients have access to innovative, impeccably manufactured, and highly effective nutraceuticals.

Quality assurance is no easy feat—even in mature industries like the highly-regulated pharmaceutical sector. Lapses in drug quality are all too common, as are recalls and FDA disciplinary actions. It is even more challenging for a relatively young industry that, despite its meteoric growth, is still dwarfed economically by pharma.

While longstanding changes remain—and new ones are emerging—the general trends suggest a strong and concerted movement toward greater truthfulness and transparency, science-guided innovation, and improved product quality.

As a clinician, you have an important role to play in holding supplement companies accountable. Don't be afraid to engage with them, and to ask tough questions. The good ones have nothing to hide. In fact, they welcome your inquiries.

We hope you find this 2018 edition of ***Quality Counts*** to be useful in your efforts to understand this extremely diverse and dynamic industry. **QC**

DSHEA: The Ground Rules For Dietary Supplement Regulation

The oft-heard claim that the supplement industry is "unregulated" is patently untrue. And it does not become any truer by its being repeated over and over again by the industry's critics.

In fact, the industry is very definitely regulated, though it is a far from perfect or fail-safe system.

It is important for clinicians who recommend or dispense supplements to understand the basics of supplement regulations, and the agencies that oversee the industry.

The Dietary Supplement Health and Education Act (DSHEA) of 1994 sets the ground rules for the manufacture and marketing of supplement products. It establishes good manufacturing procedures (GMPs), labeling requirements, and rules about permissible product claims, and it delineates enforcement jurisdiction for the Food and Drug Administration, and the Federal Trade Commission.

DSHEA sets ground rules for the manufacture and marketing of supplement products. Though DSHEA has no direct bearing on clinicians or medical practice, it greatly affects how supplement makers interact with the healthcare community.

DSHEA defines dietary supplements as a distinct and unique product category. Technically, they are considered to be "foods" as distinct from drugs. Supplements cannot be sold as substitutes for conventional foods, as meal replacements, or as therapies for specific diseases. Legal claims are strictly limited, and must be accompanied by a disclaimer that the product has not been pre-approved by the FDA.

Under the law, a supplement is, *"an ingestible product intended to supplement the diet, that bears or contains one or more of the following: a vitamin, a mineral, an herb or other botanical, an amino acid, a dietary substance for use to supplement the diet by increasing the total dietary intake, or a concentrate, metabolite, constituent, extract, or combination of any of the aforementioned ingredients."*

The Role of FDA & FTC

DSHEA gives FDA, FTC and other agencies broad powers to identify, investigate, and prosecute unsafe products, fraudulent or inappropriate claims, and unethical promotional tactics. Over the years, these agencies have proven quite capable of decisive action.

That said, enforcement has been inconsistent, in part due to meager budgets and limited federal personnel.

For fiscal year 2017, the FDA's Office of Dietary Supplements (ODS) had a working budget of about $4.3 million—half of what industry trade groups believe it needs. Given the Trump administration's anti-regulatory inclination, oversight could get even spottier.

Enforcement is also confounded by the sheer diversity of the supplement world.

DSHEA applies to everything from basic "letter" vitamins and minerals, through omega-3s, probiotics, enzymes, medicinal mushrooms, "specialty" nutrients (things like co-enzyme Q10 and N-acetyl cysteine), and a vast ecosystem of botanicals. Practically, these have little in common beyond being ingestible and not, strictly speaking, pharmaceuticals.

Many people erroneously count homeopathics as "supplements" since they're sold in the same retail outlets. But they are actually defined and regulated as a distinct subcategory of drugs.

Likewise, some people are confused about the distinction between dietary supplements and medical foods. The latter, according to federal law is a distinct regulatory category.

It is defined under the Orphan Drug act as, "a food which is formulated to be consumed or administered enterically under the supervision of a physician, and which is intended for the specific dietary management of a disease or condition for which distinctive nutritional requirements, based on recognized scientific principles, are established by medical evaluation."

Think specialized formulas for children with phenylketonuria.

Protein powders, meal replacement products or other specialized "functional" foods sold or recommended by physicians are not, *de facto*, medical foods. Over the years, the FDA has taken action against companies that promote them as such.

Though DSHEA has no direct bearing on clinicians or on medical practice, it greatly affects how supplement makers interact with the healthcare community.

Here are some important considerations:

Good Manufacturing Practices (GMPs): From the get-go, DSHEA authorized the FDA to issue GMP guidelines covering everything from production procedures through handling of consumer complaints.

But it was not until 2007 that the agency delivered final rules. That

delay was due to political opposition. As reported in ***Natural Products Insider***, Peter Barton Hutt, ex-general counsel of FDA, claims that David Kessler—the FDA commissioner at the time—"was so infuriated by the enactment of DSHEA that he ordered FDA not to enforce the new law….he was convinced if the law was not enforced and the worst elements of the DS industry were allowed to run wild, Congress would repeal the law. Of course, that didn't occur."

This means that from 1994 to 2007, supplement makers were operating without clear guidance on what was expected of them. For much of the last decade, ethical brands have been working to comply. Many have gone beyond supplement GMPs and now manufacture to pharmaceutical standards.

For practical purposes, GMPs are a starting point, not a guarantee of optimal quality. The rules define quality as "consistently meeting established specifications for identity, purity, strength and composition and limits on contaminants," but they allow each company to define its own "established specifications."

As Michael Levin, an experienced nutraceutical industry consultant puts it: "Think of current GMPs like speed limits on the road: compliance doesn't guarantee optimal safety, but non-compliance is a strong indicator of recklessness."

Currently, GMPs apply only to finished products, not raw materials. Yet the quality of a final product is heavily dependent on the quality of its ingredients. Tainted, contaminated, or intentionally spiked raw materials are far too common, as many industry experts point out. To remedy this, the Food Safety Modernization Act (FSMA)—signed in 2011 and currently being implemented—will pressure ingredient suppliers to adopt GMPs.

New Dietary Ingredient (NDI) Notifications: Under DSHEA, a brand wishing to introduce a new ingredient or novel combination must first notify the FDA, then wait 75 days while the agency reviews whether the ingredient or formula meets the definitions of "supplement," and is supported by enough data to establish a "reasonable expectation" of identity and safety.

FDA defines "new dietary ingredient" as anything not marketed in the US as a supplement prior to October 15, 1994. In theory, this means all ingredients in common use prior to that date are grandfathered.

The concept is reasonable. But since there was no official definition of "dietary supplement" prior to 1994, it can be hard to prove something was in use, pre-DSHEA. FDA's guidance on what it considers "new" is in flux. Old ingredients could be reclassified as "new"—and subject to costly review—if any aspect of a formulation changes.

In practice, both federal enforcement and industry compliance with NDI requirements have been slack. Implementation of the NDI system remains one of FDA's biggest challenges.

Labeling Issues: DSHEA established clear rules for supplement labels, which by law must display: a "Supplement Facts" panel stating key ingredients; a list of other ingredients in order of predominance; net quantity of contents (eg, "60 capsules"); the standard disclaimer stating the product quantity of contents (eg, "60 capsules"); the standard disclaimer stating the product is not intended for prevention or treatment of disease; directions for use; serving size; the name(s) and place(s) of business of the manufacturer, packer, or distributor.

Last year, FDA mandated major changes to the regulations for supplement (and other food) labels—the first significant changes in decades (See, *FDA Mandates Major Overhaul of Supplement Labels*, HPC Spring 2018). Some of these changes—elimination of the International Unit and recalculation of Folate quantities, for example—have clinical significance.

Full compliance and implementation is expected by 2020, but already many companies are working to revise their labels and, in some cases, reformulate their products to be in compliance.

Structure/Function vs Disease Claims: Prior to DSHEA, vitamin companies could not make any health claims. They were essentially prohibited from advertising altogether. DSHEA changed that, giving them the right to market, but limiting them to so-called structure/function (S/F) or basic nutrient claims.

Supplement brands cannot claim their products prevent, treat, or ameliorate diseases, health conditions, or surrogate disease markers—even if there is solid evidence that they do.

Claims can only be cast in terms of supporting healthy anatomy, improving physiologic functions, or providing specific nutrient levels.

This does not mean it is illegal to use supplements to prevent or treat disease. People—and practitioners—do so all the time. It is simply illegal for companies to communicate product benefits using disease language. Doing so automatically makes a product a "drug."

Under the law, it is the manufacturer's intended use—more so than a product's essential nature—that defines whether it is a "drug" or not.

Structure/function claims must be scientifically supported. FDA has jurisdiction over the truthfulness of structure/function claims on product labels, packaging, marketing materials, websites, and social media; FTC enforces truthfulness in advertising. Both agencies can—and often do—take action against companies with inaccurate labels and/or fraudulent claims.

Practitioner-only vs Consumer Brands: DSHEA creates special challenges for practitioner-only brands because it prohibits them from speaking medical language. In a clinical context, structure/function terms sound vague and imprecise, leading to furtive communication, as marketers try to convey the utility of their products without crossing into overt disease claims.

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Many industry leaders believe this is actually a public health issue. Structure/function restrictions impede truthful, non-misleading medical dialog between manufacturers and practitioners. Some attorneys specializing in supplement regulation believe practitioner-exclusive brands should have greater latitude, since practitioners serve as "learned intermediaries" between marketers and consumers.

The federal government makes no such distinction. Neither the FDA nor the FTC recognizes any difference between "practitioner" and "consumer" brands. All are equally subject to DSHEA.

So are practitioners who choose to work with contract manufactures to create their own private-label brands, a fact that some clinicians overlook.

Research Limitations: Because it prohibits supplement companies from making disease claims, DSHEA unintentionally discourages clinical research. In the pharmaceutical world, data can be transmuted into clear disease claims, ironclad patent protections, and ultimately, massive profit. Consequently, drug companies have strong incentive to fund large-scale clinical trials.

Supplement brands have no such incentive. They cannot use data to support treatment claims, and since supplements have lower prices and lower profit margins than drugs, companies have a harder time recouping research investments.

DSHEA actually makes it difficult to do supplement trials. A clinical study by definition involves ill people. Thus, a company-funded trial in a clinical setting runs dangerously close to disease-claim territory. On the structure/function side, it can be difficult to prove a meaningful effect in a cohort of healthy people.

There are certainly studies that show supplements have medically relevant benefits. But most are epidemiological correlations, biomarker studies, animal or cell culture experiments, or other indirect indicators. Prospective clinical trials are typically done outside the US, and seldom with off-shelf formulations.

In short, the regulations do little to foster the "gold standard" RCT research that clinicians—and regulators—want most. There's also the problem of "borrowed" science, where companies support their products by citing research done with similar though not identical ingredients. This is common practice in the industry, one that further discourages investment in original clinical research. **QC**

Is the Time Right to Revise DSHEA?

The Dietary Supplement Health and Education Act (DSHEA) has certainly had its share of critics over the 25 years since it became law.

Some contend the regulation is weak, and that it gives the supplement industry too much latitude, while providing too little consumer protection.

On the other side, many argue that the law puts a stranglehold on truthful communication about supplements, and that it creates disincentives for the type of clinical research that would advance nutritional medicine (See ***DSHEA: The Ground Rules for Supplement Regulation*** p. 6) .

To date, however, there has been little motivation from either side to push for major revision of the landmark law. Supplement industry leaders have preferred to leave well enough alone, accepting the restrictions imposed by DSHEA's structure-function claims language in exchange for freedom to market their products without FDA pre-approval.

Even the industry's most vehement critics in Congress have opted to leave DSHEA alone, partly because supplements are immensely popular, but also because regulating this industry—or any industry, for that matter—is a low priority on today's political ledger.

But all this could change in the coming years.

As supplements move from the margins to the mainstream, supplement makers are beginning to chafe at the limitations imposed by DSHEA. They want to be able to prove the benefits of their products through larger clinical trials, and they want to be able to communicate the data in clear, unambiguous language that practitioners—and administrators—understand.

Changing Attitudes

At this year's NBJ Summit, an annual gathering of several hundred nutrition industry executives, 70% of those polled said they believe the time is now right to open DSHEA for revision, with the objective of winning greater freedom to make meaningful science-backed claims.

This represents a significant change in attitude. Just a few years ago, the prevailing sentiment was that DSHEA was best left untouched, and that any attempt to revise it would subject the industry to unwanted scrutiny and ultimately play into the hands of a pharma industry bent on squelching supplements.

But over the last five years or so, there has been a gradual convergence between the supplement and pharmaceutical industries, as the former matures and the latter seeks new markets in the post-blockbuster era.

"We don't see the same antagonism coming from Big Pharma now as we did when DSHEA was passed," said Joanne M. Gray, a partner at Goodwin, a corporate law firm doing a lot of work in the supplement, OTC, and pharmaceutical industries. "They (pharma companies) are much more accepting of the science, and much more active in the (supplement) industry themselves."

Speaking at the NBJ Summit, Gray said she sees a new alignment of financial and scientific interests between pharma and nutra. Both industries are slowly discovering common ground.

"Pharma is no longer always saying that supplement companies are putting out unproven products with bad claims in violation of FDA law. Instead, they are starting to buy those companies," says Gray. "For Big Pharma, the patents are running out, the easy molecules have all been discovered. It is much harder to get a product out on the market. And even when you do, because of personalized medicine nowadays, you don't get 20 million people on it. You get smaller subsets."

The supplement industry, with its wide spectrum of ingredients, entrepreneurial spirit, and massive consumer base, is suddenly becoming attractive to pharma.

Converging Interests

Jennifer Cooper, a research & development consultant who has worked on over 300 product launches for pharma, OTC, and supplement companies, also sees a gradual softening of the historic animosity between the two industries.

"It's not nobility, necessarily. It's that the financial interests are more aligned now than ever before. There's a natural overlap (for supplements) in consumer healthcare and OTC. And there's $17 billion worth of drugs coming off patent on the Rx side in the next 8 years. They (pharma companies) are shopping for replacements for that. The gaps may not be filled with Rx products. And they certainly won't be the blockbusters that we are used to."

Pharma is strongly driven by capital markets, and investors scrutinize the R&D pipelines closely. These days, those pipelines are looking mighty dry.

The convergence between pharma, nutra and OTC actually began in the mid-1990s, when several drug companies including American Home Products and Pfizer acquired or launched supplement lines.

In general, though, the industries remained quite separate and relations between them were cool at best.

Beginning around 2012, acquisitions began to speed up: Procter & Gamble acquired New Chapter; Pfizer purchased Alacer (maker of the wildly popular Emergen-C brand); Reckitt Benckiser outbid Bayer for Schiff. More recently, Reckitt Benckiser acquired Mead Johnson Nutrition for a cool $17.9 billion.

Over the last few months, Archer Daniels Midland acquired UK-based Probiotics International for roughly $243.2 million. In March, consumer products giant, Clorox—which acquired the RenewLife line of digestive health supplements in 2016—announced the purchase of Nutranext, owner of the Rainbow Light and NeoCell brands.

Most relevant to healthcare professionals, last December, Nestlé Health Sciences purchased the Atrium Innovations portfolio of companies (including Pure Encapsulations, Douglas Labs, and Seroyal) for $2.3 billion.

Industry watchers say more pharma-nutra acquisition deals are on the horizon, and that the Rx and OTC industries may soon become valuable allies in constructively reshaping supplement regulations.

Allies for Regulatory Change?

Two-thirds of the attendees polled at NBJ believe greater pharma involvement in the supplement space will ultimately lead to positive regulatory change.

"One of the push-backs to regulatory reform has been that pharma has not wanted supplement companies to make any kind of claims besides structure/function claims, even if the claims are true. Because pharma didn't want to have their profits stepped on," Gray said.

"But as pharma companies are buying more supplement companies, they are starting to say, "Hey, let's back off on that, because we're basically eating our own children!""

Reframing Research Incentives

One need not be a regulatory expert to understand how DSHEA discourages supplement brands from funding clinical research: it prohibits them from using disease treatment or prevention studies to promote their products.

"This is where a change in the regulatory environment can really help us," said Ms. Cooper, who is chief science officer for Savant Science, an R&D consulting firm. "We're at a disadvantage, even if we want to spend good money on good clinical studies, because of the limitations of S/F claims. It's really hard to make well people more well."

When it comes to disease prevention studies, Gray sees DSHEA as essentially a gag rule. "We can fund them (clinical studies), we can run them, but we can't say what the results are, we can't use them in our marketing. We can't take those studies and convert them into helping the health of America. Who's going to run a study if they cannot use the results to sell their products?"

Reversing Side Effects: A Leverage Point

There are several types of supplements—probiotics, for example—that might help reverse the negative impact of things like antibiotic drugs or intensive cancer chemotherapies.

Under DSHEA, side effects are considered a form of disease, and therefore "amelioration of side effects" is not an allowed claim—even if there's good evidence to support it.

Gray believes the industry could make a fairly strong case for a regulatory status change on this particular issue.

"Pharma is not going to push back on us for that, because they want people to be able to continue the drugs. People go off their drugs—particularly the serious chemotherapeutic agents because they're having horrible side effects. And they get far less effective treatment, far fewer cures. So we can place ourselves in adjuvant therapy, allowing people to complete their treatments. That, to me, is a match between personalized medicine and personalized nutrition. It could help us push the regulatory status in terms of what we can say."

What a revised version of DSHEA would look like is anybody's guess, at this point. Some in the industry would like to see major revision. Others are more cautious, and would prefer to push for greater claims latitude by other legislative means.

Focus on the Farm Bill

Loren Israelsen, executive director of the United Natural Products Alliance, was among the architects of DSHEA. He worked closely with the bill's principle sponsors—Sen. Tom Harkin (D-IA) and Sen. Orrin Hatch (R-UT)—to balance the public's demand for wider access to vitamins and herbs, with the FDA's consumer protection imperative, and the pharma industry's desire to keep disease claims exclusive to FDA-approved drugs.

While encouraging the industry's desire for regulatory change, Israelsen urged caution. The political situation now is quite different from that of 1994.

Aside from the general madness of partisan politics these days, the industry's two main champions—Harkin and Hatch—are out of the

Holistic Practitioners Weigh in on DSHEA

Holistic Primary Care's 2018 practitioner survey indicates that nearly half of our 469 respondents do not even know what DSHEA is.

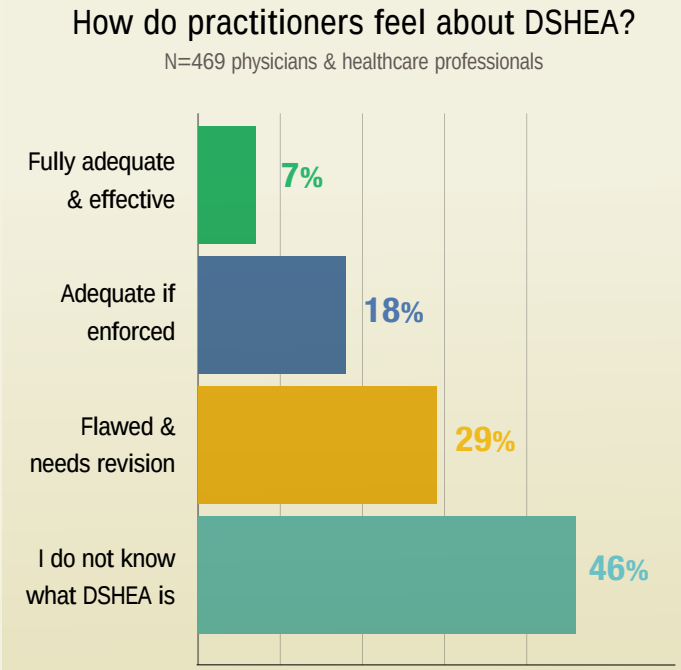
That's down from 57% in our 2016 survey, indicating a gradually increasing awareness of the law. But it's still a surprising finding given that 61% of respondents dispense supplements in their practices, and 94% of those who don't dispense are recommending supplements to their patients.

Among those who are familiar with DSHEA, there's a strong sense that the regulations need revision.

- Only 7% believe DSHEA is fully adequate and effective to protect public safety.
- 18% believe the law would be adequate if properly enforced
- 29% believe the law is fundamentally flawed and in need of major revision, up from 19% two years ago.

The verbatim comments reflect an ambivalence felt by many holistic and functional medicine practitioners: on the one hand they're concerned about malfeasance and fraud on the part of the supplement industry, while on the other they fear that the FDA is a puppet of Big Pharma bent on thwarting non-Rx alternatives.

"I have major concerns that DSHEA can be usurped by pharma companies to drive non-pharm options out of existence. On the other hand, proven lack of ingredients listed on supplement labels proves that current oversight and accountability is inadequate," wrote one survey respondent.



(Source: Holistic Primary Care's 2018 Practitioner Survey)

Another points out: "Some claims are outrageous. At the same time, they sometimes inappropriately go after small producers. FDA/FTC are understaffed."

As with so many federal regulations, the question around DSHEA really comes down to: Who is it intended to serve?

"DSHEA is good but imperfect," wrote one clinician. "However, modifications are likely to make it have greater constraints dictated by the Pharma industry, not primarily about public health." **QC**

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game. Harkin retired five years ago, and Hatch will end his long senatorial tenure this year.

"Do we have the political champions to lead a "DSHEA 2.0" initiative? The answer is No," Israelsen said. The industry's list of congressional friends is short. Without strong legislative allies, any attempt to revise DSHEA will be futile at best, dangerous at worst.

Rather than rewriting DSHEA, Israelsen believes it would be wiser to concentrate on putting new "food as medicine" provisions into the next Farm Bill.

The Farm Bill must be reauthorized every 5 years. Each time it comes up, there are opportunities to address a host of issues related to agriculture, nutrition, and health—as evidenced by inclusion of language legalizing industrial hemp—and potentially hemp-derived substances like CBD—in the 2018 bill.

The Farm Bill comes due for renewal again in 2023.

"We have 5 years to think through what we would like to see as far as supplements and nutrition-based healthcare in the 2023 Farm Bill," says Israelsen. "I believe we can achieve much of what we want as far as a "DSHEA 2.0" through a food as medicine model."

There were few, if any, medical voices involved in the development of DSHEA.

That made sense back in 1994: Only a small percentage of practitioners used supplements and herbs back then, and most were trying to stay ***out*** of the spotlight for fear of disciplinary action.

Today, the landscape is completely different. Many practitioners recommend or dispense supplements, and many of the nation's leading medical centers have integrative or functional medicine departments where supplements are part of the therapeutic tool box.

Holistic physicians will be affected by any future changes to supplement regulations; they ought to have a place at the table and a voice in the dialog. **QC**

With Its *TruQuality* Program, Metagenics Ups the Ante on Transparency

These days, "transparency" is a hot term in the natural products industry. Manufacturers recognize that health conscious people want to know as much as possible about the foods and supplements they buy.

Consequently, many supplement and nutrition companies now make claims about their transparency and their products' traceability. Few, however, publish complete, regularly updated data from their quality analysis testing for all the world to see.

This year, Metagenics—one of the top three practitioner-channel brands—has taken that step, with its new ***TruQuality*** program.

The initiative provides practitioners, patients, and basically anyone with an internet connection, full access to the data from all analytical tests performed on every lot of Metagenics' products going back for 2 years.

"This is 100% transparency," says Brent Eck, Metagenics CEO.

Any interested party will be able to see all tests and all parameters for all of the company's roughly 300 different products. For each formula, the ***TruQuality*** website lists results for every quality assurance measurement, along with reference standards for each test, allowing viewers to see how Metagenics' results stack up against accepted and validated standards.

The analytic data are fed directly from Metagenics' in-house quality control laboratory, without filtering from the executive or marketing departments, and the list is exhaustive. Each product lot is put through literally dozens of tests, including a thorough microbial analysis, tests for various heavy metals, pesticides, solvent residues, environmental contaminants, and common allergens including gluten.

If you're going to say that your products are better than mine, that your products are made to higher quality levels, then prove it by putting all your test data out there."

–Brent Eck, Metagenics CEO

Trust, But Verify

"We test every product extensively, and we've always done everything we could do. I believe we do all the appropriate and validated tests. If there's something we're not doing that we should be doing, please tell us," Eck told ***Holistic Primary Care***.

Metagenics employs 33 people in its Quality Assurance and Quality Control teams. The motto, "Trust But Verify" is the guiding principle, says Steve Sheppard, Senior Manager of QA/QC.

Sheppard, who has been with the company for 18 years and previously worked in the medical device industry, says Metagenics is extremely diligent in vetting raw materials.

"We put a ton of effort up front, working with raw materials suppliers, so we have a really strong understanding of what they're providing us. We don't just approve a supplier by itself. We approve a supplier and their manufacturing method in combination. We want full documentation on how they manufacture, so we understand how the raw materials are processed, and all the sub ingredients, processing aids…any info on allergenicity, or possible contaminants.

"Then, once we gather all this info—which includes GMO status and gluten contamination--we begin a full testing regime on the samples that they submit. And that's before we bring anything into our doors."

Reflecting on Metagenics' exacting standards, Eck added: "We are not easy to work with. We test a lot. We require three batch samples for testing before we'll even consider buying an ingredient."

But he believes such diligence is absolutely necessary to ensure the quality of the company's output.

In addition to its own in-house testing, Metagenics also has its finished products independently tested by 3rd party labs.

"We send the products—without labels—to 3rd party labs for analysis. They report back to us what they see in the products, and we label based on what these 3rd party analyses tell us, not on what we tell them," Eck explained.

The company leaders are also great believers in 3rd party certifications—such as GMO-Free and Gluten-Free—from independent organizations.

External Audits

It's a substantial investment. Eck said it took more than two years to obtain a Certified Gluten-Free seal because the certifying agency—the Gluten-Free Certification Organization, run by the Gluten Intolerance Group of North America—had to audit not only all of Metagenics' final products, but all of the company's raw materials suppliers as well, at Metagenics' expense.

Beyond that, says Sheppard, Metagenics is constantly doing in-house testing for gluten content using ELISA tests.

"I think that the FDA says it has to be less than 20 ppm to be called gluten free. GFCO says 10 ppm and that's what we aim for."

Sheppard says going several steps beyond federal safety standards is the norm at Metagenics. "From an FDA regulatory standpoint, companies are supposed to manufacture to a certain standard, but the FDA doesn't give you a "thumbs up" seal. So you don't know when was the last time FDA visited a company. With multiple third party certifications, we are being reviewed all the time. They tell us where we perform well, and where we can improve. It really drives this culture of continued process improvement."

He added that Metagenics meets or exceeds standards set by the NSF, the US Pharmacopeia, and Australia's notoriously stringent Therapeutic Goods Association.

The company's products are currently under review for certification by the Non-GMO Project. Sheppard says it is a very rigorous assessment, and it is all the more challenging because for some supplement ingredients, the bulk of what's in the supply chain is genetically modified in some way.

"We have to go all the way to the source of the material, even if it is an animal derived ingredient. We have to look at the animals' feed. Several of our products have been reviewed. We have a calcium-based product that comes from a microcrystalline hydroxylapetite. It is animal-derived, and we were able to get that non-GMO certified. We're fairly proud of that, because it is a hard thing to find.

We continue to focus on that, and we will bring out more and more products that are certified non-GMO."

Continuous Process Improvement

The production of probiotics is another key concern for Sheppard and his QA/QC team.

"We put quite a bit of effort into evaluating our probiotics, and making sure the viable count is maintained throughout the shelf life of the product. We make sure during the entire process that we keep the probiotics under as friendly environmental conditions as possible. They're manufactured under low humidity, low temperature conditions, to make sure we don't impact the viability of the organisms. We test for the activity, the viable counts on receipt of the materials at our facility, then we monitor the conditions during manufacture, and then we test them prior to release of final products, to ensure that will sustain the label claim over time."

It's a complex process, Sheppard explained. Some species are inherently hardier than others, and long-term viability is influenced by delivery form (capsules versus tablets versus liquid suspensions). Further, interactions between different organisms in a multi-strain formula can also affect shelf-life. There are many variables, and they all need to be measured and controlled.

As the supplement industry grows and matures, so do the analytical testing technologies and methodologies. Sheppard says his company routinely invests in increasing its internal testing capabilities. A recent focus is on liquid chromatography coupled with mass spectrometry (LC/MS), "to test microquantities of different actives within formulas."

Like many supplement companies, the Metagenics team is also evaluating the potential of DNA-based methods for verifying the identity of botanical ingredients. Sheppard believes that ultimately, the combination of high-performance thin-layer chromatography (HPTLC) and DNA analysis will prove to be the best method for herbal verification.

A Challenge to the Industry

In baring all of its analytical data, Metagenics is, no doubt, opening itself to criticism. Some people might take issue with the minute barely-detectable amounts of lead or other metals—all at levels far below federal safety standards—that show up on testing.

Eck says this is inevitable, especially with botanical ingredients grown outdoors. "No herbs are going to be 100% free of metals. You simply cannot get all of it out 100%. Anybody who says they can is lying. The key is to ensure your ingredients are well below the safety limits."

With the TruQuality program, Eck says he's throwing down the gauntlet to other leading supplement makers, challenging them to be equally transparent about their analytics and their product quality.

As much as the ***TruQuality*** information is intended to be useful to practitioners and patients, he also sees it as a step toward ending the rancorous infighting that occurs within the industry; each brand trumpeting its claims about quality and transparency while offering little meaningful data to support the assertions.

"If you're going to say that your products are better than mine, that your products are made to higher quality levels, then prove it by putting all your test data out there."

He and his colleagues hope that 100% transparency on analytic testing and quality validation will eventually become the norm across the industry, and especially among practitioner-focused brands. **QC**

Supplement Makers Take Action To Reduce Environmental Impact

By Kristen Schepker | Assistant Editor

From the staggering levels of plastics in rivers and oceans to the millions of tons of garbage that wind up in landfills, to the continuing surge of air, water, and soil-borne pollutants, the environmental impact of our industrialized lives is getting harder to escape.

Healthcare—with its reliance on single-use disposables—is one of the world's biggest polluters. And the natural products and dietary supplements industries—despite their "clean, green, and healthy" values—do contribute to the deluge of trash and pollution.

Fortunately, eco-conscious shoppers are seeking items that do less harm, and companies in the natural products sector are responding in kind. Among the brands leading the charge toward ecological sustainability are several practitioner-focused supplement companies, including:

- ***Klaire Labs:*** The Reno-based company has embraced a "Source to Patient" model across its complete line of over 350 products. "Every aspect of how the original raw materials are sourced, harvested and processed must be rigorously monitored," said Nigel Pollard, CEO of Soho Floridis International (SFI), Klaire's parent company. "There's a lot of upstream scrutiny. We use organic as much as possible." SFI is also innovating in its formulations to eliminate as many excipients (fillers, binding agents, flow enhancers, colors, etc) as possible. For example, SFI's KeenMind product for cognitive support, went from 8 excipients to just 2. The company also tries to maximize dose per capsule across all its products. More intelligent formulation means more efficient use of raw materials.
- ***Blackmores:*** The best-selling supplement brand in Australia, and parent of the Bioceuticals practitioner line, adopted a "closed loop" packaging process in 2014 that has cut more than 60 tons of cardboard and plastic from the company's waste stream, and diverted 69% of its onsite waste from landfills to recovery systems. Blackmores has a dedicated sustainability team responsible for cutting carbon emissions, minimizing water waste, and improving supply chain sustainability. Oh, and let's not forget the bees. The company hosts a hive of stingless bees that pollinate extensive wildflower gardens at Blackmores' main headquarters.
- ***Nordic Naturals:*** A leading fish oil brand in both the consumer and practitioner channels, Nordic Naturals obtains its oils only from non-endangered wild fish (Arctic cod, anchovies, sardines) from sustainably managed fisheries. Nordic avoids farmed fish owing to the negative impact of aquaculture on marine environments. The company's main facility in Tromso, Norway runs on biofuels extracted from leftover fish fat byproducts. Its US headquarters in Watsonville, CA, is LEED (Leadership in Energy & Environmental Design) certified, and has reduced water use by 50% since 2011. All of Nordic's bottles and packages are 100% recyclable.
- ***Metagenics:*** also has a company-wide environmental commitment that includes a LEED certified building; a Zero Water Footprint (all water used at it's Gig Harbor facility is treated and purified before being returned to the Puget Sound; and an extensive recycling program that eliminates 38 tons of waste per year, including 19 tons of cardboard. In 2014, Metagenics won the Washington State Recycling Association's "Recycler of the Year" award. The company uses recyclable glass bottles and recycled paper packaging as much as possible. "We do everything we can to empower sustainability," says CEO Brent Eck.

Making a successful switch from traditional plastic containers to recyclable or biodegradable ones can be tricky, and requires several key considerations.

The Packaging Paradox

Supplement containers must protect and maintain the freshness and integrity of products that often contain easily degradable compounds. Shielding from UV light, moisture, and microorganisms is essential. From manufacture to delivery, the products must also withstand many changes in environment.

Generally, supplements are packaged in plastic or, ideally, glass bottles, canisters, and jars -- along with cotton balls and desiccants, outer boxes, labels, tamper-evident seals, and package inserts. Products requiring precise dosing come with dispensing devices like droppers, syringes, or dosage cups, all used briefly before being discarded. While some items may contain recycled or recyclable components, many will wind up in the Pacific gyre.

Design and market appeal also play into packaging decisions. On shelves jammed with products, companies want theirs to stand out. For example, gummy supplements—a fast-growing delivery form—often come in transparent polyethylene terephthalate (PET) bottles so people—especially kids—can see the bright colors. Fortunately, PET is the most widely recycled plastic in the world.

There's also the issue of single-serving, travel-friendly, or blister-packed supplements. They're popular, but extremely wasteful. In most cases, single-serve packages and blister packs cannot be recycled.

Then there's the matter of online shopping. As reported by the *Nutrition Business Journal*, data from Slice Intelligence show that online vitamin sales are growing faster than any other e-commerce sector; 77% of all online supplement purchases are now made through Amazon alone. All that online commerce means increased amounts of cardboard and plastic packing material, as well as more fuel consumption.

Recycled vs Compostable

New eco packaging innovations are emerging, but there's lack of consensus about which are truly earth-friendly. Experts debate the merits of recyclable versus biodegradable products. Typically, production of brand new materials—even eco-conscious, compostable ones—requires greater energy input than the recycling of existing products. A remarkable variety of certified compostable bioplastics do exist, but opinions differ on which are best.

Bottles and boxes incorporating post-consumer recycled (PCR) components like plastic resins or paper are popular. Some plastic manufacturers also produce proprietary organic or biodegradable additives that enhance biodegradation of materials like PET, nitrile, rubber, or latex.

More companies are now utilizing plant-based packaging. Paper, molded fibers, sugarcane pulp, and bioplastics like polylactic acid (PLA), polybutylene succinate (PBS), polybutyrate adipate terephthalate (PBAT), and polyhydroxyalkanoate (PHA), usually made from corn, potato, or cellulose, are just a handful of the new compostable options.

But it's not like these materials dissolve overnight. Biodegradation varies significantly, ranging from two to ten years, depending on package size, thickness, weight, and the type of resins used.

Oregon-based Highland Laboratories, a private label contract manufacturer, was the first supplement company to package its products in plant-based containers. Today, all of the company's supplements come in corn-based, petroleum-free PLA bottles. "These bottles use 68% less fossil fuel than petroleum-based bottles and are the world's first greenhouse gas-neutral polymer," Highland claims.

While PLA works well for tablets, capsules, or powders, it is not a great option for liquids. Sensitive to heat, PLA can melt if exposed to direct sunlight or left in a hot vehicle for long periods. Some also worry that PLA and other green plastics or plastic additives risk contaminating the recycling stream. Unlike the more established PET, there are fewer buyers interested in recycled PLA materials.

Rainbow Light Nutritional Systems uses recycled PET (rPET) made entirely from PCR content for all of its supplement bottles. Use of rPET requires less energy and water, and generates fewer greenhouse gases than virgin plastics. It also keeps valuable reusable materials out of landfills.

In 2016, Rainbow Light launched its "Path to EcoGuard" environmental health campaign, a global effort to "activate solutions to the consumer packaging crisis and the dire toll plastics are taking on the oceans." The campaign included the launch of a microsite providing free sourcing information on its trademarked EcoGuard 100% recycled bottles, aiming "to help other conscious companies evaluate sustainable packaging options."

Rainbow Light claims its EcoGuard program eliminates approximately 10 million plastic bottles from the waste stream every year.

But even the most eco-friendly packaging is only eco-friendly if people dispose of it properly. Many labels carry messages like "100% PCR, please recycle," but there is no guarantee that users will actually do so. The reality is many communities do not have appropriate recycling or composting facilities.

Optimists expect better collection efforts and recycling capacities to emerge as demand for eco-friendly products increases. But this will require a concerted, worldwide effort.

In its June 2018 issue, *National Geographic* reported that globally, less than a fifth of all plastic gets recycled globally. In the US, that figure is less than 10%.

China's recent decision to stop accepting plastic waste from other countries is contributing to a plastic pile-up around the globe, forcing countries like the US—a major plastics disposing nation—to urgently address the management of what's arguably one of the most dangerous materials on the planet. **QC**

Eliminating Adulteration: American Botanical Council Leads An Industry-Wide Initiative

Call it the Eleventh Commandment: "Thou Shalt Not Commit Adulteration!"

Though it is not quite a divine decree, the imperative to eliminate contaminants and adulterants is one that conscientious herbal supplement companies are taking very seriously these days.

Several industry-wide initiatives over the last year show that leaders in the herbal medicine field are determined to clean up the global supply chain.

It is no secret that unintentionally contaminated or intentionally adulterated herbs sometimes make it into finished botanical supplement products.

Like any agricultural product, herbs are at risk for contamination with environmental toxins (heavy metals, pesticides, fumigants, petroleum derivatives) and biological contaminants (microbes, mycotoxins, endotoxins, helminthes, insects). More than any other supplements, medicinal herbs are also vulnerable to deliberate, economically-motivated adulteration.

It is no secret that unintentionally contaminated or intentionally adulterated herbs sometimes make it into finished botanical supplement products.

A Global Issue

Herbal medicine is big business these days. According to *Nutrition Business Journal*, herbs generated $12 billion in sales in 2017, representing 28% of the $43 billion in total US supplement sales.

Worldwide, the global herbal supplement market could reach over $86.7 billion over the next 4 years, predicted Zion Market Research, an industry analytics firm based in Pune, India. Herbs are a big part of that.

Such high demand puts intense strain on growers and raw materials processors. Sustainable agricultural practices, careful processing, and continuous quality assurance are not easy, and not cheap. The temptation for ingredient companies to cut corners—and for supplement makers to turn a blind eye—is ever present.

Some unscrupulous ingredient suppliers use cheap plant materials as substitutes or fillers for costly or rare herbs. Others intentionally spike herbs with drugs—a particular problem with weight loss, performance enhancement and sexual health products (Kosalec I, et al. *Arch Industr Hygeine & Toxicol*. 2009; Tripathy V, et al. *Phytochem Letters*. 2015).

How widespread is intentional adulteration or substitution? It's hard to say.

Several years ago, Canadian researchers used DNA techniques in a blinded analysis of 44 consumer-facing herbal products. They found 32% contained DNA from plants not listed on the labels, indicating species substitutions or dilutions. Several had potential clinical significance, like *Senna alexandrina*—a strong laxative—in a St. John's Wort product. *Juglans nigra* (black walnut) in Ginkgo and Echinacea products, could be problematic for patients with nut allergies.

Further, 21% contained undisclosed plant-derived fillers (wheat, rice, alfalfa, and soy), which could trigger reactions in people with allergies or sensitivities (Newmaster S, et al. *BMC Medicine*. 2013).

Though many experts in botanical analytics question the validity of DNA-based techniques, none dispute the reality of intentional adulteration.

Tackling a 2,000 Year Old Problem

Mark Blumenthal, founder and executive director of the American Botanical Council, an internationally renowned non-profit herb research and education organization, estimates that anywhere between 35% and 45% of the best-selling medicinal herbs—including Echinacea, Milk Thistle, Ashwagandha, Maca, Oregano, Black Cohosh, Cranberry, Saw Palmetto, and Aloe Vera—are subject to adulteration.

"That's not to say that they are adulterated, but these herbs are potentially subject to adulteration."

The US Pharmacopeia defines Economically Motivated Adulteration as: "The fraudulent addition of non-authentic substances or removal or replacement of authentic substances without the purchaser's knowledge for economic gain of the seller."

It's not a new problem. Dioscorides, Pliny the Elder, Galen and other medical authors of antiquity described the adulteration of medically valuable herbs well over 2,000 years ago, says Blumenthal, a seasoned veteran in the long fight to clean up the herbal supply chain.

Back in 1979, through his organization, the Herb Trade Association, he exposed a company selling Canaigre (*Rumex hymenosepalus)*—a Native American herb in the Dock family—as "Wild Red American Ginseng." The plant had no biological, chemical, ethnopharmacological or functional relationship to Ginseng whatsoever. He's been calling out this sort of malfeasance ever since.

Since 2011, ABC has issued 41 peer-reviewed reports on adulteration, as part of its Botanical Adulterants Prevention Program (BAPP). The series includes five lab guidance documents and 14 herb-specific adulteration bulletins.

The latest, issued in June, looks at Turmeric (*Curcuma longa*), one of the top selling herbs. Authored by Ezra Behar, PhD, at San Diego State University, with input from 18 analytical experts, the bulletin details—among other things—the use of cheap synthetic curcuminoids in place of real Turmeric root extracts.

Stefan Gafner, PhD, ABC's chief science officer says use of undisclosed artificial dyes is also an issue. "Many yellow or orange colorants, such as lead chromate or metanil yellow, may represent a health risk."

All of ABC's adulteration reports are freely accessible on the group's website (www.herbalgram.org).

More are in the works, on herbs like: Ashwaghanda (*Withania somnifera*), Frankincense (*Boswelia serrata*) Kava (*Piper methysticum*), Lavender (*Lavandula*), Tongkat Ali (*Erycoma longifolia*), Pomegranate (*Punica granatum)*, Siberian Ginseng (*Eleutherococcus*), and Black seed (*Nigella sativa*).

There is a constant cat-and-mouse game between unethical ingredient suppliers and the scientists and quality assurance officers working to detect them. Analytical techniques (see p. 21) improve over time, but adulterators evolve accordingly, growing ever more sophisticated in their deceptions.

Holly E. Johnson, PhD, the chief science officer for the American Herbal Products Alliance (AHPA) noted that several years ago, when Ginkgo hit peak popularity, some raw materials suppliers began to cut corners.

They knew USP guidelines recommended high performance liquid chromatography, keyed to three specific reference compounds. They figured out they could use leaves from *Sophora japonica*—a tree unrelated to Gingko—that produces the same three molecules, and pass USP's recommended test.

AMERICAN BOTANICAL COUNCIL
SINCE 1988

"You really have to know what to look for," says Johnson, who also serves on ABC's scientific advisory board.

Members of ABC's BAPP team are about to publish a paper titled, *Botanical Ingredient Adulteration—How Some Suppliers Attempt to Fool Commonly Used Laboratory Analytical Techniques*, in an upcoming edition of the journal, *Acta Horticulturae*.

ABC's "Search & Destroy" Initiative

ABC's mission is primarily educational, but this year, the council took a major step beyond raising awareness about adulteration: Blumenthal and his team are pushing the industry to adopt purchasing practices that will stop the problem.

Most major supplement companies have strong commitments to quality control: they do extensive analytical testing and routinely reject substandard, contaminated, or adulterated raw materials.

What happens to those rejected lots?

All too often, suppliers simply resell them to lowest-bidders. "It's the dirty little secret that's not such a secret," Blumenthal says.

ABC AHP NCNPR
Botanical Adulterants Prevention Program

Mark Blumenthal, Founder, American Botanical Council

Holly E Johnson, PhD, Chief Science Officer, American Herbal Products Association

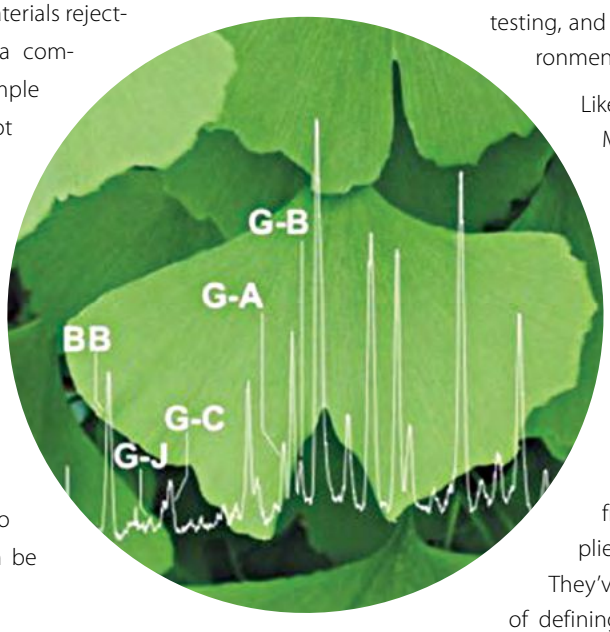
To combat this, ABC has proposed a new industry-wide Standard Operating Procedure (SOP) that would include contractual clauses mandating complete destruction—at the supplier's expense—of any raw materials proven to be adulterated or irreparably defective.

"I've been involved with this industry since 1970. Many of us have gotten fed up with the ways that people are selling substandard material, fraudulent material. It would make sense to try to develop an SOP and get it accepted by industry, to remove some of this bad raw material from the supply chain."

ABC worked closely with other industry groups, botanical experts, and legal counselors to develop the new SOP.

Michael Levin, a veteran industry consultant, quality control advisor, and contributor to HPC's 2017 ***Quality Counts*** report, developed the concept of "irreparably defective materials" at the heart of ABC's proposal.

This term differentiates between materials rejected because they do not match a company's particular specs-—for example a Ginkgo leaf powder that was not ground to the buyer's requested particle size—and materials that are contaminated, adulterated, or fraudulent, such as "Ginkgo" containing plants other than ***Ginkgo biloba***, or cut with non-Ginkgo flavonols.



"Defective" materials can be defective for various reasons, says Blumenthal. In some cases there's no malfeasance, and the materials can be remediated by the seller.

"Adulterated materials, with few exceptions, cannot be remediated. You can't fix red dye #2 or other illegal red dyes in a St. Johns Wort extract. Once it's in there you can't get it out. That stuff needs to be destroyed."

ABC's new SOP includes contract language templates that companies can use and customize; materials destruction templates; analytical testing guidelines; lists of qualified 3rd party testing labs; conflict resolution pathways; and procedures for safe and legal destruction of irrevocably tainted materials.

The proposal is still under legal review, but Blumenthal says early industry response has been very positive.

Ultimately, this SOP puts responsibility for supply chain integrity precisely where it belongs: on the manufacturers who purchase ingredients. "The buyer is key. The buyer wears the pants," Blumenthal told HPC.

AHPA: Good Ag for Good Health

ABC's efforts dovetail with other initiatives aimed at improving supply chain integrity.

Last year, the American Herbal Products Association issued a landmark guidance document, ***Good Agricultural and Collection Practices & Good Manufacturing Practices for Botanical Materials (GACP).*** It is a greatly expanded update on an earlier paper jointly published by AHPA and the American Herbal Pharmacopoeia in 2006.

AHPA holds that the purity and potency of herbs—and ultimately their clinical efficacy—depends on how (and where) they're grown, harvested, and processed. Simply put, healthy soil and healthy farming produce healthy products.

AHPA's GACP guidance fills big gaps in US and international regulations. As the authors note, there are no formal GACPs from either the USDA or the FDA for the majority of medicinal herbs. The minimum guidelines that do exist focus on microbiological testing, and have little to say on herb quality, environmental toxins, or intentional adulteration.

Likewise there are no formal Good Manufacturing Practices (GMPs) specific to herbs beyond the basics outlined in DSHEA for all dietary supplements. (see ***DSHEA: The Ground Rules for Dietary Supplement Regulation***, p. 6)

GACP provides templates that growers, harvesters, and processors—large and small—can adapt to their operations.

"A lot of companies proffering botanicals now are totally disconnected from the farmers and growers and suppliers, they don't have botanists on staff. They've lost touch with reliable old methods of defining botanical identity based on macroscopic features—the leaves, the branching patterns," says Dr. Johnson.

"Sourcing and quality assurance going all the way back to the farm is something that AHPA pays a lot of attention to. Sustainable, ethical agriculture is definitely important to our membership. If companies are in touch with their plants at that level, a lot of adulteration issues disappear," she told HPC.

Though written for industry use, Johnson believes the AHPA GACP document—available free of charge on the group's website—can provide medical practitioners with an excellent roadmap for assessing botanical supplement companies (www.ahpa.org).

Compound(ing) Interest

More specific to practitioners, AHPA also recently issued a white paper on ***Good Herbal Compounding & Dispensing Practices.*** This

document recognizes that some practitioners—especially acupuncturists, some naturopaths, traditional herbalists, and practitioners of Chinese medicine—make their own custom herbal formulations for patients.

FDA regulations do permit this, provided that, "practitioners have adequate professional training and dispense supplement products on the basis of one-on-one consultations, and the supplements dispensed have no known or suspected safety concerns." (FDA cGMP regulations, 21 CFR Part 111).

In the hands of well-trained and experienced clinicians, this is personalized medicine at its best. But the various healing disciplines all have their own methods and protocols, with no formal consensus between them.

Enter AHPA. The Herbal Compounding guidelines provide practical recommendations for ensuring quality and safety of individually formulated decoctions, powdered herbal formulas, poultices, pastes and linaments.

AHPA also publishes ***The Botanical Safety Handbook*** one of the most valuable, comprehensive, and practical guides to herbal medicine ever published. It's a reference that belongs in the library of any practitioner who recommends or dispenses herbs.

The recently revised edition—available at $95.00 for AHPA members and $119.00 for non-members—covers over 500 of the most commonly used medicinal and culinary herbs.

Among its many useful features, the ***Handbook*** divides herbs into three classes:

- Generally safe herbs with minimal potential risk that can be widely utilized without practitioner guidance.
- Herbs with specific contraindications or restrictions, such as those with potentially hepatotoxic, neurotoxic, or teratogenic effects
- Herbs with serious potential risk that should only be used under close guidance of a qualified herbal medicine expert.

The ***Handbook*** also includes a separate classification system based on interactions between herbs and pharmaceuticals. But unlike other guides, it distinguishes between actual clinically relevant and well-documented adverse interactions and hypothetical but undocumented risks.

It brings a balanced and rational perspective to its subject, dispelling the popular sentiment that all herbs are intrinsically safe simply because they're "natural," while also avoiding the alarmist tone of some reference books that place undue emphasis on the danger of herbs.

Implementing FSMA

These industry-directed efforts at supply chain improvement are aligned with the broader implementation of the Food Safety Modernization Act (FSMA) of 2011, a far-reaching set of regulations aimed at preventing and controlling contamination across the food industry, at all points along the global supply chain. Since supplements, including herbs, are officially considered "foods," FSMA applies to them as well.

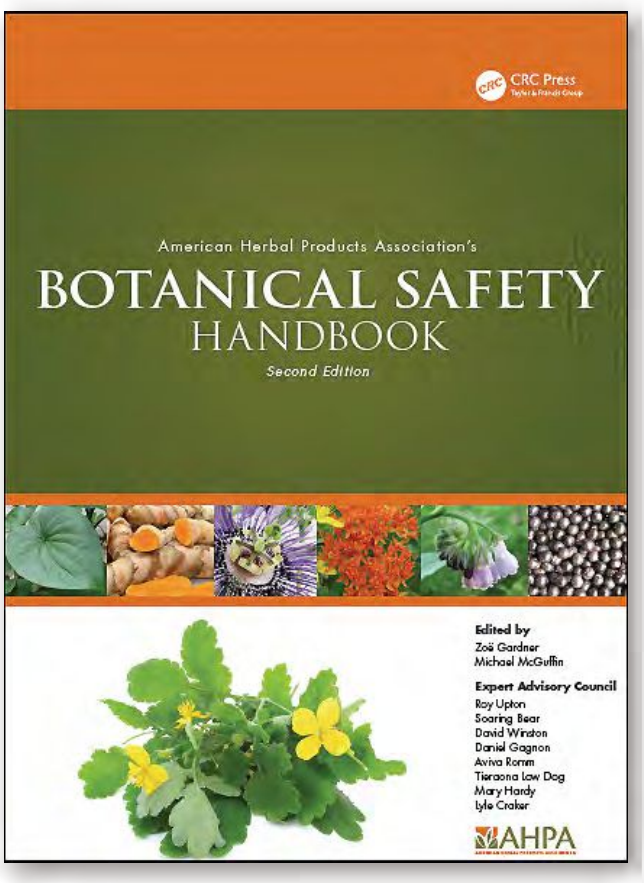
Among other things, FSMA includes ***Foreign Supplier Verification Programs*** that put increasing responsibility on food and supplement companies to ensure that ingredient suppliers outside the US comply with all US safety standards.

In June, the FDA issued draft guidance for a new Intentional Adulteration Rule, intended to mitigate risk of intentional adulteration or contamination.

One could certainly argue about the adequacy of US standards or the efficacy of FSMA in enforcing them. But supplement companies are taking the regulations seriously, and this will no doubt create much-needed "upstream" pressure on raw materials suppliers.

The effort to eliminate, or at least minimize, herbal adulteration will be a long one, says ABC's Blumenthal. "The botanical supply chain is global. Adulteration is a global challenge. The solution requires a global effort." **QC**

AHPA
AMERICAN HERBAL PRODUCTS ASSOCIATION



Common Medicinal Herbs Vulnerable to Adulteration

All herbs, like all agricultural products, are potentially subject to contamination with microbes, pesticides, environmental toxins, and financially-motivated adulteration or mislabeling.

Certain herbs, however, have been particularly vulnerable to adulteration, says Mark Blumenthal, executive director of the American Botanical Council.

Goldenseal (*Hydrastis Canadensis*), valued for its anti-inflammatory, antibacterial, and immunostimulatory effects, has a long history of being adulterated. Unethical suppliers will often cut it with other herbs containing high amounts of berberine and other yellow alkaloids.

These substitutions are not necessarily harmful, says Blumenthal. And from an ecological perspective it may even be helpful in the sense that Goldenseal is difficult to cultivate, and wild stocks are vastly over-harvested. The issue here is truthfulness in labeling. "If they're not labeling these mixtures as mixtures, and just calling them "Goldenseal," that is wrong."

Saw Palmetto (*Serenoa repens*): There are numerous documented cases of Saw Palmetto extracts, promoted for potential anti-neoplastic effects on prostate cancer, being adulterated with vegetable fats. Earlier this year, a paper came out showing that some Saw Palmetto extracts are being adulterated with animal fats. "As a vegetarian I'm not too thrilled with that," Blumenthal told HPC.

Bilberry (*Vaccinium myrtillis*), valued for its ocular and cardiovascular benefits, is one of the most highly adulterated herbs on the market. Unscrupulous suppliers will sometimes pull the anthocyanins out of more plentiful and less costly species of berries (blueberries, cranberries, elderberries, mulberries, etc), and combine them with small amounts of actual bilberry. Some really unethical ones will combine berry anthocyanins with synthetic amaranth dye and charcoal, and call it "bilberry." This combo will actually pass UV spectrophotometry tests, a common, though clearly incomplete validation method.

Black Cohosh (*Actea racemosa* aka *Cimifuga racemosa*), the fifth most commonly-purchased herbal supplement in the retail sector, is also one of the most commonly adulterated. True Black Cohosh is in short supply and is expensive. Dishonest suppliers sometimes use other less expensive species of Actea in raw materials labeled "Black Cohosh." In some cases they even use unrelated species like (*Serratula chinensis*).

Blumenthal notes that true *Actea racemosa* ("American Black Cohosh") does not grow in China, so any Certificate of Analysis claiming proof of *Actea racemosa*, and China as a country of origin, is highly suspect.

Botanical adulterations are seldom truly harmful, though they are dishonest and sometimes fraudulent. At the very least they compromise the expected efficacy of the herbal medicine.

In some cases, however, there may be clinically significant adverse impact. With Black Cohosh, there was a series of reports in 2002 attributing liver toxicity to use of this herb. However, ABC researchers believe adulteration with other plant species is likely to blame, at least in part. Later analyses found the association of true Black Cohosh with liver disease to have a weak or uncertain causal link or no causal link at all.

As industry consultant, Michael Levin pointed out in the 2017 edition of *Quality Counts*, Cordyceps mushrooms—valued for their immunostimulatory compounds—can be subject to dangerous forms of economic adulteration.

Demand for these fungi, which grow on the bodies of a particular type of caterpillar, has grown in recent years. Wild harvesters in Asia are paid by weight. So some try to pad out their bundles with potentially toxic materials. In at least one case, a supplier had stuffed the Cordyceps with lead solder. There are two reports linking lead poisoning with use of contaminated Cordyceps supplements. **QC**

Goldenseal flowering plant (*Hydrastis Canadensis*)

Saw Palmetto seeds (*Serenoa repens*)

Bilberry branch with berries (*Vaccinium myrtillis*)

Black Cohosh root (*Actea racemosa* aka *Cimifuga racemosa*)

ABC AHP NCNPR Botanical Adulterants Prevention Program

Analytical Methods Used or Botanical Ingredient Identification

Method	Applicability	Limitations: Not applicable to
Taxonomy	• Whole living plant	• Powdered or cut crude plant material • Extracts
Macroscopy	• Whole or cut crude plant material	• Extracts • Powdered crude plant material
Microscopy	• Whole, cut or powdered crude plant material	• Extracts
Genetics (DNA)	• Whole, cut or powdered crude plant material • Extracts possessing intact DNA from the parent plant	• Extracts without DNA • Materillls processed using prolonged heat, exposure to UV light, or irradiation
UV/VIS (Ultraviolet-Visible Spectroscopy)	• Extracts • Whole, cut or powdered crude plant material after extraction	• Analytes with no UV/VIS chromophore (e.g., sugars and sugar alcohols) without prior derivatization
FT-IR (Fourier Transform Infrared Spectrophotometry)	• Extracts • Whole, cut or powdered crude plant material after extraction	• Extracts containing large amounts of carriers, e.g., maltodextrin
FT-NIR (Fourier Transform Near-Infrared Spectrophotometry)	• Extracts • Whole, cut or powdered crude plant material	• Materials with variable moisture content • Extracts containing large amounts of carriers, e.g., maltodextrin
MS (Mass Spectrometry)	• Extracts • Whole, cut or powdered crude plant material after extraction	• Very high molecular weight analytes • Non-readily ionizable molecules
NMR (Nuclear Magnetic Resonance)	• Extracts • Whole, cut or powdered crude plant material after extraction	• Certain highly polymerized molecules (e.g., high molecular weight PACs)
HPTLC (High Performance Thin Layer Chromatography)	• Extracts • Whole, cut or powdered crude plant material after extraction	• Highly polar compounds
GC-FID (Gas Chromatography – Flame Ionization Detector)	• Extracts • Whole, cut or powdered crude plant material after extraction	• Non-volatile compounds
GC-MS (Gas Chromatography – Mass Spectrometry)	• Extracts • Whole, cut or powdered crude plant material after extraction	• Non-volatile compounds
HPLC-UV (DAD) (High Performance Liquid Chromatography UV Diode Array Detection)	• Extracts • Whole, cut or powdered crude plant material after extraction	• Analytes with no UV/VIS chromophore (e.g., sugars and sugar alcohols) without prior derivatization
HPLC-MS (High Performance Liquid Chromatography – Mass Spectrometry)	• Extracts • Whole, cut or powdered crude plant material after extraction	• Very low and very high molecular weight analytes • Non-readily ionizable molecules

Insights on Analytical Testing: An Interview With Elan Sudberg, Alkemist Labs

Analytical testing laboratories are at the heart of all quality control endeavors in the dietary supplement industry.

Within these highly controlled, high-tech enclaves, analytical chemists employ a variety of tools to determine the purity and consistency of the raw materials that go into supplements, as well as the potency of the finished goods before they hit the shelves.

Many nutraceutical companies have their own in-house labs. Others rely on independent 3rd party labs. The most conscientious companies use both, performing some tests in-house but employing 3rd party labs for other more specialized tests, and for confirmation of their in-house results.

Under DSHEA (see p. 6), supplement companies are required to manufacture in a way that "consistently meets the established specifications for identity, purity, strength, and composition, and limits on contaminants, and has been manufactured, packaged, labeled, and held under conditions to prevent adulteration."

In fact, ingredient identity and potency testing are the only parameters explicitly mandated under the FDA's current Good Manufacturing Practices (cGMPs). The regulations mandate that label claims about finished product potency be fully validated (provided there are scientifically valid methods for testing the ingredients in question).

In practice, there can be considerable variability in product quality, even among cGMP-compliant companies. That's partly because for many parameters DSHEA gives manufacturers wide latitude to define their own specs.

Further, analytical testing is a rapidly changing field. For some ingredients and contaminants, there's strong consensus on methodology, and well-defined reference standards. But for others, the standards may not be so clear.

The market for natural products is extremely trend-driven, especially in retail. Companies constantly seek novel ingredients for their health-crazed consumers, and the push to launch something new may be well ahead of analytical consensus.

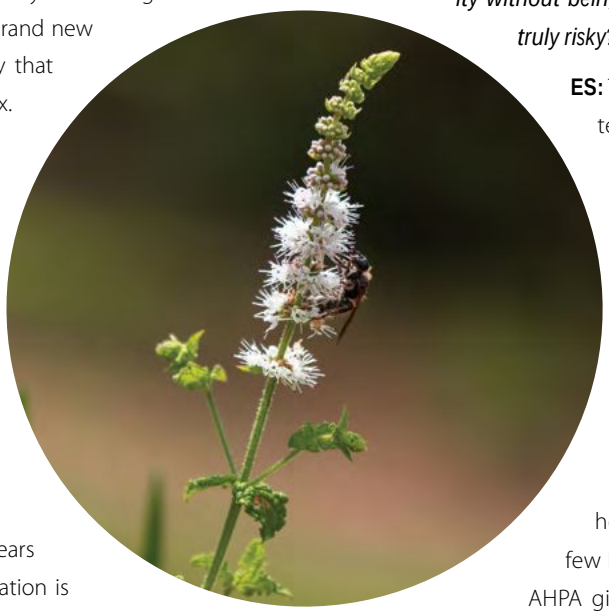
The ongoing debate over DNA tests for botanicals underscores the fact that while new and emerging techniques hold great promise, it often takes time for the scientific community to figure out the purposes for which they are most fit.

Inside Alkemist Labs' new 21,000 square foot analytical testing facility in Garden Grove, CA

Few people know more about the fascinating field of analytical testing than chemist Elan Sudberg, CEO of Alkemist Labs, Garden Grove, CA, a contract testing laboratory he co-founded with his father, Sid, in 1997.

Alkemist is one of several independent 3rd party labs that renders comprehensive analytical testing to the Food & Beverage, Nutraceutical, and Cosmeceutical industries. The lab specializes in identity and potency testing for botanicals.

Together with his father, a research chemist who also studied and practiced Chiropractic and Traditional Chinese Medicine for many years, Elan has led Alkemist to the forefront of the analytical testing world. Last Spring, the lab moved into a brand new 21,000 square foot, state-of-the-art facility that expands its working space by a factor of six.



Quality Counts asked Elan to weigh in on the most pressing issues, challenges, and innovations in the realm of product testing and quality assurance.

QC: *The American Botanical Council has stated that between 35% - 45% of herbs sold in retail are potentially subject to adulteration. Does that jibe with what you see in testing actual products/raw materials?*

ES: My experience spanning over 20 years of testing the plants tells me that adulteration is a moving target. Cheaters cheat, they always will. We have to try and get ahead of them by being diligent and suspicious, always.

That said, the labs, the industry, and the consumers are far more sophisticated these days than they were. Compliance is on the rise as indicated by our growth, so that demonstrates more testing, and less adulteration.

There are a handful of herbs that are highly suspect—herbs that are hot on the market, hard to source, or easy to adulterate. Perhaps that's where the 35%-45% figure comes from. That is certainly not the rate at which we fail herbs in our lab. The fail rate is much lower, mostly due to poor quality rather than adulteration.

Also, keep in mind there are different kinds of adulteration, the most common being attempts to boost potency of subpar material by adding substances designed to fool cursory testing or providing the wrong species, which means the label will not be accurate.

QC: *In your experience, which herbs are most susceptible/vulnerable to adulteration?*

ES: Certain categories, specifically male enhancement (ED), body building and weight loss, seem to draw the unscrupulous. Such categories are fast moving, kinda sketchy, and generally sold through online channels. Any plant intended for those categories seems to be on our list of "likely adulterated."

Hoodia is one example that burned hot and burned fast. It allegedly causes significant appetite cessation. But it is a plant that is slow to mature, and is endangered. There were several years in which more "hoodia" was sold commercially than was actually harvested.

Both the American Herbal Products Association (AHPA) and the American Botanical Council (ABC) have their lists of likely adulterated herbs that are critical for every manufacturer and for every lab, in terms of day-to-day testing.

QC: *An ingredient could be fraudulent, adulterated, or simply of poor quality without being harmful. How frequently are adulterations truly risky?*

ES: To paraphrase federal regulations, an adulterant is any component of a product for which the identity is not what is disclosed (on the label) or whose quality is such that the material value of the product is compromised in terms of quality, purity, or safety. But that doesn't mean it is harmful.

In the plant testing world, truly harmful adulterants or contaminants are so rare that I can't think of anything recent. The herbs we trade are mostly safe, and only a few have poisonous 'cousins.' In their guidance, AHPA gives a number of known potentially toxic adulterants or substitutions.

These include:

- **Eleuthero root** (*Eleutherococcus senticosus*) with *Periploca sepium* root
- **Plantain leaf** (*Plantago lanceolate*) with *Digitalis lanata* leaf
- **Skullcap herb** (*Scutellaria lateriflora*) with Germander herb (*Teucrium chamaedrys*)
- **Stephania root** (*Stephania tetrandra*) with *Aristolochia fangchi* root (Guang fang ji)
- **Black cohosh root/rhizome** (*Actaea racemosa*) with Cimicifuga root/rhizomed (Actaea spp.)
- **Ginkgo** (*Ginkgo biloba*) leaf extract standardized to flavonol glycosides and terpenes with added flavonol glycosides or aglycones (e.g., rutin, quercetin, etc.)
- **Bilberry fruit extract** with Red dye #2 (amaranth dye)
- **Hoodia gordonii** aerial parts powder with various other plant powders, possibly including Opuntia spp. and other Hoodia species
- **Grapefruit Seed extract** with Benzalkonium chloride, benzethonium chloride, triclosan, methyl paraben, or any other synthetic antimicrobials

QC: *What are the key steps in analysis of herbal ingredients?*

ES: The first step in cGMP compliance is identity testing. It makes no sense to go through all the other mandated tests (microbial, heavy metals, pesticides) if you don't even have the correct material.

Second, we analyze. This means that we test to see if the material is within limits for microbes, metals and pesticides. More exciting, though, is constituent analysis, for example, how much caffeine is in that green tea? This is critical especially if the company is bold enough to make label claims.

The next step is to verify. Most companies in our industry don't have the luxury to grow their own plants, extract from them, and then combine one extract with others from different plants. So finished product makers use ingredient suppliers and contract manufacturers. There are several hands along the chain of custody.

Each change in hands is an opportunity for failure. The most important thing, ultimately, is that pill, tablet, or drop of final product that makes it to the tongue of the customer. What's in that? Did all the ingredients make it in there? Can they be detected and match the label claims?

That's what we look for in the Verification step. Only a small percentage of the industry seems to care or be concerned about developing test methods on their finished formulas. But we predict that will change as FDA increasingly asks about that step during inspections.

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–Elan Sudberg, co-Founder, Alkemist Labs

QC: *There are a wide variety of technologies and methods used in analytical testing: Gas chromatography, thin layer chromatography, mass spectroscopy, microscopy, and now DNA testing. What are the pros and cons of these methods?*

ES: The FDA's guidance on methods is turbid at best. They basically say, "Use something that is scientifically valid." Unfortunately, that can be interpreted five different ways by three different consultants!

To start with, ID testing can be achieved for plants in whole form by macroscopic and organoleptic examinations. Such must be performed by a trained (with documentation) person. Limitations here are that the material must be in whole form, which is generally not the case in our industry. Powders are the norm.

Next is Botanical Microscopy, which is simple inspection of a powdered material under a microscope, to identify its unique cellular characteristics. This must also be performed by a trained, credentialed person. And you must have an extensive library of both reference texts and reference samples.

Botanical Microscopy has trouble speciating a handful of popular plants, and unfortunately it is a dying skill. But it is able to pick up excipients better than most chemical tests.

High Performance Thin Layer Chromatography (HPTLC) is, in our opinion, the best way to ID plants, as it's possible to do so on whole, powder, extract, liquid, and even in finished products. It is a state-of-the art technique that easily detects plant parts, adulterants, and closely related species.

HPTLC must be performed by a trained person with documentation, and there are not a lot of those. Plus, interpretation is part art, part skill, and it takes time to tune. Also, an extensive library of reference materials and methods is required.

DNA testing is the new kid on the block and there is still work to be done refining this method before it should be relied upon. In theory it has the capacity to narrow down to species and beyond. This is especially important when other techniques can't.

But DNA tests cannot determine plant parts, which is an important distinction in botanical medicine, because different plant parts contain different concentrations of desired constituents. And it is nearly impossible to get meaningful DNA results with anything but whole, raw materials.

Further, plant DNA reference libraries are closed and proprietary, so the collaboration needed to make DNA analysis a widely usable technology has not yet happened. The industry is still figuring out what to do with it. There is still so much work to do in developing DNA testing for plant identification, which is why at Alkemist, we have yet to open our DNA platform up for commercial testing.

So, we've covered the "Is it or is it not Plant X" tests, but not the methods to determine "how much."

HPLC and Gas Chromatography (GC) are the chosen techniques to quantify most market compounds. As with all these techniques, GC must be performed by a trained, credentialed person. There's a lot of skill and labor involved in all of this. The equipment is expensive to buy, run, and maintain, and they drink solvents and create gallons of chemical waste.

Undoubtedly you have noticed my recurring phrase: "Such must be performed by a trained (with documentation) person." This is absolutely crucial. These methods don't run themselves. Without well-trained humans running them, you might as well be dry-labbing.

One of the drawbacks with most in-house labs is too many of them have a small staff of people who are supposed to be proficient in all these techniques. That may look OK on paper, but in reality is a nightmare waiting to happen.

QC: *What do you consider to be the most significant and troubling quality issues in the dietary supplement space?*

ES: Do It Yourself labs and substandard testing practices are the biggest threat. At worst, something bad goes unnoticed and someone the industry, which ultimately decreases product efficacy, which undermines return customers.

Many companies think they can just buy equipment, hire some fresh grads and use that extra space in the back of the warehouse to set up a lab. Trust me, it's not that easy. The companies that sell these types of testing equipment are surely not going to tell you that though.

We see a lot of material passed by internal labs that don't meet the muster at ours.

Imagine this scenario: Jeff, who is recently promoted to Lab Director, also oversees Quality Assurance. He is best buddies with Sam in procurement. Both fear losing their jobs if they make decisions that cost a little more, because they are under pressure from their money-centric CFO. See the problem?

Then there are the so-called dry labs. These are "labs" that simply approve test samples without doing any actual tests, without actually getting their equipment "wet." Although this problem has decreased, there are still a few, and they thrive by undercutting the good labs for customers that are cheap and careless.

QC: *With the rapid growth in demand for cannabis & CBD, word is there are a lot of poor or fraudulent cannabis raw materials entering the supply chain. Is there truth to this? What are you seeing?*

ES: It's a tough market to understand. To start, California, for example, requires lab testing for all cannabis products. But lab testing of cannabis is illegal in the United States. California is in the United States. Alkemist Labs, arguably the most respected botanical testing lab in the country, is not legally able to test these products. I find it all very confusing!

The pulse of the cannabis or CBD market is a strange one. Any time there is such hype over a product, poor quality material will find its way in. There are also a massive number of new faces, new companies that are not used to the real costs of compliance. Many labs are offering "tests" that cost less than it does to actually turn on the lab equipment and make sure it is running properly.

Honestly, until the legal status gets straightened out, manufacturers don't have access to the labs with the highest level of botanical expertise to test cannabis. **QC**

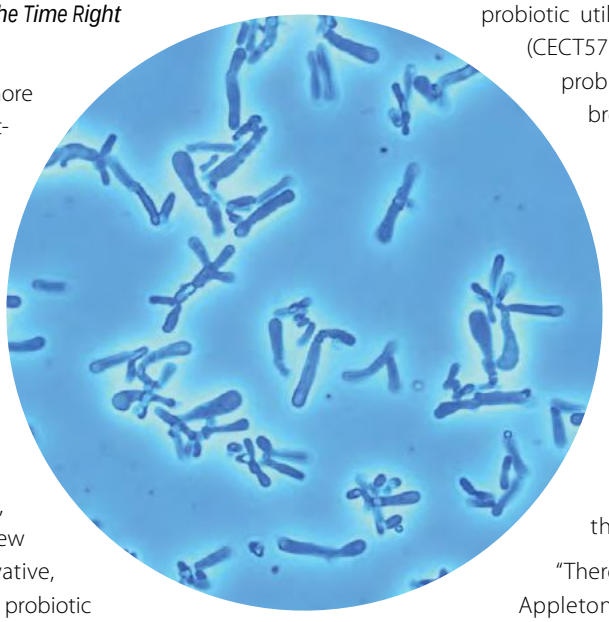
Elan (left) and Sidney Sudberg, founders of Alkemist Labs, with their team.

Formulation Innovation: How New Science Drives Product Development

Anyone who claims, "There's no science behind dietary supplements" is not paying attention.

Research on the impact of various vitamins, minerals, fats, and other nutraceutical substances is progressing at a rapid pace, despite the disincentives created by a regulatory system that prohibits supplement companies from using clinical data to make prevention or treatment claims (see, ***Is the Time Right to Revise DSHEA***, p. 9).

Nowhere is this growth in research more apparent than in the realm of probiotics. Search PubMed for this term and you'll find almost 22,000 citations, roughly half published in the last 5 years. Over the past 12 months, there were 2,775 probiotics-themed studies.



Klaire Labs, the Reno-based aggregation of three formerly separate practitioner brands (Prothera, Klaire Labs, and Complementary Prescriptions), is committed to translating the new microbiome science into innovative, highly targeted, condition-specific probiotic formulations. The company is part of a vanguard of supplement makers taking a more scientific approach to product development.

Through a creative partnership with a Dutch research & development firm called Winclove Probiotics, Klaire has brought to market several new probiotics, including Target gbX (gut-brain axis), a groundbreaking formula shown to reduce dysfunctional thinking patterns, aggression, sad moods, and overall symptom scores in people with depression.

Next Gen Probiotics

"Winclove's business model is to identify different probiotic strains, test them for potential effects against specific indications, then do the animal and pre-clinical studies, leading up to actual clinical trials," explained Nigel Pollard, CEO of Soho Floridis International, Klaire Labs' parent company. Target gbX, which contains 6 distinct species of Lactobacilli, and 3 species of Bifidobacteria, is "the first probiotic specifically formulated for components of depression," Pollard says.

Klaire's development team also works closely with Jane Foster, PhD, a behavioral neuroscientist at McMaster University in Ontario, who is among a global network of researchers who study the ways that gut bugs communicate with each other and with their human hosts. The microbiome affects human mood more than we realize. Foster and others in this field of "psychobiotics"—to borrow a term from authors John Cryan and Ted Dinan—are working to translate these new insights into the world of clinical practice.

Shortly after launching Target gb-X early in 2018, Klaire introduced Target b2 (Breast and Baby), another condition-specific probiotic utilizing a unique strain of ***L. fermentum*** (CECT5716) shown to help reduce mastitis—a problem that affects roughly one-third of all breastfeeding women. It has the added benefit of simultaneously stimulating the infant immune system.

Originally developed by a Spanish company called Biosearch Life, this strain reduces Staphylococcus—a primary pathogen in mastitis. It offers a non-toxic alternative to antibiotic drugs, which are not always effective for mastitis, but often cause significant damage to both the maternal and infant microbiomes.

"There's nothing else like this," says Jeremy Appleton, ND, Klaire's VP of Science and Education. "It is effective at very low CFUs—as low as 3 billion per day, though you can go as high as 9 billion."

Meeting Unmet Needs

Probiotics have always been Klaire Labs' strong suit, even prior to the acquisition by SFI. The company's Ther-Biotic is one of the best-selling broad-spectrum probiotics in the practitioner space, and also one of the oldest.

The company's new mandate is to build on Klaire's reputation for clean, hypo-allergenic products with new formulas backed by strong research pedigrees.

"We are in the space between commodity mass-market natural medicines and the Big Pharma model," says Pollard, who worked in the drug industry for years before a personal experience with European herbal medicines opened his eyes to other possibilities.

SFI's innovations extend beyond probiotics. On the horizon are:

Omega V: A completely vegan essential fatty acid product, derived from Ahi Flower (***Buglossoides arvensis***), a sustainably cultivated flowering plant, the seeds of which contain a near-perfect mix of Omega 3s, 6s, and 9s. Ahi also contains stearidonic acid (SDA) not found in Flax or Chia. SDA is more easily converted to

Photo: *Bifidobacterium lactis* W52 – This unique strain of *Bifidobacterium* is able to produce IL-10 and to digest lipopolysaccharides. It is one of the 9 probiotic species comprising Klaire Labs' innovative Target gbX formulation. (Image courtesy Winclove Probiotics & Klaire Labs)

EPA than flax-derived α-linolenic acid. Klaire's Omega V product combines Ahi with algal oil, providing an ideal balance between DHA and EPA.

FODMAP compliant prebiotics: Clinicians and researchers alike are starting to realize that many people have sensitivities to dietary FODMAPs (Fermentable Oligo-, Di-, Mono-saccharides And Polyols) found in many fruits and vegetables. Many common prebiotic fibers are FODMAPs, and sensitive people cannot use them. Klaire is working on a product based on alpha-cyclodextrin, a non-FODMAP fiber that is better tolerated by people on FODMAP elimination diets.

Enzymes for Starch Maldigestion: As many as 10% of all Americans have starch maldigestion problems, which are strongly correlated with IBS. Klaire is developing a high-dose enzyme product specifically for this problem. A clinical trial in the works at Baylor College of Medicine.

Appleton says the company is also in early stage development on: prebiotic/probiotic combinations for IBS and leaky gut; a product targeting gluten digestion; an intravaginal probiotic combo for vaginitis; a histamine stabilizer; a non-toxic alternative to NSAIDs; and a product aimed at brain support for people recovering from addiction.

SFI is also funding a multimillion dollar Diabetes Prevention Study at the University of Sydney's Boden Institute of Obesity, Nutrition, Exercise and Eating Disorders. The trial, currently in process, involves 400 people with metabolic syndrome, and tests whether SFI's FBCx (alpha-cyclodextrin) in combination with IlHwa's GinST-15 ginseng extract can prevent progression to Type 2 Diabetes. "We think it is the largest trial ever done for a natural product in this sector," says Pollard.

Branded Ingredients are Key

In many ways, branded ingredient companies are the research engines that drive supplement industry innovation.

Companies like Lonza, Kyowa Hakko, Kemin, Albion/Balchem, Sabinsa, PLT, FutureCeuticals, Indena, and others do not sell finished products to practitioners or consumers. Rather, they develop and market distinct patented forms of particular nutrients or herbs—a uniquely bioavailable curcumin extract, a more absorbable magnesium chelate, a more stable form of glutathione—and supply these to the industry as raw materials.

Typically, branded ingredient makers invest heavily in basic and clinical research to support their patents. They have the resources to fund the sort of large-scale trials that get published in serious journals. They also provide clear dosing guidelines for their ingredients, a safeguard against the all-too-common practice of "fairy-dusting"—using negligible amounts of popular ingredients in multi-ingredient formulas.

In short, well-researched branded ingredients engender confidence. That's especially important in the healthcare practitioner channel.

"Just because something is from the same plant as something else does not mean the two extracts are equivalent," says James Lugo, PhD, Chief Science Officer at Lonza, a Swiss chemical company that is one of the world's largest ingredient suppliers.

"Practitioners need to know they are recommending products that are most likely to deliver results for their patients. They can't afford to rely on ingredients with "borrowed science" or untested efficacy."

Motivated for Integrity

Companies like Lonza have the wherewithal –and the motivation--to hold finished product brands to task on the integrity of their formulations.

"I can't tell you how many times we've caught companies not using the clinically relevant doses of our ingredients. We know how much we sold to them, and we can check how much they sell, and what is claimed on their labels. Sub-effective doses lead to suboptimal outcomes, which hurt our brands. So we look at this stuff very carefully," Lugo said.

Generic ingredient suppliers have neither the resources nor the incentive to do the research or monitor the use of their raw materials.

Most top-tier practitioner-focused companies are using branded actives, though they may or may not promote them on their product labels. But practitioners can always ask about this: the use of well-researched ingredients is an indicator of a company's commitment to product quality.

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–James Lugo, PhD,
Chief Science Officer, Lonza

Lugo has led two clinical studies of UC-II, an undenatured form of type II chicken collagen that has become one of Lonza's top selling ingredients. The most recent trial involved 191 people with knee osteoarthritis. They were randomized to UC-II (40 mg daily), glucosamine-chondroitin (1500 mg & 1200 mg respectively), or a placebo for a period of 180 days.

The collagen group showed markedly lower overall WOMAC scores, as well as better sub-scores for pain, stiffness, and physical function (Lugo JP, et al. Nutr J, 2016: 15:14). The precise mechanisms behind the observed benefit are not entirely clear, though there is some evidence that undenatured collagen contains immunomodulatory compounds that can recruit T-regulatory cells into regions of inflammation, leading to a down-regulation of the inflammatory cascade.

Lugo acknowledged there are many other forms of collagen out on the market, however all of them are denatured or hydrolyzed by heat or chemical treatment. UC-II is undenatured, which makes it more effective at smaller doses.

"There's nothing wrong with denatured or hydrolyzed collagen. It's just that you need 6 grams per day to get the clinical effects."

Solid clinical research is a major factor driving the market success of joint health products that contain UC-II. Combined these products have shown compound annual growth rates of nearly 36% for the last 4 years, vastly outperforming other joint health supplements.

"If your product works, people will feel better, and if they feel better, they'll keep using the product," says Lugo, adding that three years ago, Pfizer began adding UC-II to its Caltrate bone and joint formula. Metagenics also uses UC-II in their joint health products.

"It's good business to do good science." **QC**

One Year On, CRN Sees Success With *Online Wellness Library*

Last year, the Council for Responsible Nutrition (CRN) launched its "Supplement OWL" (Online Wellness Library) with the intention of establishing a single, authoritative, non-government clearinghouse for specific information about the dietary supplements and herbal products out on the market.

This online label registry, launched in the Spring of 2017, in collaboration with Underwriters Laboratory (UL), is a self-regulatory initiative to increase transparency, educate consumers and practitioners, and assist regulators.

The OWL provides a one-stop library where consumers, retailers, regulators, industry representatives—and practitioners—can view the exact ingredients, label claims, dosage forms (aka "serving sizes"), intended uses, and contact information for every supplement product on the market.

"The reality is, questionable companies tend to run away from things like the OWL, because they know they would be voluntarily exposing themselves to regulatory scrutiny. We operate on the principle that fresh air is a great disinfectant." *–Douglas MacKay, ND, VP of Scientific & Regulatory Affairs, Council for Responsible Nutrition*

Though there's still a long way to go before CRN obtains 100% industry coverage—according to some estimates there are as many as 80,000 different supplements out there—the project is off to a strong start.

In the 18 months since it launched, the OWL has amassed over 11,000 product labels, with 89 supplement companies now engaged.

"Participation is moving along really well," says Gisele Atkinson, CRN's Vice President of Quality & Technical Affairs. "It is being fully supported by other trade organizations, and the FDA has also been very supportive—showing interest, asking for updates, asking for meetings to learn how the OWL works."

Steps Toward Transparency

Listing products on the OWL is voluntary, and there's no charge for companies to post their labels and basic information.

But this year, CRN added a new feature—a fire-walled commercial data exchange—where, for a small fee, companies can post all their analytical testing data, certificates of analysis, 3rd party certifications, and any other quality assurance information they want to publish.

Atkinson says the idea is to create a fast and easy way for supplement makers to share all their product specifications with buyers, including practitioners who dispense supplements.

Participation in the OWL is a way for ethical brands to show the world that they have nothing to hide.

"There was a subset of companies that really wanted to go to full transparency about their supply chain. They wanted to post all their certifications, their GMP inspection results, everything. We knew that certain audiences might misuse or misunderstand some of this information, so we came up with the idea of having a fire-walled section," explained Douglas "Duffy" MacKay, ND, CRN's Senior VP of Scientific & Regulatory Affairs.

Anyone can access the OWL's basic labels database free of charge. Access to the restricted portion of the registry is by permission only; CRN wants to ensure that only qualified people—supplement retailers, practitioners, regulators—have access to this more sensitive data.

He expects that as it grows, the OWL will be especially useful to clinicians—or their staff members—who manage in-house supplement formularies.

Several of the major practitioner channel brands, including Ortho Molecular, Douglas Labs, Innate Response, Integrative Therapeutics, Pharmax, and Pure Encapsulations, are already participating.

New Expectations

CRN does not verify or validate the label data that companies post on the OWL, but neither MacKay nor Atkinson are concerned that brands will try to game the registry with false or fraudulent information.

Says MacKay, "The reality is, questionable companies tend to run away from things like the OWL, because they know they would be

Council for Responsible Nutrition

The Science Behind the Supplements

voluntarily exposing themselves to FDA scrutiny. The companies that participate want to expose themselves because they know they are compliant, and they are confident in their products."

"We operate on the principle that fresh air is a great disinfectant," he added.

Ultimately, the CRN team hopes to set a "new minimum expectation" about label transparency.

As the industry grows and matures, it will likely come under increased regulatory scrutiny. This is particularly true in the practitioner segment, which, historically, has been too small to attract much attention from regulators.

But with practitioner sales nearing $4 billion per year, and annual growth rates between 8% and 10%, MacKay predicted that it is only a matter of time before the FDA starts taking a closer look.

And that might not be a bad thing, he says.

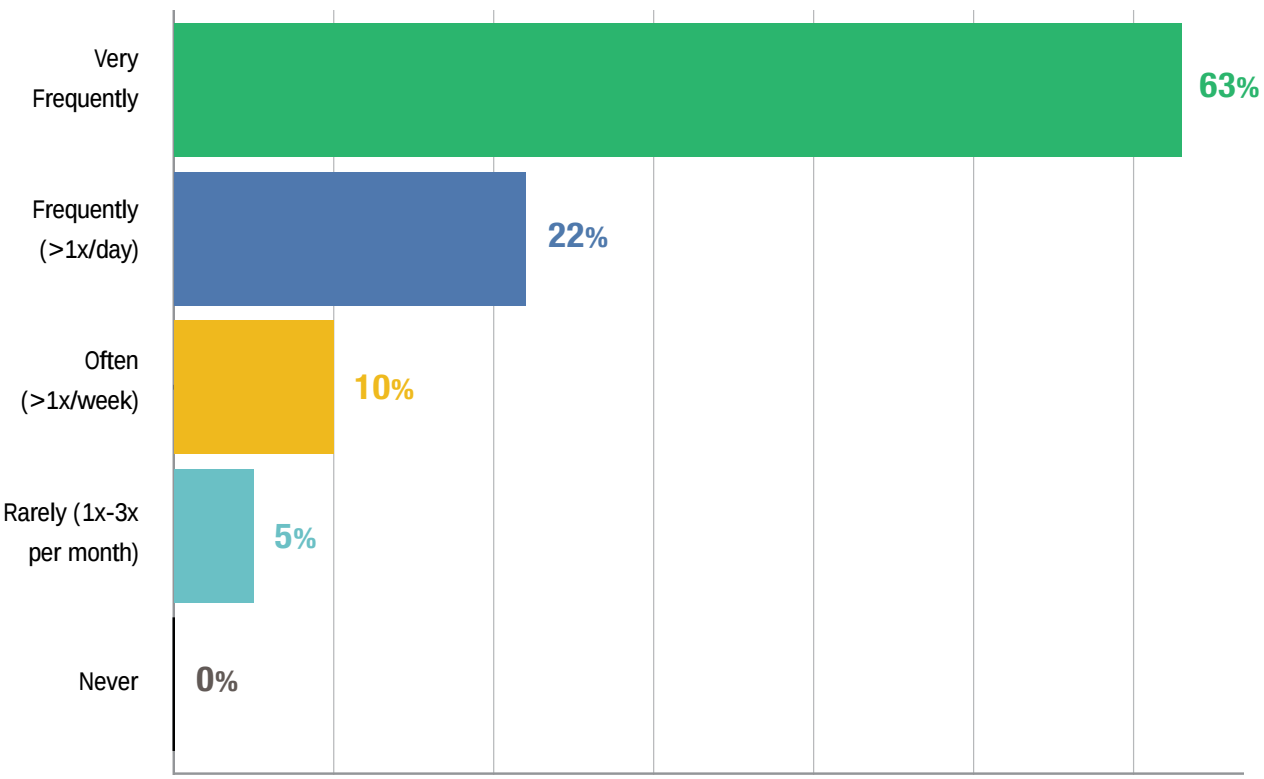
"Continued growth brings greater scrutiny. And we need that federal regulatory oversight to add a layer of legitimacy to the sector, so we can grow into the hospitals, larger clinics, federal programs, and perhaps eventually obtain insurance reimbursement."

CRN has frequent contact with the FDA and other regulatory agencies. MacKay notes that the FDA is well aware of the health professional channel, but has never put a lot of resources into policing it simply because it was not big enough. That is starting to change.

By posting their labels to the OWL, participating companies are essentially declaring their willingness to be transparent and their confidence that their products can stand up to greater scrutiny. **QC**

How often do patients ask you about supplements, herbs, and other natural products?

N=469 physicians & healthcare professionals



(Source: Holistic Primary Care's 2018 Practitioner Survey)

How Supplement Companies Walk Their Wellness Talk

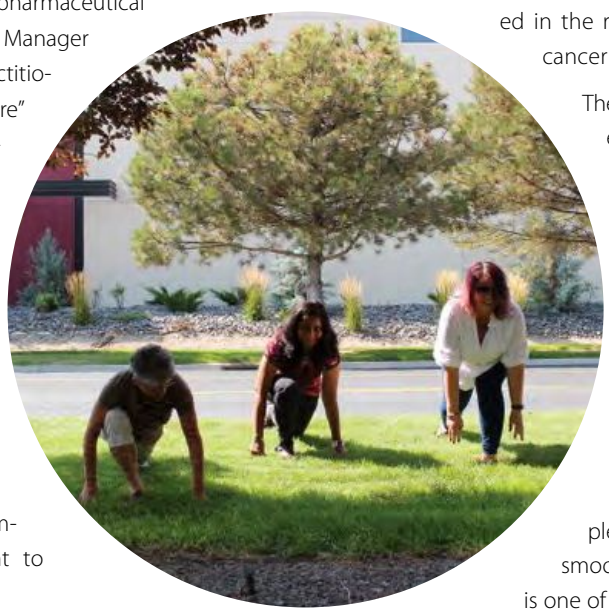
By Ellen Kanner | Contributing Writer

The supplement industry promotes wellness — that's its mission. And it's succeeding. Recent figures show wellness is a $3.7 trillion industry.

"People everywhere are looking for better alternatives to managing their own health than conventional pharmaceutical therapies," says Pam Conboy, Global Brand Manager for Klaire Laboratories, one of the leading practitioner-focused supplement brands. "Everywhere" includes the supplement companies themselves. From small businesses to multinational corporations, every company can create and promote wellness from within — it's just good business.

"If employees aren't happy," says Conboy, "they're not going to perform at their top level."

Klaire has made considerable investments in employee wellness; it is part of the brand's core values, and an important demonstration of the company's commitment to those values.



But wellness programming doesn't need to be high-tech or budget-breaking to have positive results. Klaire's most in-demand wellness initiative is its lunch and learn series.

"We get the greatest turnouts," says Conboy. "People have a real hunger for information." Presenters include integrative wellness experts but also "people who use our products." The company's high-quality, hypoallergenic supplements have a strong following within the autism community in particular. When employees connect with people who share their health challenges and who rely on the company's nutraceutical line, they "understand their work is really meaningful."

Wellness as an Ethos

"Wellness needs to be ingrained into the company's ethos," says June Lin, Head of Global Marketing, Consumer Health and Nutrition for Lonza, one of the supplement industry's major raw materials suppliers. At Lonza, basic healthcare benefits are just the starting point. The company tries hard to foster a culture of fitness.

Headquartered in Basel, Switzerland with 100 offices worldwide, the company's 14,500 workers embrace that ethos. They're excellent ambassadors for fitness, thanks to the company's fun fitness projects. Three hundred of Lonza's personnel participated in their marathon training program, Lonza Makes You Fit in 2016, including Lonza CEO Richard Ridinger. The program was such a success, the following year, the company added a cycling component. Lonza sponsored every employee who competed in the race, which benefitted a Swiss cancer foundation.

There's that old joke about whether a chef would be willing to eat in his own restaurant. At Metagenics, that's a given; everyone who works there gets to experience the benefits of the company's products.

In addition to offering fresh fruit and nuts in the break room, the company stocks its kitchen with its own line of supplements and blenders for staff smoothies. Better nutritional status is one of the hoped-for outcomes, to be sure, but the benefits include team-building, as well. "We're always sharing information and products," says the company's Human Resource Director Christina Chow.

Klaire, Lonza and Metagenics all cite community engagement as a vital part of their wellness programming, partnering with local organizations, whether it's a clothing drive for the homeless or sponsoring sports and social clubs within their communities.

Fitness, Fun & Fellowship

Yoga sessions, stress management techniques and mindfulness workshops are other effective ways to build wellness within the workplace. After all, wellness isn't just about the body, it has a strong emotional component. Group activities of any kind offer opportunities for greater bonding and office morale.

At Metagenics, "we have fun, as well. We try to add some goofy fun to wrap into our day," says Chow. But, she adds, "if you're not feeling it, you don't have to participate. We don't pressure you. Everyone has a different viewpoint as to what wellness is to them.

Photo: Klaire Labs employees stretch before their daily walk, part of the company's wellness program.

We can come up with a beautiful, awesome plan, but if it doesn't resonate within our population, it's not going to work."

Metagenics consults with partners and industry experts to make it work, to develop the right programming. The company pays attention to wellness trends, but places the highest value on employee input. Chow and her colleagues send out surveys, and have an open-door policy to get feedback about, "what employees feel is important to their life, what we should focus on and how to integrate that into our wellness program."

Four hundred employees have participated in the company's most innovative wellness initiatives, called Life-HOUSE (Lifestyle Intervention and Functional Evaluation — a Health Outcomes Survey). The program offers employees free blood panel testing and 23andMe genetics kits. After data is analyzed, employees receive personal consultations from Metagenics-affiliated clinicians, followed by customized diet and lifestyle plans, free nutritional supplements, and health coaching.

The executive team at Klaire tries to foster a corporate culture in which every employee understands that personal health is valuable. The company offers discounted memberships at local health clubs and facilities. "And we encourage our folks to use our products, available at a deep discount," says Conboy. "Employees see a difference in themselves and their families."

Sustaining the efficacy of wellness programs and maintaining employee engagement is always a challenge, especially as companies grow larger or get acquired by massive corporate conglomerates. There's always the danger that health and wellness values will get subsumed by bottom-line fiscal imperatives.

"With new and established businesses entering the nutraceuticals market, existing companies need to adapt and evolve to stay true to their core wellness values," says Lin of Lonza.

A Quality Indicator

In fact, bigger can sometimes be better when it comes to employee health and wellness.

Klaire Labs demonstrated this elegantly after being acquired by Soho Flordis International, along with ProThera and Complementary Prescriptions. According to Conboy, the three entitles have all benefitted each other. Klaire brought to the mix, "the lens of quality. Prothera and Complementary didn't have that focus on clean formulations. We removed any allergens."

Perhaps the merger's success comes from Klaire holding "true to Claire," says Conboy, referring to founder Clare Farr, an industry pioneer and champion who started the company in her own kitchen. Farr, who suffered from multiple chronic inflammatory conditions, formulated the kind of supplements she wanted for her own health — and for the health of others.

Even as the company looks towards the future, Klaire won't lose sight of the past. "We'll have our 50th anniversary next year," says Conboy. "We really started to resurrect Claire Farr. Her history and story are all over our walls," inspiring the company to honor Farr's vision and commitment. "We're still a relatively small company, growing and evolving. The important part is evolving in the right direction and taking everyone along with us."

Klaire, Lonza and Metagenics appreciate a healthy bottom line, but value a healthy workforce more. As Conboy says, "This is not about manufacturing products, shipping them out and making money. Our focus is really making a difference. That's the great joy."

It is also a subtle but important quality indicator. A company that makes a strong and sustained commitment to the health and wellbeing of its own employees is likely to be equally committed to ensuring the quality and safety of its products. **QC**

Employees of Lonza, a Swiss nutritional ingredient company, participate in the Zermatt half marathon as part of the company's "Lonza Makes You Fit" wellness program. More than 140 Lonza people made it across the finish line atop the Riffelberg, a 2600-meter mountain peak.

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