Council for Responsible Nutrition
1828 L Street, NW, Suite 510 • Washington, DC 20036-5114
(202) 204-7700 • fax (202) 204-7701 • www.crnusa.org

September 22, 2014

VIA ELECTRONIC SUBMISSION

Natural Health Product Supplement Bill
Ministry of Health
Wellington, New Zealand

Re: Natural Health Product Supplement Bill

CRN is the leading trade association for the dietary supplement and nutritional products industry, representing manufacturers of dietary ingredients and of national brand name and private label dietary supplements[1], many of which are multinational and already actively selling ingredients, finished products and services into New Zealand.

The Council for Responsible Nutrition (CRN) respectfully submits these comments to the Ministry of Health, New Zealand on the proposed Natural Health Product Supplement Bill, Government Bill 324-2, As reported from the Health Committee related to the following section:

Permitted Ingredients

> **20 Permitted ingredients**
>
> (1) The Authority may, for the purpose of this Act, declare any substance that is, or belongs to any class of substance, listed in Schedule 1 to be a permitted ingredient in a natural health and supplementary product.
>
> (2) The Authority may impose restrictions on the use of any substance it has declared to be a permitted ingredient.

[1] The Council for Responsible Nutrition (CRN), founded in 1973 and based in Washington, D.C., is the leading trade association representing dietary supplement 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 100 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.

(3) In considering whether a substance should be declared a permitted ingredient, the Authority—

(a) may conduct a safety assessment of the substance; and

(b) must have regard and give weight to, as it considers appropriate, the following:

(i) whether a recognised authority permits the use of the substance in a similar product and, if so, whether it imposes any restrictions on the use of the substance:

(ii) whether the substance is recognised in traditional medicine or pharmacopoeias:

(iii) any other matter that the Authority considers relevant in the circumstances.

(4) Every substance declared to be a permitted ingredient must be listed on the database along with any restrictions on the use of the substance.

(5) A declaration made under this section must be published on an Internet site maintained by or on behalf of the Authority.

(6) The Authority must, as soon as practicable after making any declaration under this section, arrange for publication in the *Gazette* of a notice indicating that the declaration has been made and include in the notice details of the Internet site on which the declaration is published.

(7) In this section, similar products means products that (however described) are the same type of products as natural health and supplementary products.

CRN in the spirit of the Ministry of Health requests to "Protect consumers" and "Promote trade" by enacting a NHSP Bill that (1) provides "low risk natural health products"; (2) provides "inexpensive" natural health products; (3) via a "light touch [regulatory] regime"; (4) that is "easy to use"; respectfully submits the following request when it comes to making a definitive list of "permitted ingredients".

In the United States, "active" dietary supplement ingredients, termed either old ("grandfathered") or new dietary ingredients (NDI) are permitted after they have been submitted in dossier form to the US FDA. "Inactive" ingredients may be drawn from permitted food ingredients that have either gone through an US FDA food additive petition or have successfully been Generally Recognized As Safe (GRAS) self-affirmed, with or without subsequent notification to the US FDA. Given the level of safety information required for both New Dietary Ingredient submissions and for GRAS self-affirmations with FDA notification, when either of these scenarios results in the FDA publically issuing a response of for NDI's[2] and for

[2] FDA will issue a letter of acknowledgement without objection.

GRAS self-affirmations with notifications[3], then it is reasonable to conclude that a rigorous evaluation has been conducted by Agency regulatory experts.

In short an unique / novel ingredient that is to be used in either a food additive application (via GRAS) or in a dietary supplement formulation (via NDI) must be established as safe for the intended use (concentration and exposure). A food ingredient must be reasonably certain to be safe for everyone at every exposure level for a lifetime. A dietary supplement containing a new dietary ingredient is a voluntary purchase (self-selected exposure and can stop or decrease exposure if idiosyncratic reactions occurs) and may be seasonal or sporadic and there are dosing instructions (amount per dosage form per day). A dietary supplement cannot represent itself as an item of food; therefore cannot to be used as a part of the daily caloric meals.

CRN respectfully requests that the Ministry of Health, Government of New Zealand, to include ingredients onto the "permitted ingredients" list that have been successfully determined to be "Generally Recognized As Safe (GRAS)" and/or "New Dietary Ingredients (NDI)."

[3] FDA will issue a letter stating that "FDA has no questions"

BACKGROUND

Food Ingredients

For novel food ingredients, the company-sponsored Generally Recognized As Safe determination can be conducted and marketing can occur without the FDA being notified. This is termed a GRAS self-determination and is often undertaken to protect trade secret use of a novel ingredient. Even with the self-affirmation (non FDA notification) the GRAS Expert Panel will still demand that the pivotal safety information be in the public domain (i.e., via peer-reviewed published studies), the inherent toxicity profile, the "hazard" be clearly ascertained, and the exposure projections be understood when making the final risk determination for safe use at the intended exposure level. There is no requirement that this self-affirmation be made public or the decision be submitted to any authority; however, at least one consultant has begun to track and publish these GRAS self-affirmations on a web-site entitled "GRAS Self-determination Inventory Database"[4]. The source of the information found in this database is the result of a search of information available in the public domain, primarily based upon articles in industry trade journals both in print and electronic versions. The information in this database has not been verified and instead it is simply reported as found in the public domain. Neither is this database complete as the compiler may not be aware of all GRAS Self-determinations that have been conducted. The *Food Chemicals Codex* has also instituted a section of food ingredients entitled "Provisional Monographs" to capture specifications, analytical assays, and acceptance criteria for food ingredients that are GRAS self-affirmed and not (or not yet) notified to the FDA. The down-side to such a course of action, would be the risk a company takes if contradictory information or contradictory scientific opinion would call such a GRAS determination into question, such that the company is forced to defend their GRAS self-determination, deal with financial and brand repercussions and lost market share during a recall or other bad press responses. To alleviate this risk, more reputable companies, or more risk-averse companies take the additional step to notify the FDA of the GRAS determination, and to submit all relevant data (safety and exposure) that was used by the GRAS Expert Panel. The FDA after reviewing the submission, will issue a letter to the notifier indicating that at that point in time, the FDA does

[4] http://www.aibmr.com/resources/GRAS-database.php

not have any questions surrounding the company's GRAS decision. These actions are published electronically on the GRAS list[5]

New Dietary Ingredient

A new dietary ingredient must be notified to the FDA prior to the anticipated market entry of a product containing the NDI. The submission must contain, as with a GRAS notification, the pertinent safety and exposure information demonstrating that the ingredient will not cause adverse effects when consumed per the dosing instructions. That is the dietary ingredient must reasonably be expected to cause no harm under the conditions of use. Within 75 days after the notification, you may expect a letter from the FDA acknowledging receipt of the notification and stating the date on which the notification was filed. Examples of the types of response letters FDA commonly sends include, but are not limited to: (1) a letter of acknowledgement without objection; (2) a letter listing deficiencies that make the notification incomplete; (3) a letter raising safety concerns based on information in the notification or identifying gaps in the history of use or other evidence of safety; and (4) a letter raising other regulatory issues. The letter may contain information about the Agency's review of your notification, and it may ask you to submit additional information if your notification is incomplete or raises safety questions.

Safety

Discernment of a potential ingredient's safety depends on two primary factors: (1) inherent hazard (actual toxicity per unit of measurement, i.e., mg/kg; ppm, etc.) and exposure (the amount consumed in comparison to the amount with known toxic effects). Everything is toxic, and by corollary, everything can also be non-toxic, it just depends upon the dose (exposure). When experts deliberate and make judgment on the potential for human toxicity, they develop both of these values, the inherent toxicity of the ingredient determined by relevant, well-conducted and scientifically-acceptable in vivo and in vitro studies sufficient to characterize that hazard, as well as a calculation on exposure, i.e., how much will be used in the food or dietary supplement product and how much of that product will be consumed per unit of time (usually per day). Food ingredients must have a more comprehensive battery of safety studies,

[5] http://www.accessdata.fda.gov/scripts/fdcc/index.cfm?set=GRASNotices&sort=GRN_No&order=DESC&startrow=1&type=basic&search=).

as it is impossible to gauge or estimate how much can be selectively chosen and eaten per day. If the novel ingredient is added to potato chips….one could estimate the amount of potato chips a normal (50^{th} percentile, center of a bell-shaped Gaussian curve) consumer might consume per day…but it must be safe for the unusual consumer (termed the 90^{th} or 95^{th} percentile consumer) who will eat these potato chips at the far right side of the curve.

Dietary ingredients could have a more abbreviated amount of safety information, i.e., less long-term chronic animal studies and maybe fewer esoteric end-points because overall exposure would be expected to be significantly less, less per day, less occasions per year, and only a limited portion of a lifetime. Further, dosing instructions are clearly labeled on a dietary supplement container and it is unlikely that a consumer of these products will overdose on many multiples of the daily dose of these types of products. Palatability might be an issue, as well as cost, uncomfortable nuisance side-effects, etc. However, there still must be significant conservatism built into the safety analysis such that even a very unusual very high consumer of a dietary ingredient would remain unharmed if binging on selective products.

Toxicity information usually generated

It is the wisdom and expertise of the scientific experts that determine exactly what toxicity information is needed, and the levels of statistical significance and germane end-points. The scientific experts, whether the independent GRAS Expert Panel, the Agency toxicology reviewers, the company in-house or hired expert consultants; they all must have sufficient training and capabilities to render a judgment on the safe use of the ingredient in accordance with the exposure contemplated. The higher the exposure and/or the lower the dose with some adverse effects, the more clearly the inherent toxicity most be discerned. At a minimum, for most novel food ingredients and new dietary ingredients, the experts would want to see well-conducted, acute, sub-chronic, and in vitro genetic toxicity assays. Multiple rodent and non-rodent species may also be needed depending upon nuances of the inherent hazard. Higher exposure would also dictate full-blown chronic studies, reproductive and developmental toxicity studies, metabolic fate studies, and other unique end-points in line with the targeted market demographics. Use by children (infants), pregnant and lactating women, geriatrics, active teenagers, etc., all might command specific toxicity studies and/or additional end points to be

evaluated. Human test subjects may be utilized to examine digestive actions (and reactions) and other potential nuisance effects. It goes without saying that the studies must be performed by a reputable laboratory with sufficient test animals to reach statistical significance. For GRAS determinations, the pivotal safety studies must be made public (i.e., published in a peer-reviewed scientific journal) so that anyone with contradictory data, or reliable information opposing the safety data can voice an objection. That is the basis for "general recognition". For NDI submissions to the Agency, the pivotal data must accompany the submission so that the FDA reviewers can make a similar analysis.

The US FDA safety reviewers rely upon an Agency-developed guidance document that is used by the Center for Food Safety and Applied Nutrition (CFSAN) to recommend the quality and quantity of safety studies that the Agency feels is scientifically appropriate to ascertain relevant safety, based on inherent "hazard" and proposed "exposure". This is what the Agency recommends to the submitter, and what the Agency will use to judge the quality and quantity of the submitted safety data. The original guidance document was released in 1982, with a subsequent second edition hard copy in 1993, followed in 2000 with an electronic version continuously reviewed and updated. It is entitled "*Guidance for Industry and Other Stakeholders: Toxicological Principles for the Safety Assessment of Food Ingredients*" (also known as *Redbook 2000*)[6].

Although this large compendium of relevant toxicity studies is only directly intended for manufactures submitting a bona fide Food Additive Petition (FAP) to FDA for premarket review for a novel food ingredient, it is also the "expected" internal resource that would be used by Agency toxicology reviewers who might be tasked with examining GRAS self-affirmed with FDA notification (GRASN) food ingredients, as well as New Dietary Ingredient Notifications (NDIN), as all of these submissions, FAP, GRASN and NDIN would come into the FDA Center for Food Safety and Applied Nutrition, the author of the aforementioned Redbook guidance. In the preface to the current electronic *Redbook 2000*, it states "This document delineates the toxicology information deemed appropriate for assessing the safety of direct food additives and color additives used in food," which would also conceptually include dietary supplement ingredients and GRAS notified ingredients as they are legally and from a regulatory purview,

[6] http://www.fda.gov/downloads/Food/GuidanceRegulation/UCM222779.pdf

part of the food category. This guidance document is the most transparent window into what the FDA uses when making their responses to GRASN and NDIN submissions and allow these ingredients on the market with no further Agency activity or call for data.

Conclusion

Even though the introduction of a novel dietary ingredient follows a different path of regulatory approval than a novel food ingredient, there are indeed parallel demands that the new ingredient in either category be demonstrated as safe to virtually all consumers under the conditions of intended use (exposure). There is no difference in the quality of the scientific studies to assure safety, but there may be differences in quantity, based on the expected human exposure. As previously discussed, it is hard to predict or control all aspects or levels of exposure for a novel food ingredient…there are consumers who will binge on a product and consume very high levels, day after day or even for years and years. Safe use must be built into the use of such an ingredient to cover every scenario. A new dietary ingredient must be found equally safe, with the understanding that overall daily or chronic exposure will be tempered by the use pattern (sporadic, seasonal, specific life-stage) and the recommended dosing instructions. Food ingredients and dietary ingredients are thus equally safe under their respective conditions of use.

Respectfully submitted,

James C Griffiths, Ph.D., DABT, FSB, CFS
Vice President, Scientific & International Affairs