Dietary Supplement Claims Substantiation E-Book:

How to Align Clinical and Regulatory Strategy to Support Your Product Claims

Joshua Baisley, B.Sc., Director, Clinical Trials

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In this e-book, you will learn:

- ✓ Marketing and positioning advantages of an adequately substantiated product claim
- ✓ Regional differences in permitted claims – USA, Canada, EU
- ✓ The level and type of research needed to substantiate claims for dietary supplements
- ✓ How to design a clinical trial specifically for claims substantiation
- ✓ Key factors that can comprise a claims substantiation trial
- ✓ Regulatory considerations for claims substantiation studies

Contents

Introduction

Product claims are a key component of dietary supplement brand positioning. Often driven by the marketing team, strong and engaging claims can set a brand apart from the competition by reinforcing attributes about a product's health effects, nutritional benefits and product performance.

Substantiating product claims is an important aspect of any product launch or repositioning strategy. Not having the right type or level of data required to support a product claim can put a brand at risk for regulatory consequences, negative publicity and, ultimately, a loss of market share and competitive advantage.

The purpose of this e-book is to provide detailed information and specific guidance on how to substantiate dietary supplement claims using an integrated regulatory and clinical research approach.

Too often brands will invest in just one of these two areas depending on the capabilities of their contract research organization (CRO). Why? Companies may or may not have access to internal scientific and regulatory experts to review evidence requirements and critically assess data to determine if the desired claim can be substantiated. This level of review requires assessing *both* scientific and regulatory perspectives. Attempting to substantiate claims using regulatory or clinical research alone can be an ineffective and a costly approach with increased risk of failure to achieve the goal.

Read on to learn how your brand can benefit from an integrated, well-designed regulatory and clinical research approach for claims substantiation in the US, Canada and the EU.

Regional Differences in Health Claim Regulation

Regulatory requirements vary by region, both in the types of claims that can be made as well as what evidence is required to substantiate the claim. It is important to understand which market you wish to access so that you can plan accordingly.

In the United States and Europe, dietary supplements (referred to as food supplements in the EU) are regulated as foods. While both regions have a notification system in place to inform the government when new products are being marketed, pre-market approval is not required. In other words, the evidence required to make claims is not reviewed before a product hits the market. Both the US Food and Drug Administration (FDA) and the Federal Trade Commission (FTC) have authority to take legal action against companies who make misbranded or unsubstantiated claims for dietary supplements.

In Canada, however, these products (referred to as natural health products) are regulated by the Natural and Non-Prescription Health Products Directorate (NNHPD), a division of Health Canada. Natural health products—and their claims—require pre-market approval before they can be legally sold. This is similar to how drugs are regulated.

The Canadian regulatory framework outlines a clear pathway companies can take, along with requirements to substantiate claims. In general, more aggressive claims require a greater level of data and substantiation. This pathway provides different opportunities for both clinical research and claims to achieve product differentiation. Natural health product claims in Canada can therefore be far more aggressive in terms of diseases and health conditions than their American counterparts.

Regardless of the regulatory region, clinical trials are considered to be the highest degree of evidence in terms of substantiating efficacy claims for dietary supplements. This makes clinical research a necessary step in the product development pathway. Results of clinical trials must withstand regulatory scrutiny in order to successfully substantiate the claims. To ensure the best chance for success, the clinical trial design must be robust. The documented plan will not only affect how the trial is conducted but will have an impact on the validity and reliability of data collected as well as the analysis and interpretation of results.

Acceptable Claims for Dietary Supplements/Natural Health Products

Just as there are regional differences in whether products are approved before sale, the definition of "health claim" varies between regulatory jurisdictions. However, acceptable types of claims for dietary supplements appear to be similar across different regions.

In the US, health claims are limited to describing the relationship between a food substance (a food, food component or dietary supplement ingredient) and a reduced risk of disease or health-related condition. In the EU, the definition encompasses function health claims (Article 13 claims) which relate to growth, development and functions of the body; psychological and behavioural functions; as well as weight control, children's development (Article 14(1)(b) claims) and disease risk reduction claims (Article 14(1)(a) claims). An overview of applicable types of claims by region is shown in **Table 1**.

Table 1 – Comparison of permitted health claims globally

	USA	Canada	EU
Structure-Function Claims	✓	(✓)	(✓)
Health Claims	✓	✓	✓
Nutritive Content Claims	✓		✓

The Canadian definition of "health claim" is much more expansive than that of both the US and the EU. It is subdivided based on the type of health claim (or claimed effect). In Canada, natural health products can bear claims with respect to diagnosing, treating or preventing a condition or symptom, reducing risk of condition or symptom, as well as general health-related functions (**Appendix 2**). In both the EU and Canada, structure-function claims fall under the umbrella of health claims.

Nutritive content claims (or nutrition claims in the EU) are statements like "low-fat" and "high fibre." As with all label claims, the use of terms such as "free," "high" and "low" must be accurately qualified. Canada also allows "source of" claims which identify an ingredient or constituent contained in the product (e.g., "source of probiotics"). This is a similar approach used in foods and such claims must not be false or misleading.

The Level and Types of Data Required to Substantiate Claims

According to guidance released by the US FDA in 2008, "although there is no pre-established formula as to how many or what type of studies are needed to substantiate a claim, we, like the FTC, will consider what the accepted norms are in relevant research fields and consult experts from various disciplines." While the number of studies required is not clearly defined by the FDA or FTC, the FTC has often referred to the requirement of two clinical trials in cases filed against supplement manufacturers.

This is not a hard-and-fast rule, as evidenced by the outcome of the FTC vs. POM Wonderful case. The court rejected the FTC's rigid blanket requirement for two randomized controlled trials (RCTs) to substantiate claims. Their reasoning was that the requirement was too broad, and the type and level of evidence need to be based on the type of claim being made. In the end, the panel did uphold the notion that POM provide substantiation of any future claims with at least one randomized controlled trial showing statistical significance.

Table 2 – FDA guidance on evidence requirements for claims substantiation.

Evidence that may substantiate a claim	Evidence that is supportive, but may not be adequate to substantiate a claim on its own
Human intervention studies ("randomized, double-blind, parallel group, placebo-controlled trials offer the greatest assessment of a relationship between supplement and outcome"	Animal studies
Human observational studies (e.g., case reports, case-series studies, case-control studies, cohort studies, cross-sectional studies, time-series studies and epidemiological studies	In vitro studies
	Testimonials and other anecdotal evidence
	Meta-analysis
	Review articles
	Comments and Letters to the Editor
	Product Monographs

Although the FDA has provided some guidance to industry on what types of evidence may substantiate a claim (**Table 2**), there is little guidance for industry with respect to the number and specific type of trials required to substantiate different types of claims for dietary supplements in the US.

In the EU, the European Food Safety Authority (EFSA) has released guidance documents surrounding the types of studies required to make various health claims. However, detailed guidance on the number of trials for specific claims is also lacking in the EU.

In sharp contrast, Health Canada has provided industry with guidance on the types of evidence, level of evidence and minimum number of studies required pertaining to the type and amount of evidence required to make claims. Despite this, little guidance is available on study design in Canada. Instead, Health Canada refers to guidance set forth by EFSA, Health Canada's Therapeutics Products Directorate (TPD), the US FDA and the medical community consensus or guidance documents. It is therefore worthwhile to understand the requirements of each of these jurisdictions regardless of which region the product may be marketed in.

Figure 1 depicts the level of evidence required to support claims of different levels of risk. For a more detailed overview of natural health product claims permitted in Canada, see **Appendix 2** and **Appendix 3**.

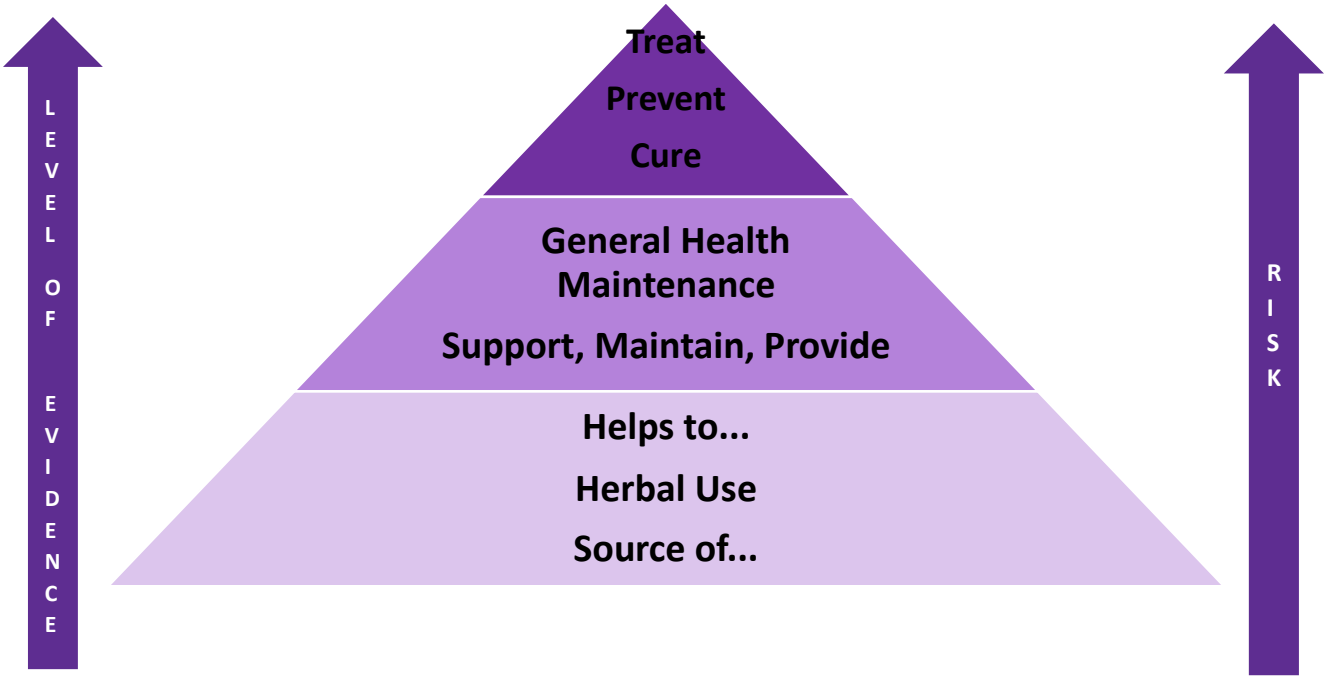

Figure 1 - Health Canada's Building Health Claims: The higher the risk of the claim, the greater the evidence must be in order to substantiate the claim.

Risks to Claim Substantiation

Recently, EFSA published a document entitled, “Guidance on Statistical Reporting” and has since discussed the article in the context of reasons for claim rejections. Deficiencies in studies submitted to substantiate claims to EFSA include inappropriate patient population or inclusion/exclusion criteria, no control or lack of appropriate control group, inappropriate statistical powering of the study, insufficient method of randomization, inappropriate statistical tests and reporting of results (**Figure 2**).

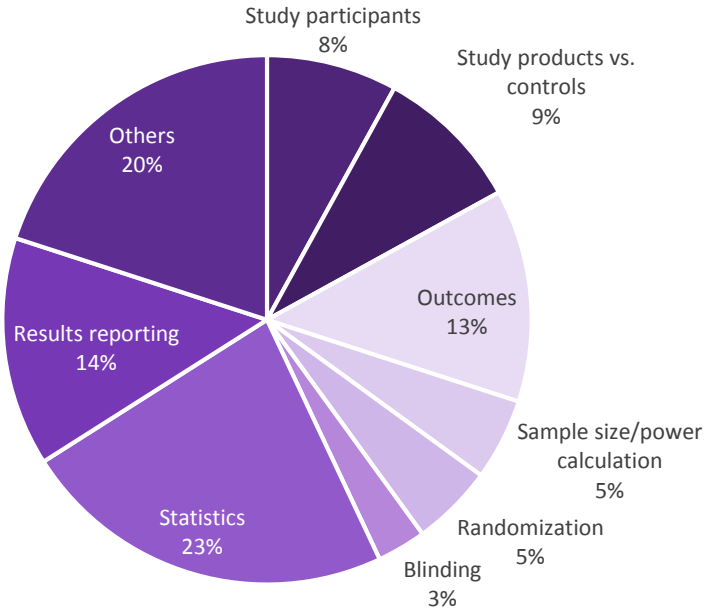

Figure 2 - Questions on studies submitted for substantiation (adapted from Guidance on Statistical Reporting EFSA Journal 2014; 12(2):3908).

The majority of issues resulted from poor planning and clinical trial design (see **Appendix 4** for a detailed list of reasons for claim rejection). It is clear that adequate time and careful planning of a clinical trial are necessary to reduce the risk of trial failure and failure of the study to substantiate the claim.

Study Population

Utilizing an appropriate study population is essential in clinical design to support successful claim substantiation. The study population should be reflective of the population that the claim will apply to in the region of interest. For example, a study conducted in Canada with Canadian citizens could substantiate a US claim as dietary habits have become increasingly similar between the two countries.

Care must be taken to carefully and explicitly define inclusion and exclusion criteria in the study protocol. This will ensure the appropriate population is targeted and will reduce confounding effects from other potential sources depending on the nature of the study design. These may include activity levels, dietary habits, concomitant medications, blood or urine markers and others.

The population should be broad enough to include the population the claim will apply to, but exclude people that may be at increased risk of safety issues associated with use of the product, interactions with other supplements or drugs, and other important confounding factors that may impact study results.

In some instances, it may be difficult to study the population the product is intended to be marketed to. Improvements may not be easily seen depending on the marker(s) or endpoint(s) of interest. EFSA has acknowledged that in some cases it is acceptable to study diseased populations and extend claims to the general population. For instance, in the guidance document for claims on the immune system, EFSA states that, “episodes of abdominal pain or discomfort occur both in healthy people and in individuals suffering from irritable bowel syndrome (IBS), and the difference between the two is the higher frequency and/or greater severity of the symptoms in IBS patients. IBS patients…are generally considered a suitable study group to substantiate claims on gastrointestinal discomfort intended for the general population.”

Inclusion and exclusion criteria are important factors that help define the study population. The population should be broad enough to include individuals the claim will apply to but exclude people that may be at increased risk of safety issues associated with use of the product. Inclusion and exclusion criteria must be adequately and thoroughly defined in a

clinical study protocol. Care must be taken to ensure the safety of study subjects and the integrity of the trial while balancing the ability to recruit subjects.

When executing and reporting a study, any deviations or waivers of subjects not meeting the inclusion/exclusion criteria must be reported transparently. Far too often investigators request waivers from a sponsor to include a subject who does not meet enrollment criteria and then notify the ethics board. This practice is not compliant with Good Clinical Practice (GCP). GCP requires that the ethics board approve enrollment of a subject not meeting inclusion/exclusion criteria prior to that subject's enrollment.

Subject Number, Effect Size and Statistical Significance

Sample size is an incredibly important aspect of clinical trials and can "make or break" a claims substantiation study. Sample size estimations are difficult to calculate for any trial, but can be more difficult in the context of dietary supplement study design depending on the ingredient(s) and the primary endpoint(s) being studied.

Sample size can be determined using many different methods. In all cases, it is important to try to estimate sample size and document this in both the study protocol and final report. Sample size calculations should include an estimate of:

- The effect size (i.e., the degree of change the product is expected to provide with relation to the primary endpoint over and above that of the placebo or comparator study arm);
- An estimate of the variability around that change (i.e., within group standard deviation of the mean effect size);
- The level of power (e.g., 80% or 90% confidence that the result is true); and
- Alpha (the level considered statistically significant [e.g., 5% or p=0.05]).

Sample size also needs to include an estimate on the withdrawal rate, also known as the attrition rate. This is the number or percentage of subjects that are not expected to complete the study. This number of subjects should be added to the calculated number required per group to ensure there is a sufficient number of subjects completing the study.

Statistical significance should not be the only consideration for sample size. The effect size—the change the product is expected to illicit—should also be clinically important.

Statistical significance, represented by the p-value, is the probability that the result did not occur by chance. For example, a $p<0.05$ means that the result has a 5% chance (or less) that the difference found in a study would occur by random chance alone. For a study with a very large number of subjects, however, the results may be statistically significant but the change itself may actually be small and/or not necessarily clinically relevant. Clinical importance is the magnitude of benefit the product provides which is relevant in the context of improving health.

In contrast, statistical significance may not be achieved due to a small sample size, but the magnitude of change seen in the study was potentially important enough from a clinical point of view that it may be wise to investigate it in a larger population. It is therefore critical that statistics be reported appropriately in the final report.

To provide the most robust sample size calculation, the estimate should be based on prior research with the specific product under study. This information may be obtained through a pilot or proof-of-concept (hypothesis testing) study conducted in a similar population with similar endpoints. Where this may not be possible, literature may be used to provide estimates on the potential change. Such a method should be approached with caution, however. The product may not be entirely reflective of those published in quantity, purity, potency, chemistry or manufacturing processes, all of which can affect the quality of the

test article and prevent direct comparability. Additional approaches can be taken to manage this risk, including increasing the power (e.g., 90% instead of 80%), or by using more conservative estimates of change and variability around the change.

The ingredient or product's effect size should be realistic and reflective of the actual substance being tested. The effect is likely not equal to or greater than that of a targeted pharmaceutical, so using a sample size calculation based upon a pharmaceutical drug study effect size would likely not be appropriate. Similarly, looking at various effect sizes to achieve the desired number of subjects that fit within a budget is likely to result in failure of achieving statistical significance.

In cases where there is a lack of information to estimate a sample size appropriately, these studies should be approached as traditional proof-of-concept studies. The expectation is that such studies would only provide guidance and information on what the product's effect size may be and could be used to guide a future clinical study designed to substantiate a claim. This is often the appropriate initial stage of a company's clinical research program and follows a more traditional product development pathway.

Selection and Measurement of Primary Endpoints

The primary endpoint of the study should be consistent with the identified claim that is to be supported. It should also be credible, validated and responsive to change. As scientific and medical knowledge increases, the number of proposed endpoints for positive health effects continues to increase. With this comes the need for determining sensitive, specific and recognized methodology for quantifying endpoints, which regulatory agencies often provide commentary on.

Keeping abreast of what the regulatory agencies consider as acceptable biomarkers and questionnaires in the context of specific claims is critical to ensuring the appropriate primary endpoint is defined and measured in the clinical study. Failure to use an appropriate endpoint can lead to failure of the study hypothesis, inadequate sample size estimations and failure to substantiate the intended claim.

For example, Health Canada, the US FDA, and EFSA are all in agreement that for weight loss and weight management studies, a change in weight alone is insufficient to support a claim. The length of study must also be sufficient to demonstrate the effect and ensure that the effect is not temporary or due to adaptation alone. In the case of weight management, for example, the study should be at least 12 weeks in duration.

For studies on gastrointestinal effects, such as stool consistency and bowel habits, the duration must be long enough to exclude adaptation, and should be a minimum of 4 to 8 weeks in duration. Questionnaires and scales used in such studies should be clinically relevant and validated (e.g., Bristol stool scale, GIQLI, etc.). Failure to use validated questionnaires appropriately can also lead to failure to substantiate a claim.

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In the case of biomarkers, timing is of similar importance. If one were to select HbA1c to determine effects of a product on blood glucose, the study period should be of sufficient duration to see a change (e.g., a minimum of 12-16 weeks to have full turnover in red blood cells).

For claims on immune function, there is often interest to look at a number of markers of inflammation including cytokines (pro-inflammatory and anti-inflammatory). Such measures often provide information on the mechanism of action but are not recognized by regulatory agencies as clinical outcomes to substantiate a claim. Clinical outcomes such as C-reactive protein alone may be enough to substantiate a claim, while the cytokines may be used as supportive information.

Minimizing Bias: Control Groups, Blinding and Randomization

Sources of bias can compromise the integrity of a clinical trial and invalidate the results. One way to avoid bias is through blinding. Blinding is the process of concealing information about the assigned treatment from individuals involved in a clinical trial. The intention is to minimize conscious and unconscious bias in the collection and interpretation of data during a clinical study. In studies intended to substantiate claims, blinding of subjects, investigators and outcome assessors is important to ensure a fair evaluation of efficacy of the investigational product. Blinding is achieved at multiple levels, from choosing an appropriate placebo to packaging the study products.

Well-designed clinical studies should include an appropriate comparison group. This can be challenging depending on the dosage form and regimen of the investigational product. Where ethical and feasible, a placebo should be used to provide an ideal comparison. The placebo should match the sensory specifications of the investigational product. Specifications may include aspects such as shape, size, weight, visual aspects, taste and smell. It is critical the study protocol clearly describes and includes appropriate rationale for the choice of placebo.

The requirement for matching should also extend to all associated packaging of the product, including labelling. The study product and placebo should be packaged in

matching containers, with labels differing only by the randomization number (randomly assigned to each subject) so as to not provide any indication of which product is contained in the package.

Randomization is a critical factor in a well-designed clinical trial. It helps prevent selection bias and aids in blinding the allocation to study products as described above. However, one consequence of randomization is an imbalance among groups with respect to some potentially confounding factors. This could lead to invalidation of study results. An alternative approach is minimization, which allocates subjects in a manner to minimize differences between groups; however, in using this approach, one can predict the allocation of the next subject.

In the context of dietary supplement trials, where the number of subjects is often small (<400 subjects), stratified randomization may be useful. Stratified randomization prevents an imbalance among groups for factors known to influence responsiveness, thereby minimizing confounding of a study's statistical results. Additionally, stratification can provide an opportunity for sub-group analysis of the data as it will provide balance between groups with respect to the factor(s) used to stratify subjects. The number of factors used to stratify should be kept to a minimum and the strata should be based only on important confounding factors (e.g., age, gender, body mass index [BMI]).

In studies intended to substantiate claims, blinding of subjects, investigators and outcome assessors is important to ensure a fair evaluation of efficacy of the investigational product.

Randomization may be simple or blocked. Simple randomization is constructed using a list of all subjects enrolled in a trial. While the method is effective for randomly assigning subjects to a group, there is risk that clusters of subjects may receive the same product in a certain period during the study. To minimize time and location effects (in the case of multi-center studies), block randomization can be used, with the preferred method of randomization being random permuted block randomization. This reduces the chance of an investigator knowing which subject will be assigned to which group.

The study protocol must describe in detail the method of randomization and assignment of study subjects to a particular group or treatment sequence. Detailed information about the placebo/control used and justification for these choices helps minimize sources of bias.

Statistical Analysis Plans

It is also important to avoid any bias in the statistical analysis. A detailed statistical analysis plan should be available prior to analyzing data sets. The a priori description should be included in the clinical study protocol and include a definition of analyses/populations to be used including inclusion/exclusion criteria. It should also clearly describe any subgroups/subset analyses and how they relate to the primary and/or secondary objectives of the study.

All endpoints to be evaluated should be described in the statistical analysis plan and detailed by both the variable name and time point. If any covariates are to be included in the statistical analyses, the plan must describe definitions and derivation rules. Missing data, or data that is not plausible, often occurs during the conduct of a clinical trial. As part of clinical trial design, it is necessary to anticipate potential issues and have detailed plans in place to manage such incidents. This will prevent occurrences and ensure there are planned methods in place to deal with any missing data.

As part of clinical trial design and preparation for statistical analyses, it is necessary to anticipate potential issues and have detailed, documented definitions and plans in place to manage such incidents. This will prevent occurrences and ensure there are planned methods in place to deal with any missing data.

The planned statistical tests should be clearly identified for specific data sets as statistical methods vary based on the type of data (e.g., binary, continuous, categorical, parametric, non-parametric). The need for tests for normality should also be included in the statistical analysis plan as many biological endpoints are prone to skewed distribution.

Assessing Prior Literature

As part of the clinical design process, the total body of evidence should be considered. It is important to review the literature for both favourable and unfavourable studies related to the claim to be substantiated and ingredient/product to be evaluated.

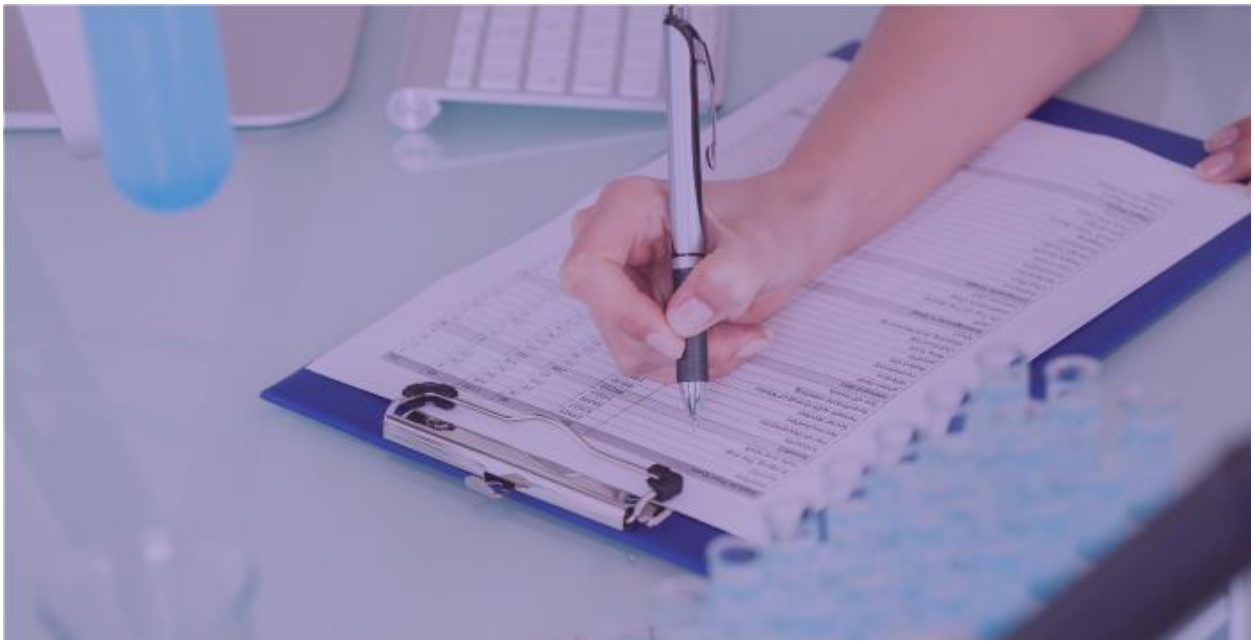
The quality of the studies should be reviewed for strengths and weaknesses in trial design, dose response, selection of endpoints and responsiveness of endpoints, reported

study limitations and confounding factors. This information should be incorporated into the study design to provide a more robust data set. It is important that resulting data from the trial be discussed in light of the literature, including justification for why the study was necessary and what was done better in the current study design compared to previous research. This will form the basis for the claim(s) substantiation dossier and address differences in results between studies.

In addition to assessing the totality of evidence, contract research organizations (CROs) provide additional benefit to manufacturers/sponsors as the CRO will often have prior experience working with similar product types and/or study designs. Ideally, the CRO would build on these experiences, sharing lessons learned to provide more robust clinical study designs to their clinical study partners.

Characterizing the Study Product/Ingredient

When conducting a dietary supplement clinical trial, it is important that the product is fully characterized. The characterization is documented in the protocol, Trial Master File (TMF) and final report to ensure there is no ambiguity regarding the relationship of any results to the product under study.



Characterization should include detailed information including the amounts of all active ingredients per dosage unit, listing of all inactive ingredients, dosing regimen including timing of dose, number of dosage units to be taken and time of dose in relation to any concomitant medications allowed to be taken by subjects in the study. The Sponsor/manufacturer should maintain documents including chemistry and manufacturing information, certificates of analysis for investigational product and placebo, batch records and stability information. This information may be maintained in the TMF, or in the case of studies conducted in Canada, will form part of the Clinical Trial Application (CTA).

The chemistry and manufacturing of ingredients, especially in the dietary supplement industry, can have profound effects on the outcome of clinical research studies. For example, botanical extracts from similar sources may be extracted with different solvents from alcohols and acids to water. The method of extraction may yield varying amounts of active constituents. If there is a different chemical profile between the investigational ingredient used in the study and that marketed with the resulting claims, the clinical trial may not substantiate the claimed effect as the difference in chemical profile could change the product's efficacy profile. Similarly, differences in formulations could result in varying degrees of efficacy. It may be appropriate to include information in the protocol on the method of preparation, potency of active constituents and stability of the ingredient or finished product.

Protocol Structure and Content

The clinical study protocol is the single most important quality control tool for a clinical trial. It details all aspects of the clinical trial design to ensure ease of implementation and execution. Consolidated guidelines for the structure and content of clinical trials are provided by the International Conference on Harmonization (ICH) and are accepted by regulatory authorities including the US FDA, Health Canada and the European Medicines Agency (EMA) (**Appendix 5**). Lack of detailed information on any of the key criteria described in the ICH guidelines can jeopardize the conduct of the trial and interpretability of the resulting data.

Thus, care needs to be taken when planning and writing clinical study protocols. Any changes to the protocol after approval of the document must be clearly documented through formal protocol amendments. This will require ethics approval and possibly regulatory approval prior to implementing the change.

Regulatory Considerations for Designing and Placing a Clinical Study

With dietary supplement regulations differing globally, it is key to understand the risks involved with study design and clinical trial conduct. Once the desired claim is understood, the clinical trial is designed around that claim. The trial design should dictate attributes of the study population, study objectives, endpoints and duration of the study, all of which are detailed in a clinical study protocol consistent with ICH and/or jurisdictional requirements. The design will also document the intent of the study, which is dictated by the population under study as well as study endpoints.

The overall intent of the research can have serious implications for a commercialization program. For example, if a study were designed in a manner consistent with the requirements of an Investigational New Drug (IND) application in the US—that is, the trial intends to study the ability of a dietary supplement to diagnose, cure, mitigate, treat or prevent a disease—this could prevent the supplement from being sold as a dietary supplement in the future. It could be classified as a drug. It is important to understand this risk as it can jeopardize commercialization of the product or other products in the future.

In Canada, product classification is driven by the nature of the ingredient/product type. For instance, natural health product ingredients/products include vitamins and minerals, herbal remedies and traditional medicines such as Chinese medicines. The safety profile of the ingredient can also define whether or not the product is a natural health product or a drug. In certain quantities, a common natural health product may be classified as a drug (e.g., Vitamin D at a dose >1000 IU/day) due to potential safety concerns.

Differences between regions can present the supplement industry with unique opportunities. A clinical research study in a pre-disease or disease state could be conducted in Canada under the *Natural Health Product Regulations* without concern for downstream regulatory categorization and effects on commercialization.

Another important aspect is understanding acceptance criteria for regulatory authorities. Some countries require claim-substantiating studies to be conducted in their region due to genetic differences in the population. The FDA requests that studies be conducted on populations reflective of the population in the US. This does not mean the study needs to be conducted in the US, but rather the population should be similar to the population

the product is intended to be marketed to. Thus, a study conducted in Canada or Western Europe could be used to support a claim on a product intended for the US as the populations in the countries are genetically similar and dietary habits are increasingly alike. Preparing, documenting and conducting a clinical trial in accordance with ICH guidelines also improves acceptance of the clinical study data with ICH member countries.

Preparing, documenting and conducting a clinical trial in accordance with ICH guidelines improves acceptance of the clinical study data with ICH member countries.

The required sample size, study population and intent of the clinical trial can have profound effects on where the study is to be conducted. If the intent of the study is to cure, treat, diagnose or mitigate a disease, an IND application may need to be filed if the research is conducted in the US. To avoid this, one strategy is to conduct the study in Canada.

Conclusion

When it comes to substantiating dietary supplement product claims, it is clear that both regulatory and clinical research strategies should be included as part of a development plan. Many commercialization opportunities are available to the supplement industry with respect to the types of claims being made and structure and design of clinical trials. Partnering with an experienced CRO can help guide you in developing an integrated regulatory and clinical research approach for successful claims substantiation.

Looking to Substantiate a Product Claim?

We can help! Established in 2002, Nutrasource is a full service contract research organization (CRO) specializing in navigating complex regulations on behalf of dietary supplement companies. With locations across North America, our experienced team partners with Sponsors to bring products to market through strategic product development, regulatory and clinical trial consulting, management and execution.

Our team of nutritional scientists, regulatory specialists, clinical research personnel and medical doctors will help you develop a strong clinical development and research strategy that meets your goal while guiding you through the complex and often challenging regulatory framework.

Clinical Trial Services Include:

- Product development strategies
- Pre-clinical program design and management
- Clinical program design and management
  - Multi-center clinical trial management
  - In-house clinical trials
- Regulatory consulting and submissions
- Claims substantiation
- Vendor management
- CMC support
- Product testing
- Bioanalytical testing

Contact us today!

Email: info@nutrasource.ca
Phone: 1-519-341-3367

Nutrasource
120 Research Lane, Suite 203
Guelph, Ontario, Canada
N1G 0B4

www.nutrasource.ca

About the Author

Joshua Baisley, B.Sc., Director, Clinical Trials

Josh joined Nutrasource in 2013, bringing over 10 years of quality assurance, clinical and regulatory natural health product experience and an additional four years of antibody research with a primary focus on pre-clinical development programs for type I diabetes. Throughout his career, Josh has compiled over 50 clinical trial applications for natural health products, drugs and veterinary products, representing over 10% of all applications received by Health Canada's Natural and Non-Prescription Health Products Directorate (NNHPD).

Working closely with Health Canada since regulations were enacted in 2004, Josh participated as an invited member on Health Canada's Canada Vigilance Expert Working Group for electronic adverse event reporting. Josh's experience in regulatory submissions and clinical trial design extends from single ingredient and multi-ingredient dietary supplements including enzymes, probiotics, botanical extracts, vitamins, minerals and essential oils to combination dietary supplement/drug products. His experience with therapeutic indications include cardiovascular health, cognitive function, detoxification, gastrointestinal health, hypertension, diabetes and pre-diabetes, men's health, women's health and weight loss among others.

Appendix 1 - Claim Categories for Natural Health Products in Canada

Diagnostic Claim	Claims relating to diagnosis of a disease, disorder, or abnormal physical state or its symptoms (e.g., detection of glucose intolerance in diagnosis of diabetes mellitus).
Treatment Claim	Claims relating to the treatment or partial treatment and mitigation of a disease, disorder, or abnormal physical state or its symptoms (e.g., symptomatic relief claims).
Cure Claim	Describe a therapeutic effect that results in the elimination of a disease, disorder, or abnormal physical state, either permanently or for a significant length of time.
Risk Reduction Claim	Claims based on significantly altering major disease risk factors for a disease or health-related condition. Preventing a disease risk factor does not imply prevention of the disease.
Prevention Claim	Claims for interventions which are proven to significantly reduce the incidence of disease.
General health maintenance, support and promotion claims	Claims for restoration, correction, or modification of a structure or physiological function in the human body in a manner that maintains, supports or promotes health.
Antioxidant claims	Products containing one or more ingredients that have antioxidant properties and claims worded as general health support claims.

Appendix 2 – Examples of Natural Health Product Claims by Health Condition (Canada)

Health Condition (Indication)	Examples
Serious disease/condition ***(High Risk)***	Helps prevent rheumatoid arthritis. For the treatment of cerebrovascular disease. For the treatment of depressive disorders. Used to prevent diabetic neuropathy. For the treatment of prostate cancer. For the treatment of high blood pressure. Used to treat diabetes.
Major disease/condition ***(Moderate Risk)***	Helps to reduce serum triglycerides/triacylglycerols. Helps to lower blood/plasma cholesterol levels. For reducing acid reflux during pregnancy. Helps to restore cognitive function/memory. Helps in the prevention of nausea and vomiting associated with conventional cancer management (chemotherapy and radiation treatment). Helps attenuate the rise in blood sugar levels following a meal. Helps improve insulin sensitivity. Helps to regulate blood glucose levels. Helps prevent glucose intolerance. Helps prevent osteoporosis. Improves joint function in osteoarthritis of the knee. Helps prevent recurrent urinary tract infections. Prevents against cavities. Helps cure migraine headaches. Helps prevent macular degeneration. Helps treat erectile dysfunction.
Minor disease/condition ***(Low Risk)***	Reduces the number and severity of acne pimples. Helps relieve nervousness. Helps relieve minor pain associated with menstruation. Used as a mild sedative (for jet lag). Soothes sore throat. Short-term relief of occasional constipation/laxative. Helps relieve minor burns including sunburn. Used for the temporary relief of muscle and joint pain associated with rheumatoid arthritis or osteoarthritis (symptom).

Health Condition (Indication)	Examples
	Helps to relieve the symptoms (e.g., sore throat, runny nose) of the common cold. Used as a decongestant to relieve nasal congestion due to hay fever. Helps to reduce the recurrence of cold sores. Relieves symptoms such as heartburn and dyspepsia associated with gastric hyperacidity (i.e., antacid). For the removal of corns and calluses. Helps prevent nausea and vomiting associated with motion sickness and seasickness.

From NNHPD's *Pathway for Licensing Natural Health Products Making Modern Health Claims*

Appendix 3 – Acceptable Minimum Efficacy Evidence by Risk Category

Low Risk Category	
Evidence Type	**Considerations**
Phase II clinical trials	***One piece of evidence of equivalent ranking or higher is required to support efficacy.*** When the evidence provided to support the claim is methodologically weak, it should be supplemented to demonstrate consistency in results and plausibility.
Epidemiological studies	Evidence only meets minimum requirements for prevention and risk reduction claims. One piece of evidence of equivalent ranking or higher are required to support efficacy.
Pilot and open label studies	***Two pieces of evidence of equivalent ranking are required to support efficacy.*** The two different studies may be of equivalent or higher ranking. When the evidence provided to support the claim is methodologically weak, it should be supplemented to demonstrate consistency in results and plausibility.
Reputable textbooks	Textbook should reflect human in vivo data if the ingredient is an essential nutrient.
Demonstration of food use	Evidence can be used to support safety only.
Medium Risk Category	
Evidence Type	**Considerations**
Systematic review other than meta-analysis	Conclusions should be based primarily on phase III trials, not phase II trials; primary evidence may be requested.
Published, peer-reviewed, detailed narrative reviews which cite detailed primary evidence	Detail should include: defining characteristics of the ingredient; primary endpoints/outcomes with statistical and clinical significance; the studied sub-population's age, gender, and health state; the dosing regimen and dosage form; the route of administration; the directions of use; any restrictions to study entry of participants based on interactions/risk; any identified adverse reactions

Phase II clinical trials	***Two pieces of evidence of equivalent ranking or higher are required to support efficacy.*** When the evidence provided to support the claim is methodologically weak, it should be supplemented to demonstrate consistency in results and plausibility.
Epidemiological studies	Evidence only meets minimum requirements for prevention and risk reduction claims. Two pieces of evidence of equivalent ranking or higher are required to support efficacy.
Published compilations referring to traditional use	Evidence can be used to support safety only.
High Risk Category	
Evidence Type	**Considerations**
Phase III or phase IV clinical trials (Randomized, controlled, well-designed)	For treatment, cure, and prevention claims or for health support claims when they imply treatment, cure, prevention, and risk reduction claims ***if the study is not multi-centered, at least two studies are required.***
Meta-analysis (controlled and well-designed)	Conclusions should be based primarily on phase III trials, not phase II trials; primary evidence may also be required
Prospective observational studies or combinations of one prospective study and one retrospective study	Evidence only meets minimum requirements for prevention and risk reduction claims. Two pieces of evidence of equivalent ranking or higher are required to support efficacy.
Evidence of a positive decision from another regulatory agency	Documentation in the form of an authorization letter or positive decision must be submitted that includes details on what was approved. A description of the regulatory requirements from the other regulatory agency should be provided.

Appendix 4 – Common problems in clinical study design leading to failure to substantiate claims

- Failure to critically assess prior literature
- Target population not reflective of study population
- Failure to specify inclusion/exclusion criteria
- Primary measures are not consistent with the target claim
- Primary measures are not recognized as valid biomarkers
- Failure to use validated questionnaires
- Failure to use validated biomarkers
- Duration of study not long enough for claimed effect
- Formal sample size calculation was not performed, under powered, or guess at effect size that is inappropriate
- Inadequate blinding
- Failure to randomize
- Stratification
- Use of inappropriate control group and/or inadequate blinding
- Failure to implement adequate bias and control measures
- Inadequate characterization of the study product/ingredient
- Failure to have a detailed, written, and vetted protocol
- Failure to detail planned statistical analyses and tests prior to conducting statistical analysis

Adapted from Clark and Mulligan, 2011

Appendix 5 – Minimum requirements in a clinical trial protocol

- General information
- Background information
- Trial Objectives and Purpose
- Trial Design
- Selection and Withdrawal of Subjects
- Treatment of Subjects
- Assessment of Efficacy
- Assessment of Safety
- Statistics
- Direct Access to Source Data/Documents
- Quality Control and Quality Assurance
- Ethics
- Data Handling and Record Keeping
- Financing and Insurance
- Publication Policy
- Supplements

Adapted from ICH E6(R1)

References

Charan J and Sazena D. Suggested statistical reporting guidelines for clinical trials data. Indian J Psychol Med. 2012;34(1):25-29.

Clark GT and Mulligan R. Fifteen common mistakes encountered in clinical research. J Prosthodont Res. 2011;55(1):1-6.

European Food Safety Authority. Guidance on Statistical Reporting. EFSA Journal 2014;12(12):3908.

European Food Safety Authority. Guidance on the scientific requirements for health claims related to the immune system, the gastrointestinal tract and defence against pathogenic microorganisms. EFSA Journal 2016; 14(1):4369.

FDA Center for Food Safety and Applied Nutrition. Guidance for Industry: Substantiation for Dietary Supplement Claims Made Under Section 403(r) (6) of the Federal Food, Drug, and Cosmetic Act. December 2008.

Health Canada. Pathway for Licensing Natural Health Products Making Modern Health Claims. December 2012.

International Conference on Harmonisation. ICH Harmonised Tripartite Guideline. Guideline for Good Clinical Practice E6(R1). 10 June 1996.