Clinical Trials: Will the Wrong Trial Design Make Your Dietary Supplement or Functional Food an Unregistered Drug?

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1. Designing clinical trials for natural health products, including dietary supplements and functional foods, is a balancing act. It requires knowledge of basic science, pathophysiology (the functional changes associated with a disease or injury), good clinical practice (GCP), clinical medicine, regulatory affairs, and even marketing. In order to maximize the likelihood of success, a good clinical trial design will take all these into account.

If a study is successful, it can yield significant returns on investment for a company. The payoffs of a successful study can include health claims substantiation, use in scientific conference presentations, and publication in peer-reviewed medical journals and company press releases—all resulting in increased sales and distribution.
Alternatively, a poorly designed and/or executed study—regardless of whether the study’s results seemed to come out positive—can generate a series of disappointments. Disappointments of a poor-quality study can range from a loss of the investment made in the study, the presence of a negative study in your regulatory file, or worse—a poorly designed or executed study can cause regulatory agencies to categorize your dietary supplement or functional food as an unregistered drug.

“Really?” you might say. An unregistered drug? How can that be? After all, you have done the responsible thing by investing in a human clinical trial to prove that your natural health product is in fact safe and efficacious.

However, as discussed ahead, what your study is designed to evaluate, and who your study is performed on, can ultimately determine how regulators regard your product.

What Regulatory Agencies Say

Let’s look at how some regulatory bodies distinguish drug studies from supplement studies.

First, what is the definition of a drug? According to FDA, a drug includes—among other things—“articles intended for use in the diagnosis, cure, mitigation, treatment, and prevention of disease…” Thus, if a clinical trial is performed in which a product is tested to diagnose, cure, mitigate, treat, or prevent a disease, FDA would classify the product as a drug.

FDA underlined this position in draft guidance published in October 2010, titled “Investigational New Drug Applications (INDs)—Determining Whether Human Research Studies Can Be Conducted without an IND.” In the draft guidance, the agency stated that human studies must be conducted under an IND if the research involves a drug, is a clinical investigation, and is not otherwise exempt from the IND requirements. Thankfully, the draft guidance specifically exempts dietary supplement clinical trials from IND requirements—as long as the dietary supplement is being used to affect the structure and/or function of the body. However, the guidance does specify that “whether an IND is needed for a clinical investigation evaluating a dietary supplement is determined by the intent of the clinical investigation [italics added].”

Also, note that IND regulations apply to studies regardless of whether there is commercial intent. This means that if a university performs a study on your product (with or without your permission and/or involvement), the study requires an IND if the study is designed to test the supplement’s ability to diagnose, cure, etc.

The bottom line is that even if you are very careful to follow DSHEA (Dietary Supplement Health and Education Act) requirements by making no drug claims whatsoever on your label and your website, your clinical trial design may in the end determine whether or not your product is in fact considered a drug in FDA’s eyes.

Across the pond, the European Food Safety Authority (EFSA; Parma, Italy) also draws differences between study designs for supplements and drugs. Specifically, EFSA has stated that studies supporting non-drug products—e.g., dietary supplements or functional food—that target a non-drug market should be performed on a non-drug population. For instance, EFSA’s July 2007 “Scientific and Technical Guidance for the Preparation and Presentation of an Application for Authorizations of a Health Claim (Revision 1)” states that health claim
applications must contain all scientific data (published and unpublished; data in favor and not in favor). Notably, among the requirements is that the “specific study group(s) in which the evidence was obtained is representative of the target population for which the claim is intended.”

To date, EFSA has rejected many health claims applications. In reviewing the rejection documents, it is clear that EFSA considers studies performed on non-healthy, diseased subjects as not applicable to health claims for healthy consumers of supplements and functional food.

**Healthy Study Subjects: Challenges**

Thus, for natural products like dietary supplements and functional food, studies should target non-diseased populations and non-drug endpoints. Statistically, however, there are challenges in performing studies in a non-diseased, healthy population. In healthy volunteers, the magnitude of a physiological change due to an intervention is likely to be smaller than it would be in diseased subjects—and as a result of a smaller effect, the likelihood of demonstrating a statistically significant difference is diminished.

How do you reconcile these seemingly competing requirements? On one hand, the natural products industry is being asked to perform clinical trials to demonstrate effects supporting health claims. On the other hand, if a study involves a diseased population or measures endpoints that are only relevant to drug products, it automatically brands the study product as a drug.

What options remain to provide scientifically valid studies that support scientific, regulatory, and consumer needs?

**Clinical Trial Design Goals**

To design the perfect study, it is always best to start with the end in mind. This means you should start by specifically determining the following goals: 1) scientific, 2) regulatory, and 3) marketing.

The scientific goals of a clinical study can include determination and demonstration of efficacy and safety, understanding and validating the mechanism of action, and understanding for whom the product works best.

The regulatory goals of a clinical study can include establishing substantiation for your proprietary product, determining that the substantiation for your finished product specifically stems from an active ingredient within your formulation, and protecting your company from legal challenges (especially class action lawsuits).

The consumer (marketing) benefits of a clinical trial can include press-worthy events (scientific poster presentations, peer-reviewed publications) and providing experts with specific documentation to reference in interviews regarding your product.

Once the goals have been established, it’s time to design the study.
The Udani Theory of Natural Health Product Clinical Trial Design

For the last decade, one of the challenges for Medicus Research has been designing clinical trials that meet a sponsor’s goals while keeping in mind a moving regulatory target. Consulting counsel, regulators, scientists, and past experience has led the company to develop a working theory on how to design studies that meet all of these needs. It’s called The Udani Theory of Natural Health Product Clinical Trial Design. This theory has three components:

1. Identify a healthy or at-risk population
2. Apply a standardized stressor to overwhelm subjects’ normal physiological mechanisms
3. Measure objective endpoints that are functionally relevant to the scientist, regulator, and consumer

When it comes to selecting a healthy, non-disease population, keep this in mind: while studies for non-drug products may not include diseased populations, non-drug studies can include an at-risk population. The rationale for identifying an at-risk population rests in understanding that the meaning of healthy is not strictly the absence of disease but rather is where an individual’s well-being sits somewhere on the spectrum between perfect health and end-stage disease. Therefore, a subject who is not diseased but who has pathophysiology representing a point on the journey toward the diagnosis of a disease is one who can most likely benefit from a dietary supplement—and is therefore the perfect subject for a clinical trial on natural health products.

The purpose of the second step, applying a standardized stressor, is to overwhelm the subject’s physiology toward the edge of control. Doing so provides the opportunity for the dietary supplement to potentially have a greater impact and demonstrate a statistically and/or clinically significant distinction when compared to placebo.

The third step, measuring objective and functionally relevant endpoints, means to select functional endpoints that have meaning to scientists (by being clinically meaningful and familiar in medical settings), regulators (by staying within the framework established by DSHEA and EFSA), and subjects (by being understandable and relevant to their health).

Clinical Trial Design Example: Immune Health

The immune system is a complex orchestration of structure and function involving several organs and cell types. Claims for immune health are equally complex. A healthy immune system is one that is vigilant, responds appropriately to the presence of an antigen, removes the antigen, and cleans up after it is done. Healthy people are exposed to environmental antigens on a daily basis. We are coughed and sneezed upon, and touch surfaces which contain potentially infectious microorganisms. Normally, our immune system recognizes these antigens, takes action to destroy them, and then returns to the quiescent phase, waiting for the next antigen to appear.

In order to design a study to support an immune-health claim, we applied The Udani Theory as follows:
1. Identify a healthy population
   a. Healthy volunteers were screened and enrolled for this study.
   b. Any subjects with an underlying immune-system disorder were excluded.

2. Apply a standardized stressor
   a. Wintertime community-based exposures to cold and flu viruses provide a stressor that may potentially overwhelm the immune system of healthy volunteers. During such an exposure, the natural (and self-limiting) immune-response function is to increase the number of circulating immune cells and to increase the function of these cells.

3. Measure objective endpoints that are functionally relevant to the scientist, regulators, and the consumer
   The progression of a viral prodrome (early virus signs or symptoms) to an upper respiratory infection is the result of the failure of the immune system to properly identify and overwhelm the antigen, leading to increased viral replication and eventually the onset of the common cold. It is the natural immune-response function that causes the viral prodrome.

   In a clinical setting, it is very specifically the reduction of signs and symptoms of the viral prodrome that is a surrogate marker for the appropriate activation of the immune system, which is the primary endpoint.

   a. To the scientist, these signs and symptoms are relevant, as they indicate the presence of the activation of a physiologic process.
   b. Regulators would not regard these as signs and symptoms of a disease; only of a normal physiologic response.
   c. The endpoint is meaningful to the consumer as well, as the average consumer understands the feeling of a viral prodrome: feeling unwell.

Therefore, the dietary supplement structure/function claim “Helps support your immune system” is measured by documenting the natural history of the self-limiting process of the viral prodrome.

This is but one example of many therapeutic categories in which The Udani Theory can be applied in order to design human clinical studies for non-diseased populations. The natural health products industry is therefore presented with an enormous opportunity by which it can firmly establish the efficacy and safety of its products—while responsibly staying within regulatory parameters.

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