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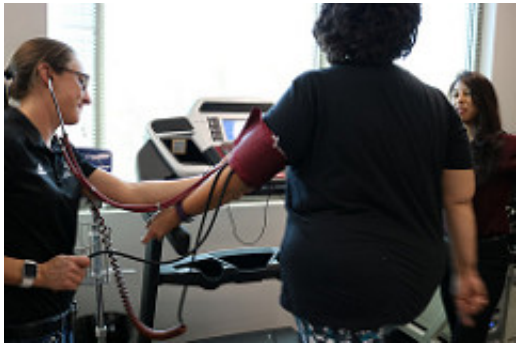
Classification and the Industry of Dietary Supplements



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Disclosures: Has received funding from industry to conduct exercise and nutrition research. Serves as scientific and legal consultant.

Dietary Supplement

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- A product that is intended to supplement the diet and contains a “dietary ingredient”.
- Dietary ingredients may include vitamins, minerals, herbs or other botanicals, amino acids, and substances such as enzymes, organ tissues, and glandular extracts.
- Dietary ingredients may also include extracts, metabolites, or concentrates of those substances.
- Dietary supplements may be found in many forms such as tablets, capsules, softgels, gelcaps, liquids, or powders, but may only be intended for oral ingestion.

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Dietary Supplement

- Dietary supplements cannot be marketed or promoted for sublingual, intranasal, transdermal, injected, or in any other route of administration except oral ingestion.
- A supplement can be in other forms, such as a bar, as long as the information on its label does not represent the product as a conventional food or a sole item of a meal or diet.
- Some energy drinks, bars, and meal replacements are listed as a dietary supplement while others are listed as foods.

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DSHEA

- The Dietary Supplement Health and Education Act of 1994 (DSHEA), placed dietary supplements in a special category of “foods”.
- This statute was enacted amid claims that the Food and Drug Administration (FDA) was distorting the then-existing provisions of the Food, Drug, and Cosmetic Act (FDCA) to improperly deprive the public of safe and popular dietary supplement products.
- DSHEA clearly defines “dietary supplements” and “dietary ingredients,” and sets certain criteria for “new dietary ingredients”.
- DSHEA prevents the FDA from overreaching and over regulating dietary supplement.

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DSHEA

- Contrary to widespread opinion, DSHEA did not leave the industry unregulated.
- The dietary supplement industry is regulated by the FDA as a result of DSHEA.
- The law ensures the authority of the FDA to provide legitimate protections for the public health.
- The Federal Trade Commission (FTC) also continues to have jurisdiction over the marketing claims that dietary supplement manufacturers or companies make about their products.
- The FDA and FTC operate in a cooperative fashion to regulate the dietary supplement industry.

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Regulatory Environment

- In the United States, dietary supplements are classified as food products, not drugs, and there is generally no mandate to register products with the FDA or obtain FDA approval before producing or selling supplements to consumers.
- However, if a dietary supplement manufacturer is making a claim about their product, the company must submit the claims to FDA within 30 days of marketing the product.
- In Canada, under the Natural Health Product (NHP) Regulations enacted in 2004; supplements must be reviewed, approved, and registered with Health Canada.
- The rationale for the U.S. model is based on a presumed long history of safe use; hence there is no need to require additional safety data.
- Each country has their own regulations which impact on whether supplements can be sold in their country or not.
- Many countries follow the lead of U.S., Canada, or European Union in terms of regulation.

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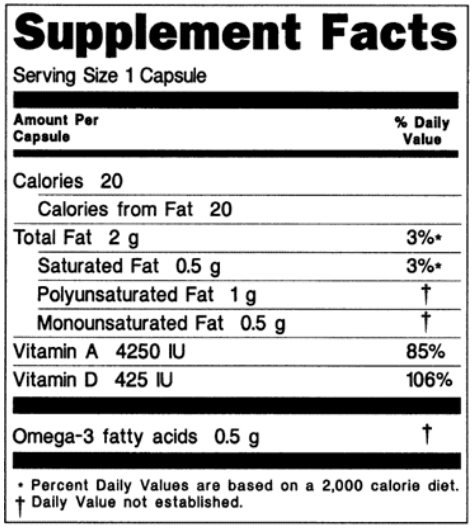
Regulatory Environment

- DSHEA also requires supplement marketers to include on any label displaying structure/function claims (i.e., claims that the product affects the structure or function of the body) the mandatory FDA disclaimer "*This statement has not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease.*"
- Opponents of dietary supplements often cite this statement as evidence that the FDA does not review or approve dietary supplements.
- However, most dietary ingredients have been "grandfathered in" as DSHEA-compliant ingredients due to a long history of safe use.
- Products containing new ingredients must be submitted by a notification to the FDA for a safety review prior to being brought to market.



Supplement Facts

Serving Size 1 Capsule

Amount Per Capsule	% Daily Value
Calories 20	
Calories from Fat 20	
Total Fat 2 g	3%*
Saturated Fat 0.5 g	3%*
Polyunsaturated Fat 1 g	†
Monounsaturated Fat 0.5 g	†
Vitamin A 4250 IU	85%
Vitamin D 425 IU	106%
Omega-3 fatty acids 0.5 g	†

* Percent Daily Values are based on a 2,000 calorie diet.
† Daily Value not established.

Ingredients: Cod liver oil, gelatin, water, and glycerin.

Supplement Facts

If a dietary supplement label includes a structure/function claim, it must be paired with a "disclaimer" that FDA has not evaluated the claim and state that the dietary supplement is not intended to "diagnose, treat, cure or prevent any disease."

Council for Responsible Nutrition www.crnusa.org

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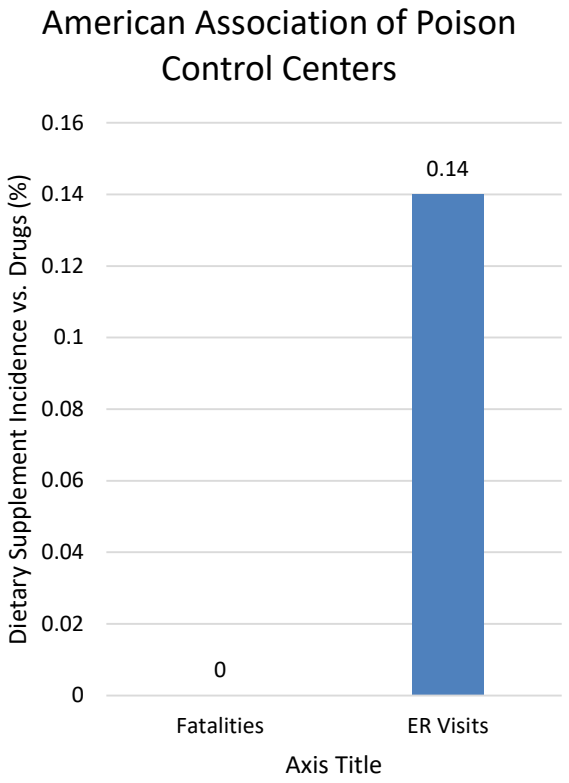
Regulatory Environment

- Although many dietary ingredients have been introduced into dietary supplements since October 1994 and have not been submitted to the FDA for a safety review, nutritional supplementation writ large is generally safe.
- While there are over 50,000 dietary supplements registered with the Office of Dietary Supplement's "Dietary Supplement Label Database", a American Association of Poison Control Centers report revealed zero fatalities occurred due to dietary supplements compared to 1,692 deaths due to drugs (*Brown. Food Chem Toxicol, 2017*).
- Comparatively, the CDC reported 2,287,273 ER visits due to prescription drug-related events compared to 3,266 ER visits due to dietary supplements (excluding cases of older adults choking on pills, allergic reactions, unsupervised children consuming too many vitamins, and persons consuming ingredients not defined by DSHEA as a dietary supplement (*Brown. Food Chem Toxicol, 2017*).



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Regulatory Environment

- In comparison, a recent Healthcare Cost and Utilization Project Statistical Brief (*Lucado et al., 2010*) reported approximately one in six Americans suffered from food borne illnesses in 2010, and food borne illnesses were associated with over 3.7 million treat-and-release emergency department visits, 1.3 million inpatient hospital stays, and 3,000 deaths.
- With that said, there have been isolated case reports of liver and kidney toxicity potentially caused by supplements containing herbal extracts (*Brown. Food Chem Toxicol, 2017*) as well as overdoses associated with pure caffeine anhydrous ingestion (*Jabbar & Hanly, Am J Forensic Med Pathol, 2013*).
- However, while available scientific literature and case reports demonstrate that dietary supplements are generally safe, dietary supplement consumption can lead to adverse events, like any food or prescription medication, in spite of DSHEA and current FDA regulations.

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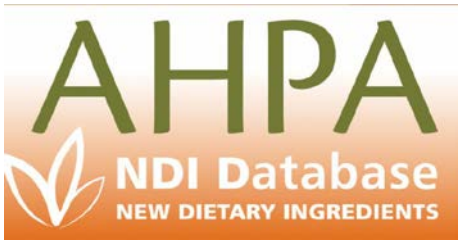
New Dietary Ingredients

- A “new dietary ingredient” (NDI) is defined as a dietary ingredient that was not marketed in the United States before October 15, 1994.
- DSHEA grants the FDA greater control over supplements containing NDIs.
- A product containing an NDI is deemed adulterated and subject to FDA enforcement sanctions unless it meets one of two exemption criteria:

    1. the supplement in question contains “only dietary ingredients which have been present in the food supply as an article used for food in a form in which the food has not been chemically altered”; or
    2. there is a “history of use or other evidence of safety” provided by the manufacturer or distributor to the FDA at least 75 days before introducing the product into interstate commerce.

- The first criterion is silent as to how and by whom presence in the food supply as food articles without chemical alteration is to be established.
- The second criterion is applicable only to NDI’s that have not been present in the food supply and requires manufacturers and distributors of the product to take certain actions.



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New Dietary Ingredients

- Companies must submit to the FDA information that is the basis on which a product containing the NDI is “reasonably expected to be safe” at least 75 days before selling the supplement including:

  1. the name of the NDI and, if it is an herb or botanical, the Latin binomial name;
  2. a description of the dietary supplement that contains the NDI, including:

     a) the level of the new dietary ingredient in the product,
     b) conditions of use of the product stated in the labeling, or if no conditions of use are stated, the ordinary conditions of use, and
     c) a history of use or other evidence of safety establishing that the dietary ingredient, when used under the conditions recommended or suggested in the labeling of the dietary supplement, is reasonably expected to be safe.

FDA GRANTED
New Dietary Ingredient (NDI) Status

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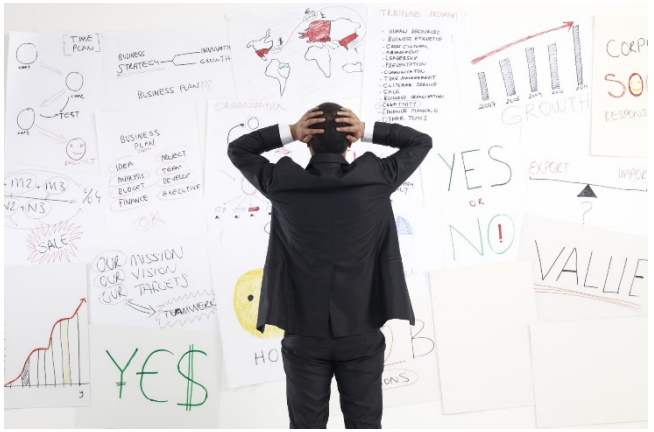
New Dietary Ingredients

- In 2011 and 2016, the FDA released Draft Guidance for Industry although it has been criticized for a lack of clarity and other issues.
- The lack of clarity surrounding the “new” Draft Guidance has led to many NDI notifications being rejected by FDA for lack of safety data and other issues.
- Other companies have opted to utilize the “Self-Affirmed Generally Recognized as Safe (GRAS)” route in order to “bypass” the NDI notification process.
- Self-Affirmed GRAS is when a company has a team of scientific experts evaluate the safety of their ingredient.
- There is no requirement that the safety dossier be submitted to FDA but is used by the company as an internal document that may be relied upon if the ingredient is challenged by the FDA.



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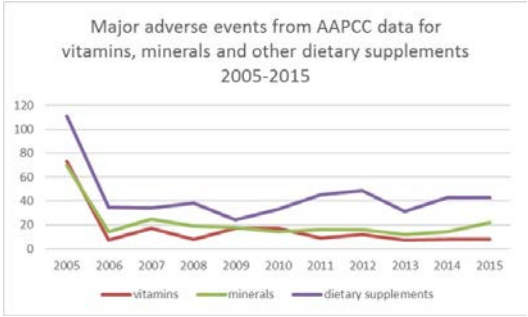
Adverse Event Reporting

- In 2006, the 109th Congress passed the first mandatory Adverse Event Reporting (AER) legislation for the dietary supplement which requires that all “serious adverse events” regarding dietary supplements be reported to the DHHS.
- The law strengthens the regulatory structure for dietary supplements and builds greater consumer confidence, as consumers have a right to expect that if they report a serious adverse event to a dietary supplement marketer the FDA will be advised.
- An adverse event is any health-related event associated with the use of a dietary supplement that is adverse.
- A serious adverse event is an adverse event that (A) results in (i) death, (ii) a life-threatening experience, (iii) inpatient hospitalization, (iv) a persistent or significant disability or incapacity, or (v) a congenital anomaly or birth defect; or (B) requires, based on reasonable medical judgment, a medical or surgical intervention to prevent an outcome described under subparagraph (A).



AAPCC data on food-related toxicities: major adverse events, 2009-15

Substance	2009	2010	2011	2012	2013	2014	2015
Other food toxicants	50	27	60	50	35	47	48
Dietary supplements	24	33	45	49	31	43	43
Minerals	18	14	16	16	12	14	22
Vitamins	17	17	9	12	7	8	8
Seafood toxins	5	8	6	6	9	17	7
Total	114	99	136	133	94	129	128

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Adverse Event Reporting

- Once it is determined that a serious adverse event has occurred, the manufacturer, packer, or distributor (responsible person) of a dietary supplement whose name appears on the label of the supplement shall submit to the Secretary of HHS any report received of the serious adverse event accompanied by a copy of the label on or within the retail packaging of the dietary supplement.
- The responsible person has 15 business days to submit the report to FDA after being notified of the serious adverse event.
- Following the initial report, the responsible person must submit follow-up reports of new medical information that they receive for one-year.

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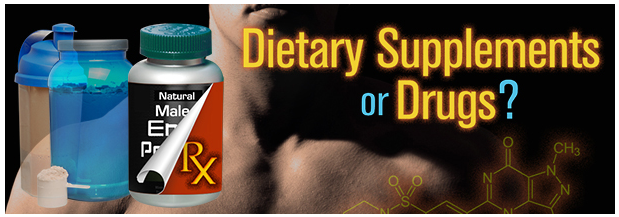
Adulterated Supplements

- The FDA has various options to protect consumers from unsafe supplements. The Secretary of the DHHS (which falls under FDA oversight) has the power to declare a dangerous supplement to be an "imminent hazard" to public health or safety and immediately suspend sales of the product.
- The FDA also has the authority to protect consumers from dietary supplements that present certain risks of illness or injury to consumers.
- The law prohibits introducing adulterated products into interstate commerce.
- A supplement shall be deemed adulterated if it presents "a significant or unreasonable risk of illness or injury".
- The standard does not require proof that consumers have actually been harmed or even that a product will harm anyone.



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Adulterated Supplements

- It was under this provision that the FDA concluded that dietary supplements containing ephedra, androstenedione, and DMAA presented an unreasonable risk.
- Most recently, FDA imposed an importation ban on the botanical Mitragyna speciose, better known as Kratom.
- In 2016, FDA issued Import Alert #54–15, which allows for detention without physical examination of dietary supplements and bulk dietary ingredients that are, or contain, Kratom.
- Criminal penalties are present for a conviction of introducing adulterated supplement products into interstate commerce.
- These actions show that the supplement industry is being watched by the U.S. Department of Justice and vigilantly protecting the health and safety of the American public.

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Good Manufacturing Practices

- DSHEA also required that the FDA establish and enforce current Good Manufacturing Practices (cGMPs) for dietary supplements.
- However, it was not until 2007 that the cGMPs were finally approved, and not until 2010 that the cGMPs applied across the industry, to large and small companies alike.
- The adherence to cGMPs has helped protect against contamination issues and should serve to improve consumer confidence in dietary supplements.
- The market improved as companies became compliant with cGMPs, as these regulations imposed more stringent requirements such as Vendor Certification, Document Control Procedures, and Identity Testing.
- These compliance criteria addressed the problems that had damaged the reputation of the industry with a focus on quality control, record keeping, and documentation.

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Good Manufacturing Practices

- However, it does appear that some within the industry continue to struggle with compliance.
- In Fiscal Year 2017, it was reported that approximately 23.48% of the FDA's 656 total cGMP inspections resulted in citations for failing to establish specifications for the identity, purity, strength, and composition of dietary supplements.
- Further, 18.47% of those inspected were cited for failing to establish and/or follow written procedures for quality control operations.
- Undoubtedly, relying on certificates of analysis from the raw materials supplier without further testing, or failing to conduct identity testing of a finished product, can result in the creation of a product that contains something it should not contain such as synthetic chemicals or even pharmaceutical drugs.
- All members of the industry need to ensure compliance with cGMPs.

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Marketing Claims

- Unsubstantiated claims invite enforcement by the FTC (along with the FDA, state district attorney offices, groups like the Better Business Bureau, and class action lawsuits).
- The FTC has typically applied a substantiation standard of "competent and reliable scientific evidence" to claims about the benefits and safety of dietary supplements.
- FTC case law defines "competent and reliable scientific evidence" as "tests, analyses, research, studies, or other evidence based on the expertise of professionals in the relevant area, that has been conducted and evaluated in an objective manner by persons qualified to do so, using procedures generally accepted in the profession to yield accurate and reliable results."
- The FTC has claimed that this involves providing at least two clinical trials showing efficacy of the actual product, within a population of subjects relevant to the target market, supporting the structure/function claims that are made.
- The FTC has acted against several supplement companies for misleading advertisements and/or structure/function claims.

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A Safer Industry Ahead

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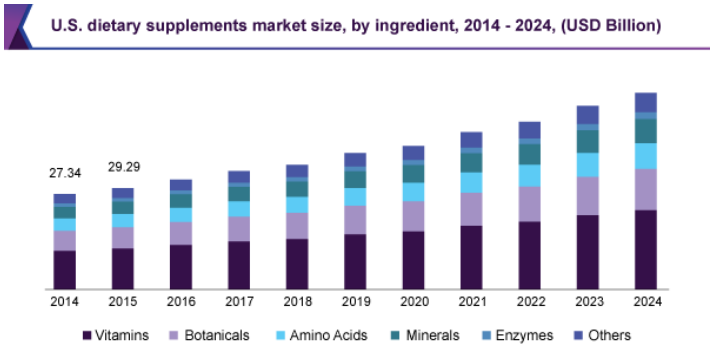
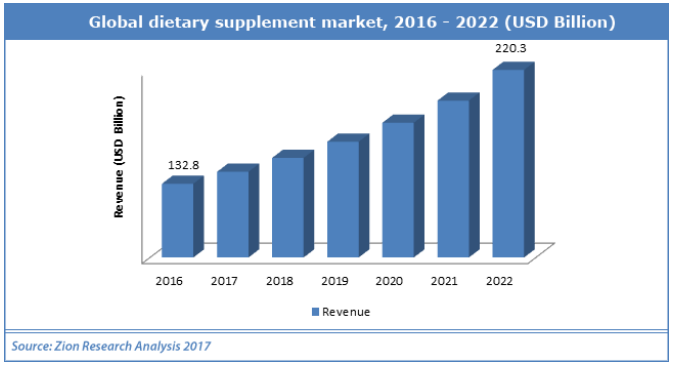
- While some argue that the dietary supplement industry is “unregulated” and/or may have suggestions for additional regulation, manufacturers and distributors of dietary supplements must adhere to several federal regulations before a product can go to market.
- Before marketing products, they must have evidence that their supplements are generally safe to meet all the requirements of DSHEA and FDA regulations.
- Over the last 20 years, many established supplement companies have employed research and development directors who help educate the public about nutrition and exercise, provide input on product development, conduct preliminary research on products, and/or assist in coordinating research trials conducted by independent research teams (e.g., university-based researchers or clinical research sites).
- These companies also consult with marketing and legal teams with the responsibility to ensure structure/function claims do not misrepresent results of research findings.





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A Safer Industry Ahead

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- While some companies have falsely attributed research on different dietary ingredients or dietary supplements to their own products, suppressed negative research findings, and/or exaggerated results from research studies, the trend in the sports nutrition industry has been to develop scientifically sound supplements.
- This trend toward greater research support is the result of:
  1. attempts to honestly and accurately inform the public about results;
  2. efforts to obtain data to support safety and efficacy on products for the FDA and the FTC; and/or,
  3. endeavors to provide scientific evidence to support advertising claims and increase sales.
- While the push for more research is due in part to greater scrutiny from the FDA and FTC, it is also in response to an increasingly competitive marketplace where established safety and efficacy attracts more consumer loyalty and helps ensure a longer lifespan for the product in commerce.
- Companies that adhere to these ethical standards tend to prosper while those that do not will typically struggle to comply with FDA and FTC guidelines resulting in a loss of consumer confidence and an early demise for the product.

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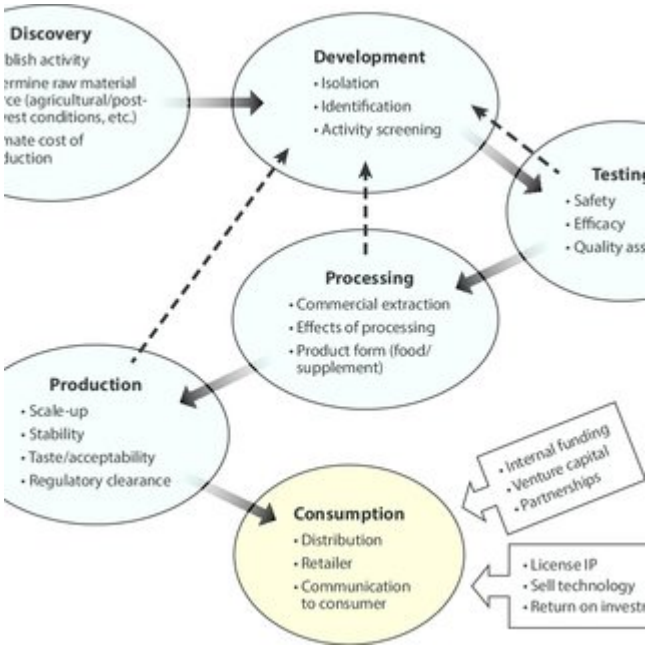
Product Development

- Established companies who develop dietary supplements have research teams who scour the medical and scientific literature looking for potentially effective nutrients.
- These research teams often attend scientific meetings and review the latest patents, research abstracts presented at scientific meetings, and research publications.
- Leading companies invest in basic research on nutrients before developing their supplement formulations and often consult with leading researchers to discuss ideas about dietary supplements and their potential for commercialization.
- Other companies wait until research has been presented in patents, research abstracts, or publications before developing nutritional formulations featuring the nutrient.



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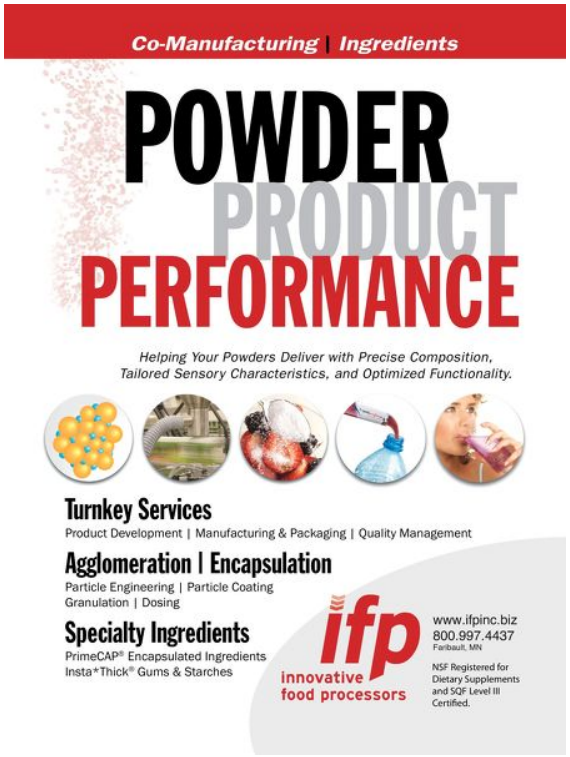
Product Development

- When a powdered formulation is designed, the list of ingredients and raw materials are typically sent to a flavoring house and packaging company to identify the best way to flavor and package the supplement.
- In the nutrition industry, several main flavoring houses and packaging companies exist who make many dietary supplements for supplement companies.
- Most reputable dietary supplement manufacturers submit their production facilities to inspection from the FDA and adhere to GMP, which represent industry standards for good manufacturing of dietary supplements.
- Some companies also submit their products for independent testing by third-party companies to certify that their products meet label claims and that the product is free of various banned ingredients.
- More recently, companies have subjected their products for testing by third party companies to inspect for banned or unwanted substances.



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Product Development

- Upon identification of new nutrients or potential formulations, the next step is to contact raw ingredient suppliers to see if the nutrient is available, if it is affordable, how much of it can be sourced and what is the available purity.
- Sometimes, companies develop and pursue patents involving new processing and purification processes because the nutrient has not yet been extracted in a pure form or is not available in large quantities.
- Reputable raw material manufacturers conduct extensive tests to examine purity of their raw ingredients.
- When working on a new ingredient, companies often conduct series of toxicity studies on the new nutrient once a purified source has been identified.
- The company would then compile a safety dossier and communicate it to the FDA as a New Dietary Ingredient submission, with the hopes of it being allowed for lawful sale.

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Colombia Dietary Supplement Landscape

- According to Euromonitor, Colombia offers intriguing possibilities for dietary supplements.
- An executive summary of the 2017 report noted:

"Dietary supplements recorded healthy growth over the review period, with sales driven by Colombians increasingly looking to prevent the onset of cardiovascular diseases and joint and bone conditions, as well as generally age without any significant health problems".

- According to DPE International consultant, David Pineda Ereño:

"After Brazil and Mexico, Colombia is considered the most attractive market due to the continuous growth in the consumption of dietary supplements and also because the Colombia regulatory conditions provide some advantages in comparison with other countries within the Latin American region. … Colombian regulations refer to the US FDA, the European Union and Codex Alimentarious."

https://www.nutraingredients-usa.com/Article/2018/05/22/Colombia-s-growth-prospects-lenient-regulations-fuel-opportunity?utm_source=copyright&utm_medium=OnSite&utm_campaign=copyright

Colombia Dietary Supplement Landscape

- The market in Colombia is still in its infancy and lacks the category differentiation characterized by markets in North America, Europe, and Asia.
- General health remained the most important positioning in dietary supplements in 2017 with over half of sales followed by bone health and digestive health.
- Dietary supplements may carry nutrition and health claims as long as they are scientifically substantiated.
- There are efforts to harmonize regulations among Latin American countries and adherence to GMP's.
- The sports nutrition market is expanding with more international and Colombian companies entering the market.

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Summary

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- The FDA and FTC regulate dietary supplements in the U.S.
- Companies are required to have research to substantiate the safety and efficacy of dietary supplements.
- Companies are required to use GMP's and report adverse events.
- The FDA and DHHS can remove adulterated supplements and/or supplements deemed to increase health risk from the market.
- Many countries, including Colombia, follow U.S., Canada, European Union, and/or Asian standards.
- The dietary supplement landscape is expanding in Colombia.


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