U.S. PERSPECTIVE ON THE CHALLENGE OF QUALIFYING BIOMARKERS FOR USE IN FOOD-RELATED HEALTH CLAIMS

Paula R. Trumbo, Ph.D.
Nutrition Programs
Office of Nutrition, Labeling and Dietary Supplements
Center for Food Safety and Applied Nutrition
Health Claims

Causal relationship between a substance and a disease or health-related condition for the general U.S. population or subpopulation

- Substance – food (salmon) or food component (EPA/DHA)

- Disease – damage to an organ, structure or system of the body such that it does not function properly (e.g. CHD, site-specific cancer), or a state of health leading to dysfunctioning (e.g. hypertension or a surrogate endpoint of disease risk) (called a health-related condition)

21 CFR 101.14
Diseases and Surrogate Endpoints of Disease Risk

CHD – Total/LDL cholesterol, blood pressure
Colon/rectal cancer – adenomatous polyps
Diabetes – Blood sugar levels, insulin resistance
Osteoporosis – Bone mineral density
Dementia – Mild cognitive impairment

Consult with NIH institutes and FDA Center for Drug Evaluation and Research (CDER)
Authorized Health Claims

• Pre-market review of a petition (sometimes agency-initiated)

• Meet the significant scientific agreement (SSA) standard – strong standard and unlikely to be reversed with new data

• Evaluated through the rule-making process

• Published as a final rule in the Federal Register and in the Code of Federal Regulations
Qualified Health Claims

- Pearson v Shalala 1999 (U.S. Appeals Court)
  - Lawsuit regarding FDA decision not to authorize 4 health claims on basis of no significant scientific agreement (First Amendment/commercial free speech)
  - Decision: FDA should provide for claims that do not meet the standard, if properly qualified and not misleading
Qualified Health Claims

• Based on scientific evidence that is credible but does not meet the SSA standard

• Include qualifying claim language to prevent consumers from being misled about the level of scientific support for the claim

• Considered under FDA’s exercise of enforcement discretion (\textit{not} authorized by regulation)
Health Claims

- Premarket review of authorized and qualified health claims

- Premarket review includes a regulatory and scientific review

- For the labeling of conventional foods and dietary supplements
Scientific Review of Health Claims

The scientific review of the evidence for SSA health claims and qualified health claims* is the same review.

The level of credible scientific evidence is a continuum.

*Require less scientific evidence than health claims and therefore require qualifying language.
Guidance for Industry

Evidence-Based Review System for the Scientific Evaluation of Health Claims
Reviewing the Scientific Evidence

- Identify relevant and reliable studies ✓
- Classify relevant and reliable studies
- Rate relevant and reliable studies for quality
- Evaluate the strength of the evidence
- Determine whether evidence supports SSA or a QHC
Health Claims Characterize a Risk Reduction Relationship Between Diet and Disease or Health-Related Condition

- Food or Food Component
- Health-Related Condition (e.g., hypertension or LDL cholesterol)
- Drug

Disease Risk Reduction

Treat/ Cure Disease, mitigate Symptoms or Signs
Fatal Flaws of a Relevant Human Study

Intervention

- No control group
- No statistics conducted between control and intervention group
- Studies conducted on a diseased or malnourished population
- Risk biomarker that is not considered a surrogate endpoint for disease risk (HDL cholesterol, macular pigment density)
- Not possible to determine independent effect of substance (e.g., an individual vitamin that is provided in a multi-nutrient supplement) – Study must demonstrate independent role of substance or substances combined (calcium and vitamin D)
- Matrix effect (e.g., phytosterols)
Strength of the Relevant Evidence

- Type of studies
- Quality of study
- Quantity of studies and study sample size
- Consistency and replication of findings
  - Beneficial findings based on statistical significance ($P<0.05$)
  - Magnitude of effect used for comparing substances within a study
- Relevance to general population or target subgroup – high risk, gender, dose
IOM Study

CFSAN funded the study and report “Evaluation of Biomarkers and Surrogate Endpoints in Chronic Disease”

Framework for the qualification of chronic disease risk biomarkers
IOM Study Recommendations

• Biomarker evaluation process should consist of the 3 following steps:
  – Analytical validation – biomarker assay method
  – Biomarker qualification – assessment of the evidence between the biomarker and the clinical outcome
  – Utilization – determine whether the above two provide sufficient support for the proposed use

• FDA should convene expert panels to evaluate biomarkers
Biomarker Qualification

- Evaluate the link between the biomarker and the clinical endpoint (Hill’s Criteria — e.g., strength of effect, consistency, exposure precedes effect, mechanism/biological pathway)
  - Clinical trials
  - Observational studies

IOM, 2010
Biomarker Qualification

• Evidence that the intervention impacting the biomarker also impacts the clinical endpoint
  – Clinical trials
    • Need to consider multiple mechanisms
    • Need to consider the population (e.g., those with other pathophysologies)

IOM, 2010
Biomarker Qualification: Optimal Situation

IOM, 2010
IOM Case Study: LDL cholesterol

- Cholesterol directly involved in process for atherosclerotic CVD
- The strength of LDL-C as a surrogate is not absolute due to the heterogeneity of CVD processes
- Therefore, LDL-C cannot fully account for all the variability that leads to a particular outcome
- However, there is a high probability that lowering LDL-C for several interventions decreases the risk of CVD

IOM, 2012
IOM Case Study: C-Reactive Protein

- Inflammation is clearly involved in the development of atherosclerosis
- CRP is an independent predictor of CVD risk, however, unclear whether CRP participates causally in the pathophysiology of CVD
- Therapeutic interventions have not specifically inhibited CRP
- The effects of absence, inhibition and lack of function of CRP has not been tested
- Incomplete understanding of CRP’s normal function or its role in the disease process prevents the use of CRP as a surrogate endpoint

IOM, 2010
FDA Center for Drug Evaluation and Research (CDER) Biomarker Qualification Program

The goals of the CDER Biomarker Qualification Program are to:

- Provide a framework for scientific development and regulatory acceptance of biomarkers for use in drug development
- Facilitate integration of qualified biomarkers in the regulatory review process
- Encourage the identification of new and emerging biomarkers for evaluation and utilization in regulatory decision-making
- Support outreach to relevant external stakeholders to foster biomarker development
CDER Biomarker Qualification

A conclusion that within a carefully and specifically stated “context of use” the biomarker has been demonstrated to reliably support a specified manner of interpretation and application in drug development
CDER Biomarker Qualification

Context of Use

Clinical trial subject selection or randomization

Pharmacodynamic assessment

Efficacy outcome measure (e.g., surrogate endpoint) ★

Toxicity biomarker

Safety biomarker

Preclinical or clinical?
CDER Biomarker Qualification Process

Submission process provided on CDER’s website--

Letter of Intent

Biomarker qualification package

Biomarker Qualification Review Team (BQRT) renders decision

CDER Director renders final decision

Letter sent to submitter
CDER Biomarker Qualification Process

The data evaluation and qualification recommendation is made by the Biomarker Qualification Review Team (BQRT). This team is comprised of primary reviewers drawn from offices within CDER (and others in FDA as appropriate). The team will have representation from each of the disciplines necessary (as appropriate) to ensure adequate breadth of expertise.
CDER Biomarker Qualification Process

- Case-by-case approach

- Evidentiary considerations (type and level of evidence) depend on context of use

- Relatively high standard for qualifying surrogate endpoints
CDER biomarker qualification focuses on “Surrogate endpoint → Clinical Outcome”
Health Claims Characterize a Risk Reduction Relationship Between a Food or Food Component and a Disease or Health-Related Condition

Food or Food Component

Health-Related Condition (e.g., hypertension or LDL cholesterol)

Disease Risk Reduction

Drug

Treat/ Cure Disease, mitigate Symptoms or Signs
CDER Biomarker Qualification

FDA has suggested that consortia through resource sharing would be a feasible way to qualify biomarkers. Some of those are listed below:

Biomarkers Consortium (Foundation for the NIH)
Osteoarthritis Biomarker Consortium
Others…

Critical Path Institute
Predictive Safety Testing Consortium (PSTC)
Coalition Against Major Diseases (CAMD)
Cardiac Safety Research Consortium (CSRS)
Others…

Oncology Biomarker Qualification Initiative (OBQI)
COPD Biomarkers Qualification Consortium
Biomarker Qualification

Foundation for the National Institutes of Health

Biomarkers Consortium – public-private biomedical research partnership with broad participation from stakeholders across the health field, including government, industry, academia and patient advocacy and other non-profit private sector organizations.

Evaluate promising biomarkers in order to help accelerate the delivery of successful new technologies, medicines and therapies for prevention, early detection, diagnosis and treatment of disease.

http://www.biomarkersconsortium.org/whatwedo.php

Developed by Pharmaceutical Research and Manufacturers of America (PhRMA) committees and tested at a workshop in collaboration with FDA and academia through FNIH.
Challenges

• Establishing causality between the risk biomarker and clinical endpoint
• Independent predictor?
• Once qualified, does the intervention (food or food component) of interest modify the surrogate? Other causal pathway?
• Cost --- return of investment
Thank you!

Paula.Trumbo@fda.hhs.gov