

# Quality Counts

A Clinician's Guide to Supplement Quality

Fall | 2017



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# Quality: It's a Clinical Issue

Dietary supplements have become an integral part of American life—and American healthcare.

By Erik Goldman | Editor in Chief

Despite the recession, the supplement industry has grown steadily at 5%-6% per year—twice the rate of OTC drugs. According to a 2011 report from the National Center for Health Statistics, more than half of all US adults regularly take supplements. A 2015 survey sponsored by the Council for Responsible Nutrition, puts the figure at 68%.

According to Cara Welch, of the Food & Drug Administration's Center for Food Safety and Applied Nutrition, there are now at least 75,000 different supplements on the US market, up from roughly 4,000 in the mid-1990s. Combined, they generated roughly \$40 billion last year.

This is not just a retail phenomenon. Supplements are part of everyday patient care in thousands of clinics. Though still a small slice of the total, sales via practitioners are growing at about 9% per year, according to *Nutrition Business Journal*, a publication that tracks the industry.

*Holistic Primary Care's* annual practitioner surveys indicate that nearly all primary care clinicians these days recommend at least a few supplements. The most recommended categories are: probiotics (89%), minerals (84%), essential fatty acids (81%) and "letter" vitamins (78%)

Currently, 63% of HPC readers dispense (ie sell) in their practices. Even among those who identify as "conventional allopathic," 8% dispense.

Despite their popularity, there are many misconceptions about how these products are defined, manufactured, and regulated.

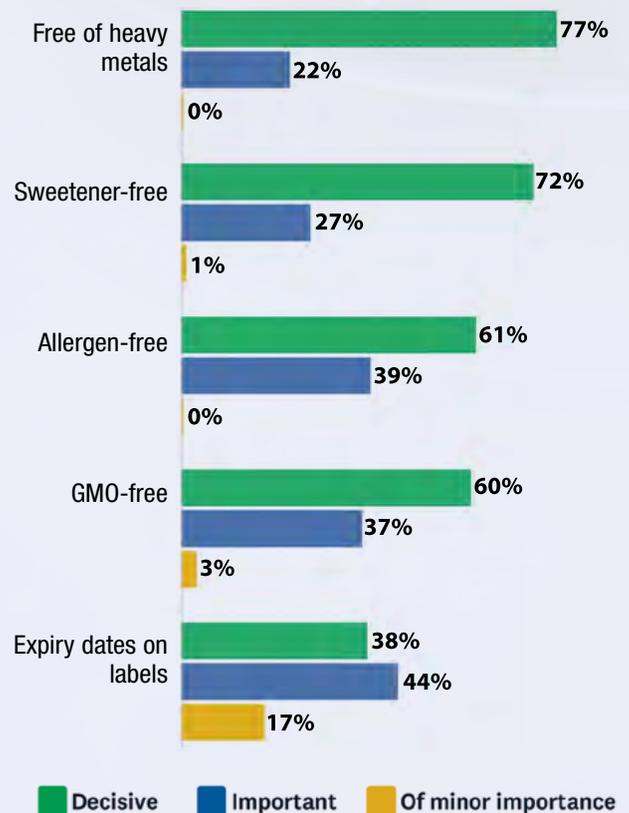
All-too-often in the media, the phrase "supplement industry" is preceded by the word "unregulated." Critics perpetuate the erroneous notions that the industry is lawless, that there is no quality assurance, and that most products are ineffective at best and dangerous at worst.

Even practitioners who routinely use supplements may not understand the regulations. Our 2016 practitioner survey showed that

57% of dispensing clinicians did not recognize DSHEA—the Dietary Supplement Health and Education Act of 1994—as the key statute governing the industry.

That said, quality is certainly on the minds of HPC's practitioners. Our 2017 survey showed the following factors to be decisive when clinicians evaluate supplements: heavy metal free (77%); sweetener-free (72%); and allergen-free (61%).

**In evaluating whether to introduce a new product or brand to your patients, how important are the following?**



## Regulated ... But How Well?

The truth is, industry regulation and quality assurance are far more evolved than the loudest critics claim. But they are also less consistent than many industry advocates want to admit. DSHEA gives federal agencies clear and far-reaching authority over supplement makers. And some companies now manufacture to pharmaceutical standards, with robust quality assurance systems.

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.

“The regulatory structure is a strange political compromise, unique to the US,” says Jeremy Appleton, ND, a naturopathic physician who has served as a medical officer for several supplement companies, and who is currently VP of Science & Regulatory Affairs for Soho Floridis International.

“If enforced, it is mostly sufficient to ensure supplements are safe. But unlike the regulations for drugs, there is no pre-market requirement to demonstrate efficacy, so there is no way for FDA to ensure supplements are *effective*.”

This special report explores the realities of supplement regulation and quality assurance.

We hope it will help you—and your patients—understand the rules, ask the right questions, and evaluate supplements more thoroughly. Concerned clinicians can play a vital role in holding manufacturers accountable to deliver safe, effective products.

The medical community was absent in 1994, when the current regulatory system was created. Given the rising role of supplements in healthcare, practitioners need to play a part in shaping the future of this dynamic industry. Consider this report an invitation to the dialog.

## Now more than ever, Quality Counts!

HPC is grateful to our industry partners for their support of *Quality Counts: A Clinician's Guide to Supplement Quality*

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# Supplement Regulations 101: What Clinicians Need to Know

By Erik Goldman | Editor in Chief

Americans certainly took plenty of vitamins prior to 1994—and argued vehemently about their benefits.

But it was not until President Bill Clinton signed the Dietary Supplement Health and Education Act of 1994 (DSHEA), that we witnessed the birth of the “dietary supplement” as we now know it.

DSHEA is a federal law that defines supplements as a distinct product category, sets basic standards for their manufacture, and regulates how they are marketed.

The statute emerged out of the then-burgeoning “health food store” movement, and was advanced by Senators Tom Harkin (D-IN) and Orrin Hatch (R-UT) in a bipartisan partnership barely imaginable today.

The law defines a supplement as 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.*

## A Balancing Act

Essentially, DSHEA mediates between the need for consumer protection and the public’s demand for open access to potentially beneficial, non-pharma health products.

Under the law, supplements are regulated as foods—more akin to hummus than Humira. As such, they are not subject to pharma style pre-market FDA approval. Just as a new brand of vegan cheese does not need FDA clearance before going to market, neither does a new brand of fish oil.

But this does not mean supplements are “unregulated,” as critics contend. DSHEA sets definite good manufacturing procedures (GMPs), labeling requirements, and rules about permissible product claims.

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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.

## Spotty Enforcement

DSHEA gives FDA and other agencies broad powers to identify, investigate, and prosecute unsafe products, fraudulent or inappropriate claims, and unethical promo tactics. Over the years, the FDA, FTC and other agencies have proven quite capable of decisive action (See *Enforcement Actions*, page 8.)

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. Trump’s 2018 budget shows no growth for FDA and no specific ODS earmarks. In fact, cuts are likely.

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.

## 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. The 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.”

Think of cGMPs like speed limits on the road: compliance doesn’t guarantee optimal safety, but non-compliance is a strong indicator of recklessness,” says Michael D. Levin, founder of Health Business Strategies, a quality and regulatory consultancy.

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 in principle. The problem is that 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. According to Cara Welch, a senior advisor to the FDA’s Office of Dietary Supplements, more than 5,000 new products hit market every year, but the agency only receives around 38 NDI notifications, amounting to just about 1,000 over the past 20 years. 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



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.

FDA's definition of "labeling" includes all marketing materials, websites, and social media.

Federal agencies are considering significant changes to food and supplement labels, including elimination of "calories from fat," an increased focus on total calories, enumeration of added sugar in gram amounts, required labeling of vitamin D content, redefinition of dietary fiber, and elimination of the International Unit (IU) in favor of micrograms for vitamins A, D, and E.

It has been about 20 years since the last major labeling changes. The timeline for the current changes is not clear, but could be as early as summer 2018.

## Structure/Function vs Disease Claims

Prior to DSHEA, vitamin companies could not make any health claims, and were essentially prohibited from advertising. 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. S/F claims must be supported by a modicum of science. FDA has jurisdiction over the veracity of S/F claims on product labels, packaging, marketing materials, websites, and social media; FTC enforces truthfulness in advertising.

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 these benefits. 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.

## Practitioner-Only vs Consumer Brands

DSHEA creates special challenges for practitioner-only brands because it prohibits them from speaking disease-centric health-care language. In a clinical context, S/F terms sound vague and imprecise, leading to furtive wink-wink communication, as marketers try to convey the utility of their products without crossing into disease claims. The S/F restrictions lead to "a dumbing down of information, to the point of technical inaccuracy, making the claims for the products difficult for clinicians to interpret," says

Jeremy Appleton, ND, VP of Scientific & Regulatory Affairs for Soho Floridis International. "The most compliant marketing materials will be the least informative for clinicians."

Todd Harrison, an attorney at Venable LLC, who specializes in supplement law, believes this is actually a public health issue. S/F restrictions impede truthful, non-misleading medical dialog. Harrison believes practitioner-exclusive brands should have greater latitude to communicate in scientific, disease-based terms, since practitioners serve as "learned intermediaries" between marketers and consumers.

The federal government does not share this view. Neither the FDA nor the FTC recognizes any distinction between "practitioner" and "consumer" brands. All are subject to the same laws.

Some practitioners choose to work with contract manufacturers to create their own private-label brands. Few understand that this makes them (or their clinics) *de facto* supplement companies—as fully liable for malfeasance, and as fully responsible for DSHEA compliance—as any major retail brand.

## Research: A Catch-22

DSHEA unintentionally discourages clinical research on supplements. Unlike the situation for pharma, where data can be transmuted into definite disease claims, ironclad patent protections, and massive profit, supplement brands have little research incentive.

They cannot use data to support treatment claims, and since supplements tend to have lower prices and lower margins than drugs, companies have a harder time recouping research investments.

The law actually makes it difficult to do supplement trials in the US. 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 S/F 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 trials, or other indirect indicators. Prospective clinical trials are typically done outside the US, and seldom with readily available 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 a very common practice in the industry, one that further discourages investment in original clinical research.

**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.**

# Who Enforces Supplement Regs?

Officially, jurisdiction over supplement regulations is shared between the Food & Drug Administration and the Federal Trade Commission, with occasional support from the Federal Bureau of Investigation and the Department of Justice.

On a practical level, state Attorneys General and class action attorneys also play a role.

## FDA & FTC

The FDA is responsible for enforcing compliance with good manufacturing practices and labeling requirements, monitoring post-market product safety, and overseeing product claims. FTC monitors the media for fraudulent, unsubstantiated or misleading ads.

"It used to seem really clear: FTC had jurisdiction over advertising; FDA had jurisdiction over labeling," said Richard Cleland, assistant director of the FTC's Office of Consumer Protection, at a recent regulatory conference sponsored by the American Conference Institute.

"But FTC takes the position that any communication intended to induce the sale of a product is "advertising"; FDA has an equally broad definition of "labeling." So in actuality there's a lot of overlap."

While they maintain separate jurisdictions, the agencies sometimes collaborate in coordinated sweeps. Cleland says FTC often relies on FDA scientific expertise.

## National Advertising Division (NAD)

A project of the Council of Better Business Bureaus, NAD is a cross-industry self-regulatory collaboration that monitors national advertising for accuracy, truthfulness, and credibility. NAD polices the mediasphere, issues warnings to companies making questionable claims, and refers cases to the FTC when its warnings go unheeded.

Kat Dunnigan, NAD Senior Staff Attorney, says many of NAD's leads come from companies reporting on their competitors. But before taking any action, NAD thoroughly reviews the reporting company, to ensure the claim is not a case of a pot calling a kettle black.

In the supplement sphere, NAD targets products making strong but poorly substantiated health claims, those that borrow science from distantly related formulas, or those that use studies done in one specific population to sell to a very different audience (ie, use of a study on mineral deficiency-related hair loss to sell products for male pattern baldness).



"The strength of your claim defines the demand for strength of evidence," says Dunnigan.

NAD has no formal authority, and its notifications are neither criminal proceedings nor binding requirements. But given the group's close relationship with FTC, it does play an important enforcement role.

## State Attorneys General

Unquestionably, there are holes in federal oversight. State AGs are actively filling those gaps.

In 2015, New York State AG Eric Schneiderman shook the industry by challenging the quality and identity of herbal products sold by 4 major retailers (GNC, Walgreens, WalMart and Target). Though the DNA technique used by Schniederman's office has questionable validity for botanicals, the high-profile action resulted in an agreement from GNC to provide the AG with twice-yearly DNA tests on raw materials. It triggered a string of class actions, and increased state and federal scrutiny of the entire industry.

Karl Racine, an AG in Washington, DC, says state AGs are preparing for what many expect will be a regulatory rollback under Trump. "We're not going to be shy when we think enforcement is important. AGs will act when the fed and state agencies will not."

Racine says AGs are driven by the need to be re-elected. Many have gubernatorial or congressional aspirations. They look for big cases involving high-impact health issues like diabetes and obesity. They share information with colleagues in other states, and often collaborate across state lines. "AGs are always talking. We're always looking for opportunities to work together."

## Class Action Attorneys

Supplement companies are frequent targets of class action suits, most of which are settled out of court. Charges range from misleading, unsubstantiated or false claims to actual physical harm. Some address legitimate grievances but many are spurious, and there is a lot of copy-cattng, where attorneys make allegations against companies that have received FDA or FTC warnings.

Class actions are on the rise, and industry insiders expect the surge to continue in a newly deregulated business environment.

# Federal Enforcement Actions



The FDA, the FTC, and other agencies have proven quite capable of taking decisive action against supplement makers.

Stephen Ostroff, MD, who twice served as the FDA's acting commissioner, points out that while FDA does not approve supplements the way it does drugs, "we do have the authority to take enforcement actions after a product is on the market—when we can establish that the dietary supplement is adulterated; misbranded; or cannot be marketed as a dietary supplement (e.g., an unapproved new drug)."

In a 2016 blog, Ostroff notes that, "We monitor the marketplace through market surveys, undercover buys, label reviews, a review of reports of illness or deaths, and product testing."

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**—Stephen Ostroff, MD,  
former FDA Acting Commissioner**

## There's been no lack of FDA action in recent years. Ostroff cites the following:

- More than 600 inspections of supplement firms in the US and abroad.
- Seizure of almost 90,000 bottles of supplements containing Kratom—an Asian herb sold as a non-opioid, non-addictive pain reliever. FDA contends Kratom is an unapproved drug. The Drug Enforcement Agency tried—unsuccessfully—to classify it as a Schedule 1 substance.
- Issuance of warning letters to "supplement" makers selling pure powdered caffeine in products that resulted in deaths of two teenagers.
- Enforcement actions against 24 companies selling supplements containing BMPEA, DMBA and picamilon—all of which are prohibited as dietary ingredients.
- A coordinated, year-long, inter-agency sweep involving the FDA, FTC, Department of Justice, and Postal Inspection Service,

that culminated in civil injunctions and criminal prosecutions against 117 companies for disease claims, misbranded products, or spiked/contaminated goods.

- Warnings against 14 companies selling supplements as cancer cures.
- More than 100 consumer alerts about "supplements" that actually contained active pharmaceuticals.

Earlier highly publicized actions include a 2003 ban on the herb Ephedra following more than 16,000 reports of serious adverse effects.

The FTC has also been quite active. Speaking at a recent conference on supplement regulations, Richard Cleland, of the FTC's Office of Consumer Protection, said the agency is paying close attention to supplements marketed for pain reduction, cognitive disorders, and weight loss. "We're also watching the opioid issues very carefully."

## Among the recent FTC actions:

- FTC vs Catlin Enterprises: A suit leading to an injunction for deceptive acts and false advertising of "Withdrawal Ease" to "significantly alleviate the symptoms of opiate withdrawal" and to "increase the likelihood of overcoming opioid withdrawal."
- Injunction against NPB Advertising for false and unsubstantiated weight loss claims for a green coffee extract supplement.
- FTC vs Quincy Bioscience, an ongoing case challenging the truthfulness of claims that Prevagen—a jellyfish-derived protein called apoaequorin—can improve memory and attenuate cognitive decline. The company cites an RCT of over 200 people. FTC says the overall data showed no significant impact, and that the claim is based on a questionable post-hoc analysis of 30 people.

# Industry Initiatives to Improve Quality

Beyond the FDA's basic criteria, there is not yet a single, national consensus defining optimal supplement quality.

Industry leaders recognize the gaps, and they're taking steps to address them.

## Dietary Supplements Quality Collaborative (DSQC)

This project, spearheaded by the US Pharmacopeia, convenes diverse stakeholders to define a "Quality Matrix" to improve quality and safety across the industry.

Participants include major industry groups (United Natural Products Alliance, Council for Responsible Nutrition, Consumer Health Products Association); educational groups (American Botanical Council); consumer advocates (AARP, National Consumers League); and medical organizations (American Medical Association, Academy of Nutrition & Dietetics).

In June, DSQC issued a 27-item first draft of the Matrix including stipulations that products be identity-tested using validated methods at every production stage; and that brands undergo FDA inspection at least every four years, and that herb growers follow the American Herbal Products Association's Good Agricultural Practices.

DSQC stresses that its goal is aspirational, not legislative. That said, leaders recently met with Steven Tave, head of the FDA's Office of Dietary Supplements, to discuss the need to go beyond federal cGMPs.

## CRN's Online Wellness Library (OWL)

The Council for Responsible Nutrition (CRN)'s new "Supplement OWL" creates a single, authoritative, non-government clearinghouse for specific supplement information. This online label registry, launched last Spring in collaboration with Underwriters Laboratory (UL), is a self-regulatory initiative to increase transparency, educate consumers and practitioners, and assist regulators.

Previous supplement databases describe ingredients in a general way. The OWL gives details about specific branded products.

"A responsible industry wants the legal requirements already in place to be enforced to promote a level playing field for all participants. Regulators need to be able to see the participants to effectively enforce the law, says Steve Mister, CRN's executive director.

CRN has invited all supplement brands to submit their data. Participation is free and voluntary. So far, more than 50 brands have responded, submitting labels for over 2,500 specific products. A number of professional-only brands, including Douglas Labs, Innate Response, Integrative Therapeutics, Ortho Molecular, Pharmax, and Pure Encapsulations, are already participating.

## Supplement Safety Compliance Initiative (SSCI)

A retailer-driven project launched in 2016 by the Natural Products Association (NPA), the SSCI aims to harmonize the diverse and often redundant certification systems in the industry.

Responsible manufacturers face the challenge of complying with multiple, often-divergent inspection standards from government agencies and industry groups. According to SSCI, there is a lack of consistency about what regulators and retailers really expect. Audit redundancy makes the process onerous and costly.

SSCI, which has buy-in from major retailers like Walgreen's, Vitamin Shoppe, and GNC, is developing benchmarks for equivalency between existing supplement certifications. According to Travis Borchardt, VP of Regulatory Affairs for Nature's Way brands, SSCI has a global vision, and though it began with botanicals, it will expand to include other supplement categories.

## Adverse Events Reporting for Dietary Supplements

As with drugs, clinicians are not legally required to report suspected supplement-associated adverse events to the FDA, but they're strongly encouraged to do so.

The FDA's Center for Food Safety and Nutrition (CFSAN) maintains a registry of food, cosmetic, and supplement-related AERs from consumers, practitioners, and supplement makers. Manufacturers are mandated by law to relay any reports of serious AEs within 15 days of receipt.

CFSAN recently made public all AERs from 2004-2016. During that period, the agency received 56,574 reports, 25,412 of which were supplement-related.

But Ashish Talati—an attorney specializing in supplement regulations—cautioned against taking these reports at face value, or considering them evidence of risk.

Many AERs lack key information (specific product used, full ingredients list, amount taken, etc), and only a handful are subject to in-depth investigation, and validation. This usually happens only when there is a distinct geographic or chronological pattern suggestive of a real problem.

"Anyone can file a report. Some are accurate, some are spurious. There's no way for the agency to monitor all of that," says Talati. "They do not prove causation."

FDA maintains a Safety Reporting Portal for clinicians and consumers wishing to submit dietary supplement AERs. For further guidance, contact the Office of Dietary Supplements at **1-888-SAFEFOOD**, or email: **ODSP@fda.hhs.gov**.

# Hallmarks of Evidence Based Quality

By Michael D. Levin | Founder, Health Business Strategies

Under DSHEA, the FDA gives a fairly clear definition of supplement quality. A *high quality product*: “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 reality, product quality can vary considerably, even among companies that comply with the FDA’s current Good Manufacturing Practices (cGMPs). That’s partly because DSHEA gives manufacturers wide latitude to define their own “established specifications.” Some companies choose to be quality leaders, others do not.

For several years, I worked closely with Cancer Treatment Centers of America®, the nation’s leading network of integrative cancer hospitals. As part of a patient safety initiative, we created the nation’s first hospital-based dietary supplement formulary to help CTCA’s clinicians identify evidence-based, high quality products they could trust.

We learned first-hand that mere compliance with company-defined specs won’t assure “superior quality.” Some companies choose, for example, to always test for a wide variety of low-level biological and chemical contaminants to assure maximum purity. Others cut corners to save money.

We read disturbing reports of sub-potent finished products, which began with Consumerlab.com back in the late 1990s. A wide range of ingredients were involved. This past March, for example, a 100mg capsule of CoQ10 was found to contain 77.9 mg of CoQ10. The test was repeated at a second lab with the same result. That means this product only met 78% of its label claim—a classic case of mislabeling.

We also know there’s a growing problem of economic adulteration in the ingredient supply chain. It’s a particular issue for herbal supplements, but definitely not exclusive to them (See p 19). Think: “Melamine in protein powders” or “Rutin-spiked Ginkgo.”

Proving ingredient identity is very technical and it’s not cheap. Some companies do a much better job than others in applying multiple technologies to prove authenticity of ingredients and freedom from adulterants.

**Proving ingredient identity is very technical and it’s not cheap. Some companies do a much better job than others in applying multiple technologies to prove authenticity of ingredients**

## All of this raises a big question: What are the most important markers of supplement quality?

I believe there are three clinically-relevant, evidence-based hallmarks:

**1) AUTHENTICITY:** Is the ingredient on the label truly the ingredient in the bottle? Consumerlab.com has published that many products claiming to have ingredients like CoQ10, alpha lipoic acid, and even B-vitamins do not contain those active ingredients!

We know that counterfeit ingredients have found their way into the market. Published research on Black Cohosh disclosed 3 of 11 off-the-shelf retail products were completely counterfeit. Products labeled Black Cohosh (*Cimifuga racemosa* aka *Actaea racemosa*) often contain less expensive *Actaea* species that are related but biologically distinct from authentic Black Cohosh.

The American Botanical Council has published surveys indicating that ~25 to 36% of the Black Cohosh sold in North American and European markets is adulterated, with the highest frequency reported in US internet sellers.

In 2014, the supplement industry was advised to “implement effective ingredient testing methods for chondroitin after a team of analytical experts identified sodium hexametaphosphate—better known as Calgon® water softener”—in chondroitin supplements marketed by a company called Zero One.

**2) POTENCY:** Does the ingredient contain the active components in the correct amounts?

The health benefit of a supplement is directly related to potency; subpotent products just won’t deliver expected results. Subpotent products may, unfortunately, be fairly common especially among “discount” brands.

One paper, which analyzed 6 retail samples of chondroitin, reported potencies as low as 16% of label claim. Over the past ten years, Consumerlab.com has identified many subpotent products, including EPA/DHA, CoQ10, B-Vitamins, Ginseng, Ginkgo, Saw Palmetto, Garlic, Zinc, and Valerian.

Under cGMPs, all potency claims must *always* be tested before leav-

Under cGMPs, all potency claims for a finished product must always be tested before leaving the manufacturing facility (unless a scientifically valid test does not exist). In fact, ingredient identity and finished product potency are the only truly mandated tests under cGMPs.



ing the manufacturing facility (unless a scientifically valid test does not exist). In fact, ingredient identity and finished product potency are the only truly mandated tests under cGMPs. Every other quality measure is fair game or free pass, depending on your perspective.

**3) PURITY:** Supplement ingredients—just like foods—can be contaminated with a wide variety of chemical and biological toxins. The list is endless. Under the regulations, companies must define which reasonable acceptable contaminants (RACs) need to be controlled for each ingredient, component, and finished product. Clinically important contaminants include heavy metals; aflatoxins in herbals (I've seen it in Milk Thistle); residual toxic solvents; pesticides; and microbes like *Clostridia perfringens*.

Some types of medicinal mushrooms present unique quality challenges. Case in point is *Cordyceps sinensis*—a peculiar fungus that sprouts from basically a mummified caterpillar. Prized in Chinese medicine, true *Cordyceps* contains immunostimulatory compounds. The problem is, *Cordyceps* is susceptible to economic adulteration. Wild harvesters in parts of 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. Two patients reportedly suffered lead poisoning associated with taking this product.

Melamine is another economic adulterant originally reported in protein products. In some cases it is added intentionally (though illegally) to raise apparent protein content.

## Quality Proxies

The products that practitioners recommend should be as free from biological and chemical contaminants as economically possible, right? First, do no harm!

Here are a few "Quality Proxies" you can use to gauge the brands you

recommend or dispense. Do not be afraid to request detailed documentation. Trust, but verify!

- **Concerned about solvents or pesticides in botanical extracts?**  
Request the raw material specs and analytical results from the last lot of raw materials received. If a company doesn't test for solvents and pesticides on every incoming lot, seek out brands that do.
- **Do you wonder if a company is cGMP compliant?**  
Ask for the table of contents of their Standard Operating Procedures (SOPs). All high-quality brands should have that. Look at public enforcement history. Regulatory action reports can now be accessed (for a modest fee) from Marian Boardley Consulting.
- **For ingredients known to be at risk of economic adulteration—**  
Black Cohosh, CoQ10, Chondroitin, Bilberry, Ginkgo, Saw Palmetto are but a few—ask for the ingredient specs with an explanation of how the ingredient is proven to be free of known economic adulterants.
- **Is finished product potency a concern?**  
Ask for specs and analytical results for the last lot of the product released to market. If they have not done this testing or if the results did not meet the label specs, ask "Why?"

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# Probiotics: Strain & Viability Define Quality

By Kristen Schepker | Assistant Editor

Discoveries about how the microbial world affects human physiology are multiplying at an astounding rate, reshaping much of what we know about health and disease.

This research is stoking a huge market for probiotic supplements, as this once obscure subject becomes a common conversation topic. Millions now take probiotics. HPC's practitioner surveys consistently rank them among the top 3 most clinically utilized supplements.

"Probiotics are a hot topic," says George Paraskevatos, Executive Director of the International Probiotics Association (IPA). "Everybody wants to be in the probiotic space—but that doesn't necessarily mean that everybody is following good quality guidelines."

The IPA is at the forefront of establishing quality standards for the probiotics industry. The group has also developed a research-backed checklist for physicians, and guidelines to help select probiotics for their patients.

Though there are many aspects to probiotic production, from a clinical perspective the key factors are the strains of organisms used, and their viability.

## Strain Selection

Researchers have studied the health impact of many diverse commensal organisms, both individually and in various combinations.

"Strain attributes do overlap, but we cannot assume that research done on one strain will apply to another," says Andrea Wong, Vice President of Scientific and Regulatory Affairs at the Council for Responsible Nutrition (CRN).

If a patient requires digestive health support, she explained, you don't want to recommend a probiotic primarily studied for immune system modulation. When choosing, it is important to familiarize yourself with the data on the expected benefits conferred by specific species and strains. They're not necessarily interchangeable.

Much probiotic research focuses on digestive issues and gastrointestinal conditions. Lactic acid-producing *Lactobacillus* is the most extensively studied genus in this context, and they have the widest range of digestive health applications. *Bifidobacteria* are a close second. Both are grown on media that contains milk proteins. This has relevance for people with dairy allergies or sensitivities.

Within each genus, there are typically dozens of species, and within each species there are many strains. ConsumerLab.com (CL) rou-



Scimat / Science Source

tinely reviews probiotics and offers good guidance on matching strains for individual needs.

## What are Colony Forming Units?

Vitamins and other supplements typically indicate dosages in terms of weight or volume.

For probiotics, weight and volume mean little. What's important is the number of living microorganisms that survive and replicate after being consumed.

The standard indicator for that is the quantity of colony forming units (CFUs) per dose. A microbiological concept, CFUs estimate the expected number of viable organisms a probiotic capsule will deliver to the intestines. It's a standard unit in probiotic research, and well-executed trials usually indicate the exact CFUs needed to obtain the observed physiological change or clinical outcome.

The quantity of CFUs needed to impart a particular benefit varies widely, depending upon strain, intended use, and desired benefit.

For common commercially available probiotics, label claims run somewhere between 1 billion to 10 billion CFUs per day—a range that conforms to a number of published guidelines. Some strains are beneficial at levels as low as 50 million viable cells per day. Others require 1 trillion CFUs daily to confer positive effects.

**In the marketplace, huge variations exist. Among probiotics recently tested by CL, the total number of CFUs per serving ranged from 100 million to 900 billion—a 900,000% difference!**

But more doesn't always mean better, and less doesn't always mean worse. When evaluating probiotics, Paraskevatos urges clinicians to request the data that guided a particular formulation. The CFUs on a product's label should be supported by data showing specific effects at that dose level.

According to CL, costlier probiotics tend to provide higher CFUs than cheaper ones. But the real question is, how much must one take to obtain a desired benefit?

"You can also compare the cost of obtaining from each (product) an equal number of probiotic organisms," the website states. The cost to obtain 1 billion CFUs can range from as much as \$1.00 down to just a few cents depending on strain and brand.

## Viability

Beyond the basic GMPs that apply to all supplements, DSHEA does not establish specs or testing requirements for probiotics.

To fill this gap, the IPA and CRN collaborated on a set of research-based voluntary guidelines earlier this year. These include scientifically-sound protocols for stability and identity testing, stated shelf lives, storage requirements, and guidelines for transportation.

Maintaining viability is of critical importance when dealing with probiotics. The organisms must be able to survive the highly acidic gastric environment—one of the body's primary defenses against food and water-borne organisms.

To assess whether particular strains or combinations will likely survive the gastric journey, probiotic companies—or their contracted analytic labs—use mechanical and biochemical reactors that mimic the human digestive tract.

Some probiotics use organisms that are too fragile to pass through the stomach. These require an enteric coating or another protective formula like microencapsulation. “Well-established encapsulation technologies are used broadly across the supplement industry to protect from harsh conditions like the acidic stomach,” says Andrea Wong from CRN.

Ultimately, microbial viability is related to product stability. The IPA/CRN guidelines urge manufacturers to commit to thorough stability testing to ensure viability from the time of manufacture to the arrival in the marketplace.

Temperature is an important variable. Several international guidelines have established clear temperature parameters for the manufacture and storage of probiotics. Stability testing should be done under the same temperature conditions as those indicated on the label.

Without doubt, it is challenging to ensure storage protocols are strictly followed down the whole supply chain. Wong suggests seeking out brands that invest heavily in scientific research. “If they invest in science,” she argues, “they will also invest in ensuring that their product remains useful throughout its entire life cycle.”

## Storage

The IPA/CRN guidelines recommend that probiotic labels carry expiration dates backed by valid stability testing. Though expiration dates are not required by DSHEA, reputable companies will provide them.

Different probiotic products carry different storage recommendations. As a general rule, heat and light are destructive to probiotic bugs, so it's a good idea to keep products sheltered. Once opened, it is important to store probiotics in moisture-free environments.

Many, though not all, require refrigeration. Numerous factors, including the strain, formulation, encapsulation, and packaging all influence whether or not a product needs to be kept cold.

Paraskevagos says shelf life is affected by strain or genus type, and by any

added excipients or therapeutic ingredients that manufacturers add to their formulas.

## Contamination Concerns

Given that probiotics are all about microbes, contamination is a natural concern. Some people fear these products might include potentially pathogenic bugs along with the friendly ones.

Regarding yeasts, molds, or other microbial contaminants, governments across the world set different thresholds for product safety, some of which are outlined in a recent paper by Sanders and colleagues.

Paraskevagos believes fears of contamination are unfounded. Reports of probiotics contaminated with pathogens are very rare.

“When receiving probiotic ingredients from manufacturers, these materials come with Certificates of Analysis (CoA), which should conform to all types of tests including but not limited to CFU counts, pathogens, contaminants, and allergens,” he says. “If the batch of probiotic ingredients does not conform, then these materials should and would not be released for commercial use.”

Analytical methods for bacteria are specific to the manufacturer, so Paraskevagos suggests checking with your preferred brands to see what specific techniques they use to detect potential pathogens. Don't be afraid to ask!

## Prebiotics

Many probiotic brands try to boost efficacy by adding prebiotics—dietary fibers that act as food sources for the beneficial bacteria, Wong explains. Fructans and galactans are the two dominant categories of prebiotics for *Lactobacillus* and/or *Bifidobacterium*.

“Including prebiotics... is like taking a two-pronged approach to your gut health,” Wong says. “They both have the same aim: to improve the composition of your gut microbiota.”

However, some people experience significant gas or bloating from products containing prebiotics. The added fiber can easily feed unfriendly organisms, and become substrates for fermentation in the gut.

Paraskevagos advises physicians to request the stability analysis for any probiotics with added ingredients. “They should have data that those ingredients work together symbiotically.”

“Not everything you might put into a probiotic will allow it to stay viable,” he explains. Acidic ingredients can kill beneficial bugs. Some manufacturers use minute amounts of vitamin C to protect against degradation, but too much can destroy microbial communities.

Both IPA and CRN are working to raise the quality bar on probiotic quality. Discerning clinicians who demand solid data and analytics can be vital allies in that process.



# Quality Considerations in the Omega-3 Market

By Kristen Schepker | Assistant Editor

According to a National Institutes of Health survey, nearly 19 million US adults regularly take omega-3s, consistently putting these products among the most popular supplements.

Omega-3s are also among the most researched supplements, with nearly 4,600 studies posted on PubMed.

Health professionals are on board, too. In *Holistic Primary Care's* 2016 survey, omega-3s are the third most commonly used supplements: 81% recommend them, and 83% take them for their own health.

Eicosapentaenoic acid (EPA) and docosapentaenoic acid (DHA) are the two main physiologically important omega-3s, though there are 11 in the family. Despite a general medical consensus that fish is healthy and people need omega-3s, there are no established Recommended Daily Allowances for EPA, DHA or the combination.

According to the Global Organization for EPA and DHA Omega-3s (GOED), a non-profit trade organization, generally healthy people should consume around 500 mg per day of combined EPA and DHA, though this will vary somewhat with age, gender, and health status. GOED's recommendation jibes with World Health Organization and European Food Safety Authority guidelines. According to the FDA, adults can safely consume up to 2 g per day of combined DHA and EPA.

Consumers and clinicians are confronted by a dizzying variety of EPA-dominant, DHA-dominant, and mixed EPA/DHA products. Some are derived from fish, others from krill, and still others from algae. How to navigate the options?

Here are some key considerations:

## Forms of EPA & DHA

DHA and EPA are available in four basic biochemical forms:

- **Triglycerides:** found in marine oil, in which trios of long chain fatty acids are bound by glycerol molecules. This is the most common form in supplements. Some brands market the triglyceride forms as they are in nature. Others unhook the DHA and EPA from glycerol, concentrate them, and then reassemble them with glycerol to create "enriched" triglyceride products.

- **Free Fatty Acids:** which are similar to the "enriched" triglycerides in that DHA and EPA are detached from glycerol and concentrated, but never reassembled.
- **Phospholipids:** as produced by krill, in which two fatty acid chains are linked to a phosphate and a choline.
- **Ethyl esters:** made by converting triglyceride forms to free fatty acids, concentrating them, then attaching ethanol molecules. Lovaza, the prescription omega-3, and its variants fall into this category, as do some supplements.

There's plenty of argument about which form is best, but little clinical data.

In 2015, pharmacist Matthew Ito reviewed pivotal trials for the prescription ethyl ester versus free fatty acid products in patients with hypertriglyceridemia. He found no significant differences. All products reliably reduce atherogenic triglycerides. To date, no one has done a prospective head-to-head clinical comparison of the various forms.

## EPA to DHA Ratio

Physiologically, EPA and DHA are different, leading to the question of what is the optimal ratio between them.

Many brands make a point of promoting specific ratios, based on the premise that people seeking particular health benefits may require higher levels of DHA over EPA or vice versa. Few studies have specifically explored this issue.

For the majority of people, ratio is a secondary consideration, says Adam Ismail, GOED's executive director. "EPA and DHA don't really compete against each other or have counteractive effects." Rather than focusing on ratios, people should make sure they're getting adequate amounts of both.

There are clinical situations, however, where the ratio does matter. In some patients with elevated triglycerides, excessive DHA can trigger an unwelcome increase in LDL cholesterol (Bradberry, J. & Hilleman, D. *Pharm & Ther.* 2013; 38(11): 681–691). If you have a patient with hypertriglyceridemia who's taking an omega-3, and you notice an unusual LDL spike, look closely at what they're using and consider switching to an EPA-dominant product.

## Sustainability of Sourcing

Most ocean-dwelling animals—including shellfish—produce omega-3 fats, but amounts and ratios vary across species. Many supplements are sourced from small, rapidly-reproducing fish (anchovies, sardines). Large wild species like cod, salmon, mackerel, halibut, and tuna produce a lot of omega-3s, but they are extremely valuable as food, and less likely to be used solely for their oil.

Responsible manufacturers source from sustainably managed fisheries, using non-endangered species. Friend of the Sea, and Marine Stewardship Council are two internationally recognized groups that monitor sustainability for fish oils (and seafood in general).

From a strictly nutritional standpoint, the source of EPA and DHA



does not matter much. But other considerations, like absorption, risk of contamination, and sustainability, are influenced by the source.

Certain forms of algae produce omega-3s, providing an acceptable source for vegetarians, vegans and others with allergies or dietary restrictions. Some algae-derived products are almost entirely EPA, others are mostly DHA. Few contain both, which is what most people need. This is much easier to obtain from fish and krill oils.

Flax is the most widely available land-based omega-3 source. Flax seed oil is roughly 55% alpha linolenic acid (ALA), a short-chain precursor to DHA and EPA. In humans, conversion of ALA to EPA and DHA is very low. Flax oil is healthy, but on its own it won't likely meet most peoples' omega-3 needs.

## Absorption

Many brands try to differentiate their products based on absorption claims. This is a key theme in the great "krill vs fish" debate.

There are small variations in absorbability. The human body does absorb the phospholipid forms in krill oil somewhat faster than the triglyceride forms in fish. Anecdotally, some consumers experience fewer fishy burps with krill. But krill oil is more costly than fish oil, a factor that may matter to some patients.

Ultimately, the choice comes down to personal preference, says GOED's Ismail. "There are differences in absorption from source to source, but they are relatively minor."

In some situations, however, a highly absorbable product might make a difference.

Some surgeons like to load patients with omega-3s preoperatively, to speed recovery, reduce inflammation, and cut infection risk. In these cases, where there's only a brief pre-op window in which to generate a rapid omega-3 surge, it makes sense to choose a more absorbable product.

For long-term health maintenance, however, there's less of a case. With omega-3a, "there is a plateau," Ismail explained. As people increase consumption of EPA and DHA, the omega 3 levels will rise to a point beyond which there's no further gain. Those who take a more absorbable product may simply reach that plateau a little faster.

## Contaminants

Given the high levels of aquatic pollution worldwide, it is reasonable to be concerned about toxins in fish oils—especially heavy metals. Several consumer watchdog groups routinely test fish oils for heavy metals and other contaminants.

**GOED has established limits for potential omega-3 contaminants, as well as methods for analyzing EPA/DHA levels. They set clear criteria for quality in this rapidly growing segment.**

The bad news, as every one knows, is that at the top of the marine food chain—large predatory fish like tuna, shark, mackerel and others concentrate mercury and other toxins. The somewhat better news is that lower down on the food chain, where most fish oils are sourced, heavy metals are less prevalent. Plus, they are easily removed in the refining process.

It is unusual for them to show up in commercial products, but top quality companies should be testing every batch to ensure freedom from heavy metals and other toxins.

GOED is one of several groups that conduct random off-shelf tests. "We've tested hundreds of products," Ismail said, and "to my knowledge, we've never tested a product with detectable amounts of mercury." Consumerlab.com did not find mercury in any of the fish oils it tested.

The International Fish Oil Standards Program (IFOS) also tests to ensure that fish oils do not contain contaminants. Created by NatraSource, a Canadian contract research lab, IFOS provides test results to the public via an online database. Top fish oil brands should be able to document their purity with clear analytical test results.

## Rancidity

Rancidity is another area of concern. When exposed to oxygen, oils oxidize and fatty acids break down. This is true not just for fish oils, but for all oils, including olive and other vegetable oils.

Oxidative rancidity is measured according to peroxide values, which indicate the amount of initial fatty acid breakdown. For most vegetable oils, international regulations set a threshold of 10 meq/kg. Olive oils are an exception; they are considered safe at values up to 20 meq/kg.

With fish oil, it's a different story. In 2002, industry representatives established the Council for Responsible Nutrition Voluntary Monograph (now known as the GOED Voluntary Monograph), setting 5 meq/kg as the limit for acceptable peroxide content.

In other words, GOED standards set a much lower acceptable threshold for peroxidation in fish oils than the standards applied to oils used as food.

"If the peroxide value of a (vegetable) oil is 10, and you safely consume a hundred times more of that than you do of fish oil, a peroxide value of 5 in a fish oil consumed at much lower levels should eliminate any concern about safety or toxicity."

GOED has also established guidelines and limits for other potential omega-3 contaminants as well as methods for measuring and analyzing EPA/DHA levels. While compliance is voluntary and none of these guidelines have the weight of a federal mandate, they do set very clear criteria for quality in this rapidly growing segment of the nutrition industry.

# Capsules & Delivery Systems: An Overlooked Aspect of Quality



By Erik Goldman | Editor in Chief

When people talk about supplement quality, the focus is usually on active ingredients. But there's another equally important aspect: the capsules and tablets that deliver the "actives."

No matter how good the ingredients, a supplement is only effective if it releases its nutrients when and where the body needs them. Delivery systems have become quite sophisticated these days, offering a vast range of properties, advantages, and disadvantages.

Enteric coatings, liposomes, microencapsulations, timed-release delivery, animal versus vegetable materials...these are just a few considerations.

A lot of engineering expertise goes into encapsulation and tableting. Though it is easy to overlook, it is an essential factor in the quality equation. Committed companies strive to match their delivery choices with their ingredient profiles and consumer preferences.

According to the 2015 *Supplement/OTC/Rx Database (SORD)* study, 42% of supplement users prefer capsules over tablets—they're convenient, clean, and easy to swallow," says Missy Lowery, Sr. Marketing Manager for Capsugel, one of the world's largest capsule suppliers for the drug and supplement industries. The data suggest that consumers who buy supplements from practitioners are particularly partial to capsules.

## Animal vs Plant Sources

Capsules are used for a wide range of powdered, liquid, and oil-based ingredients. Most are made of gelatin, which can be either soft or hard.

Both types are commonly used for pungent nutritional oils, like fish and krill oils. Manufacturers using softgels may add fragrances or flavors to mask the odors that emanate due to the micro-channels created by the soft gel's plasticizers. Hard gelatin capsules—especially those nitrogen-flushed upon filling and then hermetically sealed to prevent oxidation—can more successfully block odors, Lowery explained.

Gelatin is derived from marine, bovine, or porcine sources. While all are effective for ingredient delivery, the source is very important for some patient sub-groups. Religious Jews and Muslims, for example, avoid pork-derived ingredients of any sort. Vegetarians and vegans want to avoid all animal-based ingredients.

According to Lowery, the vegan sector is growing quickly. "We have seen extremely strong growth in demand for our plant-based, certi-

fied Vegan capsules. We're catching a rising tide for vegan supplements." Lowery estimates nearly 40% of supplement users want vegetarian options, and vegans are leading that charge.

"Vegans are loyal and passionate consumers who set trends among the full spectrum of vegetarian consumers. Millennials (ages 15-35) are the top sales drivers, with 47% of Millennial supplement users saying vegetarian/vegan is important. They look for products with a Certified Vegan seal."

In order to receive that seal, a vegan supplement—if encapsulated—must be delivered in a vegan-approved capsule. Not all vegetarian capsules qualify. In addition to being free of animal-derived ingredients, the capsules must be free of cross-contamination with animal substances during production.

Capsugel makes a range of vegetable-derived caps. The most recent innovation is the "Plantcap™" made from pullulan—a polymer derived from naturally fermented tapioca. These pullulan caps can be used for "stinky" oils, as well as for all liquid ingredients—especially those prone to oxidation, says Lowery.

Pullulan, "has a moisture content similar to gelatin, and the highest odor barrier properties of all polymers." She added that Plantcaps™ are verified by the Non-GMO Project, an added plus. They're also free of additives, preservatives, allergens, starch, and gluten as well as certified non-GMO, Kosher, and Halal.

## Gelatin Contaminants

Like the ingredients they contain, animal-derived gelatin capsules can be contaminated with environmental toxins and heavy metals. Though incidents are rare, they have a big ripple effect, given how many encapsulated drugs and supplements people take every day.

In 2012, Chinese authorities detected dangerous chromium levels in gelatin capsules made by a manufacturer in that country. The supplier, looking for cheaper ways to make drugs in response to pressures on healthcare costs, was using scrap leather as the source of their gelatin. Tanned leather contains chromium.

This affected 13 drugs and traditional medicines in the Chinese market, and prompted the Chinese Ministry of Public Security to impound 77 million caps.

While this particular incident did not directly affect US companies, it prompted worldwide concern, given that billions of capsules made in China and other nations are exported to the US and other countries for use in pharma and supplement products.

In April 2013, the US Pharmacopeia revised its national formulary monograph for raw pharmaceutical grade gelatin to insist on heavy metal testing. Many US-based manufacturers stepped up the scrutiny of their capsules.

In response to the crisis, Capsugel introduced a series of hard gelatin capsules (Coni-Snap® Sigma Series) manufactured to Six Sigma quality standards that go far beyond the tolerance levels written into current industry standards. Each individual Sigma Series capsule, whether destined for pharmaceutical or supplement application, is fully traceable to its source.

## Enteric Coatings & HPMC

Enteric coatings—made of fatty acids, waxes, shellac, plastics, plant fibers, or film resins—have long been applied to tablets, capsules, pellets, and granules (typically delivered in capsule shells) to delay ingredient release. They protect acid-sensitive ingredients during passage through the stomach, and delay delivery until the pill or capsule reaches the intestines. Most probiotics are delivered via enteric coatings of some sort.

Among recent innovations is the “Vcap” vegetarian hard capsule made of low-moisture hydroxypropyl methylcellulose (HPMC) that offers an alternative to enteric coatings. HPMC is inherently acid-resistant; it delays disintegration in the stomach but opens immediately at pH levels above 6.8, says Lowery. HPMC capsules are well suited for delivery of probiotics, enzymes, and many sports nutrition ingredients.

Delayed release capsules (DRcaps) also protect acid-sensitive ingredients for at least 30 minutes in the stomach’s pH of 1.2. They provide these benefits without any additional enteric coatings, which can be costly.

DRcaps are ideal for probiotics and enzymes, as well as plant-based powders such as ground valerian root or garlic that can trigger unpleasant burps if released in the stomach. They’re also well suited for delivery of creatine and amino acid-based ingredients like SAM-e, l-glutathione, and l-carnosine.

## Liposomes & Microencapsulation

Many supplement makers now use microencapsulation, nanoparticles, or liposomal delivery systems to increase uptake and tissue delivery of nutrients or herbal ingredients that are otherwise difficult to absorb.

Liposomal technology was initially developed more than 20 years ago, to enhance skin penetration of topical drugs. Supplement companies got onto it roughly a decade ago, and interest has grown rapidly since.

It amounts to encapsulating minute amounts of the nutrient substance—say glutathione, or curcuminoids (from turmeric)—in micro-

scopic phospholipid spheres. In some cases this is done to enhance sublingual absorption, thus bypassing the digestive tract altogether; in others it protects acid-sensitive ingredients from the low gastric pH.

The phospholipid bilayers mimic the structure of cell membranes, and actually fuse with membranes when releasing their active components.

A number of different compounds are used to create liposomes, including raw lecithin and phosphatidylcholine. The former produces larger (200-600 nm) particles that are not as well absorbed; the latter gives smaller particles (<200 nm) and faster absorption.

According to Stefan Gafner, PhD, a pharmacist who serves as the Chief Science Officer for the American Botanical Council (ABC)—the nation’s leading herbal education organizations—liposomal delivery can definitely improve absorption of botanical ingredients like curcumin. But he has not yet seen any data showing definitively that liposomes can direct plant compounds to specific tissues, as some companies claim.

As a trend, he expects liposomal delivery will continue to grow as herbal companies seek to differentiate their products based on improved bioavailability.

Capsugel recently developed a new micro-encapsulation technology called Lipid Multi-Particulates (LMP) that provides microspheres (50-300 microns) containing precisely measured microdoses of botanicals, vitamins, or amino

acids. The LMPs improve gut distribution of the ingredients, while also timing their release. LMPs also mask ingredients with unpleasant flavors. They can be used in combination with powdered ingredients via sachets and stick-packs for reconstitution in liquids, and can even be compressed into tablets.

## Nanotechnology

Nanotechnology is also a hot trend these days. It’s based on similar ideas as liposomal encapsulation, only the particle sizes are even smaller (1-100 nm). At this size, the physical and chemical properties of a nutrient or botanically derived substance begin to change.

Companies claim the small particle size enhances delivery—and therefore the benefits—of these compounds. This may be true. But there are many unknowns about nano formulations.

Given that nanotech significantly alters the biological properties of substances, nano formulations of widely used nutritional ingredients could very well be reclassified as “new dietary ingredients” under the FDA’s 2016 regulatory revisions (see p. 5). There’s no question nanotech is here to stay. But research on its real benefits—and potential downsides—lags behind manufacturer and consumer enthusiasm.

For every ingredient delivery challenge, there is an encapsulation or tableting solution. As the supplement industry grows ever more diverse and sophisticated, delivery systems will continue to evolve. Stay tuned!

**A lot of engineering expertise goes into encapsulation and tableting. Though easy to overlook, it is an essential factor in the quality equation.**

# Quality Assurance for Botanicals: A Field in Flux

Despite more than a decade of negative media and high-profile regulatory assaults, herbal medicine remains very popular with American consumers—and practitioners.

According to *Holistic Primary Care's* 2017 clinician survey, 64% of respondents use botanicals in their practices, and 49% want to learn more about them. Even among self-identified conventional allopaths, 27% use or recommend botanicals.

From a quality assurance perspective, herbs represent the most challenging segment of the supplement industry. In part, this reflects the inherent complexity of plants. Unlike discrete vitamins and minerals, herbs often contain hundreds of potentially bioactive compounds.

Like grapes for wine, herb quality is affected by growing conditions, seasonal variation, and post-harvest handling. This makes them more difficult to standardize than simple nutrients like, say, folic acid or magnesium.

Modern techniques for validating herbal identity and assessing bioactivity are works in progress. And then there are the realities of a truly global supply chain.

## A Regulatory Conundrum

Herbs are a conundrum for regulators. Though DSHEA permits use of the term “herbal supplement” (as opposed to the more generic “dietary supplement”), the law makes no distinction between herbs and other supplements.

All are subject to the same GMPs, labeling rules, and claims limitations, despite vastly different sources, manufacturing processes, and consumer usage patterns. Like all supplements, herbs are considered “foods.” That works for things like Oregano or Rosemary. But nobody makes a meal of Ginkgo leaves. On the other hand, reclassifying herbs as drugs also makes little sense.

The issue of herbal regulation became front-page news two years ago, when New York AG Eric Schniederman accused four major retailers of selling fraudulent house-brand herbal products. The action triggered heated discussion within and outside the industry.



Many botanical experts say Schneiderman’s conclusions were exaggerated and his DNA methodology was flawed. But he rightfully drew attention to gaps in the regulatory framework.

“The critics have a case. They really do,” says Roy Upton, President & CEO of the American Herbal Pharmacopoeia. Since 1995, AHP has produced independent and unbiased monographs outlining criteria for the identity, purity, and quality of medicinal herbs.

A practicing herbalist since 1981, Upton is trained in Ayurvedic, Chinese, and Western herbal medicine. As a founder of the American Herbalists Guild (AHG), and a member of the group that helped create DSHEA, he’s seen the best and the worst of the industry.

**“I have great respect for the people who are doing it well. But there are also some really bad players out there, a lot of ignorance, and a lot of apathy.”**



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## Infusions, Tinctures, Extracts

Herbs are available in many forms, from loose-leaf teas to highly concentrated powders and liquids standardized to specific biomarkers. It is important to understand the distinctions.

**Infusions & decoctions:** Hot water extractions—aka infusions and decoctions—remain very popular. But even a simple method like this has nuances.

“If it’s a root, you need longer periods. If it’s a leaf, it’s faster. If it’s a seed, like Fennel, you want to crush the seeds before extraction. For an herb like Marshmallow, you use lower temperature so you don’t destroy the polysaccharides. There’s a science to tea-making,” says Stefan Gafner, PhD, Chief Science Officer of the American Botanical Council, an internationally-renowned non-profit herb research and education organization.

Technically, infusion means steeping herbal materials for relatively short periods of time. Decoction means boiling (usually roots, barks, and seeds) for long periods—often many hours.

**Tinctures:** Gafner says aqueous alcohol extraction is the most common commercial method for preparing herbs. These tinctures typically have ethanol content in the range of 25-60%. Some go as high as 90% for herbs that are difficult to extract, but most are on the low side.

Glycerin or vinegar are also used. Though less common than ethanol tinctures, and not appropriate for all types of herbs, they are a good option for patients wishing to avoid alcohol.

**Dry extracts:** are basically tinctures that have been spray-dried to evaporate the alcohol solvent, leaving a concentrated powder that can be used in tablets or capsules. This form is very common in herbal supplements, Gafner says.

**Supercritical CO<sub>2</sub> extracts:** This increasingly popular eco-friendly method is so named because it uses of CO<sub>2</sub> cooled and pressurized below the critical threshold between its gaseous and liquid states. Liquefied CO<sub>2</sub> can extract compounds other solvents cannot. “Once extracted, you change the temperature and pressure, and the CO<sub>2</sub> becomes gas again, leaving concentrations of the desired compounds. You can recapture the CO<sub>2</sub> and recycle it.”

Over the centuries and across the globe, many volatile solvents have been used to make extracts—including methanol, ethyl acetate, dichloromethane, chloroform, and hexane. In general, says Gafner, the industry



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has moved away from potentially toxic solvents.

Ethical manufacturers will test finished extracts to ensure there are no solvent residues. But, as AHP’s Upton points out, this does not mitigate the environmental impact of these toxic solvents.

As the herb industry has become more “medicalized,” many ingredient suppliers are further processing extracts to isolate, purify, and concentrate specific compounds. The result is a plethora of branded ingredients with high degrees of biochemical uniformity and consistency.

That’s a plus from a quality control perspective. But many herbalists contend that in isolating single components, one loses the synergistic, balancing effects of a plant’s multiple active compounds.

## Validating Herbal Identity

Traditionally, herbal experts identified plants by their organoleptic properties—appearance, smell, taste, and texture. Even today, well-trained herbalists can be remarkably accurate, provided they have access to whole plants.

But in today’s high-volume herbal industry, most raw materials don’t come in as whole plant parts; they’re highly processed powders and liquids devoid of the plants’ prominent identifying characteristics. Hence the rise of analytical chemistry and, more recently, genetic analysis to validate botanical identity.

Many different methods are now in use: high performance liquid chromatography (HPLC), thin layer chromatography (TLC), gas chromatography (GC), UV spectrophotometry, mass spectrophotometry are among them. All have strengths and limitations. The problem is, there’s little consensus on methodology.

All the techniques involve detection of biochemical signatures unique to a given plant. But plants produce dozens of chemicals, and for many herbs, there’s no agreement on which ones matter.

“A lot of tests performed to establish quality are arbitrary at best. They’re not based on active compounds,” says Upton. “Nobody really knows the clinical pharmacology of St. John’s Wort. The same for Ginkgo. How do we decide what compounds to test? You can standardize St. John’s Wort to hypericin, but it’s not necessarily correlated with efficacy,” says Upton. AHP has published testing guidelines for many herbs, as have the US Pharmacopeia, the European Pharmacopoeia, and other agencies.



Upton acknowledges that all the recommendations can be challenged to some degree. But they give the industry a starting point. By standardizing to specific markers, “You can prove the product is consistent, but you don’t know that marker compound is biologically important.”

ABC’s Gafner—a pharmacist with extensive analytical chemistry experience—says many herbs are ID’d based on just one or two markers. He’d like to see the industry move toward multi-compound chromatographic “fingerprints.”

“We are moving in that direction. Many ingredient suppliers now have their own in-house libraries of biochemical fingerprints. Ultimately, I would like to see a broad, multi-stakeholder consensus library.”

Getting there won’t be easy. First, many companies consider their analytics proprietary. Second, fingerprinting herbs is not so simple. “Depending on how you process an herb, the fingerprint looks different. Alcohol extracts look different than water extracts. The root has one profile, the leaves have a different profile. It is complex.”

“Depending on what product you make, the identity testing needs to be different,” Gafner said, adding that it’s never a one-test matter. Thorough validation requires multiple methods.

## DNA Testing

### What about DNA? It has all the answers, right?

That’s certainly what AG Schneiderman thought when he took retailers to task in 2015. But again, it’s not so simple.

DNA analysis of herbs is still in its infancy. It is a reasonable option for unprocessed plants with intact cellular material. But it’s less applicable to liquid extracts or powders derived from them, because they contain little plant tissue.

This was a major criticism of Schneiderman’s action: his case was based on methods not necessarily fit for purpose.

“The more processed the material is, the less likely you’ll find DNA to evaluate,” Gafner explained. “DNA is helpful for identifying fresh plants and crude raw materials—things not submitted to heat, processing, or extraction. If you use supercritical or steam distillation, neither will have DNA, so the DNA-based methods won’t tell you anything.”

DNA is not evenly distributed in plant parts. Leaves contain a lot, but bark—think Willow or Witch Hazel—has little. So even with unprocessed materials, DNA tests are not a slam-dunk. It depends on which part of a plant you test.

For the foreseeable future, chromatography and spectroscopy will remain the mainstays of botanical identity validation. But DNA tools

are evolving rapidly, and Gafner expects they will eventually take their place among routine methods, especially for less common, difficult-to-identify plants.

DNA tests will also likely play an important role in detecting contaminants and adulterants.

## Contaminants & Adulterants

Like any agricultural product, medicinal herbs are at risk for contamination with environmental toxins (heavy metals, pesticides, fumigants, petroleum derivatives) and biological contaminants (microbes, mycotoxins, endotoxins, helminthes, insects).

Heavy metals and other industrial or agricultural chemicals find their way into plants via polluted water, soil, and air. Some, like pesticides, may be sprayed directly onto herbal crops. Some plants are particularly good at absorbing toxins—rice, for example, has an affinity for arsenic, and tea plants are good at concentrating fluoride.

But Gafner believes the risk has more to do with growing conditions than the type of herb. “If you source from a place where there’s a lot of lead in the ground, and pollution in the air, you have much higher risk regardless of the plant.”

Unfortunately, herbs are also subject to deliberate, economically-motivated adulteration. Some unscrupulous ingredient suppliers use cheap plant materials as substitutes or fillers for costly or rare herbs. Others intentionally spike herbs with pharmaceutical ingredients—a particular problem with herbal supplements for weight loss, performance enhancement and sexual health (Kosalec I, et al. *Arch Industr Hygiene & Toxicol.* 2009; Tripathy V, et al. *Phytochem Letters.* 2015).

Canadian researchers used DNA techniques in a blinded analysis of 44 consumer-facing herbal products representing 12 brands and 30 plant species. 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) found 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).

The full extent of these problems is difficult to quantify. Contamination and adulteration are not the norm, but neither are they rare occurrences.

**Though adulteration and contamination are real problems, it is important to put them in perspective. Damage caused by poor quality herbs is likely small compared to that caused by pharmaceutical overuse, or adverse effects of drugs used as directed.**

Several groups including the World Health Organization, the US Pharmacopeia and the European Pharmacopoeia, have issued testing guidelines, and maximum allowable thresholds for common contaminants in herbs. In the US, GMPs mandate that supplement brands test raw materials and finished products for all “reasonably anticipated contaminants.”

But the various guidelines do not all agree, there’s no global harmonization of supply chain oversight, and federal enforcement of DSHEA is spotty.

The American Botanical Council and American Herbal Pharmacopeia have been extremely proactive on the issue of adulterants.

Along with the University of Mississippi’s National Center for Natural Products Research, the groups established the Botanical Adulterant’s Program to test retail products, publish evidence of adulteration, and issue guidance on optimal testing methods. Stefan Gafner is the technical director, and edits the quarterly *Botanical Adulterants Monitor* to keep the industry informed.

Though adulteration and contamination are real problems, AHP’s Roy Upton says it’s important to put them in perspective. From a public health viewpoint, the damage caused by poor quality herbs is likely very small compared to that caused by pharmaceutical overuse or adverse effects of drugs used as directed.

The reality is, ethical companies that follow USP or European standards, and meet California’s stringent Prop 65 criteria, are producing clean, safe products. When evaluating herbal formulas, ask for detailed information on the company’s protocols for detecting toxins, biological contaminants and adulterants.

## Who’s to Blame?

US supplement manufacturers are quick to point fingers at Asian suppliers for the problem of tainted herbs.

It is true that some contaminated or adulterated botanicals have been traced back to sources in China and India. But Upton, who has traveled extensively in Asia and is familiar with many Chinese suppliers, says Americans need to stop throwing shade and start looking hard in the mirror.

**“The problem is not with China. It is with buyers that will buy the cheapest stuff..”**

“The problem is not with China. It is with buyers that will buy the cheapest stuff. Chinese companies produce some of the best herbal ingredients in the world, and they will also produce the lowest quality. It depends on what you want. If you want high quality, well, China produces higher quality than anybody on the face of the Earth. If you want cheap, low quality, they will sell that to you.”



Variable quality, he added, is by no means a strictly Asian phenomenon. European producers work the same way. “The customer dictates the quality, not the supplier.” Unfortunately, with retail price pressures being what they are, some brands are taking that low road.

Jeremy Appleton, ND, VP of Regulatory & Scientific Affairs for Soho Floridis (owner of Klaire Labs), echoed Upton’s view.

“There are good and bad raw materials available from most countries. Just because an ingredient comes from China or India does not mean it is bad. However, it does present challenges in terms of auditing vendors. The recourse you have with a US supplier might include a site visit, which is much more readily achieved than with an overseas supplier.”

Appleton says Klaire Labs holds all vendors to the same exacting quality standards, regardless of their location. “If they meet those standards, the country of origin is not terribly important.”

The bottom line is, high-quality comes with a cost.

“Good herbal medicine is not something that is easily achieved,” says ABC’s Gafner. “There’s a lot of expertise and knowledge that goes into doing it right. It is difficult for lay persons—or clinicians and attorneys general for that matter—to grasp how complicated this can be.”



# Clinical Considerations for Improving Supplement Quality

By Erik Goldman | Editor in Chief

As dietary supplements have moved from health food stores into clinical settings, the imperative for improving product quality has grown ever stronger.

Practitioner-focused brands have played an important role in raising the bar for safety and quality throughout the industry. The clinical communities they serve can be a potent instigator for further improvements.

“Producing high quality supplements requires a tremendous amount of attention, from beginning to end,” says Russell Jaffe, MD, PhD, a veteran immunologist and chemist, who did research at the National Institutes of Health, prior to founding Perque Integrative Health, a practitioner-focused nutraceutical company. “I am a doctor, not just a scientist and entrepreneur. I need to set high standards for safe ingredients.”

The reality is, quality costs, Jaffe stresses.

Supplements need not be egregiously expensive, and high price tags don't always guarantee top quality. But it's a good bet that people seeking bargain prices are less likely to get well-made, thoroughly tested vitamins and herbs.

Are practitioner-exclusive brands intrinsically better?

The industry veterans interviewed for this special report all agreed that practitioner-only status does not in and of itself ensure the highest quality. Likewise, there are many excellent products available in direct to consumer retail.

It really comes down to the strength of a company's commitment to safety and efficacy.

“The practitioner channel is much smaller than the retail channel, and many companies in the channel are smaller operations, with limited staff to control quality,” says Jeremy Appleton, ND, who has worked as medical advisor for several leading practitioner channel brands, and is currently VP of Scientific & Regulatory Affairs for Soho Floridis (Klaire Labs).

## Contract vs In-House Manufacture

He pointed out that many smaller players in the practitioner channel do not actually manufacture their own products. They use contract manufacturing organizations (CMOs) to produce their formulations. Use of CMOs is widespread throughout the supplement world, but brands seldom disclose this fact. In many ways, CMOs are the invisible hand in this industry.

“Using a CMO is not always a bad thing; some of them are very high-quality operations, says Appleton. “However, dependence on a CMO also means relinquishing a degree of control over quality, as well as control over sourcing ingredients, qualifying raw material vendors, having access to master manufacturing records.”

He believes its completely fair game for practitioners to question supplement brands about whether they're using CMOs, and if so, how they oversee quality control.

According to Roy Upton, director of the American Herbal Pharmacopeia, most CMOs do a fairly good job making products that contain simple vitamins, minerals, and other basic nutrients. But few have the necessary skill sets to make top-quality botanicals, particularly if a formula requires less common herbs. “A typical CMO does not have the expertise to assess the quality of something like Astragalus or Dong Quai.”

## Bioavailability

Many companies try to differentiate their products based on claims about superior “bioavailability,” a pharmacological term meaning the fraction of a given dose of something that ends up in systemic circulation.

In the supplement world, the term is used more loosely to indicate that a specific form of a nutrient or herb is better absorbed or more easily delivered to target tissues than other forms.

It's a simple concept, but physiologically the issue is complex.

First off, most bioavailability claims are not based on human pharmacological trials, but on animal studies or lab assays. Further, there is tremendous genetic variability in how different people digest, absorb, and metabolize various nutrients or herbal compounds.

Curcumin, a key compound in turmeric, is one herbal compound for which there is considerable human data on absorption and pharmacokinetics. It is often characterized as a difficult-to-absorb herb with low bioavailability. Stefan Gafner, a pharmacist and analytical chemist who is the Chief Science Officer for the American Botanical Council, says that's an oversimplification.

“It's true we don't see a lot of curcumin in the blood, but there may be metabolites that are there but we're not testing for them or they may be sequestering in the tissues. Further, curcumin may exert effects on the gut microbiome, which results in some of the benefits that we see clinically, even though the compound may not be in the bloodstream.”

Gafner says over-reliance on the classical pharmacological model developed for single-compound drugs can be misleading when applied to botanicals. “We need to recognize that herbs can be efficacious without raising blood levels of any particular compound to very high levels.”

Upton says many claims about bioavailability are overblown. “You’ll hear a claim that adding Bioperine to curcumin will raise its absorption, or that liposomal forms will give a 23% increase in bioavailability of curcuminoids. But there’s an equal chance you’ll get a 23% increase if you give a non-liposomal form to somebody in the morning versus the evening. The ability to absorb nutrients varies with circadian rhythms, stress, dietary factors.

## Gluten, GMOs, and Allergens

Many supplement users are highly concerned about gluten and other food allergens.

This is not lost on the industry. In recent years, dozens of brands have made “free-from” claims. As with everything else, if a company is claiming its products are gluten-free, allergen-free or made without GMO ingredients, you should feel free to ask for detailed documentation to prove it.

Many brands indeed work very hard to obtain clean raw materials. But even if their “actives” are free from allergens or GMOs, their excipients—the binders, flow agents, carriers, and other “inert” ingredients—may not be.

“In order to claim your products are allergen and GMO free, you need to be completely outside the conventional corn, soy, and wheat supply sources,” says Jaffe. Many excipients used in supplements are derived from one or more of these crops. Obtaining organically grown, GMO-free versions is not easy, and they cost a lot.

Companies that do spend the extra effort and capital will usually make similar investment in carefully monitoring their finished products. They should be able to provide complete detailed information about what they use, where it comes from, and how they test.

## Quality Indicators

Knowledgeable clinicians can play an invaluable role in keeping supplement makers honest and holding them to their stated commitments.

There’s no fail-safe way to know, on face value, if a company can deliver on its quality promises. But there are some characteristics that, taken together, indicate a high likelihood that a brand takes quality control seriously.

- **Is the company a member of key industry organizations?** Groups like the Council for Responsible Nutrition (CRN), American Botanical Council (ABC), United Natural Products Association (UNPA), Global Organization for EPA and DHA Omega-3’s (GOED), American Herbal Products Association (AHPA), International Probiotics Association (IPA), and International Fish Oil Standards (IFOS), have all set standards for quality and ethical conduct which they expect member companies to uphold. “When you see a company that’s a member of these groups, you know they’re concerned with quality and regulatory compliance, not just to advance their success, but because of the intrinsic value,” says Appleton.
- **Does the company have a robust Quality Assurance staff?** Size doesn’t always matter. But the reality is, good QC and regulatory compliance requires a lot of work and intelligence. Committed companies typically have teams of highly trained professionals working on these issues. If one or two people are trying to do it all, odds are slim they’re doing all of it well.
- **Is the brand compliant with the basics of DSHEA?** Marketing materials reveal a lot more about a brand than many people realize. If a company makes overt disease claims in its brochures or on its website, it is clearly not in compliance with the regs. This does not automatically mean that the actual product is unsafe or ineffective. But it should raise suspicion about other ways in which the company is skirting the rules.
- **Do the labels show expiration dates or shelf life information?** Technically, the law does not require manufacturers to put expiration



dates on supplements. But companies that are serious about quality control will do so.

- **Is there a pharmacovigilance program?** Post-market monitoring is important, and high-quality companies have well-established procedures for handling adverse events reports.
- **Can the company provide details about its raw material verification?** Committed companies go to great lengths to assure their ingredients are clean and consistent. Some have staffers that visit and fully audit raw material vendors. They also do a lot of analytic testing—either in-house or via independent labs such as Alkemist, Covance, or DiTeba. Good companies willingly share details about their vendor verification systems with interested practitioners.
- **Does the brand invest in research?** In truth, few supplement or herb companies have the financial resources to fund pharma-style trials. And the regulations prevent them from using clinical findings to make frank disease claims. Nonetheless, some brands make substantial investments in research, and in formulating with research-validated ingredients. While it's not an ironclad rule, those that are committed to science are usually committed to quality assurance as well.

## Putting Risk in Perspective

There's no question that US supplement regulations are problematic, that enforcement is inconsistent, and that poor quality products reach the market.

But even in a rigorously regulated space like the pharmaceutical industry, there are plenty of instances where poorly made substandard products make it to the market. And tight federal oversight on pharmaceuticals has not prevented problems like opioid addiction, antibiotic overuse, and a high incidence of adverse effects caused by pre-approved products.

It is interesting that the clinical community tends to take news of a drug recall or a report about life-threatening side effects in stride. There's never a chorus of medical experts vilifying the entire drug industry. The reaction to problems with supplements tends to be much more categorical.

"Conventional medical doctors don't have to defend Pfizer, Merck or Johnson & Johnson when they get busted for scientific fraud or levied huge fines for GMP infractions. They don't have to defend the quality of the drugs they prescribe," says AHP's Roy Upton.

"I don't see why functional medicine physicians and integrative doctors have to feel defensive about the nutritional and herbal products they're using within integrative medicine protocols."

**The reality is, millions of Americans take dietary supplements every day. Very, very few end up in hospitals with life-threatening complications from doing so.**

That's not to say supplement safety is a moot point. On the contrary, there's plenty of room for improvement. Clinicians who care about nutrition and lifestyle can play a vital role in helping this young and dynamic industry step up its game.

HPC is grateful to our industry partners for their support of *Quality Counts: A Clinician's Guide to Supplement Quality*

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