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Envisioning the Future of Dietary Supplement Regulation

By Erik Goldman | Editor in Chief

In the 25 years since Congress passed the Dietary Supplement Health and Education Act (DSHEA), the supplement industry has grown from cottage industry to multi-billion dollar global business.

Recent estimates put total worldwide sales of vitamins, minerals, proteins, amino acids, and herbal medicines at $124.8 billion in 2018, with a projected growth to $210 billion by 2026.

The North American market is by far the largest. Supplement sales in the US hit $42.6 billion last year, according to the research firm, *Reports and Data*.

The already burgeoning natural products sector has been turbocharged in recent years by consumer demand for cannabidiol (CBD) and other cannabis-derived products. In 2018, US CBD sales were estimated to be $390 million. But that was before passage of the Farm Bill legalizing cultivation of low-THC industrial hemp (a major source of CBD), and the decriminalization of hemp by the Drug Enforcement Agency. Industry-watchers project that CBD sales could scale to $20 billion by 2022.

Surging Sales, Straggling Regs

Rapid industry growth, the introduction of new ingredients, the globalization of the raw materials supply chain, the widespread use of genetically-modified ingredients, the emergence of ingredients produced via synthetic biology, and the growing threat of economically-motivated product adulteration are combining to challenge DSHEA in ways its original framers could not have envisioned.

An historic piece of legislation in its time, DSHEA essentially defined the concept of a "dietary supplement," and in the process gave a formal identity to what had until then been a fragmented field—albeit a very popular one. Contrary to the oft-sung refrain that "supplements are unregulated," DSHEA laid out a clear framework for oversight.

Under DSHEA, the federal government defined:

- **Clear roles and discretionary authority for the Food & Drug Administration (FDA) and the Federal Trade Commission (FTC):** FDA regulates manufacturing standards, quality assurance, permissible ingredients, product claims language, and scientific validation; FTC presides over truthfulness in advertising and marketing.
- **Good Manufacturing Practices (GMPs):** DSHEA includes guidelines and standards for everything from production procedures through management of consumer complaints.
- **Pathway for New Dietary Ingredients:** Companies wishing to introduce a new ingredient or novel combination must first notify the FDA, which has 75 days to review the ingredient(s) and determine safety.
- **Labeling Requirements:** The law defines rules for supplement labels, which must include a "Supplement Facts" panel detailing key ingredients, net quantity, serving size, manufacturer contact info, and a standardized disclaimer stating the product is not intended for prevention or treatment of disease.
- **Rules for Permissible Product Claims:** DSHEA clearly prohibits claims stating or implying that supplements can prevent or treat diseases, but permits—and actually encourages—Structure/Function claims describing these products in terms of how they support the health of specific organs or physiological processes.
- **Requirements for Adverse Event Reporting:** Though enforcement is spotty at best, the FDA does require supplement companies to report serious adverse events. It also stipulates criminal penalties for submission of false or misleading reports.

There's no question DSHEA was a compromise—some would say a devil's bargain. It permitted the then-young industry to legally advertise, while maintaining an inviolable line between supplements and pharmaceuticals by restricting the use of disease-based, symptom-oriented language that consumers and practitioners understand.

Movement Toward Revision

It is an imperfect law, and it has strong critics from all sides. Some feel DSHEA is weak and toothless, giving the industry far too much latitude to self-define and self-enforce meaningless standards. Others contend that it throttles truthful communication and discourages research—few companies are willing to invest millions in clinical trials that cannot be used for product marketing purposes.

But by and large, DSHEA has stood unchanged for more than two decades. Within its bounds, the dietary supplements and natural products industries have thrived. And despite grumbling from all corners, there have been no major steps toward revising it.

Until this year.

In February, shortly before his resignation, then FDA Commissioner Scott Gottlieb announced the agency's intention to "strengthen regulation of dietary supplements by modernizing and reforming FDA's oversight."

He stressed that, "What was once a $4 billion industry comprised of about 4,000 unique products, is now an industry worth more than $40 billion, with more than 50,000—and possibly as many as 80,000 or even more—different products available to consumers."

While most companies act responsibly and ethically, Gottlieb held that the current regulations leave holes, "for bad actors to exploit the halo created by quality work of legitimate manufacturers to instead distribute and sell dangerous products that put consumers at risk.

As the popularity of supplements has grown, so have the number of entities marketing potentially dangerous products or making unproven or misleading claims about the health benefits they may deliver."

The announcement represents the first time in a generation that the agency has signaled an intention to revisit or revise DSHEA. It heralded a volley of FDA warning letters to companies making unapproved claims about cancer, diabetes, Alzheimer's disease, and other serious disorders.

Simultaneously, the FDA announced its intention to create a new regulatory framework for hemp-derived CBD and other cannabis-related substances (See P. 6). The 2018 Farm Bill, the FDA's approval of Epidiolex, and the DEA's re-scheduling of hemp have created a chaotic and confusing landscape in which federal and state laws often clash, questionable products have flooded the market, and responsible companies struggle to comply with conflicting demands.

A few weeks later, Gottlieb resigned as commissioner. The move was unexpected and did not appear to be forced or politically motivated. Gottlieb is on record stating that while he loved his job at the FDA, it was taking a serious toll on his family life.

In the wake of his departure, it became clear that the intention to review and possibly revise DHSEA is agency-wide; it was not simply the pet project of a single commissioner.

Norman "Ned" Sharpless, MD, the acting commissioner, stated in April that, "I am not planning any radical changes from what the FDA has been trying to accomplish. Necessarily, there will be course adjustments as new facts emerge, but essentially, I feel I am walking into an organization on a good trajectory, and my main job is to figure out how to keep that going."

He added that the FDA will, "continue our efforts to modernize and reform our oversight of dietary supplements."

On May 16, the FDA held its first day-long public hearing about revising supplement regulations. The meeting included speakers from all major supplement industry trade organizations, as well as representatives of academic medicine, regulatory agencies, consumer advocacy groups, and law firms involved in the nutrition field.

In his opening remarks, Sharpless stated: "DSHEA was deliberately crafted to establish a careful balance of protecting consumers' right to access safe products and accurate information, while preserving FDA's authority to protect those same consumers against unsafe and otherwise unlawful products. While the fundamental goals underlying DSHEA have not changed, the challenge of realizing those goals has grown to a magnitude far beyond what it once was."

He said the FDA has "established an agency-wide dietary supplement working group that is looking into our dietary supplement organizational structures, processes, practices, and procedures, and identifying where we can make improvements."

Incremental Changes

Few in the industry expect major changes to DSHEA in the near future. The political process for such moves would be long and complicated under the best of circumstances. Under the prevailing conditions in Washington, and on the threshold of an undoubtedly contentious campaign year, big moves are very unlikely.

That said, the FDA did announce some significant regulatory steps:

- **Creation of the Dietary Supplement Ingredient Advisory List:** a public-facing log of potentially dangerous or unlawful ingredients detected in products marketed as supplements. "If an ingredient might be unlawful, consumers need to know so they can avoid using products with that ingredient. And responsible industry participants need to know as well, so they can avoid selling them," said Sharpless.
- **Formation of a Botanical Safety Consortium**: an assembly of academic researchers, herbal product manufacturers, botanists, chemists, and toxicologists who will meet regularly with the FDA to evaluate safety of herbal compounds in supplements, and to develop or improve analytical and toxological methods.
- **Possible Mandate for a Centralized Product Registry:** Under the current form of DSHEA, the FDA is not clearly authorized to require manufacturers to register and list all their products with the agency. Former commissioner Gottlieb had called for an amendment to DSHEA that would mandate such a central registry. Dr. Sharpless supports this move, stating that a comprehensive centralized registry would enable the FDA to respond more decisively: If the agency learned that an ingredient was dangerous, it could quickly identify all listed supplements that contain it and issue consumer warnings or mandate product recalls.

If a "DHSEA 2.0" eventually does emerge from the federal government, will it be more restrictive or expansive? It's a question that many in the supplement industry have raised.

Todd Harrison, a regulatory attorney who specializes in nutrition industry issues, believes that the current hearings are opening "a window of opportunity for a more expansive regulatory regime that allows greater innovation from industry."

Harrison, a partner with Venable LLP, sees opportunities for widening the scope of permitted dietary ingredients; improving boundaries for innovation; allowing supplements to be covered by flexible spending accounts, and finalizing a list of "grandfathered" pre-DSHEA dietary ingredients that are considered permissible for commerce.

At the same time, he believes that revisions of DHSEA, will likely strengthen the FDA's ability to take action on:

- Egregious disease claims (*e.g.*, cancer, HIV/AIDS, opioid addiction, chronic pain, Alzheimer's and other cognitive decline conditions)
- Supplements containing CBD *not* derived from hemp
- Supplements containing ingredients the FDA considers unsafe or to fall outside the current definition of dietary supplement

Regarding elimination of unlawful and potentially unsafe ingredients, Harrison says the FDA's new Ingredient Advisory List is a step in that direction.

"DSHEA was deliberately crafted to establish a careful balance of protecting consumers' right to access safe products, while preserving the FDA's authority to protect those same consumers. While the fundamental goals underlying DSHEA have not changed, the challenge of realizing those goals has grown far beyond what it once was."

—Ned Sharpless, MD,
Acting Commissioner, FDA

Ingredients Under Scrutiny

This list is for compounds that are not currently recognized as legal dietary ingredients, approved food additives, or substances generally recognized as safe (GRAS); and novel compounds that have not been submitted for pre-market notification as New Dietary Ingredients.

Harrison stressed that an ingredient's appearance on this list does not mean that the ingredient has been proven unsafe, or that the FDA has made a formal safety assessment. It simply means that the agency has concerns and is undertaking an evaluation.

Among the first wave of ingredients on the list are:

- Andarine: a selective androgen receptor modulator, sold in some muscle-building formulas
- Higenamine: a naturally-occurring compound in aconite, lotus seed, and other herbs used in traditional Asian medicine, and marketed as a weight loss and performance aid. It is a β2 agonist and is prohibited by the World Anti-Doping Agency.
- Hordenine: a phenethylamine compound found in many plants including barley, sorghum, and millet, and promoted as a "metabolic enhancer" for weight loss.
- 1,4-Dimethylamylamine (DMAA): an experimental stimulant sold widely in sports performance and body-building formulas.

Phenibut: Though not (yet) on the Ingredient Advisory List, this GABA analog is under heavy FDA scrutiny, according to Harrison. The compound is promoted as a "nootropic" cognitive enhancer by a number of supplement companies. Originally developed as an anti-anxiety drug in the Soviet Union decades ago, phenibut is a central nervous system depressant that has paradoxical stimulant effects as well. At low concentrations, it increases dopamine levels which appears to increase focus and concentration.

Phenibut is not an FDA approved drug in the US, nor is it a recognized dietary ingredient. A number of researchers have raised concerns about addiction.

The FDA recently issued three warning letters to companies marketing phenibut labeled as supplements. The letters stressed that this is not a legal dietary ingredient, and that "dietary supplements" containing phenibut are misbranded. Harrison says this is the first time the FDA has issued warning letters solely on the basis of an ingredient's status, and not citing other violations. "It signals FDA's new focus on new ingredients."

Kratom (*Mitragyna speciosa*) Native to southeast Asia, this plant produces compounds that bind to opioid receptors. Advocates say it is a non-addictive alternative to prescription pain killers and heroin. But critics say it can be just as addictive, and further, that many products marketed as "kratom" are spiked or adulterated.

Over the course of the last 12 months, the FDA has seized multiple shipments of kratom and kratom-containing products, and is urging medical professionals to report any possible kratom-related adverse effects to the MedWatch database.

Vinpocetine: In June, the FDA issued a warning about potential reproductive system effects associated with vinpocetine, a synthetic analog of a naturally occurring alkaloid in *Vinca minor* (Periwinkle). Frequently labeled as "vinca extract," vinpocetine is a common ingredient in supplements sold for memory enhancement, mental focus and visual acuity.

A recent report from the National Institutes of Health's National Toxicology Program, concluded that vinpocetine raised the risk of miscarriage and low fetal weight in rabbits and rats at blood levels equivalent to those seen in humans after a single dose of a typical vinpocetine supplement.

The findings, though based solely on animal studies, were enough for the FDA to issue a categorical statement advising pregnant women or those likely to become pregnant to avoid taking vinpocetine. The message to supplement companies? Ensure that vinpocetine products are labeled with safety warnings against use by pregnant women.

Homeopathics in Limbo

Though they are sold in the same retail aisles as vitamins, herbs, and other supplements, homeopathics are definitely not supplements from a regulatory perspective.

Under the Food, Drug, and Cosmetic (FDC) Act of 1938, a law passed long before "dietary supplement" was even a concept, substances listed in the *Homeopathic Pharmacopeia of the United States (HPUS)* were defined as a distinct category of drugs.

That's been the regulatory status of the grandfathered ingredients ever since. Homeopathics are not governed by DSHEA, and for decades marketers could make disease treatment claims —provided there is precedent for the claims in the HPUS or the historical homeopathic literature.

Homeopathics do, however, fall under the jurisdiction of both the FDA and the FTC. In recent years, they have taken steps to revamp these very old regulations on what many perceive as archaic, unscientific products and practices.

According to the FDA, "a drug, including a homeopathic drug, is considered a "new drug" if it is not generally recognized as safe and effective (GRAS/E) by qualified experts for use under the conditions prescribed, recommended, or suggested in the labeling. FDA makes GRAS/E determinations for OTC drugs marketed under the OTC Drug Review. The FDA has not reviewed any drug products labeled as homeopathic under the OTC Drug Review, because the Agency categorized these products as a separate category and deferred consideration of them."

Putting it simply, the FDA is saying that homeopathic ingredients deemed acceptable drugs in the era when nearly all were produced by independent compounding pharmacists, do not pass muster as approved drugs in today's era of industrial mass production, when homeopathy has become a $3 billion OTC industry.

Late in 2017, the FDA issued a document called *Drug Products Labeled as Homeopathic: Guidance for FDA Staff and Industry*, outlining a new "risk-based enforcement" policy that recategorizes homeopathic drugs as "unapproved new drugs" subject to the agency's enforcement discretion.

The FDA also rescinded its 1995 *Compliance Policy Guide (CPG) 400.400, Conditions Under Which Homeopathic Drugs May Be Marketed*, which, the agency says, unwittingly facilitated the marketing of prescription and non-prescription drugs, as well as non-recognized dietary ingredients unlawfully labeled as "homeopathic."

"There are no homeopathic drug products marketed in the United States that are FDA-approved. This means that the FDA has not evaluated them for safety or effectiveness. Thus, such products may not meet modern standards for safety, effectiveness, and quality," the agency said in a statement last year.

Drug Products Labeled as Homeopathic lays out the criteria likely to trigger agency action:

- Products that contain or claim to contain ingredients associated with potentially significant safety concerns;
- Products with reported safety concerns;
- Products for routes of administration other than oral and topical;
- Products marketed for the prevention or treatment of serious and/or life-threatening diseases and conditions;
- Products targeting vulnerable populations;
- Products that do not meet standards of quality, strength, or purity as required under the law

The FTC is also scrutinizing homeopathy. In 2016, it announced a plan to hold homeopathic efficacy and safety claims to the same scientific standards as apply to other OTC drugs: the claims must be supported by credible and reliable scientific evidence.

Given that homeopathic claims are often based on historical theory, traditional use, and anecdote, many homeopathic marketing pitches would fit the FTC's definition of "misleading."

As with the FDA, the FTC's enforcement resources are limited. Both agencies must choose their battles carefully. Though both agencies now have broad discretionary authority to go after homeopathic products, so far there have been few major regulatory actions.

And in a small but significant victory for homeopathy, in November 2018, the 9th Circuit Court ruled in favor of Boiron—one of the world's biggest homeopathic companies—in a deceptive advertising class action suit.

The plaintiffs claimed that advertisements for Oscillococcinum--the company's flagship flu relief product—was nothing but "water sprayed on sugar" and could not possibly deliver any flu relief. After a weeklong trial, Boiron presented sufficient scientific data to convince a jury and the 9th circuit judges that the Oscillo claims were "not false."

All of the aforementioned regulatory issues are significant, but they shrink in comparison with the challenge posed by non-prescription CBD and other hemp-derived substances.

In many ways, the CBD situation embodies all of the conflicting imperatives, tricky compromises, and technical shortfalls that have confounded the natural products industry—and its regulators—since the inception of DSHEA.

How the FDA and other federal agencies ultimately resolve the CBD issue will tell us a lot about how they are likely to regulate the entire supplement industry going forward. **QC**

Regulatory Confusion Reigns As FDA Grapples With CBD

By Erik Goldman | Editor in Chief

On July 30, former FDA Commissioner, Scott Gottlieb, published an op/ed in the Washington Post entitled, "The CBD craze is getting out of hand. The FDA needs to act."

It's a massive understatement given that there are now well over 1,000 companies selling supplements, foods, beverages, cosmetics, confections, even room diffusers claiming to contain CBD and promising myriad health benefits most of which cannot be substantiated.

It's also an ironic statement, coming as it does, from a man whose two-year tenure at the FDA will be remembered—rightly or wrongly—as the dawn of "legal" cannabis products.

Gottlieb presided over the approval of Epidiolex, the first cannabis-derived prescription drug approved for sale in the US. His time at the agency also overlapped Congress' passage of the 2018 Farm Bill legalizing cultivation and processing of low-THC "industrial hemp" (as distinct from high-THC "marijuana"), and the Drug Enforcement Agency's liberation of hemp from drug-of-abuse status.

Those moves pushed an already surging non-Rx CBD market into warp speed, with many new brands rushing in under a simplistic belief that the Fed had "legalized CBD."

The truth is far more complex. The Farm Bill permits farmers to legally grow hemp with a THC content under 0.3%. But it does not formally legalize the sale of CBD or other hemp-derived substances (with the exception of hemp seeds and hemp seed oil) in foods, beverages, or supplements. Marijuana-derived CBD—extracted from plants containing greater than 0.3% THC—remains illegal.

The Farm Bill explicitly defers to the FDA on the matter of hemp-derived CBD.

FDA, for its part, has made clear that, for now anyway, it does not consider purified, isolated CBD to be a lawful dietary ingredient. The only "approved" and legal form of CBD is the highly-purified form patented by GW Pharmaceuticals as Epidiolex.

But the agency does leave a door open for CBD companies to apply for New Dietary Ingredient status, which would subject their extracts to thorough safety review. FDA is also encouraging companies to take the longer and costlier drug development route rather than opting for the supplement fast lane.

Hemp Extracts: A Grey Area

FDA's existing rules leave a grey area regarding hemp extracts that contain CBD along with other cannabinoids (but not THC), in their naturally-occurring, non-isolated, non-purified concentrations. Hence the proliferation of "full spectrum" or "whole plant" hemp oil extracts now flooding the market.

Many companies believe the "full spectrum" designation—a marketing term that has not yet been formally defined—protects them from regulatory action. That may be more wishful thinking than statutory reality.

In many ways, CBD epitomizes all the conflicting motives and scientific ambiguities with which the FDA must constantly contend: the pharma industry's intention to protect its patents; the food and supplement industries' wish to freely market "healthy" natural products; the public's enthusiasm for non-Rx options; and the need to guard against toxic, adulterated, or fraudulent products.

Absence of clear federal policy on CBD-containing hemp extracts has created tremendous confusion about what the government does—and does not—consider "legal." This is further compounded by the fact that neither the Farm Bill nor the FDA's rules override state level cannabis laws, which vary markedly.

The result? A patchwork of local and federal regulations and enforcement policies that baffle manufacturers, consumers, clinicians, and lawmakers alike.

Historic, Inconclusive Meeting

Last winter, the FDA announced a major initiative to clarify the rules for CBD.

On May 31, shortly after Commissioner Gottlieb's unexpected resignation, the agency held the first in a series of public hearings to explore regulatory revisions that would simultaneously uphold the prescription sanctity of Epidiolex (and any future cannabis-derived drugs), while opening a channel for legal non-Rx hemp products.

Among the many issues on the table:

- Can CBD be a drug, a supplement, a food, and a cosmetic all at the same time?
- Should the commercial status (i.e. Rx vs non-Rx, drug vs supplement) of CBD be defined solely on the basis of concentration (pure CBD versus low CBD extracts)?
- How safe is CBD? For whom? At what dosage?
- What claims are permissible given the state of CBD science?
- Should synthetic CBD be permitted?
- Are available analytic methods adequate and fit-for-purpose to ensure safety and quality?

The meeting drew testimony from over 50 people—advocates and critics alike—representing the cannabis industry, supplement and food brands, consumers, medical practitioners, legislators, legal experts, and representatives of regulatory agencies.

The general consensus is that this historic hearing, though inconclusive, was a reasonable first step toward improving the current regulatory morass.

During a public comment period that ended on July 16, the agency received over 4,200 comments.

Loren Israelsen, executive director of the United Natural Products Association, and one of the architects of the original DSHEA legislation, has reviewed the entire docket with his team.

"Roughly 10% of the comments we consider substantive. The vast majority are personal experience anecdotes from private citizens," says Israelsen, adding that his organization like others are analyzing the comments in light of the FDA's stated positions on CBD, as well as the broader context of the Farm Bill.

Patent Protection vs Public Demand

CBD is a booming market that will top $20 billion in US sales by mid-decade. And legalized hemp has opened up a vast new agricultural sector at a time when American farms are hurting. The food, supplement, beverage (alcoholic and non-alcoholic), tobacco, pet product, and mass market retail industries all have a stake in the FDA's deliberations.

Nobody in Washington—including the FDA—wants to kill a Golden Goose of this magnitude.

But the FDA is also under obligation to protect the pharma industry and its investments. GW Pharmaceuticals, the maker of Epidiolex, is on record stating that in principle it has no objection to non-Rx low-dose CBD, provided that manufacturers adhere to strict quality standards, do not make disease claims, and do not borrow Epidiolex studies to support their products.

But many CBD marketers are stepping way over the line on all counts, and GW's patience is wearing thin.

Alice Mead, GW's VP of US Professional Relations has indicated that if the food and supplement makers cannot agree to play within bounds on product claims and CBD levels, GW will become more assertive of its rights as an approved drug patent holder.

Israelsen says unapproved sale of purified CBD isolates as "supplements" is perceived as a threat to the entire drug approval system. It is likely to meet with significant pharma industry pushback in the coming months.

Mislabeling is Very Common

While some brands try to get away with selling purified pharma forms of CBD as supplements, others market products that contain little or no CBD.

In 2017, Marcel Bonn-Miller at the University of Pennsylvania and colleagues subjected 84 unique CBD products from 31 different companies—oil-based hemp extracts, alcohol tinctures, and vape liquids—to triplicate cannabinoid analysis.

They found a disturbingly wide range of CBD levels. On average, the products were labeled as containing 15 mg/mL of CBD, but actual product samples showed CBD levels ranging from 0.10 mg/mL to 655 mg/mL. The median was 9.5 mg/mL, far lower than the median label claim (Bonn-Miller MO, et al. *JAMA*. 2017).

Twenty-two out of the 84 (26%) contained less CBD than indicated on the label, while 36 of the 84 (36%) exceeded their label claims. Only 31% were accurately labeled.

These findings echo a 2015 FDA analysis of 13 off-the-shelf CBD products that found only 2 were accurately labeled for CBD content.

An Herb Like Any Other?

"The May 31 meeting made it clear that the crack in the door is really for hemp extract, not CBD itself," says Douglas "Duffy" MacKay, ND, Senior VP of Scientific and Regulatory Affairs for CV Sciences, one of the nation's leading producers of CBD-containing hemp products.

"Hemp is a botanical, and DSHEA allows for botanical extracts in supplements." The problem, says MacKay, is that the FDA has not clearly defined an upper limit for CBD in supplements.

Epidiolex is 99% pure CBD, and contains no other cannabinoids. Many retail hemp extracts contain between 10% and 30% CBD along with other compounds that may or may not be disclosed. That difference explains: A) why the prescription drug is vastly more expensive than CBD supplements, and B) why Epidiolex studies cannot be cited to substantiate mixed-cannabinoid extracts with lower CBD levels.

"To some degree, hemp is just another herb. I don't mean to demean its importance in the marketplace, but it should be regulated like any other herb."

—Michael McGuffin, President
American Herbal Products Association

But that difference also begs the question of how much CBD puts a hemp extract into Epidiolex's swim lane. At this point, nobody knows.

"The FDA has never done this for any other compound," says MacKay, who was previously director of scientific affairs for the Council for Responsible Nutrition.

"They regulate by intended use and safety. Like with fish oil, it's not the level of EPA or DHA that makes the product a drug or a supplement, it is about intended use," he said, referring to Lovaza and Vascepa—two prescription fish oils approved for reducing triglycerides. It was not their omega-3 content that made them drugs; it was their disease treatment claims.

Further, the 0.3% THC distinction that the Farm Bill makes between "hemp" and "marijuana" is arbitrary. MacKay believes the FDA is struggling to deal with a set of non-scientific definitions developed by Congress which, he pointed out, "is not a science-based organization."

Cindy Sovine, a hemp and cannabis lobbyist in the Colorado State Legislature, feels similarly.

"Marijuana is a slang term that just became a legal definition," she said at New Hope Natural Media's annual Hemp and CBD Summit last spring.

A former pharma industry lobbyist, Sovine stressed that hemp and marijuana are the same botanical genus, and differ only in the relative amounts of cannabinoids they produce. And there are well over 100 known cannabinoids.

"'Industrial Hemp' is really just a catch-all for everything else that's not defined as marijuana," she said, adding that each cannabinoid could

potentially become a new therapeutic or health support product, once its physiological effects are better understood.

Complex Plant, Complex Issues

That prospect opens up another Pandora's Box for the FDA. The agency's regulatory system is well-designed for assessing and regulating isolated bioactive compounds, but it has difficulty with the inherent complexity of herbs. And cannabis/hemp is a complex plant.

But its complexity should not be held against it. "To some degree hemp is just another herb. I don't mean to demean its importance in the marketplace, but it should be regulated like any other herb," says Michael McGuffin, president of the American Herbal Products Association (AHPA).

A 40-year veteran in the herbal industry, McGuffin contends that the FDA needs to bring its authority to bear in enforcing basic good manufacturing practices (GMPs) and compliance with the safety regulations already in place.

"If you're in the business of selling products that contain hemp, that contain CBD, you need to be completely aware of and understanding all the regulations that would apply to supplements made with echinacea, or chamomile, or turmeric, or any other herb. Those all apply to your facility today. And that's really the starting point," said McGuffin at the New Hope Hemp and CBD Summit.

AHPA has been at the forefront of the herbal quality assurance effort. It has generated numerous guidance documents, technical standards, and training events aimed at improving the safety, quality, and integrity of botanical products, including those derived from hemp.

McGuffin says one of the big challenges is that many current CBD brands are start-ups with no previous experience in producing herbal products. In many cases, they're looking for a fast score on a hot commodity, and they are ignorant of the rules and standards to which established herbal companies adhere.

For their part, many legacy herbal brands have shied away from CBD because the regulatory status has been so ambiguous. But that will change. As the FDA clarifies the boundaries, "we're going to start to see hemp product extensions from some of the long-established herbal companies, the ones retailers and practitioners already trust for making really high-quality echinacea, chamomile, turmeric."

Beyond the obvious issues of product quality and prescription status, CBD and cannabis-derived products present other challenges.

Banking and Merchant Services: Many banks and merchant service companies remain wary of hemp-related businesses, especially with regard to interstate transactions. This is especially true of medical and recreational marijuana businesses. Though the DEA has de-scheduled hemp, the shadow of "illicit drug" still hangs over it.

Advertising and Marketing: The FDA has made it clear that it does not authorize disease or symptom claims for non-Rx CBD. But it has not clarified what, if any, claims are acceptable. Since the agency doesn't recognize CBD as a dietary supplement, the DSHEA allowance of structure/function claims may not apply. Or it may. Nobody's sure. Since regulatory actions have been few and far between, many marketers are taking an anything goes attitude.

Clinical Research: Everyone is calling for more clinical research on hemp, cannabis, and their derivatives. But the DEA has been very slow to increase the supplies of marijuana for scientific study.

DEA still considers THC-containing marijuana a drug of abuse. Scientists wishing to study it—and interactions between THC and CBD are an important research topic—must go through a complex application process, and can only obtain study materials from the University of Mississippi, the sole authorized grower. The agency has repeatedly promised to approve more suppliers, but this has not yet happened.

Expect a swell of FDA and FTC actions against companies making overt disease claims, as well as those claiming their products are "phytocannabinoid-rich" or "CBD-rich."

—Justin Prochnow, *attorney with GreenbergTraurig*

Wild Card Regulators

However the FDA ultimately decides to handle CBD, the reality is it will take years before any policy changes are enacted. This means confusion will reign for a long time.

And that, many industry watchers say, spells opportunity for class-action lawyers and ambitious attorneys general.

Justin Prochnow, an attorney with GreenbergTraurig, who specializes in FDA and FTC law, believes the CBD industry is extremely vulnerable. He expects a swell of FDA and FTC actions against companies making overt disease claims, as well as those claiming their products are "phytocannabinoid-rich" or "CBD-rich."

Those claims, according to the FTC, are reserved for foods or supplements that deliver at least 20% of the recommended daily intake (RDI) of a given nutrient. Since there are no RDIs for CBD or phytocannabinoids, these are false claims.

FDA and FTC warning letters are like chum for plaintiff's attorneys. Prochnow and other industry experts expect to see a lot of them in the coming months, followed by a rapid wave of class action lawsuits.

Attorneys general are also sharpening their knives. In July, a coalition of 37 state AGs called on the FDA to "cooperate with the states in protecting consumers from false advertising on cannabis-derived products, such as CBD, and the potential hazards of consuming such products in certain populations."

Even without revisions to the regulations, the FDA itself has been taking action—albeit only occasionally. It recently issued a warning letter to Curaleaf, a Massachusetts company marketing what the FDA considered unapproved CBD products with unsubstantiated cancer, Alzheimer's disease, opioid withdrawal, and pain treatment claims.

The CBD phenomenon is one of the most complex and contentious natural products issues ever to confront the FDA, the FTC, and Congress. How the agencies resolve it will likely have great impact on the regulation of supplements, foods, and drugs for years to come. QC

Quality Assurance for Hemp CBD: Key Questions to Ask

By Erik Goldman I Editor in Chief

Quality assurance is a challenge for all herbal companies. An increasingly global supply chain, the threat of economically-motivated adulteration, environmental contaminants, and limitations of analytical methods are just a few key issues.

For companies making hemp extracts, the challenges are compounded by a confusing regulatory landscape, the inherent complexity of the plant, the surging consumer demand for CBD, and the entrance of dozens of upstart brands with no prior herbal experience and little understanding of basic quality assurance methods.

Responsible and ethical brands struggle to differentiate themselves amid a sea of competitors.

Product quality begins with total control of the company's raw materials supply, says Vandana Kothari, a pharmacist who is Quality Control Supervisor for CV Sciences, one of a handful of hemp extract companies dedicating vast resources to quality assurance.

"We start with certified cultivars. When we receive oil at our door, we know exactly where it came from, and the genetics of the plants from seed to harvest. Every container is numbered, measured, sampled in house and also subjected to 3rd party testing."

CV Sciences obtains its crude extract from well-characterized hemp strains grown in the Netherlands, where the crop has long been part of the country's economy.

CEO Joseph Dowling said he is committed to eventually sourcing all raw materials from US growers as soon as the USDA finalizes its rules for hemp cultivation on US soil, and American farmers scale up for mass production.

Following are a number of other key issues to consider when evaluating hemp extracts containing CBD:

Compliance with GMPs & FSMA: Though the FDA does not consider isolated, purified CBD as a legal supplement ingredient, hemp extracts that contain CBD are herbal supplements, and companies that make them should be in full compliance with the FDA's good manufacturing practices (GMPs), and the Food Safety Modernization Act (FSMA).

FSMA requires companies to have a Preventive Control Qualified Individual (PCQI) on staff who is trained in food safety and certified as competent to manage safety programs as required by the law. Many hemp companies are not aware of these legal obligations. The conscientious ones are fully compliant.

GRAS Status: GRAS status—the acronym stands for "Generally Recognized as Safe"—is another basic quality and safety indicator.

According to FDA rules, general recognition of safety requires a company to present "the same quantity and quality of scientific evidence as is required to obtain approval of the substance as a food additive." The determination involves extensive toxicological and safety testing, and review by a panel of scientists who decide whether the substance can be deemed safe, with "reasonable certainty," when used as intended.

Hemp brands can proactively seek independent (aka self-affirmed) GRAS review from third-party labs, an expensive and laborious process. So far, only CV Sciences has done so. "It's a key step toward credibility," says Douglas MacKay, the company's VP of Scientific and Regulatory Affairs.

FDA maintains a publicly accessible Inventory of GRAS Notifications.

Analytical Methods: Techniques for identifying and quantifying bioactive compounds in herbs are constantly in flux. This is particularly true for cannabis and hemp.

The optimal method for quantifying cannabinoids in unprocessed hemp or hemp extracts is high performance liquid chromatography (HPLC) with UV detection, says Austin Stevenson, VP of Product Innovation at Nanogen Labs, a company providing herbal nanoemulsions—including hemp—to the food, beverage, and supplement industries.

Prior to joining Nanogen, Stevenson developed the hemp/CBD testing program at Eurofins—one of the world's leading analytical testing labs.

HPLC can detect all major cannabinoids including THC, THCA, CBD, and CBDA, as well as many other compounds within the plant. Gas chromatography, another common analytic method for herbs is not fit-for-purpose with hemp; the testing process decarboxylates THCA, leading to inaccurate THC readings.

Analytical testing can be confounded by the diverse delivery systems for hemp products. One cannot assume a method that accurately quantifies cannabinoids in an alcohol tincture is appropriate for edible substances, beverages, or topical formulations, says Stevenson. This is a very important detail many companies overlook.

Methodological consistency—or lack thereof—is also an issue, says James R. Ott, CEO of CFH Inc—a Colorado-based, vertically-integrated hemp grower/supplier.

"We've blind triplicate tested (hemp) with half a dozen different labs. We see a range of variability between 2% up to 20% from lab to lab. And when I blind triplicate test the same lab, it ends up showing variability of 1.5-2% on the same sample. That's about as tight as they can get. So, we've got some issues there."

Cannabinoid Spectrum: Terms like "Full Spectrum" and "Whole Plant" are popular with marketers trying to distinguish their products from purified CBD pharmaceuticals.

The problem is, there's no consensus on what "full spectrum" really means.

"It's a marketing term," says CV's MacKay. There is some industry agreement that a full-spectrum extract should contain a range of cannabinoids—there are 113 currently recognized—and only trace amounts of THC. But there's no definitive standard.

Anthony Almada, a nutrition industry consultant who heads IMAGINutrition, notes that cannabis produces over 1,000 unique chemicals, with more still to be characterized. While some brands have a clear biochemical fingerprint for a few cannabinoids in their products, the reality is that this plant has 10 "fingers."

At most, the "full-spectrum" products on the market are testing for 30-40 chemical constituents. "They're 'full-spectrum' by virtue of the limitations on what's being tested," Almada said at Holistic Primary Care's 7th annual *Practitioner Channel Forum*.

Excessive THC: "No THC" on the label does not always mean no THC in the product, says Almada. FDA studies have shown that some hemp products labeled "No THC," do indeed have THC well above the 0.3% threshold. Failure to quantify THC levels accurately is an indicator of slack quality control.

Chirality: CBD and THC have complex 3-D configurations. There are actually four mirror-image isomers of CBD, and four of THC. As is the case with many bioactive compounds—think L-carnitine or L-theanine—chiral conformation does affect physiological activity, says Almada.

"The four forms of CBD and THC are different. Chemically, with one exception, they're identical. But biologically they are different. They are four different shapes, and those shapes are like hands that fit into gloves. A right hand does not fit in a left glove. It just doesn't work."

Standard analytical methods like HPCL and gas chromatography do not detect chirality. It requires specialized tests. According to Almada, none of the commercial hemp brands are assessing chirality.

Hemp Extract vs Hemp Seed Oil: The oil pressed from hemp seeds is highly nutritious. It is rich in Omega-3, Omega-6, and other essential fatty acids. But it does not contain CBD. Only the flowering part of the hemp/cannabis plant produces cannabinoids. A true hemp extract containing CBD and other natural cannabinoids is an oil or tincture derived from hemp flowers, not seeds. Yet some unethical brands sell hemp seed oil spiked with synthetic cannabinoids and terpenes.

Toxins & Contaminants: Hemp is an excellent accumulator of toxins. That's one reason it is used as a bioremediator to clean up polluted land. But this means that analysis for toxins and contaminants is an essential aspect of hemp quality control.

According to Niagen's Austin Stevenson, manufacturers should be testing for:

Residual solvents: "What type of solvent was used to make a product in question: cold water? CO_2? Butane? Heptane? Hexane? You don't want the solvents in the finished products."

Heavy Metals: Hemp absorbs and concentrates a lot of soil metals. Companies should test raw materials and finished products for arsenic, cadmium, lead, mercury and other common environmental heavy metals. Stevenson says this should be done with Inductively Coupled Plasma Mass Spectrometry (ICPMS).

Heavy metal testing is required by law for all herbal supplements. But many start-up hemp brands are unaware of the regulations or do not have the proper quality assurance procedures or testing equipment in place.

Pesticides and Herbicides: Pesticides are an unfortunate reality in the hemp market. The plants are expensive and farmers don't want to lose them to cutworms or other hungry insects. As hemp cultivation scales up, pesticide and herbicide use will likely increase.

Extraction concentrates pesticides and herbicides in hemp. So, hemp extract companies should be testing for a full range of common agricultural chemicals using liquid and gas chromatography in tandem with mass spectrophotometry according to methods outlined in the US Pharmacopeia.

Microbiology: As with any herb, microbial contamination can be an issue with hemp. Companies should be running petri films and quantitative PCR tests for *E. coli*, *Salmonella*, and other potential contaminants. The American Herbal Products Association's (AHPA) monograph on cannabis provides thorough guidance on testing for microbes and environmental toxins.

Glyphosate: This controversial herbicide is not approved for use on hemp. According to AHPA's president, Michael McGuffin, it should be deemed a contaminant under the FDA's GMP rules. But it is not recognized as such, and few companies test for it.

Synthetic Cannabinoids and Terpenes: In addition to cannabinoids, hemp produces a spectrum of terpenes—they're what give the plant its characteristic odor.

Almada says, the cheapest way to make a "full spectrum extract" is to buy synthetic terpines—cheap and widely available—and put them in an oil base. "Companies boast about their "high terpine levels," and the products will have the intense cannabis aroma. But it's synthetic. This is a wonderful opportunity for class-action lawsuits."

Terpene profiles can be analyzed using gas chromatography and flame ionization detection (GC-FID), but few brands are testing for them.

Synthetic CBD, THC and other cannabinoids are also entering the market, says MacKay of CV Sciences. The FDA has yet to rule on whether these will be permitted in foods or supplements, but it is doubtful given that many biotech and pharma companies are working on synthetic cannabinoids for use as drugs.

Topical Delivery Systems: CBD-containing balms, creams, and other topical products are very popular. But any topical that can significantly raise blood levels of a bioactive like CBD must undergo full toxicology and cancer testing, per FDA regulations. Most brands are not undergoing that type of study. Almada expects a regulatory crackdown soon. "A product labeled as "transdermal CBD" is basically waving a red flag."

3rd Party Certification: Recently, the US Hemp Roundtable—a coalition of leading cultivators, raw materials suppliers, finished product brands, regulatory experts, and analytical scientists—launched a certification program aimed at harmonizing QA standards, assuring safety and quality, and raising consumer confidence.

The group developed stringent self-regulatory guidelines for growers, processors, and branded product makers. Certification, which is voluntary, involves thorough audits and extensive third-party lab testing of many of the parameters outlined in this article. Companies that pass will be able to include a "US Hemp Authority Certified" seal on product labels. QC

How Practitioners Define Dietary Supplement Quality

By Erik Goldman I Editor in Chief

Product quality is a high priority for dietary supplement users. Supplement brands are well aware of that fact.

Many brands claim they provide top quality formulas, made in pharmaceutical-grade production plants, with strict adherence to federally-defined Good Manufacturing Practices (GMPs).

Generally speaking, these claims are true, based on site visits *Holistic Primary Care* has made to leading brands in both the direct-to-consumer and practitioner-only nutraceutical and herbal medicine sectors.

Manufacturers have their own ideas about what constitutes top-quality. But as more healthcare professionals bring supplements into the mainstream of clinical practice, the question of how practitioners define quality becomes increasingly important.

What criteria do clinicians consider when evaluating products on behalf of their patients? Are supplement companies adequately meeting the needs and preferences of the clinical community?

Holistic Primary Care's 2019 practitioner survey gave us some insight.

The survey fielded last Winter, and generated responses from 360 practitioners, 32% of whom are conventionally trained MDs. More than two thirds (65%) dispense supplements in their practices, and 91% of those who don't dispense are recommending some supplements to patients. Nearly all (95%) take supplements themselves.

The 49-item survey included the following question:

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

For each of 10 multiple choice answers, respondents could indicate whether that factor was "Decisive," "Important but not decisive" or "Of little importance."

The top five most decisive factors among our respondents were: Free of Heavy Metals (90%), Free of Artificial Sweeteners (75%), Allergen-Free (69%), GMO-Free (67%); and Dosage Form/Frequency (43%) (Fig. 1)

What Doctors Want

The pattern of decisive criteria was fairly consistent across practitioner subtypes. In general, clinicians—regardless of background training or age—want to feel confident that the products they recommend are safe, free of toxins, artificial additives, and genetically-modified ingredients.

But there were some notable differences between younger and older practitioners.

Younger practitioners (age 30-40 yo) are much more sensitive to Dosage Form & Frequency; 75% of them identified this as a decisive factor, versus only 43% of those in the 51-60 age bracket. They are also much more concerned about prices, with 50% considering price a decisive factor, versus only 28% in the older segment.

Younger respondents are somewhat more concerned about ingredient sources, with 25% identifying US-Only Ingredients as a decisive issue, versus just 8% in the older group.

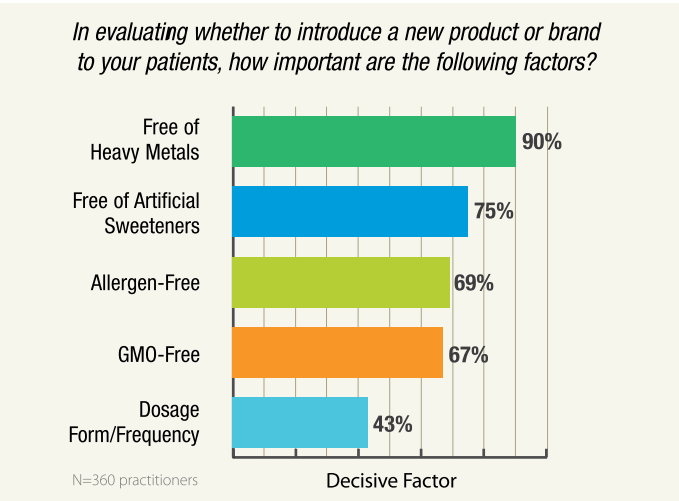


Fig. 1: *The Top Five Factors (Source: HPC 2019 Practitioner Survey)*

The written comments indicate that when it comes to evaluating product quality, practitioners are thinking far beyond the basic ingredient lists.

"Inactive ingredients are crucial in my decision," wrote one respondent, who stressed a strong preference for products free of all forms of sugar, alcohols, colorings, and additives.

Packaging is also important. As one respondent noted, "I am starting to look at brands that use glass bottles instead of plastic."

Robert Silverman, DC, director of the Westchester Integrative Health Center, and a popular lecturer on nutrition and functional medicine, has been conducting informal research among his integrative medicine colleagues to learn more about what they look for in supplements. He's found a number of common themes:

- **Easy-to-swallow liquid formulas**, especially for elderly patients and those experiencing "pill fatigue."
- **Expanded sports support lines**, especially products targeting over-zealous middle-aged marathoners and non-athletes who are just starting to exercise.
- **Gluten-free, Dairy-free, GMO-free products**.
- **Compelling visual tools for patient education**. Videos and easy-to-understand graphics help patients understand what to take, and how to take it. This increases adherence and improves outcomes.
- **Fewer tablets or capsules, and intelligent formulas**. Patient adherence is inversely proportional to the complexity of the regimen. The more pills or capsules, and the more times per day, the less likely patients will stay with the program. Simpler is always better.
- **Easy implementation protocols and online education**. Time is of the essence in any practice; clinicians want streamlined strategies for

different types of patients. "A woman who weighs 100 pounds is different from a man who weighs 270. Should each of them take the amount recommended on the label?"

- **Social media and practice development support**. Many functional medicine practitioners struggle with practice management. Nutraceutical companies that help with that become valuable allies.

Quality Goes Beyond the Products

For Jill Carnahan, MD, founder of Flatiron Functional Medicine, a thriving holistic practice in Lewisville, CO, the definition of "quality" goes far beyond a company's actual products. Top companies—the ones she prefers—are fastidious about everything from packaging to customer service.

For her, supplements are not only vital clinical tools, they represent over 40% of her clinic's total revenue. This cash stream makes possible the long, unrushed, in-depth office visits needed to care for people with complex, longstanding chronic conditions. Features she looks for include:

- **Speedy fulfillment**: "Fast, efficient, trouble-free ordering and shipping is key."
- **Solid, yet eco-conscious packaging**: "Sometimes we've gotten products that come damaged due to poor or inappropriate packaging. But eco-friendly packaging is also very important. We try to recycle as much as possible, and prefer companies that use recyclable materials."
- **Clear and detailed invoicing**: Carnahan wants to see specific product names, sizes, wholesale cost and recommended retail pricing.
- **Online ordering & autoshipping**: "We buy from over 40 different companies, and carry over 600 SKUs (stock-keeping units). You can imagine my office manager going crazy trying to figure out how to order from whom. We like companies that make it easy for us."
- **Reasonable minimums**: Some companies require practitioners to purchase several dozen bottles at a time. That's a deterrent for Carnahan. "If we have to order a minimum of 36 bottles, we may not try a new product because it will be a big waste if we don't sell it."
- **Professional and courteous customer service**: High quality companies should have phone lines answered by knowledgeable, well-trained customer care professionals. Carnahan avoids brands that only provide a general "customer service" email as the sole contact.

What Patients Want

A nutraceutical or herbal product is only as good as a patient's willingness to take it. Dr. Carnahan and her team frequently check in with patients about the products they're taking. This is part of the culture in her practice, and it often yields important insights. Patients want:

Larger sized bottles: "For many products, the standard size bottle is barely enough to get them through one month. This is especially true with antimicrobial herbal products like Allimed, Candibactin, or Candicidal, because they're usually using 2 or 3 bottles per month on higher-dose protocols. Larger bottles would be very helpful."

Auto-ship and re-purchase programs: "Patients want reminders. Amazon really has that down, with their Prime Pantry reminder system." A model like that for top quality practitioner-only supplements would be a help.

Samples: Product samples are extremely helpful especially for pain and sleep-products. Patients can find out quickly whether a particular formula will work for them, before investing in a full bottle. Brands that provide samples do their practitioners—and the patients—a great service.

Adam Perlman, MD, Director of Integrative Medicine and Wellbeing at the Mayo Clinic Florida, and former head of Duke Integrative Medicine, agrees on the importance of samples.

"Say I want to help a patient with gut healing, and I recommend a product which is a big tub of stuff, and it costs like $75 or $80. And the patient gets it home and finds out she hates the pineapple flavor! It can be a real problem."

Modern online shopping has created extremely high patient expectations. "With Zappos, if you bought a pair of shoes online and you don't like them, you can just throw them back in the box and return them. But how are we, at a medical clinic, supposed to deal with that when someone doesn't like the supplements they buy from us? I need to manage those patient expectation issues, and I need help."

Perlman, who is leading the development of an entirely new integrative health program at Mayo's massive Jacksonville campus, says product samples are an invaluable aid in averting these potentially difficult situations.

Mainstream Perspectives

The Mayo center is in its earliest developmental stages and not yet dispensing supplements to patients. But Perlman says he and his colleagues are already having discussions about product quality, brand selection, ethics, and logistics of clinic-based dispensing.

Mayo's three campuses—in Rochester, MN, Scottsdale, AZ, and Jacksonville, FL—are destination centers for people with serious, complex medical conditions. For integrative medicine to work there, it has to deliver both clinical and fiscal value.

Working within a world-renowned mainstream institution like this presents unique challenges for supplement-savvy physicians. Dr. Perlman and his integrative colleagues have experience with supplements. Most other Mayo doctors do not.

Perlman says he's evaluating supplement quality through the lens of Mayo's "Three Shields"—a set of core values that guide everything at the clinics.

"I say, "How does this address our three shields? How does it improve our clinical care of our patients? How does it contribute to the research that helps inform and heal people? How does it help educate patients and providers?

When assessing products, Perlman looks for:

- Science that is specific to that product. "That's very important. We know that different formulations of the same ingredient can be very different when used in practice."
- Product-specific studies from academic institutions or third parties other than the product's maker.
- Clear information about potential safety concerns, drug interactions, and possible side effects patients may experience.

"We all know that these issues exist. Be open about it. Put it in perspective. We write (prescriptions) for drugs that interact with other drugs all the time. This is no different. Just because something interacts with the CYP450 enzyme system doesn't mean it is dangerous. We want to be able to talk intelligently about the products we recommend." QC

Validation Testing: Insights from Inside the Analytical Lab

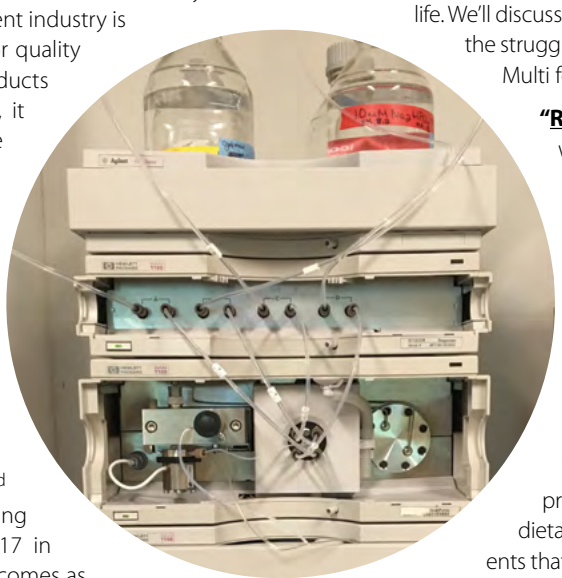
By Sarah M. Gannon I Analytical Chemist & Lab Manager
Designs for Health

From the outside looking in, the dietary supplement world can seem like a bewildering place—an extensive selection of brands and products, all using carefully worded terms to suggest that they can help with particular ailments; vast lists of unpronounceable herbs or ingredients; labels loaded with "nutrition facts" that most people don't really understand.

I'm sure many people wonder, "How is all of this being blended and manufactured? How is the quality and potency being verified?"

As an analytical chemist working for one of the nation's leading practitioner focused supplement companies, I can comfortably say that a lot of work goes into the manufacturing and testing of a supplement before it goes to market.

It's important to know that, because there's still a widely held notion that the dietary supplement industry is unregulated. While it is true that poor quality raw materials and sub-standard products sometimes make it into the market, it is also true that the major brands are extremely diligent and scrupulous about their supply chain control, their quality control systems, and their analytical testing.



For me personally, this is not just a matter of professional pride. First and foremost, I am a health nut. I was a swimmer from 3rd grade through college, and I am currently part owner of a Crossfit gym. As a competitive powerlifter, I placed 3rd at the IPL (International Powerlifting League) World Championship in 2017 in the 67.5 kg weight class. It probably comes as no surprise that diet and nutritional supplements are a necessary part of my routine. I also have a Masters in Chemistry.

When I began working at Designs for Health in 2010, I found a place where I could combine my love for science and fitness in a truly helpful way. Since I was now directly involved in validation testing and quality assurance, it also removed any doubts I had about those overwhelming ingredient lists I would read on the products I purchased for my own use.

From inside the analytical testing lab, I'd like to share some important aspects that I think all physicians should know about.

Prototyping & Blending a New Formula

A lot of time and effort goes into the development of a new supplement formula. First, the Product Development team establishes effective ingredients and dosages likely to give a desired benefit. The team then creates a Master Formula sheet, where the amounts of active ingredients are calculated to deliver the desired efficacy for the proposed label claim. The formulators must take into account, among other factors, the potency, moisture, and physical properties of the ingredients.

Properties of Raw Materials: In the case of Vitamin B1 for example, our raw materials supplier may indicate that their material delivers 98% Thiamine HCl. However, this figure represents the salt form and not the active form of Thiamine/Vitamin B1 for which our labels must declare a percent Daily Value (DV). So, our input of this ingredient needs to be adjusted based on molecular weight and the amount of moisture found in the raw material.

Then, there's the fact that some materials can degrade over time from heat, humidity, light, and oxidizing agents. So we have to calculate for that, and add overages of certain ingredients to maintain the desired shelf life. We'll discuss this more fully, when we take a closer look at some of the struggles and challenges we faced in formulating our Primal Multi formula, which contains 43 different ingredients.

"Runability" is a term we use to mean the ease with which a particular formula can actually be produced on our manufacturing equipment. Simple formulas with only a few ingredients are easy to run. But for a formula like Primal Multi, which contains so many ingredients with varying physical characteristics (ex: density, flow index, particle size, and even level of static charge), runability is one of the most difficult issues we must face.

Selection of Excipients: The first step is to create a small-scale blend (1-500 grams) of the 40+ active ingredients. We then use this to select the excipient profile. As is the case with pharmaceutical products, dietary supplements also contain non-bioactive ingredients that enable the diverse active ingredients to be blended, bound together, and stabilized.

Excipients such as silicon dioxide and tricalcium phosphate function to adjust flow rates of the ingredients through the machinery. Others, such as stearic acid or magnesium stearate, add lubrication; Still others, like microcrystalline cellulose and dicalcium phosphate, allow powders to bind. All of these aid in the manufacturing process, but they need to be chosen carefully.

Through several trial runs using test formulations, our team determined that excipient profile for Primal Multi would include 8.71% microcrystalline cellulose as the binder, 0.33% silicon dioxide for flow adjustment, and 0.57% magnesium stearate for lubrication. They tried many other compositions, but these yielded inferior performance, inadequate binding, and poor flow characteristics.

Determining Blend Times: Once the team found the optimal composition of active and excipient ingredients, the next step was to create a scaled-up version of the formula (8-10 kilograms). This is more than ten times the size of the original bench blend. This is mixed in a double cone

blender to investigate homogeneity of the blend. During the blending process, we take samples at multiple time points from various locations in the mixer, and we test for the presence of specific marker compounds.

For the Primal Multi product, 8 ingredients were selected for testing: Vitamin K1, Vitamin K2 (MK-4), Selenium, Vanadium, Calcium, Quercetin, Resveratrol, and Hesperidin. They were chosen because they represent a large range of concentrations (microgram to milligram amounts). The time point that most closely matched the desired label claim for all of these ingredients was 5.5 minutes from the start of mixing. This was designated as the best blend time for Primal Multi.

With the blend time determined, we then created another scaled up version of the formula and then we tested everything to verify label claim…yes, I mean everything. All 43 ingredients!

Scaling Up for Production: When scaling up from a cone blender to the actual production blender, we need to consider a few additional parameters. The difference in size from the cone blender to production is about 44 times, so that means 10 kilograms becomes 440 kilograms. The blend time and batch size are mathematically calculated based on equipment rotational speed and blend powder density.

In the case of Primal Multi, the 5.5-minute blend time determined in early blending steps was adjusted to 16.5 minutes of mixing time in actual production. Then, we have to run samples on an encapsulation machine to determine the optimal settings (machine speed, dosing disc size, and tamping pin settings) needed to achieve the targeted capsule fill weights.

Packaging Considerations: We select our packaging components based on serving sizes and capsule doses required to deliver the intended benefit. Based on evaluation of the physical properties of the individual ingredients in a given formula, we decide whether a dessicant is necessary to protect the product against moisture.

Once a formula is produced and bottled in its finished form, we test it yet again to validate the presence of the active ingredients.

This leads to the next question: How do we actually verify these different analytes in the product?

Chromatography & Analytic Methods

As mentioned previously, a lot of dietary supplement labels boast large lists of ingredients, particularly multivitamin formulas. Chemical analysis of all these diverse ingredients can be very challenging.

One of the most common forms of analytical testing is called High Performance Liquid Chromatography (HPLC).

This instrument is used to separate components of a mixture, and then identify and quantify them compared to a purified reference standard of the analyte(s) of interest.

The main components of the HPLC unit are the degasser, pump, sampler, column compartment, and a detector. As you would expect from the name, everything is prepared in a liquid medium; this means that full dissolution of the compounds being analyzed is very important.

The equipment takes a liquid solvent containing the sample mixture and pumps it through a column that contains solid adsorbent material. Because ingredients all have unique chemical structures, they will interact differently with this adsorbent material. Some will be retained longer, so the components will all reach the detector at different rates.

Once through the detector, the analytes will be seen as "peaks" (see Fig 1), and we can determine the concentration of each analyte based on the peak area in the sample compared to the peak area of the purified standard run.

This process may sound simple, but the unfortunate thing is that there is no single "magic method" that can test for all possible ingredients.

Much of the work happening in the world of analytical chemistry and HPLC is focused on development of methods, particularly as new ingredients and raw materials emerge in the market all the time.

There are so many variables that must be taken into consideration: What solvent to dissolve the ingredient in? What type of column to use (there are many different types of adsorbent material)? What liquid eluent should be pumped through the system for the best separation of the ingredients? What wavelength to set the detector at (particular analytes can only be seen at specific wavelengths)? These are just a few of the important variables we must think about when analyzing a supplement formula.

Things become increasingly difficult with a big ingredient list. Method development for a product like Primal Multi is very time-consuming. The good news is that there are several validated methods already published for many of the common ingredients in dietary supplements. Once these are in place in the lab, HPLC is an incredibly reliable and robust instrument for testing and validating the presence of these ingredients.

Not All Ingredients are Created Equal

We use HPLC testing to verify raw material potency and to validate consistency of blends, but it can also detect changes in ingredients

Fig. 1: Chromatogram Depicting Various B Vitamins in a Multivitamin Formula

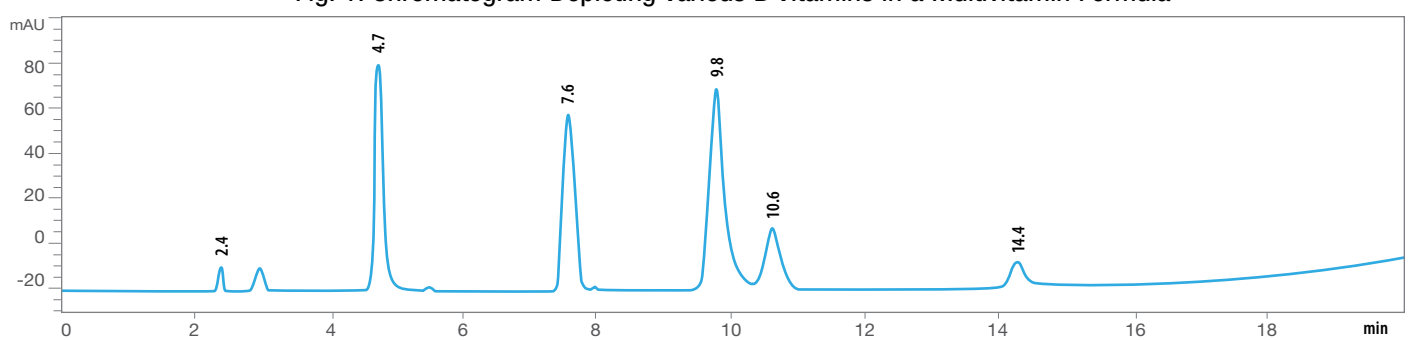


Fig. 1: HPLC chromatogram showing separation of water-soluble B vitamin peaks, as follows: Trimethylglycine (2.4 min), Thiamine (4.7 min), Pyridoxine (7.6 min), Niacinamide (9.8 min), Pantothenic acid (10.6 min) Pyridoxal-5-phosphate (14.4 min). The X axis indicates Time; Y axis indicates size of peaks in absorbance units (AU). (*Image courtesy of Designs for Health*)

over time. This is important, because most raw materials are subject to some degree of potential degradation over time. Some are very fragile and highly susceptible to degradation; others are much more stable.

Our raw materials vendors will typically give us a Certificate of Analysis on the stability of their materials, but these figures represent the materials in isolation, under ideal storage conditions. How these ingredients hold up in a finished product blend or under different storage conditions is a different story.

Stability testing to generate an expiration date for a product is common in the supplement industry. This involves simulating a long turnover time of 2 years under various sub-optimal conditions. We do this by subjecting our formulas to accelerated stability testing, where they are exposed to high temperatures and humidity (40 ^{o}C and 75% Relative Humidity) in a controlled storage chamber. One week under these conditions is equivalent to one month of real time in ambient conditions.

Over the years of testing, analytical chemists in our industry have discovered many of the characteristics and tendencies of particular ingredients commonly used in supplement formulas.

For example, we know that Vitamin B1 is highly susceptible to heat and moisture. Figs. 2A and B are HPLC chromatograms of vitamin B1 (thiamine) in the same multivitamin formula. But the test shown in Fig. 2B was run after the formula had been in an accelerated stability chamber for more than 20 weeks.

You can clearly see a decrease and change in shape of the Vitamin B1 peak at a retention time of 4.7 minutes, along with the development of other peaks, which likely represent degradation products of Vitamin B1.

When we calculated Vitamin B1 potency in the formula, we saw a reduction from 100 mg/capsule to less than 40 mg/capsule. A similar pattern of degradation was obtained on the same product when the capsules were kept in a pill box in the summer humidity in Florida.

In addition to the products themselves, we also use the accelerated chamber to evaluate different types of bottles. There are clearly some that are superior to others in their ability to protect vulnerable ingredients. For example, Vitamin D3 is another ingredient that degrades on exposure to high temperature and humidity. Recent studies have shown that Vitamin D3 retains its integrity much better in glass bottles compared with high density polyethylene (HDPE) bottles.

All of this testing allows for better planning when prototyping blends.

In the case of our Primal Multi, we adjusted the formula to add an overage to the quantities of vitamin B1 and D3 in the formula. This offsets any potential degradation that might happen during shipping or routine customer use. We also selected amber glass bottles, to provide optimal protection for the most vulnerable ingredients.

Once we finalize the formulation and packaging, we continue to conduct stability tests on our completed products in their finished form, to ensure that they meet label claim over time.

From the idea for a new formula in the minds of our product development team, to the consideration of the many intricate parameters of manufacturing, to the verification of ingredients and their stability in the analytical lab, Designs for Health consistently lives up to its motto of "Science First". **QC**

Fig. 2A: Chromatogram of Thiamine (Vit B1) before exposure to heat and humidity

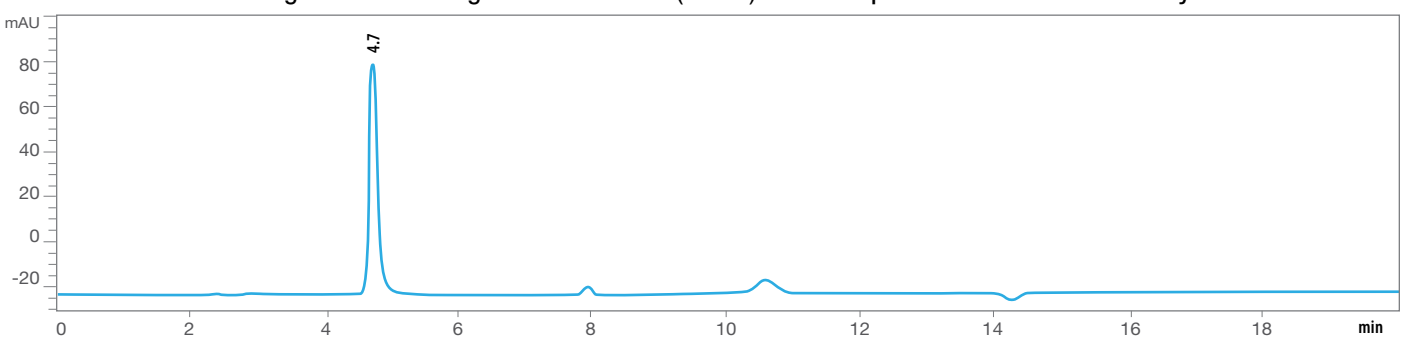
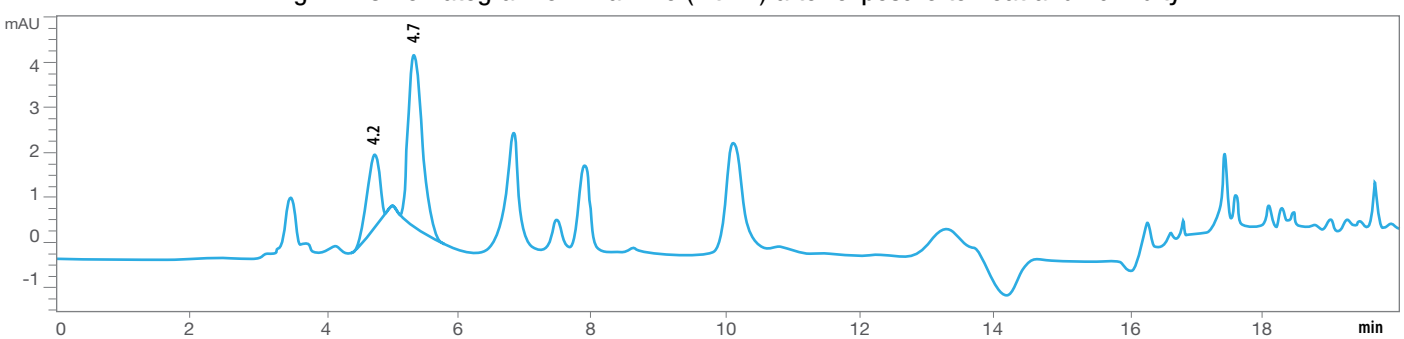


Fig. 2B: Chromatogram of Thiamine (Vit B1) after exposure to heat and humidity



Figs. 2A & B: HPLC chromatograms showing Thiamine (Vit B1) peaks before (2A) and after (2B) controlled exposure to high heat and humidity. Note that the strong 4.7 min peak in Fig 2A has broken down into multiple weaker peaks in Fig 2B, indicating degradation of the vitamin. (*Image courtesy of Designs for Health*)

The Dating Game: The Ins and Outs Of Expiration Dating for Natural Products

By Kristen Schepker | Assistant Editor

Expiration dates, "use by" guidelines, or "manufactured on" notices are printed on the labels of nearly all consumable products nowadays. When it comes to dietary supplements, who determines those dates—and what do they really mean?

What's in a Date?

"Typically, the responsible party (determining the use by date) is the one listed as the manufacturer or distributor on the label of the dietary supplement product," said Andrew Shao, Interim Senior Vice President of Scientific and Regulatory Affairs at the Council for Responsible Nutrition.

Manufacturers use stability studies—a series of experiments exposing a product to a range of different environmental conditions—to inform their expiration date calculations.

Stability testing enables researchers to examine products when stored under ideal conditions—in the dark, at room temperature, and low humidity—as well as when exposed to more extreme conditions, like those that might occur during shipping and transport: heat, light, variable temperatures.

Shao noted that supplement makers often use a combination of "accelerated" studies, where products are exposed to extreme conditions for a short period of time, and "real time" studies, exposing products to more normal conditions, and then tracking any changes that occur over a designated period.

"From a product development perspective, most products degrade over time, due to chemistry and interaction of the ingredients," explained Larisa Pavlick, Vice President of Global Regulatory and Compliance at the United Natural Products Alliance. "This is not a reflection of poor manufacturing practices—it is the nature of the ingredients," she noted.

The idea behind Use By dates is to account for the inevitability of degradation, and to set time boundaries within which a particular formula can reasonably be expected to preserve its integrity.

Voluntary Dating

While the Food and Drug Administration (FDA) mandates expiration dates on all prescription drugs and over-the-counter medications, in accordance with a federal law passed in 1979, supplements are separately regulated under the Dietary Supplement Health and Education Act. DSHEA does not mandate expiration dating. In other words, supplements are not required by law to carry expiration dates.

However, most supplement makers voluntarily choose to label their products with some form of suggested "use by" date. Some retail stores that sell a lot of supplements and herbal medicines demand that expiration dates be listed on product packages, and won't sell brands that do not do so. So even in the absence of a federal requirement, most companies do utilize some form of expiration dating.

Jay Sirois, Senior Director of Regulatory and Scientific Affairs at the Consumer Healthcare Products Association, said that according to FDA, "a firm may include [expiration dating] if it is supported by valid data demonstrating that it is not false or misleading."

If a manufacturer chooses to include expiration dates on its labels, the FDA's Current Good Manufacturing Practice (cGMP) guidelines require that the date be supported by stability testing data.

This helps to ensure some degree of scientific backing behind any label claims made, guaranteeing consumers that at least 100% of the amount of any ingredients listed on a product package is present in the supplement up until the date indicated.

"Given that requirement, manufacturers must know the shelf life of their products so they know how long they can be made available to consumers and still meet 100% of label claims," Shao said. "Most reputable manufacturers make stability testing and expiration dating or shelf-life dating a routine part of their GMP process."

Pavlick, a former FDA investigator who has inspected over 200 food and supplement production facilities throughout the western and southwestern US, pointed out that the FDA specifically requires companies to "establish specifications for identity, purity, potency, and composition, plus for any and all potential contaminants." Manufacturers must also verify that their products meet all written specifications.

"During an FDA inspection, the investigator will verify that the product meets specifications at the time of manufacturing and that any dates used on the product, whether called expiration date, 'best by' or something else, are scientifically supported. If they are not, [the manufacturers] are typically cited for not meeting specifications," she said.

Apart from facility inspections, the FDA also has the ability and authority to sample products from retail shelves in order to verify that values shown in the Supplement Facts boxes match what's in the product.

Pavlick noted that while the FDA does not currently have the resources to monitor the many thousands of nutritional supplements on the market, the agency can—and does—conduct "for cause" investigations if there is reason to suspect that a particular product may be in violation. Children's vitamins, for example, were specifically monitored during her tenure at the FDA.

Art and Science

Legal requirements aside, many modern consumers expect to find expiration dates on food, medicine, and supplement packages. Depending on the type of product, shelf life indicators—and the extent to which they should be strictly followed—can vary significantly.

In dietary supplement formulations, some nutrients are more shelf-stable than others. The degradation characteristics of single-letter vitamins, for instance, are fairly well known; water-soluble

vitamins like vitamins B and C are generally more shelf-stable than fat-soluble vitamins like A or D.

Supplement manufacturers can take these known stability characteristics into consideration during product formulation.

For companies that do put "Use By" dates on their products (and that's most companies), the ingredients must remain at label claim levels until the defined time of expiration. Because degradation occurs naturally, the FDA permits manufacturers to formulate with "intentional overages"—the purposeful addition of higher ingredient quantities to account for an eventual loss in potency.

Responsible companies will account for the known degradation of vitamins and botanical constituents by responsibly over-formulating their products.

"This means that at the beginning of the shelf life, the product may have a safe and allowable intentional overage of some ingredients to allow for the product to maintain at least the values that are shown in the Nutrition Facts or Supplement Facts box" through the date of expiration, Pavlick said.

It is "an art and a science to understand the rate of degradation and safe limits for some vitamins and components," she told Holistic Primary Care, adding that conscientious companies conduct "complex analytical testing at very specific time points to create degradation curves for their specific formulations."

Natural degradation can eventually affect a product's potency, but that does not necessarily make it any more harmful to consume post-expiration. In other words, a post-date supplement is not likely to be dangerous; it is simply less likely to deliver the expected benefit.

Storage Affects Quality

Many vitamins and other nutrients become unstable with exposure to light, air, and/or humidity.

Most supplements have shelf life of between one and two years, or an expiration date that extends one to two years post-manufacture. They are generally sold in relatively stable dosage forms, like tablets and two-piece hard-shell capsules that will maintain their quality for about two years when stored properly.

Other products, such as probiotics, liquids, and oils, are more fragile. They are highly sensitive to heat, moisture, and mold, and they have much shorter shelf lives than letter vitamins. Formulas containing these less-stable ingredients are typically labeled with special instructions—refrigeration is a common one—plus a shorter suggested shelf life.

Adverse conditions will change the characteristics of nutritional products, so proper storage is of paramount importance. Sirois urged that patients always "follow any labeling instructions regarding the proper storage of a dietary supplement to ensure that the product retains its potency."

He recommended that "if there is no expiration or best by date, or specific storage information included on the label, store the dietary supplement in a cool, dry place or contact the manufacturer if there is a question about product freshness or potency."

Pavlick says supplement users need to, "think about the impact of opening and closing supplement bottles day after day, or storing them in a kitchen window or in a bathroom in high humidity."

"Are you mail-ordering your vitamins? Do they sit in the mailbox for days in the hot sun, or left in a purse or backpack in the trunk or the backseat of a car during the summer? These conditions are often not considered by the consumer when we speak of product quality—yet they should be," she argued.

If shipped and stored carefully, many supplement products will retain their potency well beyond the best-by date. For the majority of products, the expiration date "is not a hard cut-off," says Shao.

While a product's composition will change over time, "that does not mean that all the ingredients have suddenly degraded after that date. Think of the expiration date as a general guideline," he suggested.

Quality Indicators

Despite the voluntary nature of supplement expiration dating, responsible manufacturers take stability testing seriously, and patients who use their products can trust that dates indicated are evidence-based.

"It would be odd for a dietary supplement product not to include a date of some kind, and such products should probably be avoided," Shao cautioned.

If an expiration date seems close to the time of purchase––for example, one month out on a bottle containing a six-month product supply––that's another sign to seek a different product.

Health professionals can guide patients toward high-quality products by requesting that supplement companies provide or discuss their stability data.

Pavlick recommended some key questions to ask manufacturers:

- "Do they arbitrarily assign a two-year expiration, or do they have data (to support that date)?
- Are they using intentional overages? If so, for which ingredients?
- Are toxic mega-doses being taken into consideration?"

She stressed that responsible brands will have these answers and will be happy to discuss them. "Be sure to ask your customer service or sales representative to put you in touch with the scientists in product development or within the quality department."

Other indicators can help guide patients towards higher-caliber products. A number of supplements have a USP verification mark or GMP registration seal on their labels, both of which provide additional information about a product's contents and safety.

The USP (United States Pharmacopeia) Dietary Supplement Verification Program is a voluntary program open to supplement brands worldwide. It provides independent third-party testing of quality, purity, potency, performance, and consistency, in accordance with federally recognized US Pharmacopeia–National Formulary (USP–NF) and FDA cGMP standards.

NSF is another independent certification body that registers nutritional supplement makers who meet GMP requirements. The NSF "GMP Registered" logo assures consumers that products contain the identity, strength, composition, quality, and purity of ingredients they claim to provide.

As always, "a patient-practitioner dialogue about dietary supplements is important," Sirois said. He encouraged patients to "check with their healthcare providers and read the label before taking any dietary supplement product." **QC**

A controlled storage chamber used for accelerated stability testing at Designs for Health. The chamber allows QC experts to test how well products hold up under high heat and humidity. *Image courtesy of Designs for Health.*

Encapsulating Quality: How Ingredient and Capsule Choices Impact Supplement Performance

By Barri Sigvertsen, Senior Manager, Global Innovation Marketing, Lonza Consumer Health and Nutrition

"Practitioners who recommend or dispense supplements need a high level of confidence that the products are safe, and likely to deliver on their stated benefits."

One of the many challenges for supplement manufacturers is consistently ensuring that the products they bring to market are safe, innovative, and aligned with practitioner and consumer preferences, while optimizing production efficiency, productivity, and profitability.

That's no easy feat. From the choice of bioactive ingredients, through the encapsulation or tableting process, and ultimately to the packaging and shipping, there are dozens of decisions to be made. Each choice has a potential impact on overall product quality, stability, and efficacy.

We know from numerous consumer research studies that, despite nuances between age groups and regions, the safety and quality of supplement products are the top two overriding concerns among the consumers when asked about what influences their supplement purchasing decisions (*Natural Marketing Institute, Supplements, OTC, Rx Database (SORD) Proprietary Report for Capsugel*, 2018).

The concerns are, understandably, very similar among physicians and other healthcare professionals (See *Supplement Quality in the Clinic: How Practitioners View Product Quality*, p11). Practitioners who recommend or dispense supplements need a high level of confidence that the products are safe, and likely to deliver on their stated benefits.

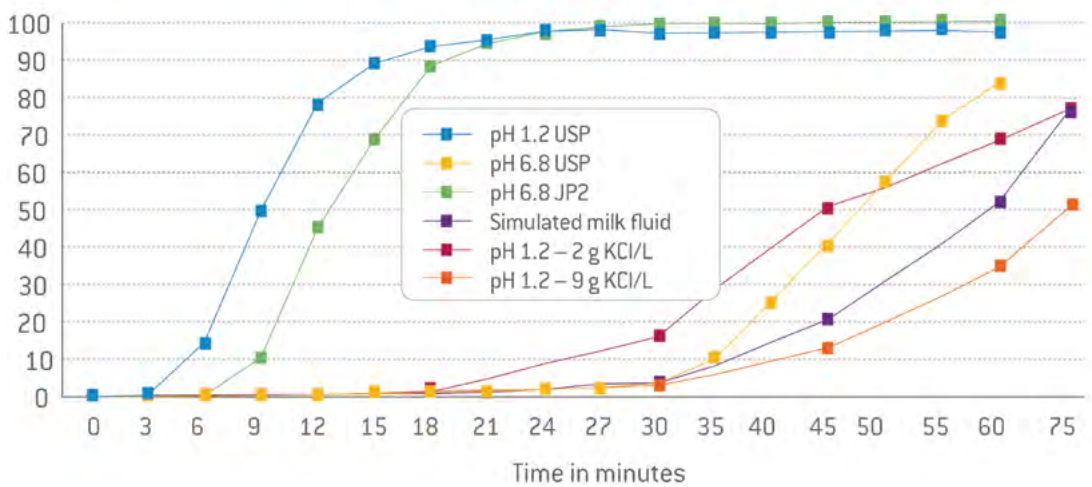
Most major supplement brands recognize customers' concerns about quality, and take them very seriously. They work with raw materials suppliers that have extensive expertise and experience in supplement technologies and manufacturing processes. There is a science to producing good quality supplements, and ingredient suppliers and other solution providers offer a wealth of support throughout the product development process. They can help with guidance on R&D, formulation, manufacturing processes, and regulatory compliance.

As one of the world's largest raw materials and capsule suppliers for both the supplement and pharmaceutical industries, Lonza is committed to helping our customers produce safe, efficacious, high-quality products to address consumers' health needs and preferences. We do this by building quality into all stages of product development, across our science-backed ingredients and functional dosage forms.

Innovative Ingredients

One important area of focus for Lonza has been on joint health, a product category in which there is high consumer demand for

Fig. 1: In-vitro dissolution of caffeine in Capsugel® Vcaps® Plus capsules



science-backed supplement solutions. Consumers want to maintain their mobility as they age, and they're seeking products that not only help alleviate symptoms of joint pain, but also truly support healthy joints.

One such ingredient, supported by multiple clinical studies, is Lonza's UC-II® undenatured type II collagen. This innovative ingredient has been shown to support joint comfort, flexibility, and mobility. One small 40mg dose, taken daily, enables healthy people to remain active for longer periods. UC-II® undenatured type II collagen has also been shown to help improve joint comfort, mobility, and flexibility in people with osteoarthritis (Lugo JP, et al. *Nutr J.* 2016. Crowley DC, et al. *Int J Med Sci.* 2009).

In a head-to-head comparison with a combination of glucosamine and chondroitin, UC-II® ingredient was found to be significantly more effective, as measured by the industry standard for mobility, the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC).

UC-II® undenatured type II collagen has a unique mode of action; it initiates cell-signaling cascades that turn on the body's natural repair mechanisms in the joints, and is thought to play a role in supporting the rebuilding of cartilage.

When taken orally, UC-II® undenatured type II collagen reaches specialized lymphoid follicles found in portions of the small intestine. These areas, known as Peyer's Patches, form a part of the gut-associated lymphoid tissue (GALT). Once UC-II® ingredient makes contact with the Peyer's Patches, it starts interacting with regulatory T-cells, which in turn produce cytokines that are transported to the joints.

These molecular signals induce resident chondrocytes to begin producing more type II collagen and other constituents that make up the structural matrix of the joint.

Lonza's UC-II® undenatured type II collagen creates the opportunity for supplement manufacturers to deliver high-quality joint health solutions that are backed by science and align with the latest consumer demands.

Delivery is Key

High quality bioactive ingredients are only one part of the quality equation.

The truth is, no matter how good or how pure the ingredients are, they will only be effective if they make it to the end-user intact and undegraded, and then—once consumed—they are released when and where the body needs them.

This is where choices about dose delivery systems—tablets versus capsules, enteric coated versus uncoated, microencapsulation, animal versus vegetable source materials, and timed-release mechanisms—come into play.

Unless you work in the supplement or pharma industries, you probably don't think too much about capsules and tablets. Nonetheless, this is a very important consideration. A lot of thought and expertise goes into the decisions about how best to formulate a product, how to optimize its absorption and pharmacokinetics, and how to protect it on its long journey from the manufacturing facility to your patient's hands.

Today's delivery systems are quite sophisticated. There are more choices than ever, each offering a spectrum of properties, advantages, and drawbacks. Committed companies strive to match their delivery system choices with their ingredient profiles and also with consumer preferences.

Consumers Prefer Capsules

We know, for example, that 43% of supplement users prefer capsules over any other dosage form (*NMI SORD* study, 2018). That's because they're convenient, clean, and easy to swallow.

Capsules also have a wide range of applicability, from powders, to liquids, to semi-solid ingredients. Many capsules are made of gelatin, which has been in use for decades within the pharmaceutical industry. Gelatin can be either soft or hard. Both types are often used for pungent nutritional oils, like fish and krill oils. Softgels are generally more porous, and may allow ingredient odors to escape. Hard gelatin capsules—especially those nitrogen-flushed upon filling and then hermetically sealed to prevent oxidation—can more successfully protect ingredients and mask odors.

Gelatin has earned its long history of use: it is durable, flexible, and cost-effective. But in today's market, it has one big drawback: it comes from animals. The gelatin used in supplement or drug capsules is derived from marine, bovine, or porcine sources.

Vegetarian vs Animal-Sourced Capsules

These days, a large and increasingly conscious market of vegan and vegetarian consumers, are seeking products that are completely free of animal ingredients. The SORD data suggest that nearly 45% of all supplement buyers want vegetarian options. This is especially true among Millennials and younger consumers.

Fortunately, there are many vegetarian and vegan options for supplement capsules.

Through its Capsugel® brand, Lonza has been at the forefront of the vegetarian supplement wave, offering the industry a range of vegetable-derived capsules. Our Plantcaps® capsules, made from pullulan—a polymer derived from naturally fermented tapioca—are ideal for oil-based ingredients with strong smells, especially those prone to oxidation.

Pullulan has a high odor barrier compared to other non-gelatin polymers, and it has a moisture content similar to gelatin, making it a good substitute for animal-sourced gelatin capsules. Plantcaps® capsules are also verified by the Non-GMO Project, an added plus in today's health-conscious market. They are free of additives, preservatives, allergens, starch, and gluten as well as certified non-GMO, Kosher, and Halal.

Pullulan is recognized on the US Department of Agriculture's National List of ingredients that can be used for "made from organic" claims. Pullulan is a product of fermentation, and will now be classified as a "non-agricultural" and "non-synthetic" substance made from food-grade bacteria. Pullulan presents the only vegetarian encapsulation material that is certified by the National Organic Program (NOP).

Lonza also offers DRcaps™ capsules. These are vegetarian hard capsules made of low-moisture hydroxypropyl methylcellulose (HPMC) that offers

an alternative to enteric coatings. HPMC is an acid-resistant polymer, which means it does not disintegrate in the stomach but opens immediately at pH levels above 6.8. HPMC capsules are well-suited for delivery of probiotics, enzymes, and many sports nutrition ingredients where a delayed release is preferable.

"Next-Gen" HPMC Capsules

In recent years, there has been a lot of innovation in the production of HPMC-based capsules, leading to great improvements in their physical properties.

A new generation of HPMC capsules, produced via a thermos-gelation process, supports a consistent and immediate dissolution. These capsules can be produced without secondary gelling agents, and they have a dissolution profile comparable to that of traditional animal-sourced gelatin capsules. They are made solely with HPMC and water, and give consistent and predictable dissolution profiles at a wide range of pH levels (see Fig. 1 - page 18).

In one dissolution study comparing Excedrin Extra Strength encapsulated in new-generation HPMC capsules versus the same formula in standard gelatin, both released 95% of their drug contents within 30 minutes, as expected. Based on tests in 24 healthy human subjects, there were no significant differences in pharmacokinetics between the HPMC capsules and the traditional gelatin.

However, when first-generation HPMC capsules are compared with animal-based gelatin capsules, there is a marked difference in onset of drug absorption.

The new form of HPMC also solves the challenge of cross-linking.

One of the issues with gelatin capsules is that some bioactive ingredients can crosslink with amino acids in the gelatin, leading to an unwanted delayed release. Since HPMC is a form of cellulose, and does not contain amino acids, cross-linking does not occur.

Further, animal-sourced gelatin has a high moisture content, typically around 13-16%, in order to maintain the flexibility of the capsule shell. Therefore, moisture-sensitive active ingredients—acetylsalicylic acid is a good example—are often incompatible with gelatin capsules because they are susceptible to degradation from the water in the capsule shells. HPMC capsules have a much lower moisture content, between 5% and 8%, making them more compatible with water-sensitive ingredients.

It's important to realize that moisture-induced degradation can happen inside a sealed product bottle, independent of environmental exposures.

A head-to-head comparison of acetylsalicylic acid encapsulated in gelatin versus HPMC showed that at 18 months, the gelatin capsules had an 8% degradation of the active compound, versus just 2% for the HPMC capsules. In both cases, the capsules remained inside unopened inductively sealed bottles for the full 18 months. The hydrolysis of salicylic acid was attributable solely to the water content in the capsule shells.

Transfer of water from capsule shell to capsule contents also affects the quality and performance of the former. Gelatin capsules that lose moisture to the hygroscopic ingredients they enclose may become brittle and more susceptible to mechanical damage. Desiccants used in supplement bottles can have the same effect, drawing moisture out of gelatin capsules and making them less flexible.

In simple terms, what this means is that choice of capsule type directly affects product shelf life and stability. This is equally true of supplements and pharmaceuticals.

There are many other considerations when it comes to dose delivery systems for dietary supplements. These include:

Enteric Coatings: A very wide range of substances—fatty acids, waxes, shellac, plastics, plant fibers, or film resins—can be applied to tablets, capsules, pellets, and granules (typically delivered in capsule shells) to delay ingredient release. These enteric coatings delay delivery. The US Pharmacopeia stipulates a 2-hour release to qualify for the enteric claim.

Acid-Resistant Capsules: DRcaps™ capsules protect acid-sensitive ingredients for at least 30 minutes in the stomach's pH of 1.2. They do this without any additional enteric coatings, which can be costly. This approach is 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. Creatine and amino acid-based ingredients like BCAA, l-glutathione, and l-carnosine also benefit from delivery in DRcaps™ capsules.

Coni-snap® Sprinkle Capsules: Many people have a hard time swallowing pills and capsules, especially infants, young children, and the elderly. This has led manufacturers to develop consumer-centric alternative delivery systems. One important innovation is the Coni-snap® sprinkle capsule, used for powders, multi-particulates, or beadlets of active ingredients..

Coni-snap® sprinkle capsules are manufactured to be five times easier to open than a standard capsule, meaning that people who have trouble swallowing capsules can simply open them and sprinkle the contents onto food or into beverages. Since these capsules can be made of either gelatin or HPMC, they can be taken orally, or used as a biodegradable carrier, which makes them an environmentally-friendly alternative to sachets.

Licaps® Capsules: Lonza's Licaps® capsule technology fuses 2-piece hard capsules specially designed for the secure containment of liquids, semi-solids, and versatile ingredient combinations.

These diverse capsule choices are only a few of the dosage delivery systems currently being utilized in the manufacture of dietary supplements. Tableting also has many variables that must be carefully considered. The popularity of chewable gummies brings with it yet another set of options and parameters.

It is essential that the dosage form is optimized for product performance, and that the manufacturer has carefully considered the bioavailability and release profiles of its chosen ingredients. Conscientious brands also consider the specific preferences of a product's intended consumer base. At Lonza, we offer a broad range of delivery forms and technologies to overcome a variety of formulation challenges and to provide tailored solutions in line with specific consumer needs. QC

The Roots of Supplement Quality Are in the Soil

By Kristen Schepker | Assistant Editor

"Happy soil leads to nutritionally dense plants. It is impossible to separate soil health from nutritional health"

The caliber of a dietary supplement is only as high as the caliber of the ingredients it contains. For supplements containing plant-derived ingredients, the quality has its roots in the soil in which the plants are grown. Recent developments in soil science and sustainable agriculture are helping conscientious companies to safeguard product quality in an era of widespread environmental degradation.

It's a simple fact: to cultivate healthy plants, you need healthy soil.

A number of different factors influence soil health, in turn affecting plant vitality and productivity. Emerging evidence indicates that the soil microbiome—the complex community of microorganisms surrounding the roots of plants—plays a far more significant role than previously recognized.

Happy Soil, Happy Plants, Happy People

"Happy soil leads to nutritionally dense plants. It is impossible to separate soil health from nutritional health," explains Christine Mason, farm operations manager at Standard Process, a pioneering nutritional supplement company that grows most of its own product ingredients.

Standard Process founder Dr. Royal Lee articulated this idea more than 90 years ago: "Whole food nutrition begins with sun, water, and fertile soil."

Lee's founding principles continue to guide the company today. "Our food cannot be healthier than the soil it is grown in," Mason stated. "Although we have beautiful crops and much to be proud of...our crowning achievement is the soil itself."

The Soil Microbiome

As with the human intestinal microbiome, diversity is a vital factor in the health of the soil microbiome. Microbes in the dirt "carry out important processes, including support of plant growth and cycling of carbon and other nutrients," note researchers Janet Jansson and Kirsten Hofmockel. But because scientists are just beginning to understand what lives beneath the dirt, most soil microbes have not yet been isolated and their functions remain largely unknown.

According to educators at Ohio State University's College of Food, Agricultural, and Environmental Sciences, there are more microbes in a single teaspoon of soil than there are people on Earth. By mass, bacteria and fungi comprise over 90% of the soil microbial community.

"The soil microbiome is the new frontier of research,"

Plants, including many that are important sources of food, have evolved over millennia to interact symbiotically with the microorganisms present in the soil. Understanding how those billions of microbes interact with different root systems and affect plant biochemistry, equips farmers with new tools to improve soil quality.

But widespread industrial agriculture has had a massive impact on soil quality, and is reshaping the natural balance of plant-microbe interactions.

The heavy application of synthetic nitrogen fertilizers, commonly seen on large industrial farms, is an effective way to increase crop yields. But in so doing, it wreaks havoc on the environment. Nitrogen-rich fertilizer overuse is now recognized as a major pollutant. Soil microbes convert nitrogen fertilizers into nitrous oxide, a greenhouse gas that traps 300 times as much heat as carbon dioxide.

Studies suggest that nitrogen fertilizers also disrupt plant root microbiomes, damaging soil health and triggering ecosystem changes unlikely to be sustainable in the long term.

Diversity is Key

In order to maximize soil life, Mason says, diversity is key. And this is true at all levels.

Diverse selections of both food and cover crops produce healthier soil, inviting in a greater mix of soil organisms. Simply put, a wider variety of plants on a farm ensures a wider variety of organisms in the soil.

Many small-scale sustainable, organic farms use techniques that inherently promote biodiversity, like crop rotation. But large-scale monocropping—a hallmark of modern industrial agriculture—does exactly the opposite.

"To me, the healthiest soils on the planet are found in undisturbed prairie or forest floor," Mason said. "These are about as far away from monoculture row crops as you can get."

Last year, at the grand opening of Standard Process' Nutrition Innovation Center (NIC) in Kannapolis, NC, Mason explained that up to 80% of

the time, soil microbes live under starvation conditions. Well-fed microbes, on the other hand "are, to paraphrase biologist Jim Fuhrer, 'soluble bags of fertilizer.'"

Harnessing the fertilization capabilities of soil microbes therefore reduces the need to treat crops with synthetic plant foods.

The 600-plus acre Standard Process farm, located in Wisconsin's Kettle Moraine basin, has been growing organic produce since the company's founding in 1929. Mason's team plants between 20 and 35 different crops every year, including cover crops grown for the sole purpose of nourishing the soil. They harvest over 6.5 million pounds of produce annually.

Alfalfa, barley grass, beets, Brussels sprouts, buckwheat, kale, kidney beans, oats, pea vine, and Spanish black radish provide the foundational base for the company's supplements. More than 80% of the raw plant ingredients in Standard Process formulas come directly from their farm.

Alongside its food/ingredient crops, the farm grows cover crops exclusively "to feed the next crop, and the microbiome of the soil that's going to encourage a healthy next crop," said Mason who, along with her husband, Steve, comes from a long line of farmers in the region. But she's had experience working in a wide variety of agricultural and industrial settings, from small family farms to major agribusinesses.

Green Manure

By intentionally and carefully choosing not only which food crops they grow, but also the cover crops they plant, Standard Process farmers can "provide a steady food source to soil microorganisms, promoting proliferation of benign organisms and crowding out and suppressing soil-borne diseases," Mason said at the NIC launch.

Beneficial soil microbes will quickly consume certain plants, like "sweet, succulent" annual legumes, but eat fibrous plants much more slowly, generating a consistent supply of organic matter and improving the soil's capacity to retain nutrients.

Again, the parallels between human and soil health are striking. "If we only eat one thing over and over, [we] are going to be nutritionally void. Same with the soil," Mason proposed. Typically, industrial farms only grow one or two crops—corn and soybeans, for instance. Their idea of crop rotation is to grow soy for a few years, then corn, then soy again.

The problem is that the various microbes residing in the soil each have a preferred diet. "If they don't have different food sources, it's harder to have an active soil life," Mason said.

She and her colleagues employ several other techniques to boost soil health. National Organic Program guidelines restrict the use of animal manure on crops grown for human consumption, so Standard Process uses green manure—made from crops grown specifically to nourish the soil—instead.

Oats, chickling vetch, and kidney beans are among the farm's top selections for natural nitrogen sources that help fertilize crops while eliminating the need for chemicals or animal feces. A 5-year crop rotation schedule assists with keeping insects and other pest populations in check, without relying on industrial insecticides or herbicides like glyphosate.

Carbon Sequestration Counters Climate Change

Growing crops organically doesn't just produce healthier soil and healthier plants—it's better for the earth, too. According to the Carbon Cycle Institute (CCI), agricultural operations are the second largest contributor to carbon dioxide emissions on the planet.

According to a March 2018 National Geographic report, "more than 75 percent of Earth's land areas are substantially degraded, undermining the well-being of 3.2 billion people." Agriculture and livestock overgrazing are two of the greatest contributors to soil degradation.

"Personal vitality is dependent on soil vitality. The nutrition in harvested portions of a plant is derived from the nutritional density of the soil."

—Christine Mason, Farm Operations Manager
Standard Process

Common conventional agriculture practices like driving tractors, tilling soil, overgrazing, and utilizing fossil fuel-based fertilizers, pesticides and weedkillers, all "result in significant carbon dioxide release," the climate-centered nonprofit says.

At the same time, carbon can also be beneficially stored in soils over long periods—decades to centuries or more—in a process known as soil carbon sequestration. This makes agriculture the one and only sector uniquely positioned to "transform from a net emitter of CO_2 to a net sequesterer of CO_2."

"There is no other human managed realm with this potential," CCI argues.

Advancements in climate science suggest that certain agricultural techniques positively impact carbon levels in both the soil and the atmosphere. Carbon-beneficial farming generates higher levels of organic matter, increasing its soil carbon sequestration capacity.

"Organic matter is approximately 58% carbon, and soils with high organic matter are the soils most apt to be able to keep up with the food demands of our planet's population explosion," Mason proposed. "Scientists are now beginning to understand that we are going to have to teach farmers and ranchers how to maximize the carbon in soil, not just for the bounty and health of the plants grown on top of it, but also for the health of the planet itself."

Growing a diversity of crops, keeping tillage to a minimum, and using organic compost are all methods for maximizing soil carbon content. While embraced by sustainable farmers, these practices aren't typically employed on conventional farms.

Closing the Phytonutrient Gap

One of the consequences of undernourished soil is low nutrient content. As Mason put it, "personal vitality is dependent on soil vitality. The nutrition in harvested portions of a plant is derived from the nutritional density of the soil."

Today, most Americans are simply not getting enough nutrients from fruits and vegetables. "8 out of 10 Americans have a phytonutrient gap," said John Troup, PhD, VP of clinical science, education and innovation at Standard Process.

Only 3 in 10 people eat adequate quantities of green fruits and vegetables, and even fewer—2 in 10—consume enough orange/yellow and red produce, Troup said. Those stats, he suggested, represent an urgent need to improve our overall nutritional quality index.

Even those who do eat their fruits and veggies might not be obtaining their full nutritional potential. "If you look at the 20-40% of people who eat fairly healthy and get the right amount of produce servings, only about 20% are able to get the recommended nutrient density from the fruits and vegetables they eat," Troup warned. "There [are] gaps in our nutrient profiles."

Fortunately, there's some good news: upping our intake of fruits and veggies results in a 5% reduction in mortality risk for each daily serving increase, Troup said, adding that it is increasingly important to document the specific effects of nutrition interventions on clinical outcomes to demonstrate the myriad ways nutrition influences health.

Commitment to Quality

"One of the powerful advantages that Standard Process has is that we're vertically integrated from basically farm to fork, or seed to supplement," Troup said. His company's "organic, natural, healthy, good-for-you" ingredients contain "all the nutritional power that food was meant to have."

Packaging that raw power into small supplement bottles requires a huge level of commitment. "I don't want people to think organic is easy," Mason stressed. "This is really hard. It's constant diligence, it's never over. It's a testament to organic farmers that as hard as it is, they choose this way anyway."

Converting land that was previously farmed conventionally into an organic farm is a massive undertaking. Before a farmer's harvest can receive formal organic certification, the farm must first be managed entirely organically for three full years. During that transitional phase, organic certification standards strictly prohibit the use of any genetically modified or synthetic inputs on the property. Certifiers conduct annual inspections to ensure compliance with organic farming requirements.

In the past two decades, Standard Process increased production at its farm by an impressive 500% on the same acreage. "We beat the conventional average in our state every year on every crop," Mason reported.

"What makes us unique is you're not buying a commodity product, you're buying something that we managed from literally the day we bought the seed, through the soil tests, to the harvest," she said. She hopes Standard Process' performance will inspire an industry wide shift in understanding that, "you can be sustainable, build soil, and feed the planet," all at once. QC

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