

Why RCTs Are Key to Substantiating Claims

by Latesha Richards

Health claims and structure/function claims communicate the benefits of dietary supplements and foods on product labels, and are often the subjects of statements made in television, Internet and print advertisements, direct marketing material and other publicly available information. But what is the substantiation standard allowing for lawful advertising of these claims? FTC has always applied a flexible approach to substantiating claims with “competent and reliable scientific evidence.” However, two consent orders this past summer set a standard for substantiating disease claims. They mandated conducting “at least two adequate and well-controlled human clinical studies...” on the product in question or an equivalent product. While these consent orders refer to disease prevention claims, the randomized, controlled trial (RCT) standard can also be extended to structure/function claims on novel products.

RCT Standards for Substantiating Health Claims

Two novel product manufacturers received letters from FDA that warned them against making explicit claims online or in labeling that their food and dietary supplements can mitigate, treat and prevent disease, as that positions the products as misbranded foods or unapproved drugs. By the summer of 2010, FTC further alleged these companies made claims that were scientifically unsubstantiated and, therefore, false and misleading to consumers.^{1,2} Both cases were brought to and settled in U.S. District Courts with the companies agreeing to pay hefty fines in addition to either ceasing making the claims altogether or substantiating them with “at least two adequate and well-controlled human clinical studies.” In addition, the court orders made clear that along with seeking FDA pre-approval for those health claims, the two human studies must be randomized, double blind and placebo-controlled on the products in question or “Essentially Equivalent Products” and conducted by independent researchers.

RCTs are not mandated for structure/function claims; however, since it is considered the “gold standard” and the most reliable form of evidence to FTC, the same proposal can be extended to support and strengthen purely worded structure/function claims and implied disease claims made on novel products.

Why the Standard is Useful

First, FDA will consider novel products as new drugs because, by definition, novel products contain new dietary ingredients (NDIs) that include whole herbs or their extracts, single-enhanced ingredients, combination ingredients, ingredients used in excess or any other ingredient that isn't GRAS (generally recognized as safe) or effective in the

medical/scientific community.³ For example, consider an advertising [structure/function] claim for an herbal Echinacea infusion in a beverage product: “Echinacea will help support the immune system.” Normally, this structure/function claim can be made; however, since Echinacea isn't GRAS and is not approved as a food additive, any claim for this product may not be allowed because the Echinacea product would be considered a new drug. And new drugs cannot be legally marketed without prior approval. Thus, RCTs to substantiate the safety of the herb, and that the dosage of Echinacea in the beverage is safe for consumption and sufficient enough to have the claimed effect would still be necessary for FDA approval and advertising purposes.

Second, claims don't always have to be worded as explicit disease claims to require rigorous substantiation. The claim “Anthocyanins in blueberries will prevent macular degeneration” is an obvious disease claim. However, many structure/function claims can be worded (usually unintentionally) to convey a similar idea, but may imply disease benefit or prevention. Words such as “maintain,” “support,” “improve,” “enhance,” “reduce,” “fight,” “promote,” “protect” or any other word coupled with specific references to signs or symptoms of disease, abnormal conditions or adverse events may be likely to imply a disease prevention or treatment benefit.⁴ For example, the advertising [structure/function] claim: “Anthocyanins in blueberries help support healthy eye sight” can be nuanced to state an implied disease prevention/treatment advertising claim: “Anthocyanins in blueberries may help restore vision back to normal” or “Anthocyanins in blueberries may help support the body's ability to stave off vision degeneration.” If a food company wanted to formulate a beverage with an anthocyanin isolate and make any of those disease prevention/treatment advertising claims, well-controlled human clinical trials would be necessary to substantiate the claim, in addition to seeking FDA pre-approval and peer-reviewed scientific literature on safety.

Third, concerns about safety from multi-ingredient interactions, ingredient dosages and efficacy of novel products would require support beyond borrowed research on individual ingredients, and into product-specific RCTs. Additionally, concerns about efficacy arise when an ingredient is being used in another dosage or application. An active compound delivered as a tablet, for example, may produce an entirely different effect than the compound delivered as a beverage. If the research does not address an equivalent product, which FTC defined in the 2010 court orders referenced earlier as “a product that contains the identical ingredients, except for inactive ingredients in the same form and dosage, and with the same route of administration as

the Covered Product," support for product claims must come from product-specific/proprietary RCTs.

Strengths of RCTs and Independent Researchers

RCTs are the most rigorous methodology that will best substantiate a claim, in that they provide the strongest and most reliable evidence that the probability of a product's attributes or claimed benefits are true and likely upon human consumption.

The words "randomized," "double blind" and "placebo-controlled" all have significant meaning in understanding why this methodology provides the strongest evidence. Randomizing a clinical trial involves randomly assigning each participating subject to either the treatment arm or control arm. The placebo control, a substance that does not contain the active ingredient(s) under study, defines a baseline for the trial. If the active product has an effect, that effect can be defined by comparison to the untreated placebo control group. Furthermore, double blinding a trial so neither clinical researcher nor subject knows if they are giving/receiving the active product or placebo eliminates the possibility of bias in recording and interpretation of results.⁵

Using independent researchers to conduct RCTs further enhances the statistical significance of the results of the trial. This helps increase the integrity of the results and is what makes claims backed by evidence from these trials difficult to refute. Thus, positive results from an RCT provide the strongest argument in favor of a claim. Other interventional studies, such as

retrospective analyses, clinical trials without placebo, meta analyses or other approaches are not as supportive and do not provide statistically significant data for substantiating health claims.

The settlements in these cases put a new RCT standard in place for companies looking to make health claims relating to disease prevention. Although companies making structure/function claims are not affected by this specific standard, the RCT is a standard to consider following since structure/function claims for novel products can imply disease prevention. For novel products to be differentiated among competitors, that may be easier said than done.

Therefore companies marketing novel products should work with independent researchers or third-party organizations such as clinical research organizations (CROs) to conduct RCTs and review the relevancy of their claims to the research. Investment in time and money must be made; but, conducting RCTs can not only mean trustworthy products and return on investment (ROI), but also fewer legal ramifications. □

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