NATURAL PRODUCTS INSIDER

March 2012 US$39.00

VIRGO HEALTH & NUTRITION

SPECIAL REPORT

Cost of Quality

The Bottom Line for Raising the Quality of Dietary Supplements

Quality control is a comprehensive program of ensuring consistent, accurate operational results. It is a system and culture that must infuse every aspect of a business. As such, deciphering costs, initial and ongoing, can be difficult and certainly requires consideration of all available data. In addition to financial investments, there are costs associated with time spent, as well as oft-overlooked costs of corrective action delays and the viral costs of poor quality.

by Steve Myers

Cost of Quality

The Bottom Line for Raising the Quality of Dietary Supplements

by Steve Myers

"The reward of a thing well done is to have done it." Ralph Waldo Emerson

"Excellence is an art won by training and habituation." Aristotle

If beauty is in the eye of the beholder, what is quality? While quality is not quite as subjective, the cost of quality is certainly as complex and as spiraling as the price of beauty. In fact, assessing quality costs requires many different considerations. There is the cost of creating and implementing quality control (QC) measures, of course, but there is also a cost associated with maintaining a quality program year after year. Then there are the more muddled costs of time spent on development, implementation and assessment of quality, including various levels of labor and training. More hidden can be the costs of failure and corrective action within the plant, as well as failure once the product reaches the end consumer. It is not just investment dollars on the table, but down-the-road costs to future sales, time and reputation.

In order to gauge the cost of quality, it is important to know what quality is. There seem to be many different definitions of quality and quality control, but they collectively focus on philosophy, education/training, standards, protocols, processes, testing, reviews, assessments and corrections. Quality is neither simple nor ready-made. "Quality is not something you install like a new carpet or a set of bookshelves," said W. Edwards Demming, who was something of a QC guru to Japanese manufacturing. "You implant it. Quality is something you work at. It is a learning process."

The dietary supplement industry's history of quality has been just that: a process of learning and effort. Back in the 1990s, supplement use exploded, thanks in no small part to the Dietary Supplement Health and Education Act of 1994 (DSHEA). With quantity and volume came some early QC problem signals. There were cases of poor supply (L-tryptophan from Japan) and lack of botanical identification leading to adulteration (digitalis-plantain mix up), as well as problems with the quality of the delivery systems, such as poor tableting and formulation. In 1999, a study published in the *Journal of the American Pharmaceutical Association* (39(1):27-31) revealed scientists testing melatonin products found some tablets showed excessive friability and failure to properly disintegrate and dissolve. They also found excessive variations in hardness.

In the late '90s, some companies such as Weider Nutrition (now a part of Schiff Nutrition) spent millions developing and implementing extensive QC programs. The National Nutritional Foods Association (now the Natural Products Association, NPA) created its first dietary supplement good manufacturing practice (GMP) certification program, which is still in use today, modified to reflect evolving regulatory developments.

However, while the responsible parts of the industry kicked into action to improve supplement quality, there was little deterrent facing unscrupulous "entrepreneurs" from making quick bucks by skirting through production with a minimum of quality measures. Such companies were certainly not the majority in the industry, but public perception has never cared about such majorities, as a few bad can stand out above the many good.

DSHEA contained several mandates for FDA to create various quality-related regulations such as new dietary ingredient notifications (NDINs), adverse event reporting (AER) and supplement-specific GMPs. However, despite making GMPs a priority—according to 2001 testimony from FDA's CFSAN Director, Joseph Levitt, to the House Committee on Government Reform—FDA wouldn't publish its first GMP proposed rule until a couple of years later. AERs and NDINs didn't begin to appear until much later.

"Unless the industry takes seriously the need to deliver clear quality standards to the public, it will suffer further."

In 2001, Susan Haeger, then the president of Citizens For Health (CFH), warned, "Unless the industry takes seriously the need to deliver clear quality standards to the public, it will suffer further." She said the passage of DSHEA promised consumers access to quality products to help them maintain good health, but instead they got a proliferation of sub-quality products with lots of inflated claims.

After almost a decade of industry urging action from FDA on GMPs, the agency published its proposed rule on dietary supplement GMPs in March 2003. Among the biggest concerns from industry were related to testing requirements for ingredients that have no validated analytical method, and the cost of testing requirements as proposed. There was also a call for a clearer definition of which entity was required to perform testing on ingredients.

In comments submitted to FDA on the proposed rule, the Council for Responsible Nutrition (CRN), said: "CRN believes FDA has grossly underestimated the costs of compliance with the proposed rule, especially the cost of testing every component of every batch. ... We believe the exhaustive testing requirement proposed by the agency would be excessively costly for firms of all sizes and is unnecessary in order to ensure quality once a company has established a well-controlled processing system."

It would take another four years for a final GMP rule from FDA. In the meantime, the perception of dietary supplement quality was taking hits. In a 2003 report in the *Annals of Pharmacotherapy*, Walter L Larimore, M.D., University of Colorado, Denver, and Dónal P O'Mathúna, Ph.D., Mount Carmel College of Nursing, Columbus, OH, looked at the industry's quality assessment programs. They concluded QC standards for dietary supplements run the gamut from good to nonexistent. "Contamination, false labeling and incomplete labeling are not uncommon problems—as are significant discrepancies in disintegration, dissolution, and in vitro release characteristics of various dietary supplements," they wrote. Until FDA finalizes and implements supplement GMPs, they said, certification programs can help provide safety assurances and help with product selection. "Although they do not testify to effectiveness (and may even inadvertently mislead some consumers), certification programs may help curb what has been called the Wild West nature of the dietary supplement industry."

They concluded QC standards for dietary supplements run the gamut from good to nonexistent.

Certification Programs

NNFA implemented its first GMP program in 1999, with Nature's Way and Wakunaga of America earning the first certifications. Passing the third-party inspections of NNFA-specified standards for safety, quality, purity and label integrity of dietary supplements meant the companies could use the NNFA GMP seal on their product labels. Specifically, the GMP certification program included specifications for testing of raw and finished materials, staff training, equipment maintenance, cleaning and recordkeeping. Auditors for NNFA's original program included former FDA staff members who were not affiliated with NNFA. Industry Congressional advocate Sen. Tom Harkin said at the time, "NNFA has picked up what the FDA dropped."

NSF International, which has a long history of third-party certification, launched a supplement quality certification program in 2001 to help address consumer and government questions on the safety and consistency of supplement products. NSF's requirements are based on Section 8 of NSF/ANSI Standard 173-2008, which it said is consistent with FDA's supplement GMPs. As part of the certification, NSF said it would verify labeled ingredients, test for contaminants and inspect plants and facilities. Certified companies can use the NSF mark on their product labels.

U.S. Pharmacopeia (USP) launched its Dietary Supplement Verification Program in late 2001, to help assure the public dietary supplements passing through its program contain the ingredients stated on the product label. The products also have to meet limits for

contaminants and comply with USP and proposed (at the time) FDA GMP standards. This program also featured a seal that could be displayed on the product's label. Pharmavite's Nature Made line of supplements was the first to earn this USP seal.

Non-GMP-focused quality certifications have also been used to gauge and recognize companies' quality efforts. These include Six Sigma, Quality Circles and ISO 9000. Other organizations created product testing programs, including those from the independent group Consumerlab.com and natural products retailer Vitacost. Such programs are aimed purely at consumers and can have an effect on media coverage of an ingredient or product, thereby possibly affecting a company's public reputation.

Many supplement companies have utilized these quality assessment programs both before and after FDA published its final GMP rule. In its efforts to ensure a top-notch quality control system and compliance with FDA GMPs, Mineral Resources International (MRI) made use of such third-party services, such as NSF certification. "We found NSF is tougher than FDA," said Val Anderson, executive vice president and director of sales and marketing for MRI.

These programs are supplemental to FDA GMP compliance and can be a good barometer for companies that have not faced FDA GMP inspection.

Shabbir Akand, vice president of sales and marketing for NHK Labs, said third-party certification programs can mimic actual GMPs, and while each program will have its own take, strategies and peculiarities on quality requirements, taking several of the programs can make your quality more well-rounded.

These programs are supplemental to FDA GMP compliance and can be a good barometer for companies that have not faced FDA GMP inspection but wonder how well they are doing with QC and compliance efforts. Thus, the cost of these programs is less in the build-up then in the registration and audits, as well as any adjustments made to the quality process following the audit. There can be a considerable time factor also. To participate in NPA's GMP program—certification is good for two years—costs the price of NPA membership, a GMP program fee of $250 and an annual renewal fee of $1,000 for certified companies. NSF's GMP registration program costs vary depending on the size and scope of the business and other factors—a larger more complex facility will need more audit days than a facility that is a warehouse or distribution center.

For certification by ISO (International Organization for Standardization), a gap analysis is recommended to highlight the changes a company would need to make to its quality

management system, which will provide some insights on the costs to meet requirements. The cost will also depend on whether a company decides to handle implementation in-house or use outside consultants. Some experts estimate about $1,000 for companies willing to handle all the implementation in-house. If using outside consultants, the price for a small company (under 25 employees) with no quality system in place can be as high as $5,000. Those with a basic or better quality system in place will have less implementation costs. Medium sized companies (26 to 500 employees) can pay up to $25,000 if no quality system is in place, and large companies (more than 500 employees) with no quality system in place can pay as much as $60,000. (info: Standards Stores) Registrar costs can be the bigger beast, with some estimates putting three-year registrar costs between $15,000 and $20,000 for smaller firms (*Center for Industrial Research and Services*). The World Standards Cooperation has information on methodologies businesses can use to calculate the potential benefits gained from standardizations such as ISO 9000 certification.

Creating a Quality System

A good quality control system will include documented procedures, responsibilities and specifications for all stages of a company's business. For manufacturers, this includes the selection and qualification of suppliers; testing of incoming raw materials; specifications for equipment used; procedures for fulfilling tasks; plant and equipment maintenance and cleanliness; in-process testing; personnel training and hygiene; corrective action plans, including procedures for out-of-spec materials; master manufacturing records; batch records; storage specifications and procedures; and many other detailed aspects of manufacturing, packaging and storing supplement ingredients and products.

Creating a quality system is more than just assembling the right information and developing sound procedures.

Creating a quality system is more than just assembling the right information and developing sound procedures. A company's leadership must communicate a culture of quality throughout every level of the company. Without a total top-to-bottom commitment to quality, to providing the highest quality products for consumers' health, some employees are more apt to not take QC seriously and corners are more likely to be cut.

QC, on its own, is a multifaceted enterprise involving numerous parts and employees in a company. Many of the more established, sometimes larger, companies in the supplement industry invested in quality long before FDA came out with supplement-specific GMPs.

Joe Archer, vice president of sales and marketing for All American Pharmaceutical (AAP), said the company had been implementing a great deal of the QC requirements long before those requirements became part of supplement GMPs. "We also started the [GMP] preparation years before these took effect," he explained. "It has helped with spreading out the costs over the gear-up time."

Spreading the costs has been a great advantage for companies that were out ahead of the GMPs relative to implementation. Akand said NHK also spread out its quality and GMP costs by investing in laboratory, equipment and other quality-related resources well in advance of the supplement GMPs. Without spreading such costs over a few years, some companies may end up going out of business because they can't sustain the investments and costs required to meet compliance, he suggested.

The departure of companies from the supplement market can be either a loss (cost) or benefit to the industry as a whole, depending on the value of the company and products. For quality companies that waited too long or simply ignored the GMP regulations—many might have thought prior FDA failures to enforce regulations were a hint of what to expect with GMPs—going out of business will take good products from consumers. On the other hand, fly-by-nighters that were never intent on playing by rules and chose to withhold investment in quality and GMP implementation will not be missed when they go out of business.

With the regulations having been effective for only a short period of time, it may be too soon to tell how many companies will fold for lack of compliance. However, with FDA continuing to increase the number of inspections, industry insiders are reporting some business departures. "Our customers have been telling us they've come across other manufacturers who are no longer in business," Akand said.

With the regulations being effective for only a short period of time, it may be too soon to tell how many companies will fold for lack of compliance.

QC is more than the GMPs, but the regulation has certainly drawn the line in the sand for supplement manufacturers (and certain distributors) as far as a quality minimum is concerned. Jeff Wright, owner of Wright's Nutrients and president of NPA, noted original predictions, including those made by FDA, anticipated up to 25 percent of the industry would leave the market in the face of compliance with supplement GMPs. "At this point, NPA is not aware of that many companies closing their doors," he said, adding the organization has instead seen some significant changes in business models and relationships. "For example, companies are

carefully assessing the cost of working with contract laboratories versus trying to bring all testing in-house." He further noted smaller private label companies are choosing to work with contract manufacturers as opposed making their own products.

"To some extent, we are still in the early stages of the smaller companies truly understanding what constitutes compliance," he continued. "As the scope and depth of FDA inspections increases, we could see more significant fallout."

For many companies the first step is figuring out how the GMP regulation applies to their business. This is where the industry has offered numerous resources. As soon as the rule became final, industry trade groups and media outlets put together tutorials, seminars, webinars and workshops on what the GMPs require and what FDA is focusing on during inspections. Many of these educational opportunities were part of trade show offerings and featured FDA staff and QC experts in an effort to clear up some questions supplement companies might have.

For many companies the first step is figuring out how the GMP regulation applies to their business.

For example, NSF-DBA has offered GMP training sessions, including both 100 and 200 level courses, at various SupplySide events. The 100 level course reviews the GMP guidelines and looks at case studies, including warning letters, to learn more about what FDA is looking for when inspecting for compliance. The 200-level course focuses on supplier qualification and auditor training, and is designed for QA/QC, regulatory and compliance, laboratory and other key personnel who are involved in the implementation of a new or modifying an existing vendor qualification program.

Such educational events can be a real value for companies that are unable or unwilling to spend more money hiring outside consultants to help develop compliance efforts. Eileen Sheets, managing director for Bioforce USA, said she would have liked to utilize a third party consultant to help figure out what the company needed to do to comply or even to get a boilerplate for standard operating procedures (SOPs), but she found the prices too expensive. Instead she turned to industry events and her trade groups. "I sat through several webinars and seminars to get an idea of what we were facing, and I had my operations manager also sit in on some," she said, noting the biggest challenge for her very small company (about 12 employees) was figuring out which areas of the GMP applied to her business, which exclusively distributes finished dietary supplements made by a network of manufacturing partners. She added the trades, especially the American Herbal Products Association (AHPA), did a good job preparing companies and providing useful resources.

Although it was one of the companies that had a head start on GMPs by investing in quality control before the final rule, MRI still found itself using a variety of outside

consultants and industry events/resources to ensure it understood and met the regulations completely. He pointed to Emord & Associates' prompt and extensive review of the final rule as a critical resource, as were industry training events that followed.

Focus on GMPs

With the dietary supplement quality landscape dominated by GMPs, the cost of achieving and maintaining regulatory compliance has dictated most QC spending of late. Once the proposed GMP rule was published, Pacific Nutritionals started to improve its processes so it could economically implement necessary changes expected in the final rule, according to company president Michael Schaeffer. "Then, following the publication of the final regulation, it was necessary for us to incur additional costs to address the differences from the draft proposal," he said.

Costs per Establishment, by Size

	Setup Costs per Establishment	Annual Costs per Establishment	Median Annual Revenue per Establishment
Very Small Establishments	$26,000	$46,000	Under $1 million
Small Establishments	$20,000	$184,000	$5 to $10 million
Large Establishments	$31,000	$69,000	$10 to $50 million
Warehouses, Wholesalers, and Other Holders	$360	$1,000	Not applicable

Source: FDA, GMP Final Rule, Cost Analysis

In its 2003 proposal, FDA estimated compliance cost to be about $100,000 per year for very small (fewer than 20 employees) and small (20 to 499 employees) companies, but many industry members disagreed, especially in the area of testing ingredients and finished products. In its final rule, FDA amended its cost estimates to $46,000/year for very small companies and $184,000/year for small companies.

The final rule contains a cost analysis of what FDA expects companies working on compliance will have to spend on personnel, grounds and physical plant, equipment and instrumentation controls, QC and laboratory operations, production and process controls, handling consumer complaints and storage of ingredients and finished products. FDA stated: "the purpose is to estimate the broad average costs of the rule." To establish baseline manufacturing costs, the agency conducted a survey of supplement manufacturers.

FDA acknowledged receiving many comments on the initial cost analysis included in the proposed rule, noting most comments said the agency had underestimated the costs involved with compliance, both first year and annual costs. Specifically, industry comments argued FDA failed to consider the costs of hiring new workers, capital equipment, holding and distributing products, holding reserve samples, and tracking product complaints.

The true, higher compliance costs argued by industry would result in opportunity costs such as decreased product choice, increased product prices to consumers and the departure of some businesses, especially very small companies, from the industry. FDA recognized the expense of compliance could result in decreased spending on other critical areas, listing examples such as worker safety, product development and marketing, or voluntary testing of the efficacy of their products.

"Companies only have so much money to spend," Anderson confirmed, adding companies have to face tough questions about how they are spending money. "Looking at your product lineup, you have to consider the regulation and its requirements and ask yourself: what makes sense to do or not to do? Ultimately, you might have to stop producing certain products," he said.

Capital costs were one point of contention between industry and FDA's analysis.

Capital costs were one point of contention between industry and FDA's analysis. FDA recognized many companies would have to make capital investments in physical facilities and equipment, as well as spend money "to perform additional maintenance, establish written procedures, keep records, carry out tests, monitor production and process controls, or execute a variety of additional tasks that they may not have previously performed."

Akand reported NHK more than doubled its lab equipment to help meet testing and analytical requirements of the GMPs. "Before, we had one HPLC machine and one FTIR, but now we a set of two of each machine, as well as other new equipment," he said. As for the physical plant, he said if there is no money for an investment in expansion, a company will have to be more resourceful with existing space and room. "We compartmentalized areas to be more efficient."

The agency noted its capital cost estimates covered the costs of minor renovations to help meet sanitation requirements—its survey of manufacturers indicated no capital investments would be needed to meet sanitation requirements—not for expanding the size of a laboratory or for some other technically sophisticated change. "Although some facilities may choose to expand laboratories, the testing requirements of this final rule should be able to be met by existing laboratory facilities within or outside of the manufacturing facilities," it stated.

Outsourcing testing to third-party labs is certainly an option, although the costs for testing in general is yet another point of difference between industry and FDA. The agency pointed out the testing requirements in the final rule are less than what was in the proposed rule that drew so many comments about testing costs.

In the final rule, FDA lists the required tests as:

- Tests of lot subsets by suppliers to create certificates of analysis (COA);
- One identity test for each shipment lot of incoming dietary ingredients;
- Tests of subsets of shipment lots for other specifications in the COA;
- Tests of subsets of batches of dietary supplements for microbial, chemical or physical contaminants;
- Tests of subsets of batches of dietary supplements for specifications; and
- Tests for meeting requirements that water used to manufacture dietary supplements complies with federal, state and local requirements and does not contaminate the dietary supplement.

To help cut costs, FDA published an interim final rule outlining a procedure to petition for exemption from 100-percent identity testing. CRN said FDA's estimate of $2,900 for the petition process is "a substantial underestimate of the true costs that would be involved," according to CRN's own analysis. "Nonetheless, even if FDA's estimates are correct, according to our analysis, manufacturers would have to receive about 50 lots per year of a given ingredient from a given ingredient supplier in order to simply break even on the costs associated with the petition process," argued Andrew Shao, Ph.D., then the vice president of scientific and regulatory affairs for CRN, in his letter to FDA. He cited information from a large-sized (per FDA's definition) CRN member company, which said it is likely to receive fewer than 50 lots per year of 90 percent of incoming ingredients. Obviously, smaller manufacturers would receive even fewer lots per year. "In short, there is very little economic incentive, if any, for companies to partake in the petition process and ultimately benefit economically from the reduced identity testing," he concluded. In the end, CRN argued identity testing for most dietary ingredients is simple and cost effective—it said FDA's estimated $60 price per identity test may even be high—and is essential to supplement GMPs.

Adjusted Total Cost for Testing	
Very Small Establishments	$11,230
Small Establishments	$19,907
Large Establishments	$7,626

Source: FDA, GMP Proposed Rule, Cost Analysis

In its estimates for identity testing, FDA concluded the minimum number of identity tests for vitamins and minerals would be a minimum of one and maximum of 30, with two tests being the norm. The agency conceded that given botanical and herbals are less easily characterized than vitamins, identifying large numbers of ingredients with a single test would be highly unlikely. It concluded one to two ingredients would be identified per test for herbal products.

One of the ways manufacturers are spreading out the costs of identity testing is in ordering or receiving larger lots. If there is one ID test required per shipment lot, it would cost less in ID testing to receive fewer shipment lots that contain higher amounts of the ingredient. While this may be a good solution for ingredients that are more stable and easy and cheap to store for extended periods of time, it would be a less viable strategy for ingredients (e.g., probiotics) that are less stable or more vulnerable to environmental factors, and those that require specific and costly humidity- and temperature-controlled storage.

For some companies, such as Pacific Nutritional, the part of the GMPs that costs the most for compliance relates to finished product and shelf-life testing. NPA expressed similar concerns. "Although identity testing is a challenge, NPA has seen that contaminant testing and finished product testing are proving to be equally or more complex and costly," Wright reported.

FDA noted the final rule allows for "sound statistical testing regimes" for finished supplement products. The agency adjusted its earlier estimates for number of batches produced per year to 444 batches for very small firms, 2,436 batches for small firms and 1,164 batches for large firms. The numbers reflect feedback from smaller companies, which said due to capacity issues they tend to produce more batches of smaller size than do larger companies. With testing batches a primary cost of GMP compliance, any time a company can find a way to produce fewer but larger batches, testing cost savings can be realized.

FDA noted the final rule allows for "sound statistical testing regimes" for finished supplement products.

NPA reported a growing knowledge base from increased FDA inspections has helped the industry develop a better understanding of FDA expectations regarding flexibility and compliance. Wright noted while there is potential to reduce the testing burden for both raw materials and finished products, companies must first demonstrate stability in their suppliers and raw materials, and confirm that their finished products meet their specifications. "This requires them to fully qualify their suppliers and verify the information on component COAs prior to relying on them versus performing testing," he explained. "Also, they must build a rationale for reduced finished product testing that includes two things—one, that data confirm the finished product meets specifications and two, that they have sufficient control over their manufacturing processes to ensure each batch of finished product will meet its specifications as established in the master manufacturing record."

Shelf-life or expiration dating is not required by GMPs, but if such dating is on the finished product label, shelf-life testing becomes a required part of the GMP testing regimen. However, most dietary supplement companies report the market demands

expiration dating, but there are few, if any, guidelines for developing stability testing programs. In 2011, NSF published a stability testing guideline to help supplement companies generate the required scientific data to support dating on product labels. The guideline, created with input from regulators and trade groups, recommends supplement companies identify the physical, chemical and microbiological characteristics under long-term storage, in addition to understanding the impact of manufacturing, packaging, labeling, distribution and holding/warehouse processes may have on a product's stability. It outlines the key factors in stability testing: dietary ingredient strength, chemical fingerprints, microbial growth, preservative content, moisture content, pH, viscosity and oxidation, among other parameters such as the product's container-closure system. This guidance is available for free at NSF-DBA's website, making it a valuable resource for companies that may help them save money.

Production and in-process controls help to ensure products are manufactured consistently from batch to batch and are free from contamination or adulteration throughout production. The GMPs require specifications for certain control points or production stages to assess identity, purity, quality, strength and composition. Specs are also required for packaging.

The GMPs require specifications for certain control points or production stages to assess identity, purity, quality, strength and composition.

FDA reasoned there may be some processes that have no critical points where a defect could occur, and these would require zero in-process tests. On the other end, the agency assumed no process would have more than five control points where defect could occur. This resulted in an estimated average of 2.5 in-process control points per batch. It further estimated an average on one test per control point.

In deciding on the costs of tests, the agency reviewed published prices from independent labs, in addition to data gleaned from FDA and industry testing experts. It found price variations relative to the frequency and complexity of testing: "Many tests require sophisticated equipment, such as gas chromatography, high pressure liquid chromatography, distillation, extraction, various spectrophotometers, and other types of equipment." In addition, while some ingredients or formulations can be properly identified via simple or single-step tests, others can require more complex and multistage testing, especially when dealing with ingredients that can easily be mistaken for another compound (e.g., plantain and digitalis). The agency noted even simple physical or organoleptic testing requires trained and experienced personnel.

It estimated a range of testing prices from $20 to $80, yet placed the average cost at $60. Many industry members argued the tests can easily cost hundreds of dollars.

Akand said NHK has doubled or tripled its lab staff to meet GMP testing requirements. He said even if a company brings most testing in-house, there will always be a need for sending some items to third party labs. He reported lead times at third party labs are already creeping upwards; it may take five to 10 days to have a test done. "If you want a rush job, it can easily be triple the regular price or more," he said.

Anderson said it is cost-prohibitive to send testing out, so MRI does most of its testing in-house. "However, we do still need third party labs to verify some results," he noted.

Still, for companies that don't have the testing capabilities or investment capital for an extensive in-house lab, partnering with independent labs may be the best option. "I believe that smaller companies can partner up with larger companies to complete some of the testing concerns and to assist with costs," Archer said.

Wright agreed using contract laboratories and contract manufacturers may prove to be more cost-effective than bringing everything in-house. "Establishing partnerships with laboratories and contract manufacturers provides an opportunity to negotiate more favorable pricing and reduce the issues that often arise when first working with contract facilities," he suggested.

Ingredient Suppliers Vital to GMP Compliance, Costs

GMPs may sit mostly on the shoulders of manufacturers, but QC extends back through the supply chain and forward through the retailer. For retailers, storage and handling are the biggest concerns. However, suppliers set the tone for quality of the entire production. If an ingredient supplier is also top quality (e.g., GMP certified) and delivers consistent high-quality, pure ingredients, manufacturers will theoretically avoid corrective costs, which can save time and money.

> Suppliers set the tone for quality of the entire production.

The industry has a split history with suppliers, as some manufacturers only buy from reputable suppliers they subject to vendor qualification, including auditing and testing, while others accept material on COA alone and target the cheapest price.

"If a manufacturer is making purchases primarily based on price, jumping from factory to factory, the raw materials aren't likely to meet their specifications," assured Bob Green, president of Novel Ingredient Services. He explained while it is the manufacturer's responsibility, under GMPs, to ensure the ingredients in its products meet to all label claims, it all relates to ingredient quality. "As a result, many U.S. manufacturers are looking more closely at their raw materials to ensure that they do not compromise quality for price," he reported. "So,

it only follows that manufacturers will push down this responsibility, at least in part, to ingredient suppliers."

Wright agreed GMP compliance requires manufacturers stop basing purchasing decisions on cost alone. He suggested long-term partnerships between manufacturers and suppliers. "The ability to demonstrate stability in your supply chain and ingredients may allow for reduced testing on incoming materials," he reminded. "Companies are learning to focus closely on ingredient specifications, both regulatory and those related to manufacturability, to reduce or eliminate production issues and ensure that finished products meet their specifications."

Documentation Requirements

If there is a bottom line, then for GMPs it is all about documentation. For Sheets and Bioforce, which doesn't manufacture but stores products as an exclusive distributor, the GMPs were largely about documentation, which was reflected in the FDA inspection. "She looked very carefully at our GMP book and remarked that it was well-thought out," Sheets reported. "I think this set the tone for the rest of the inspection—it showed we took GMPs seriously." She said the FDA inspector looked at the company's ordering and receiving procedures, as well as product documentation, warehousing, shipping and how they handle customer complaints.

Sheets made use of all available resources to keep costs down. In addition to getting the outside take—sometimes attending basically the same seminar over and over—she took advantage of in-house expertise. Some members of her staff had prior experience in SOPs and FDA inspections in other industries. She also involves just about everybody in the company, from the top down.

Every process, procedure, specification, testing method and correction, as well as all monitoring, training and packaging protocols must be written down.

In a nutshell, every process, procedure, specification, testing method and correction, as well as all monitoring, training and packaging protocols must be written down. This includes how and when a task is done, what is being tested and what the allowance are for the results.

Each formulation needs a master manufacturing record (MMR). Each batch needs a batch production record (BPR). These contain the necessary specifications for the process

and QC as well as how the product is packaged and labeled. These records must be kept for one year beyond shelf-life or, for products that don't have shelf-life dating, two years beyond distribution of the last batch associated with the record.

Also important are corrective action plans, which stipulate what actions are taken for any given failure or defect, including contamination or test result of poor quality product. This plan also stipulates who makes the decision and what factors go into the decision. This highlights another cost of quality: the cost of recognizing a problem or defect and either reprocessing the material or disposing of unsalvageable product. Either carries a cost of time and money, including delayed production, labeling, packaging and delivery to the client.

Archer has noticed GMPs have substantially increased time factors for production and has demanded increased personnel. "I believe that the labor time will be a large part of a manufacturer's costs," he said, adding one of the costliest parts of GMP compliance has been adding additional staff just to keep up with the documentation requirements.

Time is Money

"The investment [in GMPs] isn't strictly monetary," Green said. "The cost of cGMP compliance also involves additional knowledgeable staff and, especially for finished goods manufacturers, greater lead-time built into the production schedule."

The cost was not so much monetary expense, but a lot of time.

Sheets said the cost was not so much monetary expense, but a lot of time. "We spent weeks of time learning GMPs and figuring out how to meet them." In fact, FDA estimated the one-time industry burden of establishing written records at a total of more than 150,000 man-hours, with annual recordkeeping at a total of more than 900,000 man-hours.

In its proposed rule, FDA used an average manufacturing wage of $15.65 per hour in its estimates involving labor costs, including records. Industry argued the need for higher-skilled workers, such as engineers, and for Ph.D.-level employees suggests a wage range of between $23 and $72 per hour. In its final rule, FDA raised its average wage for labor cost calculations to $26 per hour, noting Ph.D.-level hires were likely unnecessary for compliance, as the requirements are mostly ordinary labor tasks such as sanitation, monitoring, and recordkeeping.

The Bottom Line

While GMP is not the totality of QC, most companies are currently focusing their quality investments on GMP compliance. The cost per company for achieving compliance and

maintaining it annually is difficult to establish. In its final rule, FDA placed total industry-wide GMP set-up costs at $41 million, spread out over the first three years of staggered effective dates. It also set annual costs at $164 million, with the two largest costs being $52 million for testing and $24 million for records.

Total Costs by Establishment Size

	Setup Costs	Percent of Total Setup Costs	Annual Costs	Percent of Total Annual Costs
Very Small Establishments	$20 million	49 percent	$38 million	23 percent
Small Establishments	$10 million	24 percent	$98 million	60 percent
Large Establishments	$5 million	12 percent	$11 million	7 percent
Warehouses, Wholesalers, and Other Holders	$6 million	15 percent	$17 million	10 percent

Source: FDA, GMP Final Rule, Cost Analysis

It is safe to say the supplement industry feels the actual cost of compliance is greater than any entity has estimated or expected. "Our industry has under-estimated the costs required for GMP compliance," Schaeffer stated. "However, industry should recognize that there are efficiency savings with well-designed GMP operating procedures."

"The cost of testing, as well as the related quality systems that are part of the testing, is greater than anticipated," Wright said. "Additionally, the overall cost of developing and maintaining compliant processes and required GMP-related documentation is proving more resource-intensive than originally anticipated." He explained emerging clarity regarding the responsibilities of each link in the manufacturing chain has resulted in more GMP-related responsibilities for all parties involved, particularly in ensuring ingredients and products meet their specifications at each step of production and before shipping. "Ultimately the cost of voluntary compliance is always less expensive than having to address non-compliance with the FDA looking over your shoulder."

With the charged climate created by cGMPs, supplement companies now need a total buy-in on quality, from the top of the organization down, equal to or greater than the consumer buy-in on addressing health and wellness via dietary supplements and other natural alternatives to pharmaceuticals. ❐

Steve Myers is senior editor for Natural Products INSIDER. He has more than 10 years of experience in the natural products industry, focusing on regulatory, financial and quality control issues. His blog, the Inside Scoop, covers the broad spectrum of current industry events and happenings.