WWW.KGKSCIENCE.COM

WHITE PAPER Q1 2023

Regulatory Considerations for Running Foreign Clinical Trials to Substantiate US Dietary Supplement Structure Function Claims Marketed to the US Population

KGK Science | Premium Clinical Research & Regulatory Expertise

Corey J. Hilmas, MD/PhD & Sandra Szlapinski, PhD

Regulatory Question and Scope of the Problem:

Do Clinical Trials on US Dietary Supplement Products Have to be Conducted in North America?

Deciding to conduct a clinical trial is a risky undertaking. How can you be assured that the data will support your product after a lengthy trial? How much risk are investors or decision makers at your company willing to take? When should you start to worry about the Federal Trade Commission (FTC) and their jurisdictional authorities over whether you have sufficient "competent and reliable scientific evidence," the substantiation standard in the US. When will FTC begin to paint a target on your back? Which competitors are sending letters to FTC and FDA questioning your evidence? Will the cost of completing a human clinical trial break my budget? It all seems to come down to cost, the Almighty Dollar, and the ultimate value proposition after weighing all of the known risks. There might be a more critical question to consider — the where — rather than the "how much". Does the clinical trial for my dietary supplement (or drug) have to be conducted in North America or can it be conducted exclusively in a foreign country?

Purported Advantages for Conducting Clinical Trials Outside North America

Running clinical trials outside North America seems too good to be true. The Australian Government is committed to improving the clinical trials environment and has invested considerable effort and resources in this area. While much has been said regarding advantages of performing clinical trials overseas, investment incentives seem to be the major driver. The Australian Government's generous Research & Development Tax Incentive encourages industry investment. It provides a 45% refundable R&D tax offset for companies with aggregated annual turnover of less than $20M; and a 40% non-refundable R&D tax offset for all other eligible companies. This new system provides for a globally competitive tax incentive for conducting R&D activities in Australia. Other foreign countries have similar tax breaks for businesses, but what does FDA and FTC, which has jurisdictional authority over marketing statements made on foods and dietary supplements, have to say about conducting clinical trials overseas:

- Do companies see these tax incentives as reasons sufficient enough to do trials abroad rather than conducting them in North America?
- Are companies weighing the regulatory risks for conducting overseas clinical trials designed to substantiate marketing claims on dietary supplements destined for the US consumer?
- What are the regulatory risks?
- Are North American subjects even needed for a dietary supplement trial?
- What percentage of clinical trial data should be comprised of North American subjects?

Clinical Trials for FDA-Approved Drugs as the Model System

FDA Acceptance of Foreign Clinical Studies Even When Not Conducted Under an IND

On April 28, 2008, the FDA amended its regulations on the acceptance of foreign clinical studies not conducted under an investigational new drug application (IND) ("non-IND foreign clinical studies") as support for an IND or a new drug application (NDA), abbreviated new drug application (ANDA), or a biologics license application (BLA) (collectively known as "marketing applications" or "applications for marketing approval"). The final rule requires that such studies are conducted in accordance with good clinical practice (GCP), including review and approval by an independent ethics committee (IEC) and informed consent from subjects. The GCP requirements in the final rule encompass both ethical and data integrity standards for clinical studies. The final rule, which took effect on October 27, 2008, is codified at 21 CFR 312.120. It is intended to help ensure the protection of human subjects enrolled in non-IND foreign clinical studies as well as the quality of the resulting data. OK, we see that FDA permits non-IND foreign clinical studies as long as they are conducted properly, but is that the end of the story? Does FDA care about extrapolation from an overseas trial to the US population? We will answer that question shortly in spite of FDA regulations supporting clinical trials performed abroad.

Different Strokes for Different Folks

For investigators and sites in the US, drug research cannot begin without the filing of an IND application. FDA reviews the IND to determine if preclinical trials support that the drug is safe enough for human testing, whether the drug can be consistently and safely manufactured, and if the proposed clinical trials have reasonable safeguards to protect human subjects. For instance, the European Medicines Agency (EMA) in Europe and the Pharmaceuticals and Medical Devices Agency (PMDA) in Japan both have rigorous policies and procedures to protect human subjects in their countries.

To enhance efficiency for sponsors, investigators and sites abroad in developing countries, the FDA permits the submission of clinical trial data in the NDA for approval without submitting an IND to the FDA. This creates a seemingly too-good-to-be-true loophole for sponsors and the contract research organizations (CROs) who carry out these projects in developing countries. Is this a theoretical possibility or a realistic scenario accepted by the Agency? In other words, does FDA require subjects from North America as part of a multi-center strategy to accept clinical data toward a drug marketing application? Is FTC similarly aligned where they require substantiation data in North American subjects in order for companies to satisfy their statutory obligation to substantiate structure function claims, directed to the US consumer, on foods and dietary supplements?

What is driving clients aimed at the US market to complete foreign clinical trials?

Two major factors drive clients to consider trials in foreign countries, namely recruitment and cost. "Can you conduct food/nutraceutical/dietary supplement studies in foreign countries to gather data for US FTC's standard for having "competent and reliable scientific evidence?"

Legally, FDA has the authority to accept foreign data as the sole basis for marketing approval of drugs. 21 CFR 314.106(b) provides for the following:

1. The foreign data are applicable to the US population and US medical practice;
2. The studies have been performed by clinical investigators of recognized competence; and
3. The data may be considered valid.

In the absence of specific FDA regulations or guidance on foods, FTC, the arm with jurisdictional authority to evaluate substantiation evidence of marketing claims on food products, would look to what other agencies or even experts have said regarding this issue. Since US drugs permit foreign clinical data, then FTC would not have a reason to reject foreign clinical studies. While foreign clinical data can be used toward drug or food marketing approval, does the buck stop there? Do you require a bridging study? Should your clinical trial strategy include the US or North American population as a necessary component for final marketing approval of a drug?

FDA typically decides at review time whether the foreign data meet the criteria listed above (for drugs), but FDA CFSAN will not be involved in a clinical trial for foods, nutraceuticals, and dietary supplements. The factors FDA will consider if the foreign data are applicable to the US population is still valid for both US FDA and more importantly FTC, in the case of foods. These factors are found in ICH E5 Ethnic Factors in the Acceptability of Foreign Clinical Data and FDA's Guidance on E5. A key concept of E5 is that data from one region must be extrapolated to another region and that significant gaps may be addressed by conducting bridging studies in the reviewing region. In other words, your risk for doing a study outside of North America in Asia or even the continent of Australia most likely would require a bridging study after it is done.

ICH E5 defines ethnic factors as arising from two sources: extrinsic and intrinsic.

- Extrinsic Ethnic Factors — These are factors associated with the location, environment, and culture where a person resides. These factors tend to be less genetically, and more culturally and behaviorally determined.
- Intrinsic Ethnic Factors — These are factors that help to define and identify a sub-population and may influence the ability to extrapolate data from one population to another.

To simplify, extrinsic ethnic factors are the influences from outside. Examples include concomitant medicine (drug-drug interaction, drug-supplement interaction, drug-food interaction), food or beverages (alcohol), smoking, malnutrition, water deprivation, and environment. Intrinsic factors are those which are related to an individual: age, gender, genetic traits to metabolize substances, and susceptibility to disease states.

Why do Intrinsic Factors matter when conducting clinical trials?

The story of aegeline in the US highlights the importance of intrinsic ethnic factors and the appearance of serious adverse events in the form of irreversible liver injury in a sensitive, ethnic sub-population of the US.[1] Aegeline was introduced into the market without filing a New Dietary Ingredient (NDI) notification with FDA. The case of aegeline also highlights the importance of following the statutory rules to file an NDI notification to demonstrate reasonable expectation of safety prior to marketing (Pre-Market Notification for dietary supplements). Aegeline was found to induce liver disease post-market in a certain segment of the population that resided in the Pacific and Hawaiian Islands. Follow-up preclinical safety studies indicated significant mortality after administration of 10X and 3X mouse-equivalent doses (MED) of aegeline product. Increases in liver/body weight ratios as well as elevations in ALT and AST were observed in female B6C3F1 mice after 2X and 1.5X MED. Similar findings were also observed in a subchronic 90-day feeding study.[2] While aegeline highlights intrinsic factors involved in susceptibility to adverse events after ingestion of a food ingredient, the same factors are important when examining efficacy.

Drug efficacy and market approval is evaluated and controlled by US FDA CDER, but foods can also make structure function marketing claims, which must be supported by competent and reliable scientific evidence, the FTC and FDA substantiation standard. FTC is the US authority which evaluates whether a firm has met their regulatory burden for providing sufficient substantiation evidence for marketing claims on consumer products like foods and dietary supplements (a category of food). There is no premarket approval of claims in foods like there is with FDA and drugs; however, FTC performs post-market surveillance of products to determine whether the marketing claims and advertisements are truthful and not misleading. FTC will not tell you that running a clinical trial overseas is problematic. FTC will not provide guidance about whether claims can be substantiated using a foreign population that is intrinsically different from the US and Canada. They will simply inform companies of a post-market issue over marketing claims made in advertisements and labeling when the time is right. Similar to FDA, the FTC requires that the participants of the study be similar and representative of the population the food product is going to be marketed in, and they would look to federal guidance, final rules, and codified federal regulations to apply this standard.

[1] Klontz, K. C. et al. (2015). The Role of Adverse Event Reporting in the FDA Response to a Multistate Outbreak of Liver Disease Associated with a Dietary Supplement. Public Health Rep. Wash. DC 1974 130: 526–532.
[2] Miousse, I. R. et al. (2017). Safety assessment of the dietary supplement OxyELITETM Pro (New Formula) in inbred and outbred mouse strains. Food Chem. Toxicol. Int. J. Publ. Br. Ind. Biol. Res. Assoc. 109: 194–209.

When would you need or not require a bridging study involving a North American population?

If a food or drug is ethnically sensitive but the two regions are ethnically similar (for example, US and Canada) and there is sufficient clinical experience with related compounds, a bridging study is not required. A bridging study using a North American population would, in some cases, not be required if the food or drug ingredient is ethnically insensitive.

What factors in foods may indicate less sensitivity to ethnic factors (ethnically-insensitive qualities)?

A food would need to have all of the following qualities listed below in order for it to be considered ethnically-insensitive:

- Linear pharmacokinetics (pK) profile
- Flat pharmacodynamic curve for both efficacy and safety in the range of the recommended dose/serving level and dose regimen
- Wide therapeutic dose range
- Good tolerability
- Minimal metabolism or metabolism distributed along multiple pathways
- High bioavailability, less susceptibility to absorption effects
- Low potential for protein binding
- Little potential for food-drug, and food-food interactions
- Non-systemic mode of action

Criticisms from Federal Agencies with Running Foreign Clinical Trials outside North America

FDA has struggled to ensure the quality of active pharmaceutical ingredients, finished pharmaceutical products, dietary supplements and nutraceuticals (or dietary ingredients) used in dietary supplements manufactured in developing countries. [3],[4] The lax oversight in developing countries coupled with stricter enforcement of laws for US domestic manufacturers has reduced domestic manufacturing capacity, caused troubling quality issues, and increased the risk of drug shortages.

Although the state of clinical trial R&D in North America is still strong, the growth of research in the US has significantly eroded as sponsors increasingly conduct trials in developing countries. According to data from the FDA and the Department of Health and Human Services Office of the Inspector General (OIG), there has been an acceleration in the movement of trials intended for FDA product approval to foreign sites. From virtually no foreign clinical investigators in the early 1980s, 22% of Investigational New Drug (IND) clinical investigators resided outside the US in 2000; this increased to 43% in 2013.

[3] White CM. Generic drugs not as safe as FDA wants you to believe. Ann Pharmacother. 2020; 54:283-286.

[4] White CM. Understanding and preventing (N-nitrosodimethylamine) NDMA contamination of medications. Ann Pharmacother. 2020; 54:611-614.

The rate of growth in foreign research sites is mostly pronounced in central and eastern Europe (41.4% growth), Latin America (27.3% growth), Asia (mostly Russia, China, India, Korea, Japan, and Turkey: 25.6%) and other emerging areas (Africa Pacific Islands: 11.0%). In 2008, 80% of applications for drugs and biologics contained data from non-US studies, 78% of all participants were enrolled outside the US, and 8.3% of new drug applications (NDAs) were conducted entirely outside the US.

While factors, including cheaper labor costs and faster enrollment rates, make overseas trials more desirable, there are structural inequities between FDA oversight of investigators and sites in the US compared to abroad. Several high profile issues have arisen that should give biomedical, researchers, clinicians, patients, and those concerned with human rights reason to pause.

What's the downside for an overseas trial?

Let's take a look at recent activity by FDA. An advisory committee to the FDA overwhelmingly voted in February 2022 against recommending agency approval of a lung cancer drug (sintilimab) that was tested only in China and sold there. Sinilimab, an immunotherapeutic drug directed against tumors was developed and tested in China by Innovent Biologics, which entered into an agreement with Eli Lilly to permit its marketing in the US, once approved. Back to the drawing board. In particular, the FDA panel debated a longstanding issue: what standards should be used in approving drugs? Should a drug tested only in China or another country outside the US be accepted without domestic trials?

The long answer:

FDA officials cited a strong preference for multiregional trials able to support broader drug approval and use, as mapped out by the International Council of Harmonization (ICH) in its E-5 and E-17 clinical efficacy standards. FDA noted in its briefing document for the Oncologic Drugs Advisory Committee (ODAC) meeting that the more recent E-17 document advances the use of multiregional clinical trials as optimal for global registration of drugs, and that data from a single country trial does not allow for evaluation of treatment effects across geographic regions and subpopulations.[5]

The short answer:

The FDA panel sided in favor of US/North American trials. The only way to resolve the issue would be to conduct a bridging study whereby Tyvyt (sintilimab) could be compared to a different antitumor checkpoint inhibitor that is approved in the US in order to demonstrate statistically significant improvement in overall survival.

[5] FDA 2022. FDA Briefing Document: Oncologic Drugs Advisory Committee Meeting. February 10, 2022. BLA 761222 Sintilimab. https://www.fda.gov/media/156021/download.

How Much Data Needs to Come from the North American population?

There seems to be two sides of the coin. On one hand, FDA has made overtures and efforts to broaden clinical trials and accept foreign clinical data as a means to represent a full range of ethnic and racial patient groups. On the other hand, a drug tested only in a specific overseas country would not be wise.

So, what is the point of doing an overseas clinical trial in Australia when FDA may reject an NDA filing using data from a foreign clinical trial where there is "inadequate evaluation for safety and/or effectiveness of the population intended to use the drug, including pertinent subsets, such as gender, age, and racial subsets."[6]

A bridging study done in a North American population is required as the next step, but how much data needs to come from North America? A typical rule-of-thumb cited by experts is that at least 20% of the supporting clinical data should be from patients in US or Canada, since the ethnic makeup of Canada is very closely related to the US population. While a review done by the Department of Health and Human Services, Office of the Inspector General, in fiscal year 2008 concluded that the majority of subjects and sites in trials supporting US FDA New Drug Application (NDAs) approvals that year were located outside the US, every study was required to include North American subjects either as part of a multi-center drug trial involving US sites, or a bridging study completed in the US. When looking at trials between 2013 and 2017, the vast majority of US FDA drug clinical trials were conducted using subjects outside the US; however, all drug approvals were required to be completed in a significant proportion of the US population (see Figure 1 below). Therefore, the 20% rule is probably a fairly accurate assumption given the historical data of approved drug applications.

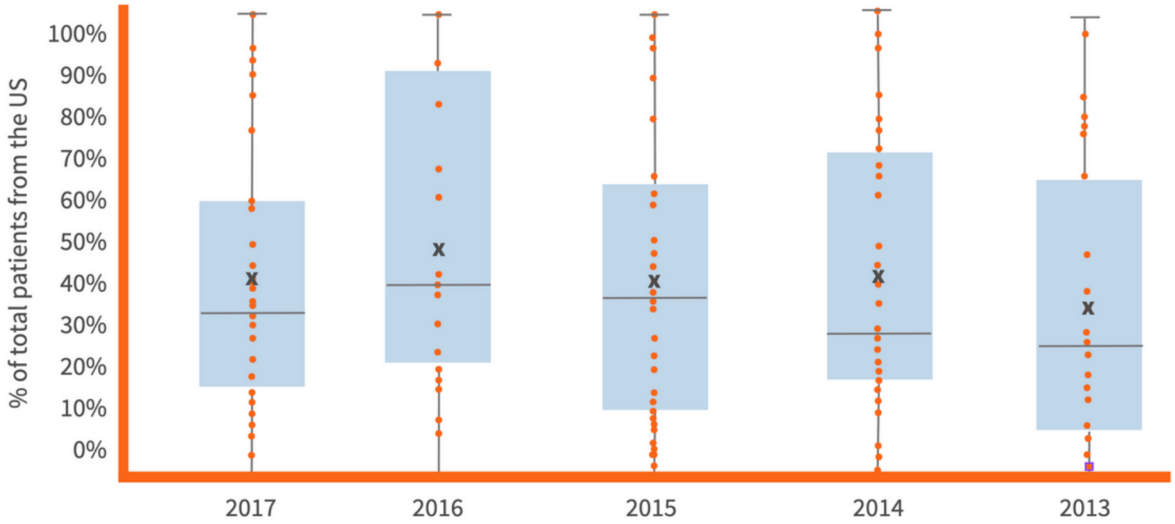

Figure 1. US Drug Approvals 2013-2017 — Percentage of Clinical Trial Participants from the US
Source: IQVA

[6] CFR 314.101(d)(3)

Does the US Government Evaluate Clinical Trials for Foods Differently Than They Do for Drugs?

Like any attorney would say, “It depends.” Foods are certainly different from drugs in the eyes of the US Government. Drugs are permitted to have side effects and therefore adverse events because there is an established benefit as a result of taking the drug for a specific therapeutic condition. The ephedrine alkaloid final rule established the risk-benefit analysis where the benefit of any food is automatically assumed to be zero (since it is not treating a disease) and therefore the safety risk of consuming that food should be zero. Unfortunately, it was an oversimplification by the courts because sponsors are conducting food and dietary supplement studies to establish a statistically significant benefit on some biomarker in healthy individuals. Foods can also be shown to reduce the risk of disease in a healthy population, enabling the authorization of a health claim for a food. Therefore, one could argue that the benefit of foods is indeed greater than zero for certain food ingredients backed by competent and reliable scientific evidence of efficacy for risk reduction of a disease marker.

Another difference is that drug trials are conducted on a specific unhealthy or diseased part of the overall population, intended for therapeutic intervention while clinical trials on dietary supplements and other foods must be conducted on the general healthy population. Therefore, marketing claims for drugs are largely dependent upon the proven benefit determined from an intervention type, randomized clinical trial (RCT) - the gold standard for competent and reliable scientific evidence. The specific language in marketing claims for drugs is therefore largely predetermined and guided by the disease population in the study and FDA’s Center for Disease Evaluation and Research (CDER); however, advertisers of prescription drugs can overplay their hand and make misleading statements, which are evaluated by the FTC. There is no equivalent organization like CDER which oversees clinical trials involving foods and dietary ingredients, other than the requirement for consent and Institutional Review Board (IRB) oversight and approval when human subjects are involved. FDA oversees labeling of food and dietary supplement products, including whether claims are disease claims or structure function claims, while FTC oversees whether those advertisements are truthful and not misleading.

FTC enforces compliance to their substantiation standard, a requirement for competent and reliable scientific evidence, behind all claims made on products or ingredients in the product. FTC also has subpoena authority to evaluate all evidence, including data from clinical trials, designed to support marketing claims made on products. It is no surprise that FTC is the government agency with authority to evaluate specific evidence in clinical trials for foods. So, while FDA CDER is reviewing the science in a clinical trial for a drug, FTC is tasked to evaluate the scientific validity and merits of a clinical trial conducted on a food making dietary supplement structure function claims.

Does the US Government Evaluate Clinical Trials for Foods Differently Than They Do for Drugs?

FTC advertising guidance speaks to the use of foreign trials only briefly, and in broad terms. Guidance on the competent and reliable standard states that the FTC will accept a clinical study conducted in a foreign country "as long as the design and implementation of the study are scientifically sound."[7] The guidance also notes briefly, and logically, that "[a]ny foreign research submitted [in a foreign language] to the FTC in the course of an investigation should be presented in English translation and with sufficient detail to allow the agency to evaluate the study."[8] The FTC's guidance alone might lead an advertiser to believe that a foreign trial will be viewed in the same light as any other trial, but recent statements by FTC staff suggest otherwise.

Statements by FTC staff have indicated growing skepticism toward foreign research from clinical trials conducted overseas, specifically regarding substation of dietary supplement structure function claims.[9] In June 2011, a trade group hosted a webinar on substantiating dietary supplement claims. Richard Cleland, assistant director of FTC's advertising division at the time, discussed the use of foreign clinical trials. He stated that although the FTC will accept any scientific evidence that meets the competent and reliable standard, many trials conducted in foreign countries "don't seem to necessarily have the same rigorous standards as the research that's conducted in the US." He stated, that "when [staff] starts looking at the underlying data [from foreign studies], we find a whole lot of garbage."

[7] See Federal Trade Commission (1998). Dietary Supplements: An Advertising Guide for Industry, pp.12. https://www.ftc.gov/system/files/documents/plain-language/bus09-dietary-supplements-advertising-guide-industry.pdf. Accessed December 12, 2022.
[8] See Federal Trade Commission (1998). Dietary Supplements: An Advertising Guide for Industry, pp.26. https://www.ftc.gov/system/files/documents/plain-language/bus09-dietary-supplements-advertising-guide-industry.pdf. Accessed December 12, 2022.
[9] Carolyn B. Phenicie, FTC Sees Red Flags In Studies Conducted Overseas To Support Claims, Tan Sheet (June 13, 2011)

In the absence of their own final rule (legally binding) or guidance (representing their current thinking on a topic), FTC will look to see what other organizations have said about the topic. FTC would therefore look to FDA CDER final rules and the Codified Federal Regulations. In short, FTC would look to what FDA CDER has to say about foreign clinical trial participants being representative of the US population. We already know that FDA CDER typically requires bridging studies in a North American population to extrapolate the results of a drug clinical trial conducted overseas.

When are Foreign Clinical Trials Representative of the US Population?

It depends… largely on the demographics of the foreign country. FTC will also look to determine whether the study population, where the foreign clinical trial was conducted, was representative of the population intended for consumption of the product (United States). For example, Canada has a melting pot of many foreign immigrants from a wide range of countries and a large group of predominantly European ancestry. The US is also a melting pot of immigrants with the largest minority group coming from Mexico.

As of 2020, White Americans are the racial majority in the US, with non-Hispanics whites representing 57.8% of the population. Hispanic and Latino Americans are the largest ethnic minority, comprising 18.7% of the population, while Black or African Americans are the second largest racial minority, making up 12.1%.[10]

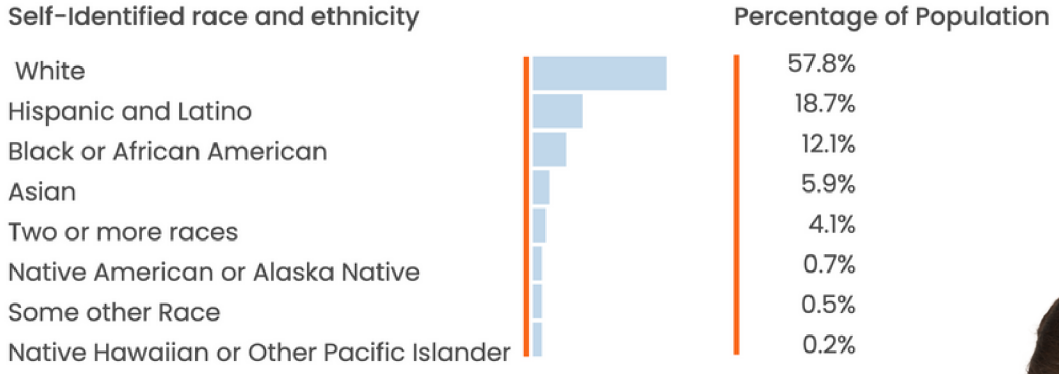

Figure 2. 2020 US Census, Including a separate category for Latino-Hispanic.[11]

In 2016, over 250 ethnic origins or ancestries were reported by the Canadian population; British Isles and those territories of French origins are still among the most prevalent. The vast majority of Canadians (close to 20 million people) have reported European origin or ancestry. Chinese ancestry (1.8 million), East Indian ancestry (1.4 million) and Filipino ancestry (837,130 peoples) are among the 20 most common ancestries reported by the Canadian population.

[10] Racial and Ethnic Diversity in the United States: 2010 Census and 202 Census. US Census Bureau. August 12, 2021. Retrieved February 14, 2023
[11] A Breakdown of 2020 Census Demographic Data. NPR. Retrieved February 14, 2023. https://www.npr.org/2021/08/13/1014710483/2020-census-data-us-race-ethnicity-diversity..

While individuals from Latin, Central or South American origins are not the predominant minority in Canada, they comprise a significant contribution to the overall Canadian population. The fact that Canada comprises Latino/Hispanic, North American Indians, and Asians, and peoples of African descent is why it is considered to be fairly representative of US population ethnicity and demographics.

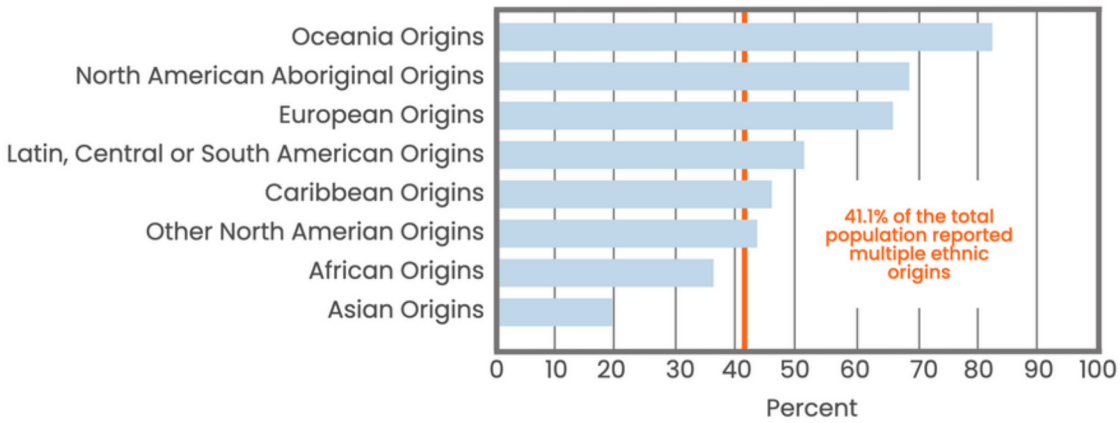

Figure 3. Percentage of multiple ethnic origin responses, by region of ethnic or cultural origin, in Canada. Source: Statistics Canada, Census of Population, 2016.

Once you see the glaring differences in ethnicity between the North American population and Asian countries, it is understandable why conducting foreign clinical trials in Japan, Korea, or China is not representative of the North American population. While Australian might be considered a melting pot, it also does not share the same melting pot diversity in ethnicity characteristics of the North American population.

Rank	Principal Ancestral Ethnicity or Nationality	Share of Australian Population
1	British	67.4%
2	Irish	8.7%
3	Italian	3.8%
4	German	3.7%
5	Chinese	3.6%
6	Aboriginal Australian	3.0%
7	Indian	1.7%
8	Greek	1.6%
9	Dutch	1.2%
10	Other	5.3%

Figure 4. Ethnic Background of Australia.

While Australia contains a significant contingent of Chinese minorities, it does not contain any significant groups of Latino/Hispanic, African, or Native North American heritage. Therefore, the results of safety, healthy biomarkers, and other efficacy endpoints evaluated on a food ingredient for a clinical trial conducted overseas in an Asian country or continent of Australia could not be extrapolated to the US population as a whole. A bridging study on a North American population would have to be conducted in addition.

FDA Changing Their Policy on “Me Too Drugs”, Requiring Data from North America

The consideration of ethnicity and the decision to conduct clinical trials exclusively in foreign countries is now being scrutinized when FDA reviews evidence for approval of “me too drugs”. In the past, FDA has approved certain therapies using exclusively limited foreign clinical data for serious diseases lacking effective treatment as well as “me too” drugs from classes that have already been previously approved using US clinical data. However, FDA has now clarified their stance on applications for “me too drugs” stating that the applications are inadequate if they present data from a single foreign study site. As described previously, an example of FDA’s stance on their new drug marketing application requirement was observed following a meeting of FDA’s ODAC in February 2022 that addressed the degree of generalizability and applicability of data from a foreign country to support approval of a drug for US patients (e.g., sintilimab). In this meeting, it was discussed whether to approve sintilimab to treat metastatic non-small-cell lung cancer (NSCLC) based on one pivotal trial conducted in China. In the end, FDA officials opposed approval of the drug, citing concerns that the drug’s pivotal study conducted in China had limited applicability to the US population. So even when there are few drug options for US patients, FDA requires a certain level of US or North American clinical data. Furthermore, FDA indicated a strong preference for multiregional trials, as they support broader drug approval and use while data from a single country trial does not permit for the evaluation of treatment effects across geographic regions and subpopulations.

Therefore, even for drug classes/categories that have already been approved, FDA is now requiring US/North American populations for “me too” drugs in the same class as others and drugs “for serious diseases lacking effective treatment”. Evidently, FDA has demonstrated that the Agency will not lower their standard for evidence substantiation and considers applications for “me too drugs” inadequate if they present data from a single foreign study. Furthermore, FTC looks to federal guidance first (updated FDA policies) when applying their thoughts on what constitutes adequate substantiation in clinical trials for structure function marketing claims made on foods and dietary supplements directed at the US consumer.

What Else is Required for Substantiation of Structure Function Claims Made for a Dietary Supplement?

If a clinical trial involving a US dietary supplement is pursued, premarket regulatory hurdles to the US market are nonexistent, unless the dietary ingredient is new. A thorough investigation of the ingredient’s regulatory status may be required. This is provided by companies providing regulatory services in the form of a regulatory status memorandum letter. If the ingredient is novel (as in Europe, for example) or new in the US, navigation of the US NDI process, which involves notification and not premarket approval, or the GRAS conclusion process may be required. This may require an NDI notification or self-GRAS conclusion. Even before that step is taken, a pathway to market analysis may help you determine whether the GRAS or NDI pathway is the best possible regulatory solution for your ingredient. Finally, a gap assessment may be useful to better understand the knowledge gaps you have in what is currently known about your ingredient and what is required for GRAS or NDI acknowledgement.

Conclusions

1. Do not rely on foreign subjects located outside of North America as the basis for any structure function substantiation study or drug application approvals.
2. Even for drug classes/categories that have already been approved, FDA is now requiring US/North American populations for “me too” drugs in the same class as others and drugs “for serious diseases lacking effective treatment”.
3. Follow the 20% rule to either do a bridging study in a US or North American population for your drug clinical trial or nutraceutical/dietary supplement clinical trial.
4. If you only have the funding to do one clinical trial for substantiation of your nutraceutical/dietary supplement product, do it in a North American population as that is the population that matters most to FTC and FDA in terms of meeting the substantiation standard for possessing competent and reliable scientific evidence.
5. Inquire as to the regulatory status of your food ingredient to know if it is a “new” dietary ingredient (NDI) or novel ingredient requiring GRAS (Regulatory Status Memorandum).
6. A pathway to market may help you determine whether the GRAS or NDI pathway is the best possible regulatory solution for your ingredient.
7. A gap assessment may be useful to better understand the knowledge gaps you have in what is currently known about your ingredient and what is required for GRAS or NDI acknowledgement.

About Our Company

MISSION

KGK Science is a leading CRO in the nutritional, cannabinoid, hemp and psychedelic industries, providing scientific and regulatory services to generate profit for our clients.

VISION

To be the premier and most trusted CRO for nutritional, cannabinoid, hemp and psychedelic scientific research by revolutionizing the way people think about evidence-based nutrition.

Corporate Facts

1997
in business for 25+ years

30,000+
Participant Database

150+
Publications

350+
Clinical Trials

Supporting Your Business with High-Quality Expertise

KGK Science is a premium contract research organization (CRO) offering high-quality clinical research trials and expert regulatory support for the nutraceutical, cannabis, hemp and psychedelic industries.

Since 1997, KGK has successfully helped hundreds of companies from custom-designed clinical trials and regulatory planning (gap assessments/pathway to market analysis) for C Suite executives to safety assessments for entering new markets. Equipped with state-of-the-art technologies, novel research techniques, and a seasoned team of industry experts, KGK Science remains at the forefront of our industry, consolidating scientific, clinical, commercial, and regulatory expertise with innovation and agility to serve the expanding needs of global business and consumers.

Pre-clinical Services

- Gene Toxicity
- General Toxicity Testing
- Neurobehavioral Toxicity Testing
- In Vitro Studies
- Proof-of- Concept Studies
- Safety for Animal Feeds

Premium Clinical Research

- Clinical Trial Design & Execution
- Clinical Research Consulting Services
- Protocol Development
- Manuscript Writing
- Pharmaceutical Trial Services

Expert Regulatory Services

- Regulatory Planning for C Suite
- Executives
- Gap Assessments Pathway to Market Strategies
- Regulatory Risk Assessment of Products/Ingredients
- Safety Dossiers/Toxicity Assessments
- Claim Substantiation Files
- Regulatory Consulting
- Product Licensing
- Serious Adverse Event Reporting

KGK Science | Premium Clinical Research & Regulatory Expertise

Stake your claim.

WWW.KGKSCIENCE.COM

Contact KGK Science today for all your clinical trial and regulatory needs.

London - Head Office
275 DUNDAS STREET
Tower A, Suite 1605
London, Ontario, Canada N6G 3L1
1-519-438-9374 | sales@kgkscience.com