COMMENTARY

The New Food Current Good Manufacturing Practices and Their Effect on Dietary Supplement Quality: What You Need to Know

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As previously reported in this journal,[1] the current Good Manufacturing Practices (cGMPs) published in June, 2007, for dietary supplements made each manufacturer responsible for establishing ingredient and finished goods specifications. This was described as "one of the biggest flaws in the whole set of final rules. It's a premier example of the fox guarding the hen house …" It is also a major reason why there can be wide differences in supplement quality: Each company defines the rules!

These cGMPs applied only to dietary supplements (finished products). What about dietary ingredients?

The dietary ingredients used in dietary supplements have been regulated under the food cGMPs (21 CFR §110, first published in 1986).[2] If we agree that the quality of a dietary supplement is measured in terms of authenticity (Is the ingredient on the label exactly and only what is in the bottle?), potency (Does the product consistently meet label claim through expiration date?), and purity (Does the product have maximum freedom from biological and chemical contaminants?), the dietary supplement industry had a clean slate on which to write specifications for ingredients for which they had, in many cases, limited knowledge about manufacturing process, packaging, handling, storage, and other factors.

Many trusted their suppliers for guidance. Some relied only on a supplier's certificate of analysis (COA) for making specifications. As too many companies learned the hard way, COAs are not always truthful. COAs did not always disclose that the botanical ingredients were processed using toxic solvents such as 1,2-dichloroethane; companies did not always know about the wide range of economic adulterants introduced into commerce used to dilute or masquerade as the high-priced ingredient (at best) and introduce deadly contaminants (at worst). Hence, the specifications they defined did not adequately address these hazards. All of these issues are at the very heart of clinical efficacy and patient safety. And all of these issues speak loudly to the "holy trinity of quality": authenticity, potency, and purity.

This first major revision to the food cGMPs in 30 years is a direct result of the Food Safety Modernization Act (FSMA) signed into law in 2011.[3] This new rule (21 CFR §117) builds and expands on the food cGMPs in clinically relevant ways.

The New Food cGMPs: What's in a Name?

As a result of FSMA, the food cGMPs (which include dietary ingredients) have been expanded to *mandate a hazard analysis and risk-based preventive controls for all foods*. Simply put, this new law requires a Food Safety Plan[4] (FSP) for all human foods. This is significant.

To understand the differences between 21 CFR §110 and 21 CFR §117 and their implications for dietary ingredients used in dietary supplements, look first to the title of the rules:

1. §110: Current Good Manufacturing Practice in Manufacturing, Packing, or Holding Human Food.
2. §117: Current Good Manufacturing Practice, Hazard Analysis, and Risk-Based Preventive Controls for Human Food.

Under §117, the provisions most directly connected to ingredient quality are:

1. §§B: Current Good Manufacturing Practices.
2. §§C: Hazard Analysis and Risk-based Controls (which mandates the FSP).
3. §§G: Supply Chain Control.

For each dietary ingredient, this means that the ingredient manufacturer *must* perform a hazard analysis.[5] This analysis, which *must* be managed by a "preventive controls qualified individual" *must* describe the steps in the process of creating that ingredient, consider what might happen at each step that could create a health hazard, determine what preventive controls are required for controlling that hazard, and document the verification and validation of those controls.

The analysis must be based on:

> experience, illness data, scientific reports and other information, known or reasonably foreseeable hazards for each type of food … at your facility to determine whether there are hazards requiring a preventive control.[6]

This includes (1) biological hazards, such as microbiological hazards, environmental pathogens, and other pathogens; (2) chemical hazards, including radiological hazards, such as pesticide and drug residues, natural toxins, decomposition, unapproved food or color additives, and food allergens; and (3) physical hazards (eg, metal and glass fragments).

For each hazard identified in the FSP, the severity of the illness or injury if the hazard were to occur and the probability that the hazard will occur in the absence of preventive controls must be evaluated and documented.[7]

Oh, yes. This FSP must be reanalyzed every 3 years (minimum). If there is a "new potential hazard associated with a food," the FSP must be reanalyzed.[8] Thallium in stevia? Time to reanalyze. Aflatoxin in herbal extract? Time to reanalyze. Azo dyes in bilberry? Time to reanalyze. Vitamin B_{12} in coenzyme Q_{10}? Time to reanalyze. And on and on …

As described previously, the sorts of hazards that must be considered are biological, chemical, physical, radiation, and economically motivated food safety hazards. Notably, this is the first time this author has ever seen economically motivated adulterants specifically included in cGMPs. This is very significant! It is a reflection of the problems we have with our fragmented, global supply chain, all of which have clinical and safety implications. And it puts the responsibility of managing ingredient safety issues where it first belongs: squarely on the shoulders of the ingredient suppliers who know their process far better than any dietary supplement company.

The sorts of controls used to mitigate the hazards can be process preventive controls, allergen preventive controls, sanitation preventive controls, and supply-chain preventive controls.[9]

Generally speaking, at time of writing, the supply-chain program (§§G: 21 CFR §117.405) is not yet enforceable and industry awaits further guidance from the US Food and Drug Administration on this section. Implementation will be daunting. Consider the dietary supplement company that buys ingredients for the products you recommend from middlemen (brokers). How many brokers, for example, will obtain FSPs for every ingredient they purchase from foreign suppliers that must be audited to be in compliance? The supplier verification activities proposed include onsite audits, sampling and testing of the raw material, review of the supplier's relevant food safety records, and more.[10]

One complaint and question I've heard from supplement companies is:

> Why do supplement companies have to do all the heavy lifting in defining cGMP-compliant ingredient specifications? My supplier won't tell me about his process, so how am I to really know what's important? What are the reasonably anticipated contaminants I should consider in my specs? Which analytical methods should I use?

The FSP required for every dietary ingredient addresses these issues.

And from researchers, I have heard similar questions. Proper characterization and analysis of ingredients and products are as critical to research as they are to food safety.

Why §117 Matters

As mentioned previously, under the dietary supplement cGMPs (§117), each company must define specifications for ingredients and finished goods. For the very first time, the dietary ingredient suppliers are required under law to have an FSP that comprehensively addresses all potential food safety hazards, controls them, and manages them through a verified supply chain control program, using ingredient-specific, verifiable and validated methods. The dietary supplement companies now have another evidentiary basis for developing their ingredient specifications based on an FSP provided by their ingredient suppliers.

Summary

The ground rules have changed. The new food cGMPs offer a regulatory framework for addressing ingredient quality issues and controlling these problems throughout the entire ingredient supply chain. That said, aggressive enforcement is required to assure compliance.

Health care practitioners interested in learning more about a specific ingredient will, one day, be able to review the FSP for any ingredient from any cGMP-compliant ingredient manufacturer.

Once fully implemented, §117 will theoretically empower dietary supplement companies to use suppliers' FSPs as an important basis for developing fully cGMP-compliant ingredient specifications that truly links ingredients from the source through the supply chains to finished products. This will become a standard for best practices.

And that would be a very good thing!

What You Can Do

Researchers should request an FSP for any ingredient undergoing an institutional review board-approved trial. Although we will never totally eliminate the possibility for fraud, this is an important first step afforded by these regulations. Trust, but verify.

Practitioners should ask their favored supplement companies about their plans for handling these new food cGMPs that require FSPs for ingredients. It is important to

start the conversation. Though it will take years for us to see full adoption of rules that will help assure clinical efficacy and patient safety, it is our moral obligation to move this agenda forward. It is the right thing to do. Successful supplement companies will respond to customer requests, particularly those required by law. Know this law and its potential. Enforcement of this new law began in September 2016.

The time is now.

References

1. Pizzorno JP, Levin MD. FDA's natural product cGMPs—A missed opportunity. *Integr Med Clin J*. 2007;6(5):8-9.
2. 21 CFR §110.110.
3. US Food and Drug Administration. FDA Food Safety Modernization Act (FSMA). FDA Web site. http://www.fda.gov/Food/GuidanceRegulation/FSMA/. Updated September 6, 2016. Accessed September 6, 2016.
4. 21 CFR §117.126(a)(1).
5. 21 CFR §117.126(b)(1).
6. 21 CFR §117.126(a)(1).
7. 21CFR §117.130(c)(1)(i).
8. 21CFR §117.170.
9. 21 CFR §117.135.
10. 21 CFR §§117.410(a) and (b).