A Legal and Regulatory Overview of Dietary Supplements

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A previous edition of our China Practice Newsletter included an article addressing many of the regulatory and legal issues surrounding cosmetics (See Holland & Knight's China Practice Newsletter: May-June 2019). This article provides similar information with respect to dietary supplements.

WHAT IS A DIETARY SUPPLEMENT?

Dietary supplements occupy a unique place in the regulatory scheme administered by the U.S. Food and Drug Administration (FDA). Many of them have the visual appearance of drugs, because they are usually in the form of tablets or capsules that are packaged in the kinds of bottles associated with over-the-counter pharmaceuticals. From a regulatory perspective, however, they are much closer to food than to drugs. The key to understanding the basics of dietary supplements is to appreciate that the two main points from a legal perspective are 1) what's in the bottle (the ingredients) and 2) what's on the bottle (the label). Integrity of the manufacturing process is also important, but this is more of a process issue mostly overseen by regulatory personnel (not by lawyers).

As suggested by the word "supplement," a dietary supplement must not be represented as conventional food or as the sole item of a meal. For example, a nutrition bar would not qualify as a dietary supplement because it is a conventional food, and a meal-replacement beverage would not qualify as a dietary supplement because it is represented as the sole item of a meal. Accordingly, these items are each regulated as food, not as dietary supplements.

The nutritionally active ingredient of a dietary supplement is called a "dietary ingredient" (discussed below). A supplement can have a single dietary ingredient, or a combination of them (as in the case of multivitamins).

The law specifies what types of ingredients are permitted as dietary ingredients. It also specifies what types of dietary ingredients are prohibited.

WHAT ARE PERMITTED DIETARY INGREDIENTS?

The statute governing dietary supplements defines "dietary ingredient" as a vitamin; mineral; herb or other botanical; amino acid; dietary substance for use by man to supplement the diet by increasing the total dietary intake; or a concentrate, metabolite, constituent, extract, or combination of these. Examples include conventional vitamins and minerals (vitamin C, vitamin E, folic acid, iron, magnesium, and zinc); food items often used in cooking such as garlic, green tea and turmeric; less common food items such as cranberry extract and fish oil; and extracts of purportedly medicinal plants such as ginkgo biloba, St. John's wort (*hypericum perforatum*) and saw palmetto (*serenoa repens*). Weight-loss supplements generally contain combinations of caffeine and botanicals. Sports nutrition supplements include protein powders, creatine and purported testosterone boosters.

The dietary ingredient must also satisfy one of the following three conditions:

1. it was lawfully marketed as a dietary ingredient in the United States before October 15, 1994

2. it has been present in the food supply as an article used in food, and is used as a dietary ingredient in the same form (no chemical alteration), or

3. it has a history of use or other evidence of safety establishing that when used as specified on the label, it reasonably will be expected to be safe; and the manufacturer has given the FDA at least 75 days prior notice before the product is sold

As can be seen, the first category is a "grandfather" provision that permits the continued sale of dietary ingredients that were lawfully on the market before the current statute took effect, and the second permits the use as a dietary ingredient of something that is already used as a conventional food. However, it can be difficult to determine if a particular dietary ingredient is permitted under the grandfather provision, because there is no official list of dietary ingredients that were lawfully used in dietary supplements before October 15, 1994. It is the manufacturer's responsibility to determine if this was the case. If this cannot be done, and if the second condition (has been used as a conventional food) is not satisfied either, the manufacture should provide advance notice to the FDA to qualify it under the third category.

The third category is the way in which a manufacturer can introduce new dietary ingredients, or use a dietary ingredient that cannot be shown to have been on the market in a supplement before October 15, 1994. As can be seen, there is no requirement for FDA approval of new dietary ingredients, just the manufacturer's submission to the FDA of its intent to begin sale. The submission must also include the basis on which the manufacturer has concluded that the dietary ingredient is safe.

Although the requirements to introduce a new dietary ingredient are relatively lax, not every potential new ingredient will pass muster. As an example, the FDA took action in 2016 against manufacturers of dietary supplements for weight loss that contained the new dietary ingredient *acacia rigidula* (also known as *vachellia rigidula*, blackbrush acacia or chaparro prieto), which is a botanical for which there was no evidence of prior use and for which no advance submission had been made. It is unclear what position FDA would have taken if the manufacturers of these products had made an advance submission, but it appears that no such submission has been made as of the date that this article was prepared in Winter 2019.

The advance submission can made electronically through a portal accessible via the FDA website, which also contains instructions on how to submit them.

WHAT ARE PROHIBITED DIETARY INGREDIENTS?

Generally, a dietary supplement must not contain an ingredient that has been approved in the U.S. as a drug, or that has not yet been approved but is in clinical trials for possible future approval. An exception to this rule is if the ingredient had already been in use as a dietary supplement before it was approved as a drug. For example, fish oil was approved in 2004 as a drug (under the generic name of "ethyl esters of omega-3 fatty acids"), but had already been in use as in dietary supplements well before that, so it may continue as such.

Another exception, which is rarely if ever used, is if the FDA makes an official determination that a drug product may also be used as a dietary supplement. Persons interested in approval of cannabidiol (CBD) as a dietary ingredient may pursue this approach, which would be necessary because it was not lawfully sold as a supplement before it was approved by the FDA as a drug.

The statute governing dietary supplements also prohibits generally the sale of adulterated items. By definition, a dietary supplement is adulterated if it contains a dietary ingredient "that presents a significant or unreasonable risk of illness or injury under the conditions of use recommended or suggested in the labeling." As an example of the FDA's use of this provision to address safety issues, the FDA took action in 2018 against sellers of pure caffeine powder, which had a suggested serving size of 1/16 teaspoon or no more than 200 mg,

in part because consumers could not be expected to reliably measure such tiny amounts, and even modest overages in measurement could result in a toxic dose of caffeine.

WHAT ARE THE LABEL REQUIREMENTS?

The statute and regulations control what must be on the label and what must not be on the label.

A dietary supplement must be labeled with the phrase "dietary supplement." The label must also include 1) a statement of identity; 2) the net quantity of contents; 3) nutrition labeling (supplement facts) in a prescribed format; 4) a list of the ingredients; and 5) the name and address of the manufacturer, packer or distributor. There are specific standards for how to present this information, and additional rules for different categories of products. They are not difficult to comply with, but are very detailed and should be followed without deviation.

The most common violation of the labeling rules appears to be including a claim which states (or suggests) that the dietary supplement is useful to treat or prevent a disease. As readers of our cosmetics article may recall, there is a similar issue for cosmetic labeling. In both cases, a label (or advertisement, including statements on a website) that makes a disease claim has the undesired effect of turning what would be a supplement or cosmetic into an item that is regulated as a drug. And because no supplement (or cosmetic) that is formulated, manufactured and labeled as such will ever be in compliance with the law governing drugs, the result is a violation of multiple sections of the law governing drugs.

In the case of supplements, the line between permitted and prohibited claims blurs, because "disease" claims are prohibited but "structure/function" claims are permitted (with qualifications). For example, "relieves sadness" and "prevents rashes" are disease claims, while "supports a healthy mood" and "promotes skin health" are structure/function claims. Similarly, "helps prevent the common cold" is a disease claim, while "supports the immune system" is a structure/function claim. Many have questioned the wisdom of such distinctions, finding them nonsensical.

At the threshold, a good way to avoid inadvertently turning one's supplement into a drug by making an impermissible disease claim is to avoid the use of any medical or clinical term, or the name of any disease or ailment (even a colloquial or layperson's term). For example, do not use words such as ache, allergy, arthritis, asthma, blister, cancer, depression, diabetes, diarrhea, eczema, fever, headache, heartburn, hypertension, indigestion, infection, itch, pain, rash or ulcer. Next, avoid words such as cure, prevent, reduce, treat or stop.

The typical (permissible) structure/function claim uses the words "supports" and "healthy." Examples include "supports healthy joints" or "supports joint health," and "supports prostate health" or "supports a healthy immune system." Finally, when using a structure/function claim, the label must include the following disclaimer verbatim (in singular or plural, corresponding to the number of claims):

> "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," or
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> "These statements have not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease."

A manufacturer that use a structure/function claim must have substantiation that the claim is truthful and not misleading, and must submit to the FDA a notification with the text of the claim not more than 30 days after it is first used in the market place. As indicated by the required disclaimer, the FDA's failure to object to these notifications does indicate that it has approved them.

Finally, as noted above, there are also formal rules governing many aspects of the labeling, such as how to name ingredients, how to present the supplement facts, and such.

WHAT ABOUT MANUFACTURING?

Dietary supplements must be manufactured in accordance with current good manufacturing practices (cGMP) that are specified in regulations adopted by the FDA. A detailed review of them is beyond the scope of this article, and most involve process requirements that are usually handled by regulatory professionals (not by lawyers).

One area that deserves mention, however, is the problem of overreliance on a supplier's certificate of analysis. For example, most manufacturers of dietary supplements obtain their raw materials from other companies. These materials include both the dietary ingredients and the inactive ingredients (excipients) such as binders, disintegrants, lubricants and other tableting aids. Ingredients are oftentimes sourced through brokers or other intermediaries, and not purchased directly from the actual manufacturer.

In the case of dietary ingredients, the cGMPs do not permit the supplement manufacturer to rely solely on the certificate of analysis provided by the ingredient supplier to substantiate the ingredient's identity. Rather, the manufacturer must conduct "at least one appropriate test or examination" to verify the identity of dietary ingredients, unless a specific exemption has been sought and granted by the FDA. The cGMP regulations do not specify what tests must be conducted, and state that it is the manufacturer's responsibility to determine the appropriate test(s) or examination(s). However, they also provide that the tests and examinations "are appropriate, scientifically valid methods" that must include at least one of "(i) gross organoleptic analysis; (ii) macroscopic analysis; (iii) microscopic analysis; (iv) chemical analysis; or (v) other scientifically valid methods." Thus, the manufacturer must have in place some reliable, documented method to verify the identity of each dietary ingredient that will be included in its supplements.

IS CANNABIDIOL (CBD) A PERMITTED DIETARY INGREDIENT?

In a word, "No." As of this writing (Winter 2019), cannabidiol (CBD) is not permitted in dietary supplements. The reason is the prohibition against using as dietary ingredients a substance that is approved in the U.S. as a drug, unless it was already being lawfully used as a supplement before approval as a drug (and before public knowledge of clinical studies being conducted in furtherance of an application for approval as a drug).

Here, the issue is that cannabidiol was approved as a drug in the U.S. in September 2018; the brand name is Epidiolex. It was publicly known well before that date that the pharmaceutical company developing this product was conducting clinical studies of it to treat rare forms of childhood epilepsy. And even if cannabidiol had been marketed in the U.S. as a dietary supplement before the existence of these studies became publicly known, it would not have been lawfully marketed because until a change in the law that took effect in 2018, extracts of the cannabis plant (also called marijuana) were illegal drugs. Thus, even though cannabidiol would qualify as a dietary ingredient in the abstract (as a constituent or extract of a botanical), it is excluded because it has been approved by the FDA as a drug.

As noted above, the FDA has authority to grant exceptions to this rule on a case-by-case basis. There is significant public and political pressure for the FDA to do this in the case of cannabidiol, which is perceived in the popular imagination as a remedy for everything from anxiety to diabetes to hypertension to Parkinson's disease. Paradoxically, this clamor for access to cannabidiol for purposes that are clearly for the treatment of diseases — which is exactly the type of use that is not permitted for dietary supplements — may weigh against the goal sought by these proponents of cannabidiol.

Notwithstanding the prohibition on use of cannabidiol in dietary supplements, dozens if not hundreds of CBD products are openly sold as dietary supplements in stores and online. The FDA has sent warning letters that primarily focus on drug claims for CBD products, i.e., claims that these products are useful for serious diseases. As of Winter 2019, the FDA has not pursued large-scale enforcement programs against companies selling CBD products without improper disease claims. The general lack of action does not mean that sales of these products as dietary supplements is legal — it is not — nor does it mean that no large-scale actions will be taken in the future. Additionally, companies attempting to import CBD products into the U.S. run the risk of having them refused admission and potentially destroyed by customs officials.