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## Ensuring Dietary Supplement Safety with Transparent Testing

**Multi-faceted approaches to supplement safety in a transparent environment**

Dietary supplement consumers increasingly demand more information and transparency around the safety of dietary supplements, and brand owners face many potential safety regulations. Unlike other areas of dietary supplement testing, ensuring safety requires a multi-faceted approach that can involve toxicology and tolerability studies, microbial testing and various risk assessments.

# Ensuring Dietary Supplement Safety with Transparent Testing

## Multi-faceted approaches to supplement safety in a transparent environment

*by Steve Myers*

**S**afety is not a single compound or constituent that can be identified and fingerprinted in spectroscopy. Ensuring the safety of products and their ingredients requires multiple tests and assessments. Safety is as much about what is in the product as what is not in the product; it involves assessments about how the product is likely to act in various environments, especially in the human body; and it can be influenced by production and handling conditions. Brand owners, whether they manufacture the product or contract with a manufacturing partner, must be involved in how their products' safety is ensured and find a way to better relay this information to consumers, who are demanding more transparency on safety.

Besides the ethical responsibility to ensure products ingested by consumers are safe, there are several regulations brand owners may encounter that demand safety data. Foremost is the dietary supplement good manufacturing practices (GMPs, introduced in 2007), which levy several testing requirements on manufacturers and other responsible parties including private label brand owners. The testing requirements focus on identity, purity, strength and composition—the first part of being safe is to make sure the product is what it is supposed to be.

GMPs are intended to ensure safe, quality supplements are made in a consistent, reproducible and documented manner. Testing is one part of this process and is to be conducted on incoming material, at various points during the manufacturing process and on outgoing finished products. Beyond testing, the requirements also demand regular maintenance and cleaning of equipment, proper personnel hygiene and training, clean and uncontaminated facilities, and proper storage of product to prevent degradation and cross-contamination, all areas that can affect product safety.

The GMP testing requirements do not specify any particular test method or reference material, as the agency allows the manufacturer/responsible party the flexibility to select the most appropriate test method for the ingredient or product. However, in its final rule, FDA said testing should include at least one of organoleptic, macroscopic, microscopic, chemical or other scientifically valid analyses. In the end, the manufacturer will have to prove why a given method is appropriate for a given product. Many find it useful to rely on compendia from USP (U.S. Pharmacopeial Convention) or official validated methods from AOAC International, but FDA only recommends, not requires, these types of resources.

GMPs are a minimum requirement for dietary supplements in the United States, but many companies also follow hazard analysis and critical control point (HACCP)-type systems, which are a mainstay in the food and beverage industry. HACCP identifies potential hazards in production that can render a finished product unsafe. Following a HACCP plan helps minimize the risks of such hazards. Ingredient suppliers are not directly regulated by supplement GMPs—manufacturers subject to GMPs are required to qualify suppliers and test incoming materials to established specs—but there is some speculation the implementation of the Food Safety Modernization Act (FSMA, signed into law in 2011) may require supplement ingredient suppliers to follow a HACCP plan.

The food and beverage industry is also influencing dietary supplements due to the increasingly blurred lines of dietary supplements versus functional foods/beverages. While regulators continue to sort out the lines of distinction between these product types for purposes of regulation, companies making and selling these types of products—some beverages and foods are marketed as dietary supplements—are increasingly turning to GRAS (generally recognized as safe) status to designate their ingredients as safe for use in foods and beverages, including functional products.

“The safety standard for GRAS ingredients is the same as that for food additives: reasonable certainty of no harm,” explained Claire Kruger, Ph.D., president of Spherix Consulting, a division of Chromadex. “The evidence of safety is the same as that required to support approval of a food additive petition in terms of breadth and quantity of information as well as quality of information. In addition, for GRAS determination, the pivotal information must be publicly available and accepted.”

The most common route these days is the self-affirmed GRAS process. For self-affirmation, the company performs and/or gathers all the data that shows safety, and this evidence must be reviewed by an independent, expert scientific panel. The evidence can include published literature on the substance, toxicological studies, history of use, adverse events and all the data on composition, properties and production of the specific substance under review.

GRAS status is for a specific substance and a specific use. While not a regulatory requirement, companies typically notify FDA of a successful expert panel review and submit the required information to the agency. FDA then issues either a letter of no objection, which carries more weight in the marketplace, or a letter

Between 1998 and 2008, FDA issued a “no objection” letter to 77 percent of GRAS notifications, according to the Government Accounting Office (GAO).

noting insufficient evidence, which often results in the discontinued use of the that substance for the intended use or the resubmission of GRAS notification with additional evidence.

While dietary supplements came out from under food regulations after the passage of DSHEA (the Dietary Supplement Health and Education Act of 1994), which mandated GMPs and other requirements, FDA continues to work on the rule for new dietary ingredients (NDIs). In the mean time, the industry has relied on the food industry's GRAS method to show safety. Per DSHEA, NDIs are defined as supplement ingredients that were not on the market before Oct. 15, 1994, but the agency has said any ingredient significantly altered from the form marketed before that date would also be considered an NDI. Another mandate of DSHEA, NDI notifications (NDINs) provide FDA a pre-market period of time (at least 75 days) to evaluate the safety of an NDI and issue any objection. Information included in NDINs is similar to that for GRAS, and can include scientific data on identity, human studies, toxicology studies, history of use and other safety and toxicology references.

While FDA agreed to rework the guidance after much industry criticism of its original guidance (released in July 2011), one part of FDA's initial guidance that industry has adopted is the exemption from NDIN requirement for ingredients that have already been listed or affirmed as GRAS, as long as that ingredient has not been chemically altered from the GRAS form. Ingredients exempted through the GRAS pathway are still subject to the NDI draft guidance adulteration standard if not marketed before Oct. 15, 1994. A GRAS ingredient would be considered adulterated if there is insufficient data to reasonably assure it does not present significant or unreasonable risk of illness or injury. An NDIN for such ingredients would provide FDA, which is primarily concerned with dosage amounts of supplements relative to GRAS, with additional evidence of safety.

In California, supplements are subject to additional safety requirements under Proposition 65, which was enacted as a ballot measure in 1986. If content of certain heavy metals is above a certain threshold in a supplement, that product must bear a label warning about containing a carcinogenic substance. The enforcement of this regulation is by private parties, which has created so-called "bounty hunter" lawyers who enjoy significant financial benefit from the cases.

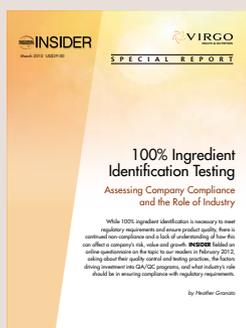
In fiscal year 2012, FDA objected to 85 percent of new dietary ingredient (NDI) notifications, according to Emord & Associates.

Besides the bounty hunter environment, the technical criticisms are focused on the strict limits for metals such as lead, arsenic, cadmium and mercury, which are found in almost all agricultural and botanical products. Marine products are another target category for Prop 65 due to metal levels in oceans. The Prop 65 limits were far below guidelines established by USP limits for nutritional supplements, as well as FDA's Total Tolerable Intake levels (for lead).

Prop 65-driven heavy metals testing, court, labeling and reformulation costs were high, but an early 2013 California judicial ruling deemed dietary supplements as foods under Prop 65. This is relief for supplement companies, as chemicals naturally occurring in foods are exempt from Prop 65 warning requirements. This ruling may ease some of the burden, but supplement companies and retailers may still have to prove chemicals are naturally occurring, which will require data from test screens.

## Generating Safety Data

Among the scientific data used to show safety, animal toxicology studies are used for hazard identification and can involve a number of methodologies including a screening genotoxicity battery, repeat dose toxicology such as a 90-day rodent or non-rodent subchronic study, chronic/carcinogenicity studies, one generation or multi-generation reproduction studies, developmental toxicity studies and absorption/distribution/metabolism/excretion studies.



## ➤ Check Out this FREE Report 100% Ingredient Identification Testing

While 100-percent ingredient identification is necessary to meet regulatory requirements and ensure product quality, there is continued non-compliance and a lack of understanding of how this can affect a company's risk, value and growth. This **INSIDER**

Report discusses the findings from a February 2013 industry questionnaire, including how industry execs rate their companies' QA/QC programs; what primary compliance obstacles are challenging identification testing; and how industry can work together to ensure product safety and quality.

Kruger explained animal models are selected on the basis of their ability to extrapolate results to human health assessment. The researchers consider bioavailability, nutritional requirements/limitations, metabolic parameters and developmental stage.

“The study must be designed to prevent differences in pharmacokinetic handling or dietary imbalance from confounding toxicology results,” she said, noting the goal of the study design is to differentiate those effects which are: local or systemic; reversible or irreversible; and immediate or delayed. “Determination of the hazard or target organs of toxicity is utilized in a subsequent risk assessment.”

Risk assessment estimates the risk of adverse health effects from exposure or ingestion of chemicals. This involves scientific, mathematical analyses, and both quantitative and qualitative conclusions on the likelihood of harm or illness. In risk assessment, the potential hazards of a chemical must be identified, taking into consideration data on human exposure to the chemical, and dose-response relative to toxic effects.

### Risk Assessment Checklist

- Hazard identification:** the qualitative assessment of the intrinsic toxicity of the substance.
- Dose-response assessment:** the quantitative assessment of dose and toxic effect.
- Exposure characterization:** assessment of the intensity, frequency, and duration of contact, the route of the substance across the boundary, the resulting amount of substance actually crossing the boundary and the amount of substance absorbed (internal dose).
- Risk Characterization:** risk is the product of hazard and exposure; the characterization summarizes and integrates information from the preceding steps of the risk assessment to synthesize an overall conclusion about risk

*Source: Spherix Consulting*

Risk assessment poses challenges for the dietary supplement industry. For NDIs or GRAS substances, the specific data and information that demonstrate safety depend on the characteristics of the substance, the estimated dietary intake, and the population that will consume the substance. “Complex products can necessitate the use of different and innovative approaches to develop

documentation of a safe level of ingestion," Kruger advised. "For example, natural products are of interest due to their nutritional and functional properties, but they are chemically complex, making them challenging to characterize for the purpose of a carrying out a safety evaluation."

She suggested one way to address this challenge is to establish the safety of the "whole" natural product by defining its composition in a rigorous and systematic manner, and then using this information to evaluate the safety of the components that make up the whole extract. "It is important to note that, for dietary ingredients, the amount and frequency and duration of consumption can determine status as an old or new dietary ingredient and changes in these parameters for dietary ingredients can necessitate the need for toxicology testing," she said.

What safety data is required depends on the specific ingredients, product category and intended use, all which will determine which regulations are in play as well as possible chemicals and hazards.

For instance, botanicals and marine ingredients likely contain some heavy metals from their environments. "In addition to batteries of USP assay tests for potency and other parameters, we have, for safety testing, emphasized heavy metal breakdowns for the so-called 'big four,' namely arsenic, cadmium, lead and mercury," said Weiguo Zhang, president of Synutra Ingredients, which guarantees its chondroitin sulfate is adulteration-free. "For material or product safety, we typically provide a 50- to 100-percent endpoint cushion to limits of monograph or official documentary standards, if applicable; for certain line items, such as the big four, we prefer a 10-times or more endpoint cushion for rare but possible contaminant surges due to accidental environmental contamination." He advised under these circumstances, safety testing is only complementary to broader and systematic quality assurance (QA) and quality control (QC) measures to prevent process compromises resulting from external factors, such as ground water contamination.

Some nutrients are essential and require balancing the need to minimize risk with the need to avoid deficiency, according to Alan Boobis, pharmacologist from Imperial College London.

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Compromises from the production and storage environments is another area of safety concern where specialized testing may be warranted. Mark Calmann, senior marketing manager for Accugenix, noted regulations require manufacturers to adopt methods and limits to demonstrate environmental control of the production area relative to microbial contamination. "In addition, raw materials and samples of final products are also tested to ensure the safety of the product or the strain type used in a probiotic is always the same," he said. "Alert and action limits are set by individual companies based on the nature of the product, the intended recipients, capability of the product to support growth or sustain the microorganisms and interference of the organism with active ingredients, test methods, product stability or container/closure system." He noted investigations are based on action levels and alerts manufacturers set for their facilities and the organisms they consider objectionable.

### Marketing Safety

Transparency is the best strategy, according to Suzanne Shelton, founder and president of the Shelton Group, who said these days, consumers are looking for information online. "A company's website needs to address quality questions and issues honestly and directly," she recommended, noting all the studies on social media show that when companies answer questions and concerns directly, it grows consumer loyalty, and this would apply to websites as well. "You lose them if you get too technical, so don't let the science staff finalize the copy."

Shelton further suggested quality programs should be part of a company's marketing message on an ongoing basis, but the quality has to be legitimate. "You should also have a crisis communications plan in place so that if there is a negative issue you need to address, you have all the tools to act promptly," she added. "Delays look fishy, and your silence, if you don't speak up quickly, becomes a negative message."

For Karena Dillon, partner in the Baker Dillon Group, branding might be a good marketing avenue. "Make measurements of quality part of the branding itself (GMP manufactured, laboratory tested, purity guaranteed, etc.), then back the messaging up with a certificate of analysis (CoA) on the product page,"

The World Health Organization (WHO) estimates more than 25 percent of the global burden of disease is linked to environmental factors, including chemical exposure.

she suggested, indicating such a move shows full transparency. “The CoA is label proof and ensures the quality of the product ...if the company doesn’t have one, consumers should look for a different product from a company that provides CoAs.”

The importance of transparency is driven by growing concerns in the marketplace over the safety of dietary supplements. Whether or not the concern is warranted or overhyped by media coverage, consumers seek brands and companies they can trust. Trust and safety are not achieved overnight, but by a long-term commitment to compliance with quality and safety regulations. This requires careful considerations of the various methods of analyzing safety and assessing risk, as well as sound partnerships with expert, capable labs and contract manufacturers. □

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