

Evaluating an Immune Health Ingredient?

Ten questions to ask the researchers.

Immunity has emerged as a worldwide health concern, prompting food, beverage and supplement manufacturers to seek new ingredients that deliver real immune benefits to consumers. The challenge for manufacturers is evaluating the research behind the increasing number of ingredients that claim to enhance immune system function. At stake is dominance of the growing immune health market that spans virtually every product category. A 2007 Healthfocus International study of 32 countries on five continents identified interest in "immune benefits" as a global trend. In Western Europe, foods that boost the immune system rank in the top five topics that shoppers want to learn more about. The demand may be even stronger across the Atlantic. Fully 87% of Americans currently consume, or are interested in consuming, foods and beverages that improve immune system function, according to a 2008 survey by the International Food Information Council Foundation.

The opportunities for immune-enhancing products have triggered an increase in ingredient suppliers touting immune benefits. The quality of the research behind these claims falls all along the credibility spectrum. Several major US food manufacturers were criticized last year for touting immune health claims for beverages and vegetables based on vitamin content. While acknowledging that A, C, E and other vitamins are important for the functioning of many systems in the human body, a consumer group blasted the companies because there is little evidence to show that these vitamins would have any specific effect on a person's immune system. To separate the good science from the bad, the credible claims from the bogus, manufacturers would serve themselves well by asking the following 10 questions:

1. Is the research peer-reviewed? The peer-reviewed publication of study results in a technical journal remains the gold standard for research quality and credibility. Often, companies will cite data that was never peer-reviewed or published and, sometimes, research is presented at credible scientific conferences and the abstract gets published. Always review the depth and breadth of the published research supporting ingredient claims. Unpublished data can provide secondary support if the science has been firmly established by peer review.

2. What type of study was conducted? Latin phrases may provide an air of validity to a study, but there is a wide gap in the significance of research conducted *in vitro*, *in vivo* and *ex vivo*. *In vitro* studies are done in a Petri dish or test tube. *In vivo* studies are conducted inside a living plant or animal and *ex vivo* studies involve living tissue studied outside the host and in a sterile environment. As a rule of thumb, preclinical *in vivo* (animal) studies and controlled human clinical studies most closely replicate what occurs in the human body. If conducted in animals, the more closely the animal species and human physiology match, the more significant a study.

3. Did the study measure biomarkers? Many immunity studies focus on human biomarkers. Biomarkers can provide evidence of change within the immune system; but, the problem is determining which biomarkers are most relevant. It has been said that if you ask 100 immunologists to name the most important biomarker, you'll get 100 different answers. Biomarkers reflect the complex role that various cells, antibodies, cytokines and other messengers have on the immune response and overall immune function. The question to ask is whether a particular biomarker is meaningful and whether it correlates to an immune health benefit. Are there data showing the linkage between the change in the biomarker and beneficial immune function? For example, antioxidants remove free radicals, the byproducts of normal cellular function that may be harmful in large amounts. Is there research to support how effective a particular antioxidant is in clearing free radicals? Can the immune system benefit of removing free radicals be measured?

One of the biomarkers demonstrating the efficacy of Wellmune WGP, a natural immune ingredient from Biothera that activates innate immune cells, is phagocytosis. Wellmune WGP activates a natural immune mechanism to increase the ability of macrophages to phagocytose or engulf and destroy foreign challenges. Studies also demonstrate that Wellmune WGP increases the oxidative burst that other innate immune cells called neutrophils use to rupture the cell membrane of bacteria and other intruders. One potentially controversial group of biomarkers, cytokines, are chemical messengers that signal to cells that a health challenge is present. Cytokines play a critical role in communicating

between immune cells and mounting an immune response, but some cytokines may produce inflammation. When looking at cytokine data, be wary of immune ingredients that elicit high levels of pro-inflammatory cytokines, such as TNF-alpha and IL-1B. Some immune ingredients purport to increase the number of Natural Killer cells. Like boosting cytokine production, increasing the number of immune defenders in the body may over-stimulate the immune system and result in harmful side-effects.

4. Did the study include clinical endpoints? Unlike biomarkers, clinical endpoints are easier to understand; for example, did the subjects get sick? Evidence of positive clinical endpoints may increase confidence in an ingredient's efficacy. Savvy marketers will pay attention to the endpoints used because the link between research and the claims that marketers intend or desire to make may be weak or unsupported. In other words, research is often not designed to be the support that marketers need, which is one of the reasons why studies with Wellmune WGP have focused on stress-related health challenges. The impact of psychological and physical stress on the immune system is well documented; consumers can relate to the toll of stress in their lives. In addition, stress management claims are not disease claims.



5. How was the study designed? Study design is critical to eliminating unintentional bias on the part of researchers or study subjects. The study should include a control group that is treated with a placebo. In evaluating the results, it is important to note whether the study was conducted with a single blind (the researcher knows how each subject was treated), open label (the subject knows the treatment received), double blind (neither researcher nor subject knows the treatment) or crossover (the two subject groups switch treatments during the study period). All are valid study designs; however, a double-blind study is considered to be the best design. A crossover study design is equally good as it eliminates data variations owing to the particular physical make up of each treatment group.

6. How large was the study? The study should include enough subjects to generate statistically significant or valid results. It is often difficult for researchers to determine the number of subjects needed without knowing the specific clinical outcome that defines product efficacy in a study population. Also, real world financial constraints sometimes dictate study design and outcome selection. Therefore, it may be necessary to look at the entire body of research supporting an ingredient. This will provide a more complete picture of an ingredient's safety and efficacy.

7. How were the results evaluated? It is important that a well-established methodology of statistical analysis was used to evaluate the results. In statistical hypothesis testing, p-values represent the probability of obtaining a result at least as extreme as the one observed. The lower the p-value, the less likely a different result or outcome would be observed in a larger population under the same conditions. p-values of 0.05 or less are considered to be "statistically significant." Did selection of 'n' (number of subjects) involve power calculations based on the desired clinical outcome? Conducting small human studies to evaluate specific outcomes can help to determine appropriate outcomes upon which to base power calculations.

8. What kind of research was conducted? Every immune health ingredient for human consumption must be supported by credible safety/toxicology and efficacy research. Look for safety and toxicology data that has been published in peer-reviewed journals. In addition to solid efficacy research, another essential type of research relates to mechanism of action. Is it understood how the compound works at a cellular level to effect a beneficially immune response? How and why an ingredient works provides a more complete understanding of safety, dosing and efficacy.

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9. Does the ingredient have government recognition or approval? Has the safety or efficacy research been reviewed by a government or regulatory agency? Companies that have submitted their research for government review or approval such as US FDA GRAS, Australian TGA or EU Novel Food have set a high standard for their ingredients. Government approval builds confidence in the product.

10. Is there a total data package to review? Look for a documented history of research data that has been published in peer-reviewed journals. The data package should include published safety data, preclinical (animal) efficacy studies, human clinical studies and mechanism of action. By reviewing the "totality of the data," you will do your company and customer base a credible service.

For more information

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