August 16, 2023
Council for Responsible Nutrition Response

Council for Responsible Nutrition: Written Response Questions to GAO Inquiry

Safety of Prenatal Supplements, Job Code: 106689

1) *Can you provide an overview of CRN—including why CRN was formed and the purpose it serves?*

The Council for Responsible Nutrition (CRN), founded in 1973 and based in Washington, DC, is the leading trade association representing dietary supplement and functional food manufacturers and ingredient suppliers. CRN companies produce a large portion of the dietary supplements marketed in the United States and globally. Our member companies manufacture popular national brands as well as the store brands marketed by major supermarkets, drug stores and discount chains. These products also include those marketed through natural food stores and mainstream direct selling companies. CRN represents more than 200 companies that manufacture dietary ingredients and/or dietary supplements, or supply services to those suppliers and manufacturers. Our member companies are expected to comply with a host of federal and state regulations governing dietary supplements in the areas of manufacturing, marketing, quality control and safety. Our supplier and manufacturer member companies also agree to adhere to additional voluntary guidelines as well as to CRN's Code of Ethics. Learn more about us at www.crnusa.org.

2) *Why would a prenatal supplement manufacturer join CRN?*

    a. *What are the incentives for membership and what are the benefits that a company would receive for being a member?*

CRN members receive timely, valuable intelligence on developing issues critical to the industry and also have the opportunity to shape public policy related to the supplement industry. CRN is recognized as a strong voice for the industry, both proactively and responsively. As the leading trade association for the dietary supplement and functional food industry, CRN provides members with the most comprehensive representation of the supplement industry. Serving the dietary supplement industry since 1973, CRN offers specialized expertise in scientific, legislative, regulatory and communications disciplines in support of the industry and its consumers.

    b. *Approximately how many members do you have in dietary supplements in general and then specifically in terms of prenatal supplement manufacturers?*

As noted above in response to Question 1, CRN has more than 200 members that manufacture dietary supplements or ingredients, or that supply services to the dietary supplement industry. A list of CRN members can be found here. Of these 200 companies, approximately 65 manufacture dietary supplements and/or ingredients for dietary supplements.

Of these members, we do not specifically track what products they manufacture. CRN, however, maintains a dietary supplement database – the Supplement OWL. Members are required to include current supplement product labels in this database. A search of this database for "prenatal" returns 150 labels. Non-members are permitted to post labels to the database, so these labels are a mix of member and non-member products.

3) *Do you have a sense of how many dietary supplements on average are on the market?*

CRN does not maintain a list of all dietary supplements that are on the market, but as indicated above, requires our members to include all their products in the Supplement OWL. Since there are

manufacturers with products in the marketplace that are not members of CRN, we don't keep an official record of those products, unless the non-members voluntarily include their products in the Supplement OWL. The National Institutes of Health (NIH) maintains a database of dietary supplement labels (*i.e.,* Dietary Supplement Label Database (DSLD)). This could be a mix of current products on the market and discontinued products no longer being sold. According to the DSLD website, "It catalogs all information printed on labels of dietary supplement products sold in the United States. The database resulted from specific recommendations to NIH from Congress in 2004 that encouraged the Office [of Dietary Supplements] to develop, create, regularly update, maintain, and make available to government and research entities a database of all supplement labels sold in the United States." The DSLD can be accessed here.

a. *Do you know how many prenatal supplement products are on the market?*

We do not have this information but a review of the NIH DSLD and the CRN Supplement OWL provides an overview of the type and approximate number of products on the market.

4) *Can you expand on the "additional voluntary guidelines" mentioned on your website that your membership must adhere?*

There are a myriad of regulations and laws governing the dietary supplement industry and, in addition to following these requirements, CRN members voluntarily adhere to a number of principles and guidelines that have developed by CRN. The CRN Code of Ethics and a list of voluntary guidelines/best practices (and the guidelines/best practices themselves) are provided on our website and linked in this document.

a. *Is participation in the National Institute of Health's Dietary Supplement Label Database a requirement of member companies?*

Yes, through a member company's participation in the CRN Supplement OWL. Participation in the Supplement OWL is mandatory for CRN members and CRN provides publicly available label information from the Supplement OWL to the NIH DSLD.

i. *If not, are you aware of how many member companies voluntarily participate in the NIH Dietary Supplement Label Database?*

See above.

5) *What measures, if any, does CRN take to ensure that member organizations produce quality products and meet federal and state regulations?*

a. *Does CRN require manufacturers to report quality assurance test results of ingredients and final products?*

i. *If so, what are the guidelines for this testing by manufacturers?*

CRN reviews companies that manufacture dietary supplements and/or their ingredients before they join CRN. This review helps provide CRN with general assurances that the company has an understanding and respect for applicable legal and regulatory requirements, and safety considerations, such that the applicant genuinely would be able to commit to CRN's Code of Ethics and are in compliance with applicable laws. CRN's review includes a review of Food and Drug Administration (FDA) enforcement actions to determine if FDA has cited a company for violations of good manufacturing practice (GMP) legal requirements or other regulations that are enforced by

the agency. GMPs, described in more detail below in our answer to Question 6, govern how a dietary supplement product or ingredient is manufactured. These requirements are intended to ensure that a dietary supplement contains what the manufacturer intends it to contain. GMP regulations require testing of ingredients and finished products at different stages during the manufacturing process.

More information on CRN's membership policy can be found here.

6) *What quality assurance protocols for supplement and ingredient manufacturing do you commonly see from your member companies?*

    a. *Do these protocols generally differ between final product manufacturers and ingredient manufacturers?*

As noted above, dietary supplement products are subject to GMP legal requirements that ensure consistent and controlled manufacture of safe and quality dietary supplements. Manufacturers must (1) ensure that dietary supplements are produced using a master formula and in sanitary facilities; (2) set and meet specifications for their products related to identity, purity, quality, strength and composition; (3) establish controls to prevent contamination of ingredients and supplements; and (4) produce and keep master manufacturing records and batch production records to ensure the correct amount of dietary ingredients are used and that correct labels are applied to final products. The GMPs require manufacturers to establish specifications for raw materials (e.g., identity), finished products (e.g., levels of contaminants), in-process production, as well as for labeling and packaging, and to verify that the established specifications are met through appropriate testing or other procedures. Manufacturers must establish written protocols for all operations and maintain records to demonstrate that GMPs have been followed. Whether a company has followed appropriate GMP requirements is the subject of FDA manufacturing facility inspections. Dietary supplement GMP requirements are found in the Code of Federal Regulations (CFR) at 21 C.F.R Part 111.

Manufacturers of dietary ingredients are required to follow similar GMP practices – the Current Good Manufacturing Practice, Hazard Analysis, and Risk Based Preventive Controls for Human Food established at 21 C.F.R. Part 117. These requirements ensure the production of safe food and prevention of foodborne illness or injury. This rule emphasizes current good manufacturing practices; hazard analysis; preventive controls; supply chain program; and recordkeeping.

7) *How many member companies seek 3rd party verification of their supplements from the US Pharmacopeia or other external validation services such as NSF International?*

Supplement companies may seek third-party verification of their supplement products for a variety of reasons. For example, verification may help a company demonstrate that products meet retailer quality standards, or it can be used in marketing material to emphasize to consumers that a neutral third-party has reviewed the quality of the product.

Also of note, the Department of Defense (DoD) recognizes the importance of third-party verification. Specifically, the military is taking steps to ensure that servicemembers are using products that have been verified by one of four certification bodies. DoD's Consortium for Health and Military Performance (CHAMP) has developed a comprehensive program focused on dietary supplement use by the military. Operation Supplement Safety (OPSS) provides critical resources related to supplements, notably including a scorecard, where service members can answer several yes or no questions based on information from a supplement label. The first question asks if third party certification seals are present on the label; these include seals from the Banned Substances

Control Group (BSCG), Informed Sport, the National Science Foundation (NSF), and US Pharmacopeia (USP). The scorecard then tallies the number of "yes" responses and determines whether the supplement is safe for consumption.

8) *How do member manufacturers decide what vitamins and minerals to include in prenatal supplements?*

The formulation of a prenatal supplement takes into account scientific evidence on the impact of nutrients, including vitamins and minerals, on maternal and fetal health and development. Manufacturers also consider medical and scientific authoritative body recommendations, such as the American Academy of Pediatrics. Additionally, data on the amount of nutrients consumed from food sources by pregnant people help manufacturers identify nutrient gaps that could potentially be filled by prenatal supplementation. Technical factors (*e.g.*, ingredient-ingredient or ingredient-matrix interactions, chemistry, processing parameters like time, shear, and temperature, stability) are also taken into consideration when developing a prenatal formula.

9) *How, if at all, does CRN interact differently with final product manufacturers compared to ingredient manufacturers?*

The CRN membership and other standards for final product manufacturers and ingredient suppliers are the same. Both types of members are subject to the same type of new member review and adhere to the Code of Ethics and follow the other guidelines discussed above.

10) *What concerns do your member companies have and what challenges do they face regarding the manufacturing or validation testing of prenatal supplements?*

Dietary supplements, including prenatal supplements, are sometimes limited in their formulations due to their delivery format. For example, calcium can add undesired bulk to a tablet, which in prenatal formulations can contain 20 or more nutrients. This bulk can reduce consumer appeal and swallowability.

To meet consumer preference for alternative delivery formats, industry has developed innovative delivery formats such as gummies. A challenge associated with manufacturing prenatal dietary supplements in gummy form is selecting nutrients that can be delivered in meaningful amounts and still taste good. For example, iron has a metallic taste, fish oil providing omega-3 fatty acids taste fishy, and vitamin B1, vitamin B2, and choline do not taste good. Additionally, some nutrients can interact with each other or with the gummy matrix, e.g., iron is a pro-oxidant for fish oil.

Prenatal supplements are complex formulations containing a broad array of nutrients often including vitamins, minerals, fatty acids, and other actives. Dietary supplement manufacturers have a responsibility to ensure that all actives are delivered at label claim through the entire product shelf life. Given the complexity of prenatal formulations, this often requires analytical methods that are optimized for the specific product matrix. Analytical variability between testing laboratories is also a challenge.

With respect to analytical testing of prenatal supplements in gummy form, there are challenges associated with sample preparation prior to testing. These include separation from the gummy matrix, solubility issues, and uniformity concerns, since there is a need to have a representative sample for testing.

a. *Members of CRN have publicly backed legislation that would require manufacturers to register with the FDA as a means to provide FDA with better oversight over the market of dietary supplements. Why did CRN back this legislation?*

CRN is a longtime supporter of FDA's calls for a federal dietary supplement listing program as a critical new tool for the agency, retailers, and consumers offering more transparency of the dietary supplement marketplace in the US. CRN's Board of Directors, which drives the association's policies and legislative strategy, has repeatedly endorsed both the general policy and the specific legislative aspects of a dietary supplement product registry for several years. As referenced above, CRN launched in 2017, and manages, the Supplement OWL as a model of a product registry. Participation in the database is required for CRN members who market supplements in the U.S. – but many non-member companies voluntarily submit their labels to the database as well.

b. *Is CRN aware of additional legislation in the works?*

CRN will continue to work with elected officials to support a dietary supplement listing program that will advance FDA's oversight of the marketplace and demonstrate the industry's commitment to be held accountable among retailers and consumers, but we are not aware of any impending specific legislation at this time.

c. *What else, in your opinion, could be done to ensure appropriate oversight of dietary supplements—specifically prenatal supplements?*

CRN is committed to transparency and believes that providing the agency with a federal dietary supplement listing database is an important first step. Without proper insight into what products are actually on the market, FDA could be stymied to enforce their existing authority against illegal, adulterated or misbranded products.

11) *How, if at all, does CRN coordinate with federal agencies, such as FDA, or other expert groups regarding prenatal supplements?*

CRN regularly engages with federal agencies and expert groups regarding prenatal supplements and nutrition. A few examples are described below.

CRN develops science-based self-regulatory initiatives that reflect expert group recommendations. In 2015, CRN issued guidelines, "Iodine Quantity in Multivitamin/Mineral Supplements for Pregnancy and Lactation," recommending dietary supplement manufacturers and marketers to include a daily serving of at least 150 mcg of iodine in all multivitamin/mineral supplements intended for pregnant and lactating women in the U.S. These guidelines were developed in response to recommendations from authoritative medical organizations, including the American Academy of Pediatrics, the Endocrine Society, and the American Thyroid Association, that pregnant and lactating women receive a daily multivitamin/mineral supplement that contains 150 mcg of iodine. Adequate iodine is critical early in pregnancy when the fetal brain is growing rapidly.

CRN also engages in the Dietary Guidelines for Americans (DGA) process each 5-year cycle, providing input supported by scientific data to help guide the development of the guidelines. For example, in comments regarding the 2020 – 2025 DGA, CRN encouraged USDA and HHS to ensure the guidelines reinforce current expert recommendations regarding nutrient supplementation during pregnancy, lactation, and birth to 24 months, as these life stages are critical periods of growth and development.

Another critical nutrient for early development is folic acid. Supplementation with folic acid is proven to prevent neural tube defects, and CRN has advocated for the U.S. Preventive Services Task Force (USPSTF) to maintain its recommendation that all women who are planning a pregnancy or are capable of becoming pregnant to supplement with 0.4 to 0.8 mg of folic acid to avoid experiencing this serious birth defect. Additionally, when FDA proposed lowering the Daily Value for folic acid on the Nutrition and Supplement Facts label, CRN advocated for maintaining the Daily Value of 400 mcg, which is the amount recommended by numerous health organizations for women of childbearing age.

Since prenatal dietary supplements play a key role in maternal health and in fetal/infant development, it is important to ensure appropriate regulatory federal regulatory resources are directed to this category. In 2016, CRN strongly supported the elevation of the former Division of Dietary Supplements into an Office, a designation that brought more priority to FDA's oversight. Since then, the industry has successfully lobbied Congress to more than double annual funding to the Office of Dietary Supplement Programs (ODSP) to assure increasing attention and enforcement. However, FDA's proposed reorganization of its Human Foods Program would eliminate ODSP under the current Center for Food Safety and Applied Nutrition. FDA proposes to insert the regulation of dietary supplements into a new combined office that will be called the Office of Food Chemical Safety, Dietary Supplements and Innovation. This apparent downgrade means less attention and priorities will be given to dietary supplements, including prenatal supplements.

12) Are there any other experts or agencies you would recommend we talk to about prenatal supplements?

We recommend discussing prenatal supplements with Vitamin Angels, which is a non-profit organization that is working to increase access to prenatal vitamins and minerals. https://vitaminangels.org/our-work/interventions/prenatal-vitamins-and-minerals/

We also recommend the Association of Official Analytical Chemists as a resource to discuss challenges associated with analytical testing.