Controlled Testing: The Cornerstone of All Quality Natural Products

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"It is always the right time to do the right thing."
— Martin Luther King

***Disclosure**: Dr Liva has been involved in dietary-supplements manufacturing since 1985 and is the president, CEO, and director of Quality Control and Quality Assurance at Vital Nutrients, a company certified by the Natural Products Association for current Good Manufacturing Practices.*

Quality control testing is *the* key to producing quality natural products—an essential counterpart to good manufacturing practices (GMPs). As surprising (and, in truth, disturbing) as it might seem, a manufacturer can comply with the US Food and Drug Administration's (FDA's) recently released current GMPs (cGMPs) and still conduct inadequate testing.* Thus, in the end, they have a poor-quality product. Comprehensive, thorough, and adequate testing is the *only* real way to ensure quality.

Recent Quality-Control Testing Failures

I am the quality control/quality assurance (QC/QA) director for my company. As such, I have overseen the testing of several-thousand raw materials and finished products over the past 9 years. Following are some routine quality control testing results from the past few months.

Adulterated Product: An extract of hops (*Humulus lupulus*) was sent to the QC lab for identity testing via thin-layer chromatography. The test report stated that the sample did not meet the profile for *H lupulus* but instead appeared like burned maltodextrin.

Herbicide Residue: An extract of Asian red ginseng (*Panax ginseng*) was sent to the QC lab for herbicide and pesticide testing. The testing found and quantified quintozene, a fungicide that is illegal to use on herbal products. The FDA has zero tolerance for quintozene, which, in translation, works out to be an acceptable limit of <10 parts per billion (ppb)—which, as it also works out, is the lowest limit of detection possible using the FDA testing method for quintozene.

This ginseng extract was purchased from a well-known, high-quality European supplier used by many American companies. The supplier was resistant to taking back the material because the representative said the product passed the US Pharmacopeia test method, which showed it had <1000 ppb of quintozene. The rep argued that the company was not going to be held to the higher standard of <10 ppb. I pointed out that the legal limit is <10 ppb and nothing more is acceptable. The rep capitulated after checking with the company's legal department and finding this to be true. As it turns out, the supplier was not aware of the legal limit for this fungicide, which floored me because I assumed it would, by necessity, have such information.

Herbicide Residue: An extract of wild yam (*Dioscorea villosa*) was sent to the QC lab for herbicide and pesticide testing. The testing again found and quantified quintozene, the fungicide that is illegal to use on herbal products. The amount was 51.9 ppb. Exactly the same scenario unfolded as outlined in the example above.

Solvent Residue†: In an effort to find a suitable backup supplier that could provide milk thistle (*Silybum marianum*) extract 80% that has the proper strength and is clean (ie, a lack of toxic solvents), I sent a sample from a new supplier I was trying out to the QC lab for a strength assay and solvent-residue testing. The supplier of this product claimed on its certificate of analysis that the solvents used to make this extract were ethanol and water. (Ethanol is a Class III solvent, which is considered less toxic and of lower risk to human health than solvent Classes I-II).

A solvent screening test told a whole other story. A first test revealed benzene residue, a known carcinogen. Trying to quantify the amount of benzene to see if it was within acceptable limits, I had the lab run a second test using gas chromatography/mass spectrometry (GC/MS). Although the benzene was unable to be quantified due to interference from another compound, this test found 30 total peaks showing solvent contamination. Thirty peaks! You can see these in Figure 1. The important point to note is that GC/MS accurately identifies a compound, so you know without a doubt that the compound exists.

Other solvents identified by the GC/MS included hexanes (a Class II solvent, which should be limited in use because of their inherent toxicity), heptanes, and pentanes (a Class III solvent, so less toxic)—nothing related to ethanol and water. Despite the lab's inability to quantify the amount of the benzene, I am convinced that this is a dirty and contaminated milk thistle extract, which is something I have found many times before despite high-quality claims by supposedly reputable suppliers.

The question is, if this product was extracted using "ethanol and water" only, where did these 30 compounds come from?

*If you find it surprising that the FDA's cGMPs leave open the possibility of inadequate testing and poor-quality products, please read 2 articles in *IMCJ*'s Oct–Nov 2007 issue: "New FDA cGMPs for Supplements: Smoke or Substance?" by Rick Liva, ND, RPh (*IMCJ* 6.7:28-32); and "FDA's Natural Product cGMPs—A Missed Opportunity" by Joseph Pizzorno, ND, with Michael D. Levin (*IMCJ* 6.7:8-10).

†For more information on solvents and their classifications, please see "Seeking High-Quality Products: Whose Definition Should We Believe? Part II" in the Feb–Mar 2009 issue of *IMCJ* (*IMCJ*, 8.1:36-40).

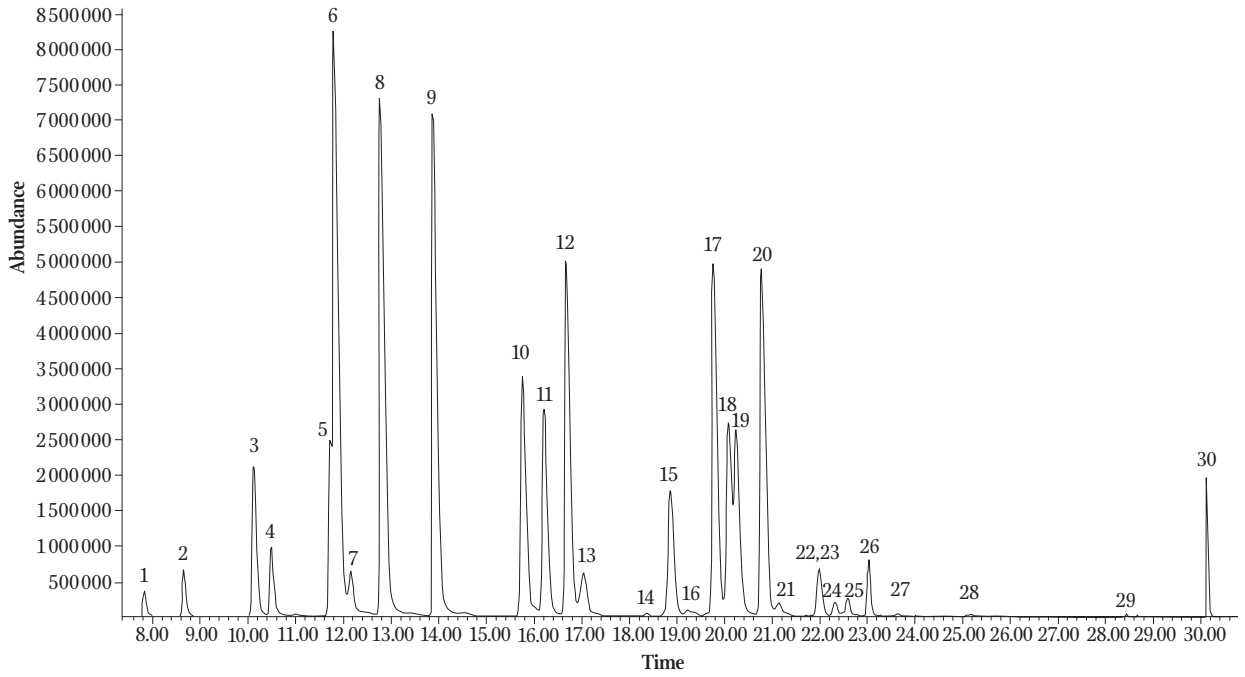

Figure. Gas Chromatography/Mass Spectrometry of Milk Thistle 80%

Each peak represents a solvent residue. The peaks are as follows: 1) 2-Methylbutane 2) Pentane 3) 2,2-Dimethylbutane 4) Acetone 5) 2,3-Dimethylbutane 6) 2-Methylpentane 7) Cyclopentane 8) 3-Methylpentane 9) Hexane 10) 2,2-Dimethylpentane 11) 2,4-Dimethylpentane 12. Ethylcyclobutane 13) 2,2,3-Trimethylbutane 14) 2,4-Dimethyl-1-pentane 15) 3,3-Dimethylpentane 16) 1-Methylcyclopentane 17) 2-Methylhexane 18) Cyclohexane 19) 2,3-Dimethylpentane 20) 3-Methylhexane 21) 1,1-Dimethylcyclopentane **22) 3-Ethylpentane and Benzene coelution** 23) 5-Methyl-1-heptene 24) cis-1,3-Dimethylcyclopentane 25) trans-1,3-Dimethylcyclopentane 26) Heptane 27) 2-Methyl-2-hexene 28) Methylcyclohexane 29) Toluene 30) 4-Methyl-3pentane-2-one

They don't naturally occur in milk thistle. One has to ask, did the supplier even know these compounds were in there, and, if not, what does that say about their quality control?

The Clinician's Crucial Role

My question is always this: As a clinician, would you have bought the final products made from these contaminated sources and put them on your shelves? If you never ask about quality, the answer would have to be *yes*—why wouldn't you? The marketing says the quality is good. For that matter, how do you know the products that you are dispensing and your patients are consuming right now don't have similar issues?

Let me put it this way: You would never knowingly use a faulty x-ray machine since you are fully aware that a radiation overdose can lead to tissue damage, sickness, and an increased risk of cancer. Doesn't it make sense to apply the same standards of conscience to the products you ask your patients to ingest? In the milk thistle example, benzene is a known carcinogen and quintozene has been banned for herbal use by the FDA. Many people use ginseng, wild yam, and milk thistle in large amounts and over long periods of time. Is selling contaminated supplements really so very different from using a faulty x-ray machine?

For the time being, until (if and when) the current laws change, the responsibility of quality verification must rest with the clinician who prescribes the dietary supplement. Why? Because there is no one else to implicitly trust. The FDA has regulatory power over this industry, but it doesn't have enough funds to adequately police and ensure a level playing field, and it is not likely to get sufficient funds given the economic challenges facing our government. The FDA cGMPs that were finalized in June of 2007 do not cover raw material suppliers to this industry (a big hole there), and the regulations are so loosely written that they will surely invite minimal compliance by many dietary supplement manufacturers. The prescribing clinician cannot assume quality but, rather, must take the responsibility to assure high quality through a thorough examination of scientifically valid and legitimate proof of comprehensive testing. Easier said than done, and the information presented here will forward that objective.

Of the approximately 1200 to1500 or so manufacturers of dietary supplements in the United Sates, we really don't know who is and who isn't following the FDA's dietary supplement cGMPs and performing adequate authenticity, strength, and contamination testing to verify quality. Until the government steps in with strict enforcement, it is up to individual practitioners to educate themselves about quality manufacturing regulations and hold the individual manufacturers from whom they buy accountable for following those regulations.

My goal in writing these columns is to help you understand the issues at hand and to choose natural product suppliers/manufacturers that follow established FDA cGMP regulations and routinely perform adequate and thorough testing to produce uniform, authentic, consistent, and potent finished goods that are as pure as possible.

Understanding What Quality Looks Like

High quality, superior quality, or just quality? Though the marketers like to throw the words around, in truth, it is either a quality product or it is not; ie, it either meets quality-control

standards or not. If not, it is a low-, lower-, or poor-quality product for various reasons.

So, what are the elements of producing a quality product? It is very uncomplicated and straightforward and includes just 2 elements: 1) A manufacturer must establish superior raw material and finished product specifications and 2) then test to make sure those specifications are met.

First: Get proof (evidence) of routine testing on *each* batch of raw materials for:

1. Identity (verifies authenticity)
2. Strength (verifies potency claim if applicable, eg, milk thistle 80%)
3. Purity and contamination

For Botanical Raw Materials: A typical testing profile would include heavy metals, pesticide residue, solvent residue, aflatoxins, microbial content, and yeast/mold content. In some circumstances testing for genetically modified organisms and industrial pollutants may be indicated.

For Nonbotanical Raw Materials: A typical testing profile may include solvent residue, microbial content, and yeast/mold content. In some circumstances testing for 1 or more heavy metals such as mercury and lead, rancidity markers, and industrial pollutants such as polychlorinated biphenyls (PCBs) and dioxins may be indicated.

Second: Get proof (evidence) of finished-product testing to verify the label claim for its declared strength.

Third: Get proof (evidence) of stability testing to verify that the label claim for strength is met throughout the expiration dating period.

Comprehensive raw material testing, finished product testing, and stability testing are the right steps to take and the most important key elements in producing a high-quality product. That said, based on the QC results I've seen over the years, I've found that many, if not most, companies are just not doing this level of testing. Why? No one makes them. Some day the FDA may step in and enforce the regulations industry wide and level the playing field, but what happens in the meantime?

Widespread lack of quality control creates a "buyer-beware" scenario. As a clinician, when you procure supplements from a supplier or manufacturer and make them available to your clients, you need to be able to judiciously obtain and interpret a company's quality information and find the truth about the level of quality they are providing.

Obtain Objective Evidence of Quality Testing and Evaluate

The road to ensuring high quality is successfully traveled when clinicians ask for and obtain valid evidence (test results) of a product's identity (authenticity), purity (maximum freedom from contamination), and shelf-life strength. Then, once you have the test results in hand, they must be evaluated for scientific validity.

To this end, a number of years ago, I developed and wrote a questionnaire entitled "The Manufacturer Quality Assurance Self-Audit Form," which was published in the Aug-Sept 2006 issue of *IMCJ* (*IMCJ* 5.4:41-44) and has been available since on the *IMCJ* website (www.imjournal.com). The form is intended to give clinicians a basis upon which to question manufacturers and/or suppliers about their quality control and quality assurance practices.

After these several years of use and feedback, I have now developed a new, more simplified questionnaire that clinicians can use as a quality testing tool for the products you buy. This new questionnaire is considerably shorter than the original and focuses primarily on asking for the test data used to ensure quality. We will print it in the next issue, so look for it upcoming.

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