

Mandatory Laboratory Testing

Laboratory Quality Assurance

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How does mandatory laboratory testing apply to the practicing clinician?

Recently I received a solicitation from a professional products company that was pushing its contract manufacturing business to clinicians. They touted their customer service, great pricing and quick turn-around time. This is what they had to say about their quality assurance: “We use high-quality ingredients and require a certificate of analysis (COA) for each ingredient that enters our doors, certifying purity, potency and freshness.” This statement essentially says, that they do “zero” for quality assurance verification themselves—ie, they accept the COA at face value and do no testing to determine if it is true.

As a clinician this is unacceptable and truly offensive. Unacceptable because by now we clinicians should know that the only way quality can be assured is using objective evidence obtained through scientifically valid lab testing where we are absolutely certain of the testing standards. Don’t ever rely on a supplier COA, which is simply a piece of paper that can say whatever the writer wishes and should never be trusted. This solicitation is truly offensive because it’s marketing hype and is all about money, not about quality verification. I say this because a comprehensive quality-assurance and quality-control program is very expensive. Having no quality program means a lot more money in the pocket of the stockholder or owner. Unfortunately, it also means that you, as the buyer, have no idea what ingredients are giving to your patients.

I constantly find raw materials that are subpotent, inauthentic, or contaminated in some way. These deficiencies come to light because we conduct a comprehensive quality-assurance and lab-testing program. How about that wild yam (*Dioscorea villosa*) root I just rejected because it had 65 parts per billion (ppb) of aflatoxin (FDA limit 20 ppb, German limit 4 ppb). No patient will have to endure that contamination. Relying on a COA would never have prevented that.

The bottom line is, if you are providing dietary supplements to your patients from manufacturers that don’t test their raw materials or finished products, you are putting your patients at risk. The risk comes from selling products that are inauthentic, sub- or super-potent, or contaminated. Without testing, these quality deficiencies will get through to your patients. Unfortunately, even if the company claims to do the necessary raw-material and finished-product testing, it would be wise to verify their testing claims and know something about the quality of the in-house or contract labs they are using for the verification process.

Current State of the Contract Lab Industry

To the best of my knowledge, neither a manufacturer’s in-house lab nor a contract lab that tests dietary supplements have oversight by any city, state or governmental agency. Any company wishing to operate a lab needs no specific credentials, level of training, license or certification. The lab itself is under no obligation for inspection. It is the wild, wild, west out there in laboratory land. When I first discovered this, I was mortified. How can I trust the results I pay for with this as the situation? Over time I have learned how to determine if a lab is serious about quality and how to evaluate it. However, this was only after I encountered many dirty secrets. Problems exist with some contract labs that perform QA testing, dry labbing or method rigging or the use of poor-quality reference standards.

What, you may ask, are these?

Dry labbing is when a manufacturer sends in a sample for testing and gets back exactly or close to the results it desires. However, actual analysis was never done—ie, it was dry labbed. How wide spread this practice is I'm not sure, but I have seen it many times. It is easy to spot if you know what you are looking for. An example: A company reports that their lab has tested a prostate formula containing extracts of saw palmetto (*Serenoa serrulata*, *S.repens*, *S. serulata*), pygeum (*Prunus africana*; formerly *Pygeum africanum*) and nettle root (*Urtica dioica*) mixed together as a finished product. The lab report shows the marker compound, beta sitosterol, in 3 separate amounts coming from each plant extract. However, it is scientifically impossible to separate the beta sitosterol and relate an amount to each individual plant extract.

Method rigging is when a lab performs a test method and tweaks it in such a way as to get the desired results. In other words, they improperly skew the scientific validity of the method to satisfy the customer. Again, this is something I have seen many times. How do I know it occurs? An example: schisandra (*Schisandra chinensis* or *S. sphenanthe*) extracts I received that claimed to be 10% schisandrins by high-performance liquid chromatography (HPLC) testing. I asked for the method and had an expert evaluate it. Turns out the claimed HPLC method is not appropriate for testing this botanical constituent, but instead was designed for an entirely different purpose. In addition, there are only a few commercially available standards for schisandrins. Using those standards and an appropriate, scientifically valid HPLC testing method, I had the product tested along with several other schisandra samples from other vendors. The total schisandrins in all samples come out very low in the 2-3% range. Getting 10% is impossible without method rigging.

Reference standards are highly purified compounds that are well characterized. They are the most commonly used material in determining scientific validity. Basically, reference standards are used to qualify and quantify an ingredient and are necessary to set up process controls that establish the validity of a test method. When it comes to testing specific chemicals, they are essential. Qualification involves identifying that the ingredient really is what it says it is, and quantification identifies that the ingredient really is at the potency it claims. For example, when a manufacturer buys curcumin (*Curcumin longa*) raw material that claims 90% potency for total curcuminoids (curcumin, and 2-3 other curcumin compounds), they either lab test it themselves or send a sample to a contract lab. The lab must have authentic curcuminoid reference standards that have a documented potency level. The sample in question would be compared against these “known” reference standards and a calculation would be made to quantify how the sample measures up for potency.

A brief description of reference standards is in order.

Primary Standard is an analytical reagent of generally high purity that has documentation confirming the results of 4 or 5 of the following authenticating tests: HPLC, nuclear magnetic resonance (NMR), gas chromatography (GC), thin-layer chromatography (TLC), liquid chromatography with mass spectroscopy (LCMS), Karl Fischer (used to determine water content by coulometric titration) and a residual solvents analysis. The method's testing parameters (basically the recipe for how to test the product) will be provided along with the testing results.

It is important to note that for a substance to be considered primary, the authenticating tests must be made using methods specific for defined constituents of the substance—generally a therapeutic active or a marker compound.

Materials designated as a Primary Standard are excellent for use in a variety of analytical applications including instrument calibration, method performance, quality control (QC) and analyte identification (AI). These compounds are also suitable for *all* other general applications requiring high-purity materials.

Secondary Standard is generally of a lesser purity than a Primary Standard, however the defining difference between the two is that Secondary Standards have only 1 or 2 authenticity test results, usually HPLC and one other. These standards also list the method (recipe) of testing. Materials designated as a Secondary Standard are suitable to be used in a variety of analytical applications, including instrument calibration and method performance, and *some* quality control and analyte identification. These compounds are also suitable for other general applications requiring high-purity materials, but are *not ideal* for use in *all* applications and must be used judiciously in quality control and analyte identification—for instance, in applications where absolute certainty is not necessary.

Reagent/Standard Grade is separated from Primary and Secondary Reference Standards due to a lack of characterization and documentation of the batch compound. There is a Certificate of Analysis provided with the compound, however no guaranteed method of analysis will be provided. Methods may be available, but they may not necessarily refer to the specific details on how that compound was produced or tested, thus leaving a gap in necessary information and documentation.

Materials designated as Reagent or Standard grade can be used for analytical standards in a variety of applications including instrument calibration and method performance, but are very limited in use for quality control and analyte identification.. These compounds may also be suitable for other general applications requiring high-purity materials, *but may not always provide consistent or homogenous results when quantifying a compound*. If a Reagent Grade Standard is used it may under or over quantify the potency of the test material. In this case the potency result obtained will be incorrect. The incorrect data provided to the customer will be used to formulate a product based on inaccurate results.

Many, many labs inappropriately use reagent-grade chemicals as quantifying reference standards because they are cheaper. Most, if not all, reagent-grade chemicals do not have verified potencies, ie, the actual potencies differ from what is claimed. This can significantly distort the lab test results.

Primary and secondary standards are preferred for the most accurate quantification results. Ideally, Reagent Grade Chemicals should not be used as for this purpose.

A Quality Check List for Lab Analysis

As you can see from what has been discussed, the integrity of a manufacturer's house lab or contract lab is paramount. To ensure both integrity and quality, the lab must have experienced employees and a solid infrastructure. When you are looking at a manufacturer's products, how do you know whether they had a good lab or not? A quality checklist of items to review with a manufacturer about their contract lab would include:

Laboratory Accreditation

- Is the lab accredited? Accreditation services info can be obtained from:
 - American Association for Lab Accreditation, www.a2la.org,
 - American Council of Independent Laboratories, www.acil.org,
 - Assured Calibration and Laboratory Accreditation Select Services, www.aclasscorp.com,
 - Association of Official Analytical Chemists, www.aoac.org.
- Does the lab operate under Food and Drug Administration (FDA) GLPs (Good Lab Practices) or current good manufacturing practices (cGMPs)?

Laboratory Organization

Here you'll need to use a little common sense or defer to an expert you can trust who will know if all the bases are covered or if there are organizational holes. To evaluate the organization:

- Request an organizational chart to see who is responsible for what and who reports to whom.
- Request job descriptions and CV's to determine experience and qualifications.

Quality Assurance Unit (QAU)

- Does the lab have an independent QAU?
- Request an organizational chart for the QAU (again, if you can't determine if there are holes, ask someone who can).

Laboratory Experience

- Request a description of previous projects.
- Review types of analytical methods being employed and determine if they match your needs..
- Review experience with dietary-supplement testing.

Laboratory Equipment

- Request a list of all analytical equipment and compare it to the CV's of those who run the equipment to make sure they have the qualifications to do so. If you don't understand what something is or you're not sure if the equipment is sufficient, ask someone you can trust.

Standard Operating Procedures

- Request the table of contents from the lab's Standard Operating Procedures (SOP). Ideally they would have SOP's that outline procedures for every function in the lab.

You may also choose to visit the manufacturer's contract lab for a visual audit. Given the state of the dietary-supplement contract-lab industry, one cannot assume a lab is providing "quality" testing unless they are verified or checked in some comprehensive manner.

Proposed FDA-GMP Dietary-Supplement-Testing Requirements

The Department of Health and Human Services and the FDA published proposed rules for dietary ingredient and supplement GMPs, called the "Current Good Manufacturing Practice in Manufacturing, Packing, or Holding Dietary Ingredients and Dietary Supplements," in the Federal Register (21 CFR Parts 111 and 112) on March 13, 2003, in Volume 68, Number 49, pages 12157-12263. Word on the street is that these long-awaited GMP rules will be finalized in early 2006.

I have made the assertion in this column on a number of occasions that a large percentage of dietary supplement manufacturers do absolutely no raw-material or finished-product quality-assurance testing. Once the FDA GMP rules are in place, testing will be mandatory for finished products, although, ironically, *not* mandatory for raw materials unless an appropriate test of the finished product is unavailable (more on that later). Whether manufacturers comply with the rule is another question. It is not yet known what kind of enforcement the FDA will bring to bear in ensuring compliance with these rules. The greater the enforcement, the greater the percentage of the industry that will comply. The non-compliers will be faced with search, seizure or recall of product along with fines and shutdown.

Why is Mandatory Testing So Important?

Every end user of dietary supplements deserves to know that the product was manufactured and tested in a way that assures authenticity, lack of adulteration, claimed potency and maximum freedom from contamination. The Proposed rules in Sec. 111.35(h) would require that an appropriate test or examination determine whether specifications are met for a particular final product (but again, not necessarily raw materials) .

An appropriate test is one that uses a scientifically valid analytical method. If there is an AOAC (American Organization of Analytical Chemists) or FDA method available that is appropriate, your manufacturer should use that test method. If an AOAC or FDA method is not available, a scientifically valid analytical method is one that is based on scientific data or results published in, for example, scientific journals, references, textbooks, or proprietary research.

Why is this so important? The scientific validity of the method is everything (assuming proper application, instrumentation, appropriate reference standard, etc.) in the search for a true result. If a method is inappropriately applied or changed in some way, the true result will be distorted.

The specifications for a particular final product required by the FDA to be tested for are:

1. identity (assurance of authenticity without adulteration),
2. purity (assess contamination levels),
3. quality, (with, however, no parameters of what determines quality)
4. strength, (verifies the claimed potency).
5. and composition (the proper ingredient mix).

These should be ascertained upon receipt of the raw material at points during manufacturing, and at the finished-product batch stage.

The rules further require that the manufacturer test *each and every* finished batch of the dietary ingredient or dietary supplement produced before releasing it for distribution to confirm that specifications are met for the identity, purity, quality, strength, and composition intended. Thus, if a manufacturer gets in 40 kilo of vitamin C and uses only 25 kilo in a first batch and 15 kilo in a later batch, they need to test both.

The FDA gives some wiggle room for finished product testing. The rules state that since certain tests for identity, purity, quality, strength, or composition for certain finished products may not be available, the manufacturer must then test all the raw materials that went into the finished product—the only time it requires such raw material testing. Ironically, when it is possible to test a final product, the rules only put forth the *recommendation* that raw material testing occur. “If you are able to perform testing on each finished batch of dietary ingredient or dietary supplement to confirm that specifications are met for the identity, purity, quality, strength, and composition intended, *then we would recommend, but would not require* [italics introduced], that you also test raw materials received for these same specifications to ensure that they are the right ingredients and so that you do not end up having to destroy an entire batch of finished product after using an erroneous ingredient that could have otherwise been identified earlier before being added to a batch.” (68 Federal Register 49:12157, at 12197-12198: March 13, 2003)

Most importantly, the rules state that using a Supplier Certificate of Analysis (a piece of paper that accompanies the material verifying various parameters of quality) in lieu of performing testing on each shipment lot of components is not appropriate because it is possible that a supplier's certification or guarantee may not ensure the identity, purity, quality, strength, or composition of a component, dietary ingredient or dietary supplement.

Hence my points in this column!

This is a lot to cover so far. In the second part of this column I'll go over sample analysis and lab method validation and will interview Mark Roman, PhD, director of research and development at Chromadex Analytics, a supplier of botanical reference standards in Clearwater, Fla., and chairman of the Methods Development Committee on Dietary Supplements for AOAC International (formerly the Association of Official Analytical Chemists).

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