



Editorial

*“Seen a man standin’ over a dead dog, lyin’ by the highway in a ditch
He’s lookin’ down kinda puzzled, pokin’ that dog with a stick
Got his car door flung open, he’s standin’ out on highway 31
Like if he stood there long enough that dog’d get up and run”*

Bruce Springsteen, Reason to Believe

June 25, 2007, what we all were thinking was a dead dog *did* get up and run, albeit on three legs. The Current Good Manufacturing Practice for Dietary Supplements (GMP’s) 21 CFR Part 111 was finally published as a final rule and made law. The rule is indeed a compromise, taking into account the various industry voices that all chipped away at the needed regulatory teeth.

The new GMP’s do the basic job of outlining the requirements for many aspects of manufacture, cleanliness, and quality control. However, the industry is still in many ways in need of some even more stringent requirements. Even worse, many in this industry claim to follow self-imposed GMP’s, but do not properly do that, and probably will not, even with the publication of these GMP’s.

Example 1. The machine pictured below was offered for sale by an equipment dealer and was in operation when inspected and photographed by my Quality Assurance Director in 2006 at a contract manufacturer’s facility in New Jersey. This filthy machine was being used in the production of products, which were being made and private-labeled for major retail companies. The machine was in a dirty room with cobwebs in the air-handling exhaust system and was being used by improperly garbed employees. On their website, the facility proudly displayed they were inspected and had GMP certification by the NNFA (National Nutritional Foods Association). It would appear they only expend the time to clean their machines when being inspected.



Photo of a filthy machine taken in a plant
“certified and approved by one of the independent
organizations.”

Example 2. About six years ago, physicians noticed a change in product color, but no label change, in an encapsulated product from a “professional” company. Upon questioning by several doctors, the owner of the company stated that even though the product filler was labeled “glycine,” he had started using “rice powder” as the filler. He stated that he was “just using up the old labels and would change it on the next label run.” It is *vital* that economics *not* dictate GMP compliance. Today, although the company does not even have an in-house laboratory, they claim to have the best quality in the nutritional supplement industry.

Example 3. An Ontario softgel manufacturer, licensed to manufacture pharmaceuticals and over-the-counter (OTC) drugs, also manufactures softgels for the dietary supplement industry. For the pharmaceutical and OTC products they *claim* to follow drug GMP, analyzing raw materials, in process products, and finished products. *However*, when I questioned their “Business Development Manager” about why they do no analysis on incoming raw materials or finished product that is a dietary supplement, his arrogant response was that, “It’s done only if the customer requests it, and pays an additional charge, and his company would never change that policy.” Economics again, not concern for quality.

Example 4. A “professional” company which provides a certificate of analysis (C of A) from an “independent laboratory” with each product purchased by a customer and a CD with representative analysis of all their products. I had a pharmacist purchase a multi-vitamin-mineral from the company, which he received along with a C of A from an “independent laboratory.” He divided the product into two new bottles and sent them back to the same laboratory for analysis of three of the vitamins. He claimed that one bottle had about 70% of the already analyzed vitamins and that the other bottle had about 130% of the already analyzed vitamins. The laboratory sent back results, which were almost exactly the levels he *claimed*, even though they were far below or far in excess of the *previous* analysis. Without an in-house laboratory to verify and *validate* the results of an “independent laboratory,” the company does not have the capability to determine if the lab is quality or not. If your *finished product* analysis is not reliable, can you rely on your *raw material* analysis and claim that your products are *pure*?

Example 5. The x-ray (right), from a U.S.P. website link, shows calcium supplements taken for three days which have failed to disintegrate. The photo shows a tablet lodged in the appendiceal remnant which had to be dislodged into the cecum with forceps. Such products *might* disintegrate in a laboratory setting using the acid-base standard U.S.P. disintegration test, but when subjected to the differences in individual patient digestive systems, laboratory results mean little. Standards should require disintegration (and dissolution of soluble ingredients) within an hour, in *any* pH found in the digestive tract, be it acid or neutral.





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Let's look at language and some of the requirements that have potential for misuse. When a raw material comes into a manufacturer's plant, the proper quarantine and recordkeeping must be done, followed by sampling of the product for identity and analysis. The FDA's new GMP states:

"*Representative sample* means a sample that consists of an adequate number of units that are drawn based on rational criteria, such as random sampling, and that are intended to ensure that the sample accurately portrays the material being sampled."

"(a) Before you use a component, you must:

- (1) Conduct at least one appropriate test or examination to verify the identity of any component that is a dietary ingredient; and
- (2) Confirm the identity of other components and determine whether other applicable component specifications established in accordance with 111.70(b) are met. To do so, you must either:
 - (i) Conduct appropriate tests or examinations; or
 - (ii) Rely on a certificate of analysis from the supplier of the component that you receive, provided that:
 - (A) You first qualify the supplier by establishing the reliability of the supplier's certificate of analysis through confirmation of the results of the supplier's tests or examinations;
 - (B) The certificate of analysis includes a description of the test or examination method(s) used, limits of the test or examinations, and actual results of the tests or examinations;
 - (C) You maintain documentation of how you qualified the supplier;
 - (D) You periodically re-confirm the supplier's certificate of analysis; and
 - (E) Your quality control personnel review and approve the documentation setting forth the basis for qualification (and re-qualification) of any supplier."

There is a *lot* of wiggle room in this section.

We have all seen for years on the internet and in the literature of companies that claim to have non-governmental body "certified" GMP's, that they send out to an "independent laboratory" for raw material analysis on every "batch" of raw materials sampled. What *should* happen is that *every* container of every lot from a supplier should be sampled and tested, whether one or one hundred. Once that process has been done for a significant time and the raw material has been verified as meeting quality standards, then, and only then, can the supplier and subsequent shipments of raw material be considered *validated*. Even then, after validation of the supplier, one must take the square root of the number of containers of a given lot, round it up, and add one. For example, 50 containers would require

that 9 samples be randomly taken and identified by analysis. Since only a small number of manufacturers have an in-house laboratory, this becomes expensive and may likely not be done. As shown in Example 4, above, although there are many good “independent laboratories,” there are very unscrupulous ones as well. Unlike blood analysis laboratories, there are no FDA mandated Clinical Laboratory Improvement Amendments (CLIA) for laboratories that analyze dietary supplement ingredients. It is an open marketplace.

Now, let’s go back to that laboratory analysis you receive with the product you ordered. You know, the one that states the 40 exotic ingredients *analyzed* to the microgram. Well, in many cases these ingredients can only be analyzed accurately as an individual raw material. Even with supercritical extraction methods, no analytical procedure known to man can actually show results claimed by many laboratories when these ingredients are mixed together. The FDA recognizes this when it states that there may be:

“...no scientifically valid method for testing or examining such exempted product specification at the finished batch stage. In such a case, you must document why, for example, any component and in-process testing, examination, or monitoring, and any other information, will ensure that such exempted product specification is met without verification through periodic testing of the finished batch; and (2) Your quality control personnel must review and approve the documentation that you provide under paragraph (d)(1) of this section.”

Additionally, there are so many variations of final ingredient combinations in the dietary supplement field that it is impossible to publish monographs, such as U.S.P. drug monographs, for each dietary supplement. Since there are no standards, such as CLIA, one must question the calibration of equipment and freshness of chemical standards used in analysis.

This industry needs to *follow* the new GMP ruling, quit complaining, and in fact *exceed* what the FDA has outlined. The quality questions about dietary supplements will then shuffle away on four legs.

Al Czap,
Publisher



Tablet lodged in the orifice of the appendiceal remnant, in a 70 year-old woman who had been taking a variety of vitamin and mineral supplements. The tablet was dislodged into the cecum using a forceps.