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ORIGINAL CONTRIBUTION

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Weight of evidence needed to substantiate a health effect for probiotics and prebiotics

Regulatory considerations in Canada, E.U., and U.S.

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Summary Successful and responsible introduction of probiotic and prebiotic products into the worldwide marketplace requires labelling for health benefits that meets consumer needs, adheres to regulatory standards and does not overextend scientific evidence. Regulations differ among countries, but underlying all is an emphasis on scientific credibility of any statements of health benefits. This paper considers the value of different types of evidence offered in substantiation of efficacy and reviews different regulatory approaches to labelling for health claims. Limitations of *in vitro*, animal and different types of human studies used for efficacy substantiation for probiotics and prebiotics are discussed.

Key words probiotics – prebiotics – regulatory – health claims

Introduction

As part of the 2003 meeting of the International Scientific Association of Probiotics and Prebiotics held at Henley-on-Thames, UK, a discussion group was convened to address the scientific issues associated with one of the most difficult endeavors facing those in the probiotic and prebiotic fields – substantiation of efficacy needed to support claims of health benefits. Tremendous progress has been made over the past decade documenting in well designed human studies the impact of probiotics on health [1]. Assuring that product claims, based on these emerging data, are truthful and not misleading is a clear goal of national regulatory agencies worldwide. This requires that such claims be adequately substantiated, based on valid science. Exactly what constitutes "adequate" was the focus of this discussion, which included perspectives from different countries' regulatory approaches, including both the level of substantiation deemed "adequate" for different types of claims and the kinds of scientific evidence regarded as credible in providing substantiation. It should be noted that within the EU, principles for assessing the scientific support of health claims are being addressed by the Concerted Action PASSCLAIM.

It is also important to validate markers which provide predictors for efficacy on human health. This is a difficult process requiring mechanistic and epidemiological studies for validation. One large barrier to development of biomarkers relevant to the study of probiotics and prebiotics is that the composition of the human gut flora is not fully characterized and the significance of the presence, absence or certain levels of different genera, species or strains of bacteria is not understood.

What is the value of different types of efficacy evidence?

In vitro evidence

It was generally agreed that *in vitro* approaches are usually too simplistic and fail to mimic successfully the conditions in the human organism, limiting their usefulness in predicting efficacy or safety in humans. Care must be exercised not to over-extend the meaning of results from *in vitro* tests until they are corroborated by *in vivo* analyses. For example, many published papers have asserted the importance of the production of bacteriocins for probiotic efficacy. The biochemistry, biology and genetics of bacteriocin production in many probiotic strains have been established by elegant *in vitro* experiments. Unfortunately, no study with isogenic strains of bacteriocin producing and non-producing variants has been published comparing relative efficacy *in vivo*. Therefore, the relevance of bacteriocin production to probiotic efficacy remains unknown.

Recognizing these limitations, many *in vitro* evaluations are quite useful and necessary as precursors to *in vivo* studies or in their own right by providing important strain characterization data. *In vitro* tests can be used as the first step of screening for probiotic safety and efficacy. Valuable *in vitro* efforts include genomic analysis, DNA-based and phenotypic strain identification and measurement of viability. These approaches are useful for the following purposes:

- Quantifying bacteria in sample/product
- Identifying and characterizing the strain(s) being studied
- Characterization of strain- or species-specific differences among a range of probiotic bacteria
- Insuring product quality and consistency
- Screening for survivability in the upper gastrointestinal tract
- Conducting mechanistic studies with cellular models
- Identification of potential safety risks

Animal models

Numerous animal model systems have been developed and are used widely for the study of physiological effects of a wide diversity of bioactive components and diets. However, there are important anatomic, metabolic, and physiological differences between animals and humans. Thus the results obtained during animal experiments cannot be used as proof of efficacy but only as indications, especially when doses used in animal studies are not reflective of realistic doses to be used in humans.

Preliminary substantiation of safety, efficacy and a plausible hypothesis of effect in animal models can be important in gaining approval for human studies by institutional review boards, as only limited tests can be performed in humans due to ethical issues. Furthermore, animal models allow the acquisition of tissue from a living animal host that would not be accessible from a human. These tissue samples can be of great value to advancing the understanding of the impact of probiotics and prebiotics on animal physiology. Valuable applications for animal studies also include establishment of efficacy for products destined for animal use.

Although *in vitro* and animal studies may provide useful insights on probiotic efficacy, action and safety for products targeted for human use, in general such experiments cannot be considered as adequate substantiation for claims for humans, and well designed and controlled human studies need to be performed.

Human case studies

Observations from a single case study are at best only suggestive of a more general effect. Most often, they only reflect peculiar effects in a specific condition and are not representative of the general population. Single case successes should be used only with caution, as they do not provide sufficient evidence of probiotic or prebiotic efficacy and it is tempting to overextend the meaning of the results. Results are likely to be biased towards a specific case and there is no mechanism for similar reports of product failure. The sample population size is always important in proving efficacy in the general population. Although human case studies can raise public awareness, they should always be confirmed by well-designed, randomized, double blind, controlled trials.

Caution should also be exercised in evaluating case studies as they relate to safety. Individual reports of rare adverse incidents can be difficult to interpret without context for evaluating the relative risk [2].

Human trials

Well-designed, randomized, double blind, controlled trials are the cornerstone of efficacy substantiation and have been conducted on some preparations [3–8]. However, some factors complicate this approach, especially when applied to evaluation of functional foods. It is important to define the active ingredients of a product as it is sold in the market, but this is often difficult as the product may undergo changes with time and storage conditions. Effects of the functional ingredient may vary when put in different food matrices, so products should be tested as they are intended to be sold. Although placebo-controlled trials are the ideal, it can be difficult to develop an appropriate placebo for some studies, especially for food delivery systems. However, even if the

placebo is not indistinguishable from the test product to the subjects, it is still possible to blind a study as long as none of the participants knows which product is test and which is placebo. If a placebo-controlled trial is not possible, it is still important that the trial is randomized. Another important factor is the reproducibility of the study. There should be coherence of data when the study is repeated at different sites.

Open-label studies might provide useful information, especially in evaluating the effect of the product in a "real world" situation. For marketing of functional foods, the psychology of the product may be an important factor. However, although important from a marketing point of view, establishment of a psychological placebo effect would not be convincing evidence of efficacy for either scientific or regulatory scrutiny. If an open-label approach is used, randomization is still an important study design element and results must be reproducible to be considered valid.

Epidemiology was considered to be valuable, but the large degree of experimental "noise" in these studies makes it difficult to detect small effects. Obtaining reliable information from consumers regarding their dietary intakes is difficult, and such studies can be costly and time consuming. Observational studies can also be valuable, but do not provide conclusive evidence.

Performing long-term intervention trials is also important, especially in order to observe the improvement of wellness. Most studies with probiotics and prebiotics are short-term (< 12 week) studies. If, for example, a risk factor can be reduced with probiotic or prebiotic administration, long-term trials are necessary to investigate whether the effect will persist with time. Post-market surveillance is important in order to monitor the long-term beneficial (or adverse) effects. It is a difficult task to perform though, since diet is not easily monitored accurately.

Definition of test product

An important aspect of conducting studies is developing the appropriate format for the test product. Many factors enter into product definition, such as inclusion of other potentially bioactive ingredients, use of a blend of probiotic strains, combined use of probiotics and prebiotics, method of growth and preservation of probiotic strain(s), levels of probiotics or prebiotics used, and delivery matrix. The mode of delivery to the human body will clearly influence the target site of the product (e. g. enteric-coated capsules may be impacted less by stomach acid). But conducting human studies on all marketed formulations can be an unreasonable financial burden, and is perhaps not necessary if justification can be provided that two different products are substantively the same regarding expected biological activity. It is not ethical to conduct trivial human studies. But a scientific, not a financial, justification of the case for functional equivalence must be made.

Regulatory perspectives on substantiation of efficacy

Canada

In Canada the newly created Natural Health Product Directorate (NHPD) oversees the regulations concerning probiotics and prebiotics (www.hc-sc.gc.ca/hpfb-dgpsa/nhpd-dpsn/index_e.html). These new regulations became law as of January 1, 2004 and control all aspects of Natural Health products from manufacturing, packaging, labelling, distribution, storage, importation and sale. The new NHPD regulations allow therapeutic claims as well as risk reduction and structure/function claims. Under Item 8, the Included Substance List (Schedule 1), the term "probiotic" is defined as a monoculture or mixed-culture of live micro-organisms that benefit the microbiota indigenous to humans (www.hc-sc.gc.ca/hpfb-dgpsa/nhpd-dpsn/overview_nhp_regs_e.html#21). It clearly states that probiotics are limited to non-pathogenic microorganisms following the recommendations of the FAO/WHO report 2001 (p 18; ftp://ftp.fao.org/es/esn/food/probio_report_en.pdf). However, provisions have been made for dead microbes or other microbes, not considered or labelled as "probiotics", under Item 1 and 2 of Schedule 1 where bacteria and fungi and their extracts are specifically listed. Food products such as yogurts or other products containing microbes or fibers are not controlled by the NHPD but by the Food Product Directorate (FPD). Direct-fed microbes for animal nutrition are under the jurisdiction of the Canadian Feed Inspection Agency (CFIA). Some probiotic products that were previously controlled as pharmaceuticals by the Therapeutic Product Directorate (TPD) and have a Drug Identification Number (DIN) will automatically be transferred to the NHPD. Prebiotics were not specifically addressed in the Included Substance List of Schedule 1 but they would generally fall under Item 1 which includes plants or plant materials, algae, bacteria, fungi or non-human animal materials.

Under the new regulations from the NHPD the claim made on a probiotic or prebiotic product will depend on the "Standard of Evidence" that is submitted with the claim application. These standards of evidence are loosely based on the "levels of evidence" ranking generated some 20 years ago by the Canadian Task Force on the Periodic Health Examination (Can Med Assoc J (1979) 121(9):1193–1254). The "Standards of Evidence" presented by the NHPD are clearly defined criteria that are used to evaluate the safety, quality, and efficacy of a

Natural Health product. They define the amount, credibility, strength and quality of data required to support all conditions of use associated with a product. Claim application types will either be: i) Compendial, that is citing a monograph in the NHPD Compendium of Monographs, or ii) Non-compendial, that is requiring a full review. Different evidence requirements apply to both different types of Claim applications. However, in all applications the evidence must be given in totality; a summary of both favourable and unfavourable evidence from all relevant sources must be provided and the balance of the evidence must support safety and efficacy.

Claims can be of the following types: i) structure/function, non-specific; ii) risk reduction; or iii) treatment (www.hc-sc.gc.ca/hpfb-dgpsa/nhpd-dpsn/evidence_for_safety_efficacy_finished_nhp_e.html#21). Structure/function describes the effect of an ingredient on a structure or physiological function, or its support of an anatomical, physiological or mental function. An example would be "prebiotics maintain a healthy intestinal flora". Yet even non-specific claims under this section must still be supported by evidence. Risk reduction describes the relationship between using a medicinal ingredient and reducing the risk of developing a specific disease or abnormal physiological condition. This is usually based on observational studies that demonstrate a significant change in the major risk factor or factors in the development of a chronic disease or state. An example of this type of claim might be "probiotics reduce the risk of colon cancer". The treatment claim refers to the diagnosis, treatment, mitigation or prevention of a disease, disorder or abnormal physical state or symptoms. An example of this type of claim might read "clinical trials have shown that probiotics can be used in the treatment and prevention of pouchitis". If any potential risk to consumption of the product is perceived, the level of the supporting evidence required for such a claim will increase. Also considered is if the active ingredient is used as sole or adjunct therapy, whether it is intended for symptom management or treatment and the seriousness of the condition.

In the NHPD the products can be considered as either "traditional" or "non-traditional". Traditional products must have at least 50 consecutive years of use and can be considered for all three types of claim (i. e. structure/function, risk reduction or treatment). The labelling claim must use the phrasing "traditionally used in the…". Traditional evidence requires two independent references to traditional use that support the health claim or an expert opinion report if only one written reference exists. Some probiotic preparations in Canada have been on the market for this long and may possibly be able to claim "traditionally used to maintain the intestinal flora" or "traditionally used to reduce gassing and bloating". However, at this time it is not clear if such claims will be accepted outright by the NHPD. Safety reports must also be submitted with such claims and the applicant must search the scientific literature for information regarding adverse reactions and known interactions. As well all applicants must answer each of the specific questions posed under "Safety Factors" (www.hc-sc.gc.ca/hpfb-dgpsa/nhpd-dpsn/evidence_for_safety_efficacy_finished_nhp_e.html#81).

Non-traditional claims are all other claims not covered under the "traditional" definition. Most probiotic and all prebiotic preparations will fall under this section. The evidence to support this claim must be based on scientific data and again all three types of claims (i. e. structure/function, risk reduction or treatment) will be considered. Again, the amount and type of evidence required will depend on the type of claim and severity of the symptoms or condition. The evidence will be assessed on the basis of its strength, credibility and quality.

Very specific criteria have been developed in these regulations for documenting the range of the evidence (Table 1), credibility of the evidence (Table 2), and the quality of the evidence (Table 3). These questions prepared by NHPD are not only useful guides for the re-

Table 1 Canadian Natural Health Products Directorate approach to assessing the range of evidence provided to support a health claim for a Natural Product (www.hc-sc.gc.ca/hpfb-dgpsa/nhpd-dpsn/evidence_for_safety_efficacy_finished_nhp_table_2_e.html)

Level I	– Well-designed systematic reviews and meta-analyses of randomized controlled trials or other clinical trials OR at least one well-designed, preferably multi-centered, randomized controlled trial.
Level II	– Well-designed clinical trials without randomization and/or control groups.
Level III	– Well-designed descriptive and observational studies, such as correlational studies, cohort studies and case-control studies.
Level IV	– Peer-reviewed published articles, conclusions of other reputable regulatory agencies, previous marketing experience and expert opinion reports.
Level V	– References to traditional uses.

Table 2 Canadian Natural Health Products Directorate approach to assessing the credibility of evidence provided to support a health claim for a Natural Product (www.hc-sc.gc.ca/hpfb-dgpsa/nhpd-dpsn/evidence_for_safety_efficacy_finished_nhp_e.html#51)

1. Is the reference generally available?
2. Is it widely recognized and used?
3. Are the authors knowledgeable in their field?
4. Do the authors cite their sources?
5. Has the reference been peer reviewed?
6. Is it used in other jurisdictions?
7. Does it present balanced data?
8. Is it based on the totality of existing evidence?
9. Has it been commercially published?
10. Is it the most current information or edition available?

Table 3 Canadian Natural Health Products Directorate approach to assessing the quality of evidence provided to support a health claim for a Natural Product (www.hc-sc.gc.ca/hpfb-dgpsa/nhpd-dpsn/evidence_for_safety_efficacy_finished_nhp_table_3_e.html)

1. Were the objectives of the study defined?
2. Were the outcomes, measures or endpoints clearly defined?
3. Was there a clear description of the inclusion and exclusion criteria?
4. Was the sample size adequate and justified (e. g. by a power calculation)?
5. Were the methods of statistical analysis adequate and well described?
6. Was there at least one control (comparison) group?
7. Was the study randomized?
8. Was the study double-blinded?
9. Was any risk information described, such as adverse reactions or reasons for participant dropout?
10. Was the medicinal ingredient in the study adequately identified (e. g. proper name) and characterized (e. g. DNA fingerprint)?

viewer but also provide a solid basis for any researcher or company wishing to undertake a thorough investigation.

By using this assessment guide, a reviewer will be able to score the weight of the evidence and thus decide on the "sufficiency" of the evidence. Sufficiency represents the relevant level of evidence, the totality and balance of the information provided and the credibility of the sources, and compares this information to the intended claim. Hence, stronger claims require stronger evidence. A medicinal product which has less than sufficient substantiation will be required to present further information before allowing the claim.

Part 4 of the new NHPD regulations outlines the considerations for clinical trials on Natural Health Products (on-line guidelines are not available at this time). Applications must be made to the ministry for clinical studies as currently required by the Therapeutic Product Directorate for pharmaceuticals. The NHPD clearly states that the clinical studies must comply with International Committee for Harmonization (ICH) guidelines and local ethical principles and laws in order to ensure the safety of the subjects. The clinical trials are undertaken to ascertain the safety and efficacy of the product and must also conform to Good Clinical Practices (GCP) which are designed to ensure the protection of the rights, safety and well-being of everyone associated with the trial, including the trial staff and the trial participants. The principles of GCP are detailed in section 74 of the new guidelines and will not be covered here. The trial must be approved by a research ethics board which can not be affiliated with the sponsor company. Where human trials cannot be ethically performed, animal trials will be accepted.

The new NHPD guidelines in Canada allow for qualified claims based on the weight of evidence provided. The design of clinical trials to assess probiotic and prebiotic products will follow the precedents of ICH and GCP already in place for pharmaceutical products.

European Union

The European Food Safety Authority (EFSA), Regulation EC No. 178/2002, was established January 28, 2002. These EC regulations call for "a strong scientific base" and outline the responsibilities of scientific committees and permanent scientific panels (article 28). The committees are responsible for the consistency of the scientific opinion procedure and the panels, composed of independent scientific experts, will be established for specific groups of products or ingredients. The proposal also covers nutrition and health claims used in labelling, presentation and advertising of foods. This legislation is proposed to cover substances with a physiological effect, such as prebiotics and probiotic bacteria. Any claims must be based on and substantiated by the generally accepted scientific data. All health claims (overt or implied) that cannot be scientifically verified will not be allowed. For example, statements such as "excellent for your organism", "preserves youth" or "helps keep your body feeling good" or other unsubstantiated behavioral claims are not acceptable. The EC regulations will prohibit any claims referring to the prevention, treatment or cure of a human disease (in contrast to that proposed by Canada and the United States) for a food. However, risk reduction and structure/function claims are allowed. Risk reduction and structure/function claims will be authorized only once they are reviewed and confirmed by an independent body within the EU. Thus, "scientific evaluation of the highest possible standard" is required and will be assessed by the EFSA. Principles for assessing the scientific support of these claims will be set by the Concerted Action PASSCLAIM. Regulations at the national level may advance more quickly than those set out by the EFSA and may be used as models for future EFSA regulations.

United States

The use of health claims in food labeling in the U. S. was first authorized by the Nutrition Labeling and Education Act of 1990 (NLEA). The Food and Drug Administration (FDA) promulgated regulations to implement this legislation; the regulations concerning health claims appear in the Code of Federal Regulations (CFR) at Section 101.14. As discussed below, the standards of evidence needed to substantiate health claims in the U. S. have been clearly elucidated over the past decade, and have been the subject of extensive public discussion as well as legal challenge and resulting case law.

Statements of nutritional support, often referred to

as structure/function claims because many of them describe the effect of a dietary substance on the structure or function of the body, were first formally authorized in the Dietary Supplement Health and Education Act of 1994 (DSHEA) (www.cfsan.fda.gov/~lrd/fr000106.html). Initially, such statements were regarded as being available for use only in the labeling of dietary supplements, not foods, but FDA extended the use of these claims to foods in September, 1997, in a *Federal Register* notice (FDA notices at www.cfsan.fda.gov/label.html) that stated that it would be appropriate for cranberry juice cocktail to make the same claims regarding urinary-tract health as would be permitted to a dietary supplement containing cranberry extract (Federal Register 62:49859–49868, September 23, 1997). Structure/function claims are distinguished from health claims by the fact that they may not state or suggest that the product is useful in the prevention of disease. FDA has not yet attempted to outline criteria regarding the kinds or extent of substantiation required to support such claims. Although DSHEA clearly states that structure/function statements must be truthful and not misleading, FDA has never asked for substantiation of any structure/function claim appearing on a food or dietary supplement label. Indeed, FDA has never challenged a structure/function claim with regard to its truth.

Health claims, which are defined in the U. S. as any claims that expressly or by implication characterize the relationship of a dietary substance to a disease or health-related condition, must be pre-approved by the FDA or (as provided by the FDA Modernization Act of 1997) must be issued as authoritative statements by an agency of the U. S. government with responsibility for dietary guidance or public health (e. g., the National Institutes of Health or any of its institutes, the FDA itself, the Department of Defense, the Department of Agriculture) or by the National Academy of Sciences or one of its units. Approval is based on the totality of the publicly available evidence.

Although health claims are regulated by different agencies if they are part of food labeling (FDA) or used in advertising (Federal Trade Commission–FTC), the agencies coordinate their reviews so that substantiation standards for acceptable health claims in labeling and in advertising are similar. Unlike FDA, FTC has published a number of policy documents setting forth its approach to evaluating substantiation of both health claims and structure/function claims, most notably *Dietary Supplements: An Advertising Guide for Industry*, which is available on the FTC website (www.ftc.gov/bcp/conline/pubs/buspubs/dietsupp.pdf).

The FTC does not differentiate between health claims and structure/function claims, but rather requires that the advertiser must have a reasonable basis for all express and implied product claims of all types. This judgment is based on the totality of the scientific evidence using accepted norms in the relevant fields of research, i. e., what experts in the relevant area of study would generally consider reasonable or adequate. In addition, the FTC imposes the "reasonable consumer" standard. In other words, if a reasonable consumer would interpret an advertising message to mean something which cannot be substantiated, then the advertising message is not allowable. Furthermore, since consumers tend to ignore disclaimers, the FTC discourages their use.

In proving a case for efficacy to substantiate a health or structure/function claim, a variety of sources of information may be compiled, including experience, long-standing traditional use, ethnomedical uses, animal studies, case reports, *in vitro* experiments and clinical or human volunteer trials. Elucidation of a plausible biological mechanism is not absolutely required, but is regarded as extremely valuable in substantiating a claim of a relationship between a dietary substance and a structure or function of the body, a disease, or a health condition. In general, interventional studies provide the strongest evidence for causality. The U. S. regulatory agencies consider the "gold standard" for interventional studies to be the randomized placebo-controlled clinical trial. In some cases (e. g., cancer), interventional dietary studies are not feasible due to the long latency in the development of the disease and supporting evidence may have to be derived from observational and mechanistic studies (FDA, *Significant Scientific Agreement in the Review of Health Claims for Conventional Foods and Dietary Supplements*. December 22, 1999; www.cfsan.fda.gov/~dms/ssaguide.html).

The FDA has recently ranked the persuasiveness of the type of research supporting efficacy (FDA, *Interim Evidence-based Ranking System for Scientific Data*. July 10, 2003). This ranking, in descending order, is as follows:

- Randomized controlled clinical trial
- Cohort (longitudinal) study
- Case-control study
- Cross-sectional study
- Uncontrolled case series or cohort study
- Time-series study
- Ecological (cross-population) study
- Descriptive epidemiology
- Case report

Animal and *in vitro* studies alone would not adequately support a health claim. Human data are required. Furthermore, the FDA has never approved a claim based on meta-analysis alone; such analyses are regarded as corroborative but not alternatives to primary data.

When the NLEA was enacted, authorizing the use of health claims on food, the FDA established that it would approve a health claim "only when it determines, based on the totality of publicly available scientific evi-

dence…, that there is significant scientific agreement among experts…that the claim is supported by such evidence." [Federal Register, 21 CFR 101, 14(c)] Significant scientific agreement in practice is a very high standard of proof, and indicates that there is a sufficient body of evidence that shows consistency across different studies and researchers and permits the key determination of whether a change in the dietary intake of the substance will result in a change in a disease endpoint. Furthermore, there must be agreement that the relationship is not likely to be reversed by new and evolving science.

In recent years, companies have been unhappy with the use of the significant scientific agreement standard. Objecting to FDA's rejection of a number of proposed health claims, a dietary supplement company sued the FDA on the basis of restriction of free speech as guaranteed by the First Amendment to the U. S. Constitution. This amendment has long been held to protect "commercial speech" as well as political and private speech. The court case, Pearson v. Shalala, was decided in favor of the company by the U. S. Court of Appeals for the District of Columbia. As a result, the concept of "qualified health claims" emerged. The Court ruled that the FDA must "favor disclosure over suppression" and cannot prohibit a claim unless:

- The substance that is the subject of the claim is unsafe; or
- The claim is untrue or "inherently" misleading and incapable of being made non-misleading by providing appropriate qualification (such as, "Recent scientific studies suggest, although they do not yet prove, that…"), as would be the case if there is a preponderance of evidence against rather than in support of the claim.

In response to this ruling, the FDA developed a draft system of evaluating qualified health claims (FDA, *Guidance: Interim Procedures for Qualified Health Claims in the Labeling of Conventional Human Food and Human Dietary Supplements*. July 10, 2003). This interim procedure is still open for general comment and a final ruling has not been promulgated; nevertheless, FDA is currently evaluating qualified claims under this interim procedure and has approved several of them. The FDA also declared in December of 2002 that it will use the same "reasonable consumer" standard used by the FTC, a change from the agency's historical position that its mission is to protect "the ignorant, the unthinking, and the credulous" from label statements that might mislead them (FDA, *Qualified Health Claims in the Labeling of Conventional Foods and Dietary Supplements*. December 18, 2002).

According to the interim procedures, the degree of qualification needed and the level of evidence supporting a health claim will be judged by the following rating system:

- A: significant scientific agreement exists – no qualifications are necessary
- B: the evidence is not conclusive
- C: the evidence is limited and not conclusive
- D: there is little scientific evidence supporting the claim

The types of studies supporting claims will be rated:

- Type 1: Randomized controlled intervention trial
- Type 2: Prospective observational cohort study
- Type 3: Non-randomized intervention trial with concurrent or historical control
- Type 4: Cross-sectional study, case study

The strength of the total body of scientific evidence will be rated according to:

- Quantity: the number of studies and number of individuals tested, weighted by study type and quality
- Consistency: similarity of results from high quality studies of design types 1 and 2
- Relevance: magnitude of effect (observed in high quality studies of design types 1 and 2) and whether the effect is physiologically meaningful and achievable

This new approach to health claim approval will undoubtedly open the door for many more claims than are currently in use. It is now more likely that a product containing probiotics and/or prebiotics would qualify for some level of health claim on food products in the U. S.

Conclusions

In conclusion, good agreement generally exists between science and regulatory agency approaches to establishing efficacy. Controlled human trials are essential for the substantiation of efficacy in humans. Some important issues remaining unresolved for the probiotic and prebiotic field include:

- Definition of test products, so that the active biological function is identified and quantified for the product being administered.
- Development of appropriate biomarkers which can reduce the burden on human subjects for study and provide indicators of risk as well as measures of wellness.
- Additional studies which reveal information on the benefits of long-term consumption, dose dependency of effect and wellness compared to disease.

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