

2006 Cardiovascular Biomarkers And Surrogate Endpoint Symposium

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The Use of Biomarkers for FDA Regulatory Decision Making – Health Claims

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The Center for Food Safety and Applied Nutrition (CFSAN) is delighted to co-sponsor this symposium, and as you will see, surrogate endpoints are critical in evaluating the efficacy of foods and food components, such as nutrients in the risk reduction of chronic disease in the general healthy population. Within CFSAN, I am in the division of Nutrition Programs and Labeling. This division is responsible for the authorization of health claims, which you may have seen on various dietary supplements or conventional foods. This division is also responsible for regulating the nutrition/supplement facts label that provides the key nutritional components within a conventional food or dietary supplement.

Now, let me first explain health claims because this is where surrogate endpoints are extremely important for our evaluation process. The definition of a health claim, based on the Code of Federal Regulations, is that it characterizes the relationship between a substance and a disease or a health-related condition. A substance can be one of two things. It can be a specific food, such as salmon, or it can be a food component, such as omega 3 fatty acids that are present in conventional foods or in a dietary supplement. We review health claims for various diseases, including cardiovascular disease, cancers, macular degeneration, Type II diabetes, osteoporosis, and osteoarthritis. A health-related condition can be one of two things. It can be a condition that is so equivalent to the disease, as to be indistinguishable from the disease, such as hypertension for cardiovascular disease. It can also be a surrogate endpoint for disease risk, for example low-density lipoprotein (LDL) cholesterol for coronary heart disease.

We evaluate the evidence to determine if a food or a food component (and this is getting to be more and more interesting with bioactive food components) can either modify the surrogate endpoint or actually alter the onset of the disease. It can take a very long time with dietary and nutrient interventions to determine the benefits on a clinical disease endpoint, so most studies that we review measure risk biomarkers or surrogate endpoints.

Health claims are for the labeling of conventional foods and dietary supplements and proposed health claims are petitioned by the food and supplement industry. Petitioners are required, as detailed in the Code of Federal Regulations, to submit the total body of scientific evidence that is related to the petitioned health claim. Within the petition, the

company will tell us what health claim they would like for FDA to review. So via petitions, we can receive many articles. Petitions can include meta-analyses, animal studies, in vitro studies, studies that are not relevant at all to the substance-disease relationship, and then preferably, we receive human intervention and observational studies. These petitions can include up to 500 articles. We are not involved up front in the design of the study to ensure that once the study is completed, that it will provide answers to address the health claim. Therefore, the studies that are submitted in the petition are usually not designed with the intention of supporting a health claim.

Authorized health claims first came about in 1993, based on the Nutrition, Labeling and Education Act. It was determined that the level of scientific evidence must meet the significant scientific agreement standard – the demonstration that there is a relationship between the food or food component which is recognized by qualified scientific experts. This is the type of claim found on a food product or on a dietary supplement which states that “substance X may reduce the risk of disease Y” with the understanding that disease is multifactorial and nutrition is a small part of that in primary prevention. The FDA, in response to the petition, drafts the proposed rule which goes out for public comment and then based on the public comment and other information, the final rule is drafted.

In the early 1990’s when FDA first evaluated ten claims that Congress directed FDA to evaluate, six were approved. There were four that the agency determined did not meet the significant scientific agreement standard, and so they were denied. Subsequently the FDA lost in court over First Amendment commercial free speech. It was determined that if there was a way to qualify these health claims to reflect the level of scientific evidence, even though the evidence was fairly minimal, then FDA was required to do that. As a result, qualified health claims have been around since 1999. There is less scientific evidence required for qualified health claims than for authorized health claims; therefore, some type of qualifying language is required. Some examples of qualifying language include “limited evidence suggests” or “its highly uncertain”, which reflects the level of scientific evidence. Qualified health claims are issued through letters of enforcement discretion.

Finally, there are FDAMA health claims which are based on authoritative statements from scientific bodies within the US Government, such as HHS, USDA, CDC, and the National Academy of Sciences. The purpose of FDAMA notifications is to help bypass the agency’s extensive scientific review process and to issue a health claim that reflects the language that is cited in these authoritative reports. The level of scientific evidence for these claims must meet the significant scientific agreement standard.

When FDA is reviewing the studies included in a petition, the relevant studies are reviewed through an evidence based review system. We first identify the substance and disease and then determine what studies are going to help us in evaluating the scientific evidence for this particular relationship. Next, we identify the human interventional and observational studies that can support this specific relationship. We also use animal data to understand the causal mechanism by which this relationship can occur. Once we have identified the relevant human intervention and observational studies, we evaluate certain

aspects of each study, such as how the disease is measured and the use of biomarkers or surrogate endpoints for risk of a chronic disease. Next, we categorize the studies as interventional, cohort, case controls, or other types of observational studies and rate them for their methodological quality. Then we rate the strength of the body of the scientific evidence.

When we evaluate the evidence for a particular claim, the incidence of the disease is considered to be the most reliable endpoint, but we also look at studies that have measured validated surrogate endpoints, in consult with NIH and CDER. For cardiovascular disease, we currently rely on three surrogates for predicting risk: total and LDL cholesterol and blood pressure. It is recognized that not all nutrients work through these surrogate endpoints and that some nutrients may reduce the risk of cardiovascular disease through mechanisms other than through these endpoints. It is a challenge to determine what to do with studies that are measuring endpoints, such as inflammatory markers, where the evidence does not yet validate their use as surrogates of cardiovascular disease. For example with some foods, such as green tea, the mechanism of action is still questionable.

Some examples of where FDA has used surrogate endpoints in reviewing qualified health claims include: monounsaturated fatty acids and blood total/LDL cholesterol (heart disease); tomatoes, lycopene and colorectal polyps (colorectal cancer); chromium picolinate and elevated blood sugar and insulin resistance (type 2 diabetes); and calcium and bone mineral density (osteoporosis). Some examples of the authorized health claims that have met the significant scientific agreement standard include sodium and hypertension, saturated fat and coronary heart disease, fruits and vegetables that contain a certain level of fiber and heart disease, soy protein and heart disease and most recently the phytosterols and heart disease. All of these heart disease claims relied on total and LDL cholesterol levels for evaluating the relationship between the nutrient or food and the disease.

In conclusion, we hope that there can be increased interaction between those interested in surrogate endpoints for primary prevention (risk reduction) of cardiovascular disease and those that are interested in surrogate endpoints for secondary prevention and treatment of disease. It is expected that there are common mechanisms by which nutrients and drugs are beneficial for chronic diseases, such as cardiovascular disease.