

### FDA Releases Final Guidance for Evidence-Based Review System for the Scientific Evaluation of Health Claims

On January 16, 2009, the Food and Drug Administration (FDA) announced the availability of a final Guidance for Industry entitled, "Evidence-Based Review System for the Scientific Evaluation of Health Claims" (Scientific Evaluation of Health Claims Guidance).<sup>1</sup> The new Guidance represents FDA's current thinking on the evaluation of scientific evidence for both significant scientific agreement (SSA) health claims and qualified health claims (QHCs). The Guidance replaces two FDA guidance documents, "Interim Evidence-based Ranking System for Scientific Data," which addressed the scientific review of qualified health claims, and "Significant Scientific Agreement in the Review of Health Claims for Conventional Foods and Dietary Supplements" (SSA Guidance).<sup>2</sup>

Thus, instead of separately reviewing SSA health claims and QHCs, FDA intends to use a single approach as set forth in this Guidance for evaluating the scientific evidence in petitions that are submitted either for an SSA health claim or for a QHC. Under the steps outlined in this Guidance, FDA will determine whether the scientific evidence meets the SSA standard or, if not, whether the evidence supports a qualified health claim.

#### FDA's Evidence-Based Review System

FDA's evidence-based review system of health claims involves a systematic science-based evaluation to determine the strength of the scientific evidence to support a proposed claim about a substance/disease relationship.<sup>3</sup> FDA states that it will evaluate the scientific evidence for health claims through the following series of steps:

- Identify scientific studies that evaluate the substance/disease relationship;
- Identify surrogate endpoints of disease risk;
- Evaluate human studies;
- Assess the methodological quality of the scientific studies;
- Evaluate the totality of the scientific evidence;
- Assess SSA;
- Analyze the specificity of the claim language of a QHC; and
- Reevaluate existing SSA claims and existing QHCs.

<sup>1</sup> 74 Fed. Reg. 3060 (Jan. 16, 2009), available at <http://www.fda.gov/OHRMS/DOCKETS/98fr/E9-959.pdf>.

<sup>2</sup> According to FDA, this Guidance does not reflect any change in FDA's understanding of what constitutes SSA and many of the explanations of SSA in this Guidance are taken verbatim from the 1999 SSA Guidance.

<sup>3</sup> FDA's approach as outlined in this Guidance overlaps with the approach FDA set forth in its recently released Guidance for Industry, "Substantiation for Dietary Supplement Claims Made Under Section 403(r)(6) of the Federal, Food, Drug, and Cosmetic Act" (Substantiation Guidance). See 74 Fed. Reg. 304 (Jan. 5, 2009); see also, Covington & Burling LLP E-Alert, "FDA Releases Final Guidance for Substantiation of Dietary Supplement Claims" (Jan. 9, 2009) (available by clicking [here](#)).

## Identifying Scientific Studies that Evaluate the Substance/Disease Relationship

First, FDA will review the scientific studies that are submitted in petitions seeking health claims and will search for and review on its own initiative any additional studies that are relevant to the proposed health claim. FDA will then focus its review primarily on human intervention and observational studies, which the agency believes provide evidence from which scientific conclusions can be drawn about the substance/disease relationship in humans.

Next, FDA will determine whether the studies identify a substance that is measurable. For example, a food component that is the subject of a claim could be a nutrient or a dietary ingredient.

FDA will also consider whether the studies identify a specific measurable disease or health-related condition. For example, because FDA considers cancer a collection of more than 100 separate diseases, FDA will evaluate studies for each form of cancer individually in a SSA health claim or QHC petition to determine whether the scientific evidence supports the potential substance/disease relationship for that type of cancer.

Finally, FDA will categorize the studies by type as either intervention studies or observational studies. FDA states that it will find the most convincing scientific evidence to support a health claim from a well-conducted intervention study.

For any given study, however, FDA will not extrapolate evidence conducted on selected populations to different populations if such extrapolation is not scientifically valid. For example, FDA will not extrapolate an association between a substance and a reduced risk of juvenile diabetes to the risk of diabetes in adults.

## Identifying Surrogate Endpoints of Disease Risk

FDA will determine, when relevant, whether appropriate biomarkers were used in the studies in place of onset of disease. Because there can be multiple pathways to a specific disease, an acceptable surrogate endpoint that is involved in a single pathway may not be applicable to certain substances that are involved in a different pathway. For example, LDL cholesterol levels cannot be used in evaluating the relationship between the long chain omega-3 fatty acids and risk of cardiovascular disease because these fatty acids generally have no effect on LDL cholesterol levels, even though omega-3 fatty acids have been associated with a lower risk of cardiovascular disease.

## Evaluating Human Studies

At the heart of FDA's evidence-based review process is FDA's evaluation of each human study.

In evaluating whether to use an intervention study as scientific evidence of the substance/disease relationship, FDA will analyze:

1. Whether the study subjects were healthy or had the disease that is the subject of the health claim. FDA will consider evidence from studies using subjects with the disease only if it is scientifically appropriate to extrapolate to individuals without the disease.
2. Whether the disease that is the subject of the claim was measured as a "primary" endpoint. Most often, scientific conclusions about a disease endpoint cannot be

drawn from a study unless the study evaluates that outcome as a primary endpoint.

3. Whether the study includes an appropriate control group. Without an appropriate control group, FDA believes that scientific conclusions cannot be drawn about a substance/disease relationship. Special protocols need to be taken in studies that analyze the effect of whole foods rather than food components.
4. Whether the study was designed to measure the independent role of the substance in reducing the risk of a disease. In many studies involving food components, it may not be possible to determine the independent effect of the food component when whole foods or multi-nutrient supplements are used. Such studies will be less likely to provide scientific evidence of the substance/disease relationship.
5. Whether the relevant baseline data was significantly different between the control and intervention group. Studies in which the baseline levels between the control and intervention groups are significantly different are unlikely to provide scientific evidence of the substance/disease relationship because of uncertainty in interpreting the findings.
6. Whether and how the results from the intervention and control groups were statistically analyzed. FDA intends to use only studies that include appropriate statistical analyses between the control group and the intervention group.
7. Whether the biomarker used and measured was appropriate. FDA intends to use only studies that measure appropriate surrogate endpoints.
8. How long the study was conducted. FDA does not intend to use studies in which the study is run for a short period of time such that FDA cannot evaluate the effects of the substance.
9. If the intervention involved dietary advice, whether there was proper follow-up to ascertain whether the advice resulted in altered intake of the substance. FDA does not intend to use studies that involve dietary advice in place of a prescribed diet unless the studies assess whether the dietary advice resulted in a change in intake of the substance.
10. Where the studies were conducted. FDA does not intend to use studies conducted in study populations that are not relevant to the general U.S. population or subgroup identified in the proposed health claim if differences in the study population mean that the study results cannot be extrapolated to the U.S. population or subgroup.

In evaluating whether to use an observational study as scientific evidence of the substance/disease relationship, FDA will analyze:

1. The type of information collected. When biological samples are used, the study should demonstrate a strong correlation between the intake level of the substance and the level in the biological sample.
2. Whether the study used scientifically acceptable and validated dietary assessment methods to estimate intake of the substance. Dietary assessment methods such as 24-hour diet recalls, diet histories, and food frequency questionnaires each have limitations and must be validated.

3. Whether the study evaluated the relationship between a disease and a food or a food component. FDA is unlikely to use observational studies as scientific evidence of a relationship between a food component and a disease, because it is difficult to ascertain the effect of an individual food component in such studies. FDA will, however, use observational studies as scientific evidence of associations between a whole food and a disease.

### **Assessing the Methodological Quality of the Scientific Studies**

FDA will independently rate the methodological quality of each remaining study with a high, moderate, or low quality rating. FDA will base the quality rating on study design, data collection, the quality of the statistical analysis, the type of outcome measured, and study population characteristics. FDA will eliminate any studies receiving a low quality rating from further review.

In rating intervention studies, FDA will consider whether the studies (1) were randomized, blinded, and placebo controlled, (2) provided the inclusion/exclusion criteria and key information on the study population, (3) assessed and explained subject attrition, (4) verified subject compliance, (5) provided baseline data for all subjects initially enrolled or for subjects who completed the study, (6) measured disease incidence or a surrogate endpoint of disease risk, and (7) verified onset of disease using reliable sources.

In rating observational studies, FDA will consider whether the studies (1) adequately adjusted for confounders of disease risk so that observed effects on risk of disease that may be due to confounders are not incorrectly attributed to the substance of interest, (2) used reliable dietary assessment methods to estimate dietary intake, (3) measured disease incidence or a surrogate endpoint of disease risk, and (4) verified onset of disease using reliable sources.

### **Evaluating the Totality of the Scientific Evidence**

FDA will evaluate as a whole, the strength of the total body of publicly available scientific evidence. The strength of the totality of the scientific evidence will depend on (1) the type of studies conducted (intervention or observational), (2) the number of each type of study and the number of subjects per group, (3) the methodological quality rating (high, moderate, or low), (4) the outcome of each study (e.g., beneficial effect, no effect, adverse effect), (5) the consistency among the studies (the greater the consistency among the studies showing a beneficial relationship, the greater the level of confidence that a substance/disease relationship exists), (6) whether any of the study results have been replicated, and (7) the relevance of the evidence to the general U.S. population or to the target subgroup. Based on the totality of the scientific evidence, FDA will determine whether the scientific evidence meets the SSA standard or whether the scientific evidence is credible to support a qualified health claim for the substance/disease relationship.

### **Assessing SSA**

FDA will rely on the approach it has used in the past for determining SSA, which is its best judgment as to whether qualified experts would likely agree that the scientific evidence supports the substance/disease relationship that is the subject of a proposed health claim. FDA accords the greatest weight to the conclusions of federal government scientific bodies and typically finds SSA when the validity of a substance/disease relationship is supported by such conclusions. For health claims that meet FDA's SSA scientific standard, FDA will authorize these claims as it has in the past by publishing a final rule or an interim final rule in the Federal Register.

## Analyzing the Specificity of a QHC

If FDA determines that the totality of the scientific evidence for a substance/disease relationship is credible but does not meet the SSA standard, FDA will require the proposed claim to include qualifying language that expresses the level of scientific evidence to support the relationship. For a QHC supported by credible evidence, FDA will issue a letter stating its intent to exercise enforcement discretion.

## Reevaluating Existing SSA Claims and Existing QHCs

Finally, as an ongoing effort, FDA will use the steps as outlined in this Guidance to reevaluate existing health claims, either on its own initiative or in response to a petition. FDA intends to evaluate new information that becomes available to determine whether it necessitates a change to an existing SSA health claim or an existing QHC. Such new information could support the revision of health claim language, support the change of an SSA claim to a QHC or vice versa, or raise safety concerns about a substance so that there is no longer support for an existing health claim.

If you have any questions concerning the material discussed in this client alert, please contact the following members of our food & drug practice group:

Eugene Lambert	202.662.5422	<a href="mailto:elambert@cov.com">elambert@cov.com</a>
Jeannie Perron	202.662.5687	<a href="mailto:jperron@cov.com">jperron@cov.com</a>
Miriam Guggenheim	202.662.5235	<a href="mailto:mguggenheim@cov.com">mguggenheim@cov.com</a>
MaryJoy Ballantyne	202.662.5933	<a href="mailto:mballantyne@cov.com">mballantyne@cov.com</a>

---

This information is not intended as legal advice, which may often turn on specific facts. Readers should seek specific legal advice before acting with regard to the subjects mentioned herein.

Covington & Burling LLP is one of the world's preeminent law firms known for handling sensitive and important client matters. This promotional communication is intended to bring relevant developments to our clients and other interested colleagues. Please send an email to [unsubscribe@cov.com](mailto:unsubscribe@cov.com) if you do not wish to receive future emails or electronic alerts. Covington & Burling LLP is located at 1201 Pennsylvania Avenue, NW, Washington DC, 20004-2401.

© 2009 Covington & Burling LLP. All rights reserved.