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Identity, Purity, Strength, Composition

Testing under the Dietary Supplement GMPs

by Steve Myers

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"You failed to conduct at least one appropriate test or examination to verify the identity of a component that is a dietary ingredient before using the component, as required by 21 CFR 111.75(a)(1)." This is, unfortunately, one of the common GMP (good manufacturing practice) violations noted in warning letters to dietary supplement manufacturers.

Among the biggest challenges dietary supplement companies face in the new world of GMPs is increased testing. The uncertainty for many companies surrounds the kinds of testing required at various points in the manufacturing process—who does what and when? The regulation (21 CFR 111) provides some introductory guidance for when testing is required and by whom, but the regulation does not specify testing methods, other than saying companies should use "appropriate" tests. Thus, the onus is on the "responsible party" to determine which test is the best, but this decision has to be substantiated if questioned by FDA.

Who Should Test

The "responsible party" is primarily the manufacturer, but in cases of contract manufacturing, the brand owner or marketer has responsibility to ensure its products are made in compliance with GMPs. Also, firms that package, label and/or hold dietary supplements also have a burden to ensure GMPs are met during those processes, all of which can affect the quality of the products. (Think label accuracy, package integrity, storage conditions, etc.)

When to Test

For ingredients and components, testing starts with identity before the material is ever used in production. Gone are the days of relying on certificates of analysis (CoAs). One of the biggest quality control (QC) issues in the supplement industry is adulteration, either intentional or accidental, so ensuring the correct identity is the first step toward quality supplement manufacturing. Confirming the ingredient is what it is supposed to be is elementary.

The regulation says at least one "appropriate" test must be conducted to verify the identity of any component used to make the dietary supplement. FDA published an interim final rule offering an avenue for exemption from 100-percent identity testing, but it requires scientific data and rationale showing a specified alternative testing plan would ensure identity as well as 100-percent testing, when the component is sourced from a specified supplier.

Similarly, firms have the opportunity to forgo their own testing of incoming components and use the CoA, but only if the reliability of the supplier and CoA are confirmed through testing. The CoA must state the testing method used and show actual test results, and these must match the tests used to qualify the CoA. As with every GMP requirement, documentation on the process and frequency of this qualification must be maintained by the firm, which must periodically confirm the qualification through testing.

Once identity is confirmed, it is equally important to determine if the lot has contaminants, the right potency and profile of key actives or markers.

Under GMPs, firms need to verify identity, purity, strength and composition at all points in the manufacturing process where it is necessary to ensure these quality parameters are on track. How is that for open-ended guidance? It is a given that these tests need to be conducted for incoming lots of ingredients and components as well as outgoing finished product, but for everything else in between, it is the firm's responsibility to figure out the in-process control points that ensure a quality product. Thus, specifications for identity, purity, strength and composition must be set for each of the in-process control points the firm has determined is critical to QC.

Not only must these specs be established, but there must also be "adequate documentation" showing why these specs for control points and components will ensure an unadulterated, high-quality product. Further, the specifications for components and in-process control points must be reviewed by QC personnel.

What to Test for?

The product owner must set specifications for the purity, strength and composition of components, including dietary ingredients. Firms should know their products better than regulators, so FDA left plenty of space in the GMPs for companies to decide what should be tested for in their ingredients and finished products. For example, heavy metals are a particular concern for botanicals (see [Guidance on Heavy Metals from the American Herbal Products Association \[AHPA\]](#)), marine-based ingredients (see [Voluntary Monograph from the Global Organization for EPA and DHA Omega-3s \[GOED\]](#)) and some minerals, so susceptible ingredients—determined on a risk-based basis—should include heavy metal screens in their testing protocol.

Heavy metals are only one type of contaminant. Many botanicals have known adulterants that should be included in specifications for purity and identity. The American Botanical Council (ABC)'s [Botanical Adulterants Program](#) is a great resource for details on known adulterants, both intentional and accidental, including some testing recommendations.

Botanicals aren't the only supplements susceptible to adulteration, as sports nutrition, sexual health and weight management are three supplement categories recently plagued with pharmaceutical adulteration. Protein is another category

ripe for adulteration. Given these trends, companies with products in these categories should consider testing for sildenafil and its derivatives in sexual health ingredients, hormone and stimulant compounds in sports ingredients, and melamine in protein ingredients. The [U.S. Pharmacopeia \(USP\)](#) is a great resource for information on the many economically motivated adulterants that plague such ingredients as well as the testing methods used for detection of adulterants—HPLC (high-performance liquid chromatography) and infrared spectroscopy are among most common.

NSF International, a global public health and third-party certifying organization, tests supplements and dietary ingredients as part of its dietary supplement certification program. The NSF supplement certification process includes a label review, a toxicology review, a contaminant review, facility inspections and ongoing monitoring to verify compliance through periodic auditing and testing.

NSF's Certified for Sport® program tests products for more than 200 banned or prohibited substances such as narcotics, steroids, stimulants, hormones, diuretics and other masking agents, and other related substances. The goal of these programs is to help consumers, athletes coaches and trainers make more informed decisions when choosing dietary supplements.

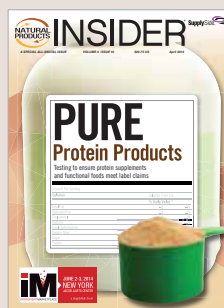
Companies sourcing or selling ingredients and products in Asia can also take advantage of NSF's Shanghai Testing Laboratory, which complements its product certification services in China.

When a company establishes the specifications for identity, purity, strength and composition, it must document why these specs will ensure a consistent, quality and unadulterated product, and why the selected testing methods are appropriate.

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Which Testing Method?

According to GMPs, the tests must be “appropriate” and “scientifically valid.” Testing certain components, including botanicals, probiotics and multi-ingredient premixes can be challenging, and may require costly technology and multiple techniques. For instance, with probiotics distinguishing between different strains from the same genus and species is difficult due to similarities, so the best method

for probiotics identity may be genetic fingerprinting. However, this testing requires expensive equipment and training.

Many firms are unsure how to apply the term “scientifically valid” to testing under GMPs. The regulation requires the use of at least one of the following types of analysis: macroscopic, microscopic, gross organoleptic, chemical or any “scientifically valid” method.

Several botanicals, such as ginkgo, are commonly tested using HPLC, which reveals constituents in a sort of fingerprint of peaks and valleys. This can be useful in the search for known or common adulterants. However, gas chromatography (GC) is the industry standard used to quantify docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) in omega-3 fatty acids, while a combination of GC and high-resolution mass spectrometry (MS) is the standard for PCP and dioxins in marine omega-3 ingredients; a number of different tests, including FTIR (Fourier transform infrared) spectroscopy and nuclear magnetic resonance (NMR) spectroscopy, are used to analyze oxidation of lipids such as omega-3 oils.

In [a detailed article for INSIDER](#), James Neal-Kababick, director of Flora Research Laboratories, and Kathryn Lawrence, formerly a business development manager at W.R. Grace, listed several testing technologies, including HPLC, GC, MS, high performance thin layer chromatography (HPTLC), flash chromatography, infrared (MIR, NIR, FTIR) and ultraviolet visible spectroscopy (UV-VIS). They suggested advanced flash column chromatography (AFCC) as an alternative separation technique that can complement other technologies quickly and at a reasonable cost. In fact, Flora Research created the [One Pass Flash technique](#) using flash chromatography to efficiently obtain concentrated and purified fractions that can be used in MS to analyze for constituents, including adulterants such as steroids in sports supplements.

Labs such as Flora Research, Covance, Chromadex, Alkemist Labs and others are great sources of testing methods, as well as standard reference materials, samples of various ingredients of known (via testing) and common constituent profiles that can be a baseline for testing components under GMPs.

Several resources are available for firms looking for validated or scientifically valid methods. A partnership between the Office of Dietary Supplements (ODS) and AOAC International for the [development, validation and dissemination of analytical methods for dietary supplements](#). The project uses single-lab and collaborative study validation, and many methods from the program are published in the Journal of the AOAC and in [AOAC's Official Methods of Analysis](#). ODS also partners with the National Institute of Standards and Technology (NIST) on developing standard reference materials (SRMs) for use in validating methods and in analyzing raw material lots for [constituents and contaminants](#).



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Monographs can also be useful for detailed information on ingredient constituents including actives and markers, as well as possible contaminants and analytical techniques and methods. [USP's Dietary Supplement Compendium](#) houses more than 400 National Formulary (NF) dietary supplement monographs and information on tests and assays; it has 200 Food Chemical Codex (FCC) monographs for ingredients used in foods and supplements, including protein, as well as FCC appendices with testing and assay information. The compendium offers similar information for more than 175 excipients commonly used in supplement manufacturing.

Botanical monographs from the [American Herbal Pharmacopoeia \(AHP\)](#), [ABC's German Commission E library](#), the [European Pharmacopoeia](#) and the [World Health Organization](#) (WHO) are just a few resources for finding more information on botanical constituents and testing.

AHPA, which has been very tuned into the California Proposition 65 regulation on heavy metals, has more than just the guidance on heavy metals. It offers [guidance on mycotoxins and microbiology for herbal ingredients](#), which can help in setting specifications. Also, the [AHPA Botanical Identity References Compendium](#) serves as a centralized and collaborative resource on the chemical profile and analysis of medicinal plants. The compendium provide physical characteristics and analytical test methods, including HPTLC, macroscopy, microscopy and organoleptic techniques, for more nearly 200 botanical species.

As stated, probiotics and DHA/EPA omega-3s present unique testing challenges. While there is no specific regulatory requirement, [FDA has adopted the WHO guidelines in recommending phenotype and genetic testing](#) to determine the genus, species and strain of probiotics.

➔ **Check Out the INSIDER article,
"Probiotics Quality Control Challenges"**
for more information on testing and labeling.

In both cases, probiotics and omega-3s, industry members active in those market segments who had strict quality and purity practices worked together on voluntary standards and guidelines for quality of those ingredients. GOED maintains and updates the voluntary monograph, which was created by a working group spearheaded by the Council for Responsible Nutrition (CRN). The monograph covers EPA and DHA (triglyceride and ethyl ester forms) from fish, plant or microbial sources. The European Pharmacopoeia has a monograph for cod liver oil, and USP has a new monograph for krill oil.

The [International Probiotics Association \(IPA\)](#) gathers industry and academia to share info and ideas on probiotics, including technology. It has composed voluntary guidelines, but they focus on labeling. [The International Life Science Institute \(ILSI\) Probiotics Task Force produced a monograph](#) that touches on the techniques used to analyze probiotics, but a more detailed presentation of testing information can be found in the [Probiotic Appendix of FCC from USP](#).

While there are numerous sources of information on testing methods for various dietary ingredients, there are also some circumstances in which there is no “scientifically valid” test for certain finished products, such as when a test works for a particular ingredient on its own but not in a multi-ingredient formula. FDA has acknowledged this possible void by allowing for an exemption to certain finished product testing in the GMPs. Such cases require documentation explaining why component and in-process testing and other information will sufficiently ensure a quality finished product without testing the finished batch.

The Choice is Yours

Manufacturers have no choice but to follow GMPs if they want to produce legal product for the U.S. market, but they do have the choice in what specifications to set and what tests to perform. This isn't total freedom, as all these choices must be appropriate and scientifically valid, not to mention documented. Dietary ingredients and finished products present unique challenges to identity and purity testing, and companies will have to determine whether they have the funds, expertise and personnel to set specifications and perform testing in-house or if it is best to work with consultants and third-party labs. Certainly, companies would be smart to consider the numerous resources available to determine what component and finished product constituents should be, what contaminants and adulterants are possible, and what testing methods and control points are best to ensure the products are made consistently and of a high quality. In some cases, companies have to create their own test methods and, preferably validate them through single lab or collaborative study validation. Whatever the approach, proper testing must be performed under GMPs, and it is up to the companies to determine their own testing protocol. □

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