

New FDA cGMPs for Supplements: Smoke or Substance?

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I recently had a visit from a representative for a very high-quality botanical manufacturing company in Europe. I had not seen him in the past 2-3 years. Because the herbal products his company makes are considered drugs in several European countries, the company is a licensed pharmaceutical manufacturing facility. As we sat down to discuss products, the conversation quickly turned to the quality assurance (QA) measures his company takes. The herbal materials he sells are more costly because of a high level of QA testing. He explained to me that many, if not most, of the U.S. manufacturing companies he visits don't buy his materials very often. I asked why. This man has been in the industry for more than 10 years, and he explained that, in his experience, the U.S. manufacturing companies want the cheapest materials possible so they can stay competitive and maximize profits. They buy his material only if the client requests it.

This prompted me to ask if the manufacturers he visits do any independent testing themselves. He replied that, from small companies up to even the largest, the vast majority do little or no testing of their raw materials or finished products. Even though I've heard it before many times, his response was a bit shocking. When I hear something like this, it is upsetting and I want to shout from the rooftops, "buyers beware!"

Is your supplement company testing to verify quality assurance, or are they turning the proverbial blind eye (as the botanical rep above points out) and using whatever they get with little or no verification? How would you know? Do you ask for proof? If not, I'd ask you, why not? Does it matter to you? By what means could you tell if the products you buy are subpotent, superpotent, or contaminated? If you have no idea, you are doing your patients a decided disservice. As a clinician, when you procure supplements to pass along to your clients, you need to obtain and interpret a company's QA information and find the truth about their quality assurance testing practices to evaluate if they are adequate.

Ah, you say, but why? This problem is taken care of by the Food and Drug Administration (FDA), in particular with the recent filing of the finalized dietary supplement good manufacturing practices (GMPs). Big brother is on our side.

Well, maybe, sort of, in theory, on our side.

New FDA cGMPs

You may or may not know that in June 2007, the FDA finalized the current GMPs (cGMPs) for dietary supplements—a ruling specifying guidelines that manufacturing companies must follow to ensure the safety, consistency, quality, purity, and potency of their dietary supplements. The ruling is encased in an 800-plus-page document entitled *Current Good Manufacturing Practice in Manufacturing, Packaging, Labeling, or Holding Operations for Dietary Supplements; Final Rule*. It stipulates that

manufacturing companies with more than 500 employees have 1 year to comply with the new FDA cGMPs, companies with more than 20 employees have 2 years, and companies with fewer than 20 employees have 3 years to comply.

The new FDA cGMPs are a milestone for the industry, no question. However, there are 4 huge problems with them—what I call the “highly likelies.”

1. It is highly likely the FDA will do little to enforce consistent compliance with the rules due to a lack of resources.

2. The new rules have so many holes, loopholes, and unspecified areas that it is highly likely manufacturing companies will follow these rules in a very diluted fashion.

3. It is highly likely that companies will hide behind the new rules as a guise—saying, “Of course we have excellent products; we have to, the FDA requires it.” However, due to the lack of enforcement resources mentioned in #1 and the holes/loopholes mentioned in #2, this may not be the case at all. The question is, how would someone ever know unless they received specific proof and objective evidence of a company's QA testing and practice methods? It's easy to hide behind words and *say* that you are doing something when in action you are really not.

4. The suppliers of raw materials to the dietary supplement manufacturing facilities are “exempted” from the new FDA cGMPs. Thus, suppliers do not have to follow cGMPs and the burden of quality assurance is on the manufacturer. Not only is this unfair, it is more than highly likely, almost certain, in fact, that a large number of raw material suppliers will simply ignore quality issues (they already do). Objections to this imbalance have already been made—for more information see the sidebar, “AHPA Petitions FDA to Amend New cGMP Guidelines.”

These 4 issues will breed massive confusion in the industry and for the consumer. In particular on numbers 1–3, if 25 companies say they are following FDA cGMPs for dietary supplements, how would anyone know who is really in compliance? In short, it is not possible to tell without evaluation of the company's quality practices and testing parameters. There is a simple solution. I provide it at the end of the article.

What Others Are Saying About the New FDA cGMPs

From NUTRAingredients-usa.com/7/17/2007/: “Controversial supplements industry watchdog ConsumerLab.com has criticized the recently issued Good Manufacturing Practices (GMPs), saying they are not strong enough to prevent a company manufacturing a ‘bad’ supplement . . . ConsumerLab.com levels that the GMPs are insufficient since, while they require all ingredients going into supplements to be tested, they do not specify testing methods and standards . . . Company president Tod Cooperman said that the absence of a limit on lead and other contaminants is also problematic [because] . . . GMPs leave it up

to individual manufacturers to determine acceptable levels”¹ and specifications.

From *The Integrator Blog* 7/14/2007: After 12 years of an “unsteady and politicized process,”² the US Food and Drug Administration last month finally issued its new Good Manufacturing Practices (GMP) for dietary supplements. “Were they worth the wait? Yes and no.

“Yes, because the FDA now has the regulatory framework necessary for enforcing dietary supplement manufacturing practices. All companies must be in compliance by no later than August 2010 . . . If they aren’t, and there’s a problem, FDA can point to the chapter and verse by which to take legal action against the offender.

“No, because the rule requires that manufacturers, not the FDA, define quality specifications for their products—and those specifications can (with very few exceptions) be as loose or as tight as determined by each manufacturer. The law simply requires the manufacturer to define the specifications and to make certain that the processes in place guarantee that the finished products meet those specifications. Huh?

“Bottom Line: The new GMPs will not assure any improvement whatsoever in the quality of dietary supplements in the US. The rules are comprehensive, detailed and very clear: it’s up to the market to define quality. Some companies will continue to do a good job, and some will continue to do a poor job. In this environment of food safety concerns, contamination and economic adulteration, it’s only a matter of time before another problem surfaces. Hopefully . . . the companies themselves will stand tall and act responsibly to protect the public health. We’ll see.”²

From the *Wall Street Journal*, June 23, 2007: “Consumer advocates criticized the rules as too lax, saying they don’t specify how manufacturers should carry out the tests or adequately address safety problems posed by some supplements.”³ The new regulation “is an example of better late than never” said Sen. Richard Durbin, an Illinois Democrat. But he said the rules “do not appear to go as far as they could have.”

Personal Communication From John Atwater, PhD, RAC, senior analytical reviewer, U.S. Pharmacopeia (USP) Dietary Supplement Verification Programs: “My first impression is that the GMPs are somewhat weak. USP will want to keep our standards high, which can be a point of differentiation with the minimum requirements of the GMPs. Also, the FDA will not have the resources to police the industry; they will take a risk-based approach to enforcement. Therefore, there is no guarantee for the consumer that companies will follow the GMPs in their entirety.”

Need I say more? Others see the same glaring holes that I see.

What Do The New FDA cGMPs Say?

As mentioned, the new cGMPs fill more than 800 pages. Here is an outline and summary of what I think are most of the critical pieces.

Who is subject to this law?

Anyone who manufactures, packages, labels, or holds (such

AHPA Petitions FDA to Amend New cGMP Guidelines

The American Herbal Products Association (AHPA) announced in July that it is requesting changes in the newly minted current good manufacturing practices (cGMPs).

The guidelines, released by the U.S. Food and Drug Administration (FDA) June 25, are a statute of the 1994 Dietary Supplements Health and Education Act (DSHEA) and will provide standards for inspectors to check for purity, safety, and legality in manufacturing supplements. The ruling applies to companies that manufacture, package, or store dietary supplements. Critics of DSHEA have complained that GMP legislation has had numerous holes.

Among the rule’s requirements, manufacturers will be compelled to evaluate the identity, purity, strength, and composition of their dietary supplements, thereby ensuring that finished products contain actual labeled contents without adulterants such as pesticides, bacteria, or heavy metals. If dietary supplements contain contaminants or do not contain the dietary ingredient promised on the product’s label, FDA would consider those products adulterated or misbranded.

In response to the FDA’s long-awaited recommendations, AHPA submitted a petition asking for 7 amendments. According to AHPA, the points in question are potentially confusing, contrary to the public interest, or detrimental to manufacturers with no corresponding benefit. Of primary concern is that the new cGMPs put the burden solely on manufacturers and not suppliers.

AHPA offers the following changes as means of improving and clarifying the guidelines:

1. Clarification that a dietary ingredient manufacturer or supplier cannot be made subject to the final rule based on how its customers use its ingredients.
2. Removal of a potential loophole allowing companies that package products made by someone else to avoid some parts of the rules on verifying that product specification are met.
3. Addition of definitions for the terms “manufacturing,” “packaging,” “labeling,” and “holding.”
4. New language that allows master manufacturing records to include a range of batch sizes rather than specific batch sizes.
5. Removal of language that would have the effect of barring any single-employee companies from being in the dietary supplement business, to be replaced with appropriate options that will ensure product quality even in such small firms.
6. Allowing personnel to conduct examinations for correct labels (now currently limited to electronic or electromechanical examination) to qualify for exemptions in label reconciliation.
7. A requirement that the batch, lot, or control number assigned to dietary supplements actually appears on finished products.

For further explanation of these amendments, go to <http://www.ahpa.org/Default.aspx?tabid=69&aId=411&zId=1>.

—Anne Lanctot, *IMCJ* staff

as a distributor warehouse) a dietary supplement, including:

(1) a dietary supplement a company manufactures that is packaged or labeled by another person;

(2) a dietary supplement imported or offered for import into any state or territory of the United States, the District of Columbia, or the Commonwealth of Puerto Rico.

Comment: This means all dietary supplement companies are supposed to follow the same procedures no matter if they manufacture a supplement or simply label, package, or hold it—and no matter what country the company is in.

What are the requirements to implement a production and process-control system, and what specifications must be established?

(1) Companies must first establish written specifications (ie, a master manufacturing record) and then implement a system of production and process controls for any point, step, or stage in the manufacturing process where control is necessary to ensure dietary supplement quality—with the intent that the supplements are packaged, labeled, and held as specified in the master manufacturing record.

(2) In specific, for each ingredient used, a company must establish:

- (a) an identity specification;
- (b) ingredient specifications necessary to ensure that the purity, strength, and composition of the dietary supplements are met;
 - (i) within purity, a company must establish limits on those types of contaminants that may adulterate or may lead to adulteration of the finished batch of the dietary supplement to ensure the quality of the dietary supplement.

Comment: This says a company must establish written specifications to ensure the identity, purity, strength composition (uniformity), acceptable levels of adulterants, and storage parameters of all the dietary supplements it manufactures. It doesn't say what standards need to be met when establishing these specifications.

What must a company do to determine whether specifications are met?

- (1) Before using an ingredient, the company must:
- (a) confirm the identity of all dietary ingredients (ie, vitamin C or calcium citrate) and all other ingredients (ie, fillers or binders) and determine that specifications are met. To do so, it must conduct either:
 - (i) appropriate tests, or
 - (ii) examinations.

(2) A company must ensure that the tests and examinations used to determine whether the specifications are met are appropriate, scientifically valid methods.

(3) The tests and examinations used must include at least one of the following:

- (a) gross organoleptic analysis;
- (b) macroscopic analysis;
- (c) microscopic analysis;

(d) chemical analysis; or

(e) other scientifically valid methods.

(4) A company must establish corrective action plans for use when an established specification is not met.

Comment: This says that after a company establishes its written specifications, it must then use appropriate, scientifically valid tests to verify that a finished batch of the dietary supplement meets these product specifications for identity, purity, strength, composition, and adulteration (for limits on those types of contamination that may adulterate or that may lead to adulteration). Once again, it doesn't say what standards need to be met, nor does it state parameters on identity, purity, strength, composition, and adulteration.

What must a company do if established specifications are not met?

(1) For established specifications that are not met, quality control personnel must reject the ingredient, dietary supplement, package, or label.

(2) Dietary supplements that don't meet company specifications for identity, purity, strength, and composition may not be released for distribution.

Those Are the Rules, Now What Is the Reality?

Who determines these specifications?

As should have become clear by now, the companies themselves come up with their own specifications.

Comment: Herein lies one significant crux of the problem. This leaves interpretations wide open and unregulated. For example, a company can “dummy down specifications” and decide to test only for bacteria but not for pesticides or aflatoxins (or whatever). And how does a buyer know which company is doing what? Additionally, a bit of a round robin has been set up. Since the companies determine specifications and then decide if these specifications are met, what is to keep them from changing the specs to fit their needs of the moment? This is a case where the FDA clearly needs to issue the guidelines.

What requirements apply to laboratory methods for testing and examination?

A company must:

(1) identify and use an “appropriate scientifically valid method” for each established specification for which testing or examination is required;

(2) establish and follow written procedures for laboratory operations it conducts to determine whether specifications are met.

Comment: This means that, theoretically, a company shouldn't be able to use flunky methods or labs just to manipulate data and get the results it wants. The problem, as I have stated in other articles many times, is who is enforcing whether or not a lab is using appropriate and scientifically valid methods—because there is no one who has to approve them.

What are the requirements for the laboratory facilities used?

A company must use adequate laboratory facilities to perform

whatever testing and examinations are necessary to determine that it meets established specifications.

Comment: What is adequate?

What are the requirements for laboratory control processes?

A company must establish and follow laboratory control processes that are reviewed and approved by quality control personnel, including the following:

- (1) use of criteria for establishing appropriate specifications;
- (2) use of sampling plans for obtaining representative samples of:
 - (a) ingredients, packaging, and labels;
 - (b) in-process materials;
 - (c) finished batches of dietary supplements;
 - (d) product received for packaging or labeling as a dietary supplement (and for distribution rather than for return to the supplier);
 - (e) packaged and labeled dietary supplements;
- (3) use of criteria for selecting appropriate examination and testing methods;
- (4) use of criteria for selecting standard reference materials used in performing tests and examinations;
- (5) use of test methods and examinations in accordance with established criteria.

Comment: This is a step in the right direction. If universal guidelines were given and enforced, we'd be getting somewhere.

Our Hero the FDA?

If you are still thinking the FDA will basically be of service, consider the following.

Many raw materials or dietary supplements come from China and India where sanitation and quality practices are not always what we hope for or would expect. If a dietary supplement manufacturer is buying materials from these countries (lots of them do) and doing no testing what so ever, what does that mean for you?

I paraphrase from the *Wall Street Journal*, June 14, 2007, "Are Chinese Export Products Unsafe?"⁴

China struggles to contain an escalating crisis of confidence in the safety of food and other exports. The Chinese government initially denied responsibility for tainted pet food exports that resulted in 4,000 consumer reports of pet deaths in the United States, though the FDA has confirmed only 16 deaths. China has gradually acknowledged systemic safety issues, confirming that it had shut down 180 food processing factories since December and in August banned an antifreeze chemical that had been used in toothpaste. Last month, the United States blocked shipments of farm-raised catfish, shrimp, and other seafood that had high levels of antibiotics and chemicals, adding to the list of recalled products that includes about 450,000 defective tires and 1.5 million toy-train parts with high lead content.

The FDA is responsible for inspecting about 80% of the U.S. food supply (the U.S. Department of Agriculture is responsible for other 20%, like meat, poultry, and dairy). Despite the on-paper requirement of 80%, in reality the FDA has historically inspected only about 1.7% of the stated 80%. And as bad as that sounds, in the

past decade, FDA food inspections has decreased to about 1%.⁴

That's comforting! A huge amount of dietary supplement raw material is imported from China. Do you think the FDA will do better with that than with food? Since we can't trust the FDA to scrutinize it, the assurance of quality must fall upon the manufacturer. But, what if the manufacturer does not test to assure quality?

In his last editorial (*IMCJ* 6.4:9), Dr Pizzorno asked me to answer this question, "What is your best estimate of the percentage of raw materials not meeting quality standards?" I respond with the following. There are estimated to be 1,200-1,500 manufacturing companies in the United States. Given what I have seen in the past several years and verified by the sales rep from the beginning of this article, the majority of them do NO or extremely little QA testing to assure identity, purity, strength, or consistency of raw materials and the same is true for finished products. My estimate (as well as the estimate of other GMP auditors I have spoken with) is that 70-90% don't test. Since most companies don't test, it is almost impossible to determine what percent of raw materials don't meet quality standards. From my own testing experience, if I include identity, comprehensive contamination testing, and potency parameters, I have found that 30-50% of raw materials have some sort of quality "issue" that does not meet specifications. And that's after buying from companies known for higher quality. Many manufacturers buy cheap materials, which would lead, almost without question, to much higher numbers—as one would expect a higher failure rate from cheap raw materials.

The Bilberry Example

Azo dyes (synthetic, inorganic chemical compounds) have been used to spike the results given for anthocyanin content (measured via ultra violet [UV] spectrophotometry) in bilberry (*Vaccinium myrtillus*). Anthocyanins have a certain depth of color that is read by the UV method. By substituting dyes, the spectrophotometer is fooled. This is done to either make poor-quality bilberry look more potent or to make fake bilberry look potent and real. Azo dyes also have been found in imported spices such as chili and curry. The European Union views one of the illegal Azo dyes (Sudan I) as both genotoxic and carcinogenic. Mandatory testing for Azo dyes in spices and processed foods was passed into European law.

One news report states, "Calls from the bilberry industry for better testing of imported extracts are growing louder."⁵

Because the UV spectrometer has proven so unreliable, the Italian botanical derivatives supplier Indena developed a high performance liquid chromatography (HPLC) method to verify the anthocyanin profile and the concentrations of various polyphenols such as found in bilberry. According to the company's routine analyses, at least 15 to 20 per cent of the bilberry samples they collected on the market were adulterated,⁵ though not all from the Azo dyes (black mulberry [*Morus nigra*] and black bean skins are also used). The HPLC method has been adopted by the European and Italian pharmacopoeias and is being evaluated by the U.S. Pharmacopeia (USP). This is another great lesson in the value of using higher-precision tests (which equals more expensive tests) to assay raw materials.

The price per kilo for high-quality bilberry is reported to be around \$500–600. Yet, companies selling bilberry at \$400 or much less are “cleaning out the market” according to the referenced NUTRAIngredients.com article. It is highly possible that anyone buying for less than \$400/kg is getting a fake bilberry.

This is just one more example of how an industry has failed to communicate the value of raw material quality in its value proposition. As the natural products industry has succumbed to price competition, the biggest losers are the public health and the reputation of the industry.

What Can You, as a Clinician, Do?

The goal of all of my articles on quality assurance is to impress on you the urgent need to obtain valid evidence of a product’s identity (authenticity), potency, and purity (maximum freedom from contamination). To help you do this, I developed and wrote a questionnaire for clinicians to question manufacturers and/or suppliers about their quality assurance practices. It is available at *IMCJ*’s website, www.imjournal.com. In the menu bar on the left, click on “Quality Assurance” (located near the end), then click on “Manufacturer Quality Assurance Self-Audit Form.”

Please send this form to each of your natural products manufacturers and/or suppliers and see what comes back. It directs them to answer a series of questions but also asks for documentation that helps provide verification that they are, in fact, doing what they claim they are doing. The questionnaire asks for proof as well as yes-or-no answers. It is easy to answer *yes* to a question on a form; it is more difficult to provide proof.

Ask, ask, ask, and ask again for proof. Never stop asking for proof of quality assurance testing. If you are not asking, you are burying your head in the sand and risk using inauthentic, subpotent, or contaminated product. The manufacturers that supply you with independent proof are testing, and the manufacturers that give you double speak and supply nothing are not testing.

If you are unfamiliar with quality assurance issues or need further clarification, I am available to answer your questions and provide information. Please contact me at rickliva@center4health.com.

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