GUIDELINE CONCERNING THE SAFETY AND PHYSIOLOGICAL EFFECTS OF NOVEL FIBRE SOURCES AND FOOD PRODUCTS CONTAINING THEM

Guideline No. 9
Issued by the Food Directorate
Health Protection Branch
Health Canada
Ottawa, Ontario
K1A 0L2

Revised November 1997

Contents

GUIDELINE CONCERNING THE SAFETY AND PHYSIOLOGICAL EFFECTS OF NOVEL FIBRE SOURCES AND FOOD PRODUCTS CONTAINING THEM

1. Introduction

1.1 Purpose

This guideline explains further the policy outlined in Information Letter (I.L.) No. 736[1], Dietary Fibre, with respect to new or novel fibre sources.

In keeping with the definition used in I.L. No. 736, "novel fibre" or "novel fibre source" means a food that is manufactured to be a source of dietary fibre, and

a) that has not traditionally been used for human consumption to any significant extent, or

b) that has been chemically processed, e.g. oxidized, or physically processed, e.g. very finely ground, so as to modify the properties of the fibre contained therein, or

c) that has been highly concentrated from its plant source.

There are safety considerations unique to novel fibre sources which must be taken into account in the evaluation of their acceptability as foods. Also, since knowledge of the physico-chemical nature of the dietary fibre in a food cannot reliably predict the potential benefit of that food, the physiological efficacy of the food must be demonstrated by scientific evidence.

I.L. No. 736 indicates that, if a novel fibre source or novel fibre-containing product is not safe for human consumption, it may be in violation of Section 4 of the Food and Drugs Act. Similarly, if a product is represented as containing dietary fibre, but does not have the effects the public has come to expect of dietary fibre, the product may be in violation of Subsection 5(1) of the Act. This guideline has been developed, therefore, to assist manufacturers in identifying the procedures which will be considered to verify the safety and physiological efficacy of new products which they wish to represent as dietary fibre sources and dietary fibre-containing food products. It is primarily intended to provide basic direction and rationale

rather than to specify procedural details, and is subject to revision as research in the dietary fibre area progresses.

1.2 Safety Considerations

Adverse effects which have been observed for fibre sources include reduced mineral bioavailability and undesirable changes in the structure and function of the gastrointestinal tract mucosa. These are related to the physico-chemical properties of the fibre source, e.g., presence of natural toxins or contaminants, abrasiveness, hydratability, ability to complex with minerals, and microbiological profile.

1.3 Physiological Efficacy

This will be considered in terms of the effects identified by the Expert Advisory Committee on Dietary Fibre[2], and reiterated in Section 3 of I.L. No. 736, as being verifiable for dietary fibre sources and products, i.e. laxation, normalization of blood lipid levels, and attenuation of blood glucose responses. The evidence relating to the potential ability of fibre-containing products to suppress appetite was considered by the Committee to be unconvincing[2].

2. General Principles Relating to Product Testing

2.1 The nature and extent of testing to be undertaken will depend upon the novelty of the fibre source and the amount of existing data relating to its composition, safety and intended effect(s).

2.2 Established specifications for the composition and physico-chemical properties of a novel fibre source should be available prior to initiating safety or efficacy studies, since they will influence the choice of parameters to be studied. The specifications should be adhered to in order to ensure that the material on the market corresponds to what was tested.

2.3 The safety of the novel fibre source should be tested in animals prior to testing in human subjects.

2.4 A novel fibre source should be tested for physiological efficacy in typical end-products, in the same form and at levels relevant to those in products intended for sale.

2.5 If a novel fibre-containing product is intended for use by a special group, it may be advisable to test the product directly in that group.

3. Information Necessary to Evaluate the Acceptability of a Novel Fibre Source as a Potential Dietary Fibre Ingredient

3.1 Form, Manufacture and Intended Use

3.1.1 Origin and physical form

3.1.2 Method of manufacture, i.e., a description of how the novel fibre source is derived from the raw agricultural product, in sufficient detail to assess whether processing may have significantly altered the properties and/or the nutritional value of the source.

3.1.3 Potential applications and levels of intended use in products.

3.2 Physico-chemical Specifications

3.2.1 Nutrient composition, i.e., dietary fibre (total and constituents)[3-5], protein, fat, carbohydrate, ash, energy value and, where appropriate, vitamins and mineral nutrients.

3.2.2 Properties, e.g., particle size, hydratability.

3.2.3 Chemical analysis, as appropriate, for presence of natural toxins, antinutritive components and contaminants, including toxic metals, pesticide or solvent residues.

3.2.4 Functional properties in foods.

3.3 **Microbiological Specifications**

3.4 **Safety**

3.4.1 Detailed reports of tests made to establish the safety of the novel fibre source.

Guidelines for the testing of novel foods have been published by the U.K. Department of Health (1991)[6] and by the Codex Committee on Vegetable Protein (1987)[7].

3.5 **Physiological Efficacy Evaluation**

3.5.1 Animal experiments, to provide information on *in vivo* properties of the novel fibre source, e.g., apparent digestibility, or to measure parameters not easily measured in humans, e.g., fecal volume.

3.5.2 Clinical studies, to investigate one or more of the physiological effects noted in 1.3 above, to assess acceptability and tolerance and to monitor possible adverse effects.

These studies may follow principles outlined in Annex I of I.L. No. 700, "Report of Expert Advisory Committee on Dietary Fibre" (attached, Appendix 1), with the exception of laxation studies. With regard to the latter, a guideline entitled "Guideline for Planning and Statistical Review of Clinical Laxation Studies for Dietary Fibre", has been prepared to replace part 1 of the above Annex I of I.L. No. 700 and is appended to this document (see Appendix 2).

The Branch will be pleased to comment on the design of clinical protocols, and on the acceptability of novel fibre sources and fibre-containing products, in accordance with this guideline.

References

1. Information Letter No. 736. **Dietary Fibre**. Health Protection Branch, Health and Welfare Canada, February 5, 1988.

2. Health and Welfare Canada, Report of the Expert Advisory Committee on Dietary Fibre, Ottawa: Supply and Services Canada, October, 1985 (available from the Nutrition Evaluation Division on request).

3. Mongeau, R. and R. Brassard, Enzymatic gravimetric determination in foods of dietary fiber as the sum of insoluble and soluble fiber fractions: summary of collaborative study. J. AOAC Int. 76:923-925, 1993.

4. Prosky, L., Asp, N-G., Furda, I., DeVries, J.W., Schweizer, T.F. and Harland, B.F. Determination of total dietary fibre in foods and food products: collaborative study. J. Assoc. Off. Anal. Chem. 68, 4:677-679, 1985.

5. Englyst, H., M.E. Quigley, G.J. Hudson and J.H. Cummings, Determination of dietary fibre as non-starch polysaccharides by gas-liquid chromatography. Analyst 117:1707-1714, 1992.

6. United Kingdom, Advisory Committee on Novel Foods and Processes. Guidelines on the Assessment of Novel Foods and Processes. Department of Health, Report on Health and Social Subjects No. 38 London: HMSO, 1991.

7. Proposed draft guidelines for testing the safety and nutritional quality of vegetable protein products. Codex Committee on Vegetable Protein, 4th Session, February 2, 1987, Havana, Cuba.

8. Information Letter No. 700. Report of Expert Advisory Committee on Dietary Fibre. Health Protection Branch, Health and Welfare Canada, December 6, 1985.

APPENDIX 1

PROPOSED GUIDELINES FOR CLINICAL STUDIES

Annex I from

INFORMATION LETTER No. 700:
REPORT OF THE EXPERT ADVISORY COMMITTEE ON DIETARY FIBRE

December 6, 1985

ANNEX I

PROPOSED GUIDELINES FOR CLINICAL STUDIES

It is not possible at this time to define precise protocols for a given situation. The following are suggested as appropriate guidelines for clinical studies which may be used to validate claims for physiological effects associated with dietary fibre products.

1) This section from the original Annex I of IL No. 700 is replaced by Appendix 2

2) **The effects of dietary fibres on lipid metabolism**

The study would preferably involve subjects with raised lipid levels, consuming their habitual diets. The number of subjects would be that appropriate to achieve statistically significant differences in lipid levels between test and control periods. There should be an equal distribution of men and women across the age group included in the study. Since it is important to have an accurate idea of what the subjects ate, dietary studies would be essential. It is suggested that there be a control three-week observation period and a three-week fibre treatment period performed in random order. Blood samples should be taken at least at the subjects' entry into the study, and at the end of the observation and treatment periods. (Sampling at the end of the control period would indicate if there were a fibre effect). It would be preferable, if possible, to take blood samples weekly, bearing in mind that individual levels are variable and, depending upon the time of the study, could be slightly influenced by seasonal variation (Kritchevsky, 1984)[1]

In man, the end-points would be serum lipids and their lipoprotein distribution. Apolipoprotein measurements might provide some information, however, these measurements would not be essential. Important measurements would be serum total and HDL-cholesterol, together with serum triglycerides. These would allow serum LDL-cholesterol to be calculated. Lowering of LDL-cholesterol with slight or no change in HDL-cholesterol would be desirable results. Lipid values could be expressed as proportions e.g. LDL-/HDL-cholesterol or HDL-/total cholesterol in addition to absolute levels.

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[1] Kritchevsky, D. Variation in serum cholesterol levels. (submitted Nutrition Update, Vol. II).

3) The effects of dietary fibres on glucose tolerance

The number of normal volunteers required would be that which would show a significant 20-30% reduction in glycemic response resulting from the fibre treatment. There should be an equal distribution of men and women across the age group included in the study. It is questionable whether products which produce lesser reductions than this, by comparison with bread, would have significant physiological impact in the context of a mixed diet.

The effect of the test fibre could be demonstrated by measuring blood glucose responses at 15-minute intervals over 1 to 2 hours following test meals. Reduction in the peak rise or area under the blood glucose curve should be observed, either by comparison with a placebo food of the same composition but lacking fibre, or a bread control containing the same amount of available carbohydrate. Tests should be performed, in random order, in the morning after an overnight fast, and significance of the difference between test and control periods should be assessed by paired Student's t-test.

Similarly, insulin levels could also be measured although, in the absence of large differences in protein or fat in the test product, these would likely contribute little additional information. Evidence of increased sensitivity to insulin could also be obtained in longer studies where supplements have been fed daily and a standard carbohydrate challenge given before and at the end of the experimental period.

Finally, it is important that the foods concerned should be sufficiently low in fat and sugar to fit the internationally recognized guidelines for the nutritional management of diabetes.

4) The effects of dietary fibres on weight control

A protocol which aims to test the efficacy of dietary fibres as weight controlling agents or adjuncts should be specifically directed in design, target populations, extent of supervision and measurements involved, towards the nature of the product and the type of claim the manufacturer wishes to make. If the manufacturer wishes to make a weight reduction claim for a fibre-containing supplement for example, an effective clinical trial would involve free-living individuals consuming their regular (weight-maintaining) diets with or without the fibre supplement. An appropriate model would be a randomized, controlled clinical trial in which, following an initial run-in period, subjects are randomly assigned to the fibre-containing or control diet for 6 weeks, then to the alternative regime for another 6 weeks. Evidence of weight loss in the treatment compared with the control period would be considered acceptable for a weight loss claim. This type of protocol would likely be

directed toward moderately obese individuals (at least 20% above ideal weight) and could be carried out in a setting such as a weight loss club, under the supervision of a physician, and possibly other professionals (psychologist, nurse, nutritionist, fitness expert). Rigorous dietary supervision would not be necessary, however, accurate assessment of dietary intake, including the fibre supplement, would be essential to ensure that observed effects were due to the fibre product, rather than other factors relevant to weight control. Either a seven-day food diary or a three-day weighed food record should be collected, initially and at the end of each treatment period. In addition, a diary noting any adverse effects, levels of exercise and stressful events, would be useful. Health surveillance would involve initial and periodic physical examinations, including blood pressure, and appropriate biochemical and haematological measurements. The investigator may wish to assess the capacity of the product to induce satiety. This could be subjectively evaluated using a four-point scale ranging from "no hunger" to "marked hunger". Evidence of reduction in hunger scores alone, however, would not be adequate for weight control claims.

If the product is a fibre-containing meal replacement or a fibre product intended to supplement a restricted energy diet (1000 kcals or less), a more intensive paradigm would be required. Such a protocol would likely involve severely obese subjects and be conducted under careful medical supervision e.g. in a hospital obesity clinic. The energy-restricted diet would have to be nutritionally adequate, with appropriate vitamin and mineral supplements as necessary. Safety measures would be more rigorous, according to the judgement of the physician, and would likely involve additional procedures such as initial ECG and additional blood and urinary measurements. Intervals between measurements would be closer than those of the trial outlined above. Laboratory tests could include: electrolytes, liver function tests, Mg, Ca, Fe, TIBC, total protein and complete blood count. Food intake assessment and symptom records would also be necessary in this context.

Since the more intensive model would likely be accompanied by strict dietetic supervision, it may be more difficult to achieve significant differences in weight change between fibre-treatment and control periods i.e. acceptable weight loss may occur in both periods. In this case the product may be shown to be beneficial by increasing adherence to the calorie-restricted regime. Compliance would be expressed as per cent of initial subjects to complete treatment and control periods. The nature of the response to the fibre product should, in any case, be clearly stated e.g. "this product will assist in adherence to a 1000 kcal dietary regime".

The following general study conditions apply to either of the paradigms outlined above: the subjects should be over 18 years of age and at least 20% above desirable weight for their height and body frame*, matched according to age, sex, dietary habits, physical activity and any other demographic parameters which the investigator believes necessary. There should be an equal distribution of men and

women across the age group included in the study. The subject number would be that calculated to achieve statistically significant results. Subjects should not have any obvious organic disease such as cardiac, renal, hepatic or endocrine dysfunction. Volunteers should be desiring to lose weight but not concurrently participating in another weight control program.

* 1983 Metropolitan Life Insurance Company table.

APPENDIX 2

GUIDELINE FOR PLANNING AND STATISTICAL REVIEW OF CLINICAL LAXATION STUDIES FOR DIETARY FIBRE

Food Directorate
Health Protection Branch
Health Canada
Ottawa, Canada

June, 1994

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GUIDELINE FOR PLANNING AND STATISTICAL REVIEW OF CLINICAL LAXATION STUDIES FOR DIETARY FIBRE

INTRODUCTION

This Guideline is intended to assist applicants and reviewers in the planning, presentation and review of clinical laxation studies submitted to the Health Protection Branch as part of the evidence needed to demonstrate the acceptability of a novel source of dietary fibre. This evidence would consist of data related to both safety and efficacy.

A novel fibre or a novel fibre source is a food that is manufactured to be a source of dietary fibre, and

a) that has not traditionally been used for human consumption to any significant extent, or

b) that has been chemically processed, e.g. oxidized, or physically processed, e.g. very finely ground, so as to modify the properties of the fibre contained therein, or

c) that has been highly concentrated from its plant source.

In 1988, the Health Protection Branch published a Guideline Concerning the Safety and Physiological Effects of Novel Fibre Sources and Food Products Containing Them. The Guideline was developed to assist manufacturers in identifying the procedures which would be considered to verify the safety and physiological efficacy of novel fibre sources. Laxation is one of the physiological effects of fibre for which a given novel fibre source may be tested to demonstrate its value as a source of dietary fibre. Since there was a need for a standardized protocol for conducting laxation studies and criteria for evaluating the outcome, the present Guideline was developed.

This Guideline is presented in two sections. The first section (parts 1 to 4) deals primarily with the **PROTOCOL** planning phase of a clinical trial. The second section (parts 5 to 9) deals with statistical considerations involved in the final **SUBMISSION REVIEW**.

This Guideline replaces Appendix B (1) of the Report of the Expert Advisory Committee on Dietary Fibre: "Proposed Guidelines for Clinical Studies - (1) Laxation effects of fibre-containing foods", which is the same as Annex I (1) of Information Letter No. 700 concerning that report. Similarly, it replaces the reference made in the document, "Guideline Concerning the Safety and Physiological Effects of Novel Fibre Sources and Food Products Containing Them", to Annex I(1) of I.L. No. 700.

In developing the Guideline, the Branch drew on the 1985 Report of the Expert Advisory Committee and held an expert consultation in August, 1992 with Canadian scientists working in the field of dietary fibre. These scientists assisted in establishing the basic requirements of the study protocol and defined the criteria for meeting the primary objective. (For further information, see "Expert Consultation" under References at the end of this Guideline).

I. PROTOCOL

1. STUDY OBJECTIVES

1.1 A statement of the specific objectives of the study should be provided. The primary objective and secondary questions or objectives should be clearly stated, preferably in the form of hypotheses to be tested and criteria to be satisfied. This information is necessary for assessment of the adequacy of sample sizes and power.

1.1.1 The **primary objective** of the study is to demonstrate a positive laxation effect. There are two steps in demonstrating that this objective has been met.

The first step is to test a null hypothesis. In statistical hypothesis testing, the rejection of the null hypothesis constitutes evidence in favour of the alternative hypothesis. The **null hypothesis** for this study would be stated as follows:

> *The average daily fecal output with the diet including the test fibre is not greater than that of the diet without the test fibre, the "negative control".*

The **alternative hypothesis** would, therefore, be that *the test fibre fecal output is greater than that of the negative control*.

The second step is to meet the following criterion which provides a measure of the biological significance:

> *The observed change in average daily fecal output with the addition of the test fibre to the basic diet is at least 50% of that seen with the addition of the standard wheat bran (AACC coarse hard red wheat bran), the "positive control".*

The change in average daily fecal output between the test or the positive control treatments and the negative control will be expressed in grams wet fecal weight per gram of added fibre from the test or positive control source.

For further discussion of secondary questions and objectives see subsection 3.1.

1.1.2 The study must produce results that can be considered to be a conclusive, as opposed to a preliminary, demonstration of a laxation effect.

2. STUDY DESIGN

2.1 Study Population

2.1.1 The study population should be clearly defined in terms of subject inclusion/exclusion criteria. These criteria should provide assurance that subjects are suitable for the purpose of the study.

2.1.2 The study population should be normal, free-living, healthy individuals with an equal distribution of male and female subjects between 18 and 65 years of age. If a product is targeted towards a specific age group, then an equal mix of female and male subjects from that age group should be used. The exclusion of people with either very high or very low fibre intakes is reasonable. When premenopausal women are included, each treatment period should be timed to begin at the same stage in each woman's menstrual cycle.

2.2 Treatments

2.2.1 The treatments should be identified in terms of the doses, frequency, duration, adjustments, concomitant variables, etc. Items such as baseline periods, proposed treatment comparisons and control groups should be described.

2.2.2 The "negative" control diet, i.e. the diet consumed by the subjects during the study aside from the addition of the fibre sources under study, should be similar to the average diet of the population. It should provide 10-15% of energy as protein, 30-35% as fat, and 45-55% as carbohydrate. The dietary fibre contributed by the control diet should be 13 to 20 grams per day. The diet should be planned, prepared and weighed out by the research team, in other words it should be a "metabolically-controlled diet".

The use of a non-metabolically-controlled diet would increase the risk of non-statistically significant results. A larger number of subjects would be required and careful dietary record keeping by subjects would be essential. While the non-metabolically-controlled diet may appear to be a less costly approach, this needs to be

weighed against the possibility of not obtaining a clear answer. A metabolically controlled diet is strongly recommended and its use will be assumed, for the most part, throughout the remainder of this document.

2.2.3 One of the treatments must be AACC (American Association of Cereal Chemists) coarse hard red wheat bran which will act as a positive control or standard against which the performance of the test fibre will be measured.

2.2.4 Specifications for the test fibre source which are sufficient to clearly identify and characterize the product must be provided.

2.2.5 The amount of test fibre source added should be that which is sufficient to have an effect while maintaining acceptability of the diet and producing no adverse gastrointestinal effects. This would best be determined through preliminary tests. The test fibre source should be incorporated into foods of the type in which it is expected to be used. The positive control fibre source must be added at the same dose on the basis of the fibre content and incorporated into the same foods as the test fibre source. Apart from being incorporated and cooked into foods in the same way as the test fibre, the AACC coarse hard red wheat bran should not be otherwise modified physically or chemically, e.g. bleached, precooked or finely ground, since such modification may alter its effectiveness in laxation.

2.2.6 The duration of each treatment period should take into account the time required for the subjects to acclimate to the test fibre and the time required for passage of the fibre through the digestive tract. A minimum of seven days at the beginning of each treatment period is needed for acclimation to the test fibre and a further 4 days, at least, for collection of feces (see also section 3.2.2). A longer period for both acclimation and collections would be more sensitive and would increase the precision of the results.

2.3 Experimental design

2.3.1 The description of the experimental design should include identification of the study configuration (crossover, balanced incomplete block, multiple investigator, etc.) and the randomization procedures. There should be an explanation of the design's suitability for the treatment and effect under investigation. Details of stratification or blocking used to control known sources of variation should be provided.

The randomization procedures should guard against possible selection bias arising from either known or unknown sources of variation which were not controlled through stratification.

2.3.2 Three diets will be tested: test, positive control and negative control. Factors which could affect response should be controlled and monitored during the course of the study.

2.3.3 A three period crossover design where subjects act as their own controls is suitable for laxation studies. A balanced incomplete block design may also be suitable. Studies should be carried out as double-blind studies as far as possible.

2.4 Blinding

2.4.1 A description of the type of blinding (partial-blinding, single-blinding, double-blinding) should be provided along with an outline of the specific procedures to be followed to ensure blinding. There should be a discussion of whether the level of blinding is sufficient to minimize potential bias on the part of subjects, observers and analysts.

2.4.2 As stated in paragraph 2.3.3, laxation studies should be as close to double blind as possible.

2.5 Study conduct details

2.5.1 Additional information to be provided in the protocol would include planned interventions, study duration, handling of potential drop-outs, monitoring of compliance, quality control, etc.

2.5.2 A schematic layout of the planned experiment may be useful.

2.6 Ethics Committee Review

2.6.1 The planned protocol should be reviewed by a committee of the institution charged with ensuring studies are carried out in an ethical manner.

3. EFFICACY MEASURES AND STATISTICAL METHODS

3.1 Primary and secondary variables

3.1.1 The major variable measured will be average daily wet fecal weight expressed as total wet fecal weight divided by number of days of collection. All stools produced during the collection period must be collected and weighed and the time and date of each stool noted.

3.1.2 Frequency of defecation and individual stool weight must be reported as these will be evaluated as secondary variables, acting as validity checks.

3.1.3 Subjects should keep a daily diary throughout all phases of the study which should document time of defecation, symptoms of gastrointestinal function, changes in exercise patterns and stressful events and any other observations considered relevant by the investigator. In addition, the following specific questions should be asked at the end of each period:

Did abdominal pain appear?
Did distension (bloating) appear?
Did you have any fecal incontinence (difficulty preventing defecation)?
Did you have any other problems?

This information will help to determine if there are any acceptability problems with the test fibre and if uncontrolled factors might have had an impact on the results.

3.1.4 The fibre content of the test source should be measured using one of the three methods listed at the end of these guidelines. All the fibre measurements, including that of the AACC wheat bran, should be done using the same method since full equivalence cannot be assumed. Also, depending on the nature of the material, the particle size should possibly also be measured using the method of Mongeau and Brassard (1982) or equivalent.

3.2 Types of measures (continuous, categorical)

3.2.1 The measurement frequency and measurement techniques should be described. For variables involving assignment of scores the scoring procedures should be explicitly defined to assure accurate and consistent reporting.

3.2.2 The fecal collection must be carried out over 4 consecutive days or more. The reason for this is that, if the collection period is too short, the results can be highly variable depending on the time and spacing of the subjects' bowel movements. This problem is less important with a longer observation period. Although markers are recommended (see 3.2.3), marker or transit time adjustment of the fecal wet weight measurement should not be used as an alternative to an adequate collection period. There is no simple linear relationship between fecal output and rate of appearance of markers in the stools.

3.2.3 It is recommended that radiopacque markers be used to monitor the completeness of stool collection. At least 95 % of the markers would be expected to be recovered during the study.

3.2.4 All stools must be collected on consecutive days with collection periods of the same duration for both test and control periods.

3.3 Statistical methods

3.3.1 Proposed methods of analysis should be outlined in sufficient detail to demonstrate the appropriateness of methods with respect to the objectives, the type of data and the study design.

3.4 Planned interpretation of results

3.4.1 The basis for conclusions and interpretations should be described.

3.4.2 The change in average daily wet fecal weight compared to negative control values, i.e. with added test and positive control fibres versus without, must be expressed in grams per gram fibre added rather than percentage of initial fecal weight.

3.4.3 Details of the primary objective and the two steps required to meet that objective have been discussed in Section 1. These provide the basis for interpretation of the results of the study.

4. SAMPLE SIZE DETERMINATION

4.1.1 The basis for sample size calculations should be provided. This may involve both statistical and practical considerations. Formulas for sample size and power should be given along with their derivations and/or source of reference. Estimates used in the formulas should be given and explanations provided as to how they were obtained.

4.1.2 A minimum of 12 subjects for the three period crossover design is required. More than this number would likely be required for a balanced incomplete block design. The actual number used should be based on the calculations noted in 4.1.1. Subject numbers will depend in part on the degree of control the study administrator has over the subjects. Larger numbers may be required with free living individuals than with subjects staying in metabolic units and with individuals consuming non-controlled diets than consuming controlled diets.

II. SUBMISSION REVIEW

5. PROTOCOL REVIEW

5.1 The review of a submission would begin with a review of the **PROTOCOL**. This includes STUDY OBJECTIVES, STUDY DESIGN, EFFICACY MEASURES AND STATISTICAL METHODS, SAMPLE SIZE DETERMINATION, DEVIATIONS FROM PROTOCOL, BASIS FOR DEVIATIONS, MODIFICATIONS, ADDITIONAL ANALYSES, etc.

5.2 The actual study conduct details should be provided along with the results. Any important change in the protocol or conduct of the study made after the study was initiated should be described and its implications considered.

6. DATA FILES

Example:

SUBJECT	CENTRE	AGE	SEX	VARIABLE1	VARIABLE2	VARIABLE3
#001	CODE 1	#	M	VALUE 1	VALUE 2	VALUE 3
#002	CODE 1	#	M	VALUE 1	VALUE 2	VALUE 3
#003	CODE 1	#	F	VALUE 1	VALUE 2	VALUE 3
#004	CODE 1	#	F	VALUE 1	VALUE 2	VALUE 3

6.1 Data files can be submitted on diskettes or tape. These data files should be stored in a two-dimensional array (subject by variable). This would allow the reviewer to examine rapidly the individual subject data underlying critical group comparisons.

6.2 Files can be divided into categories (e.g. demographic, efficacy, clinical, laboratory).

6.3 Files should be documented so that data can be easily identified and retrieved if additional analysis is required.

7. DOCUMENTATION OF STATISTICAL METHODS

7.1 Statistical model underlying the analysis

7.1.1 The statistical model underlying the analysis should be specified precisely and completely. The model must be consistent with the study design and underlying assumptions should be specified. Where reasonable, it should be shown that the data satisfy crucial assumptions.

7.2 Assumptions underlying the statistical methods and verification of assumptions where reasonable

7.2.1 Statements of clinical claims tested should be expressed in terms of null and alternative hypotheses. Statistical methods applied to estimate effects, construct confidence intervals, etc. should be specified and references should be included where appropriate. It is important to consider the extent to which the analyses were planned prior to the availability of the data and, if they were not, how bias was avoided in choosing the particular analysis used as a basis for conclusions.

7.3 Tests of clinical claims

7.3.1 The test statistics, sampling distributions under the null hypothesis, values of test statistics, p-values, and intermediate summary data should be provided in a format that allows quick and easy verification. For each different type of analysis used, a sample computer printout of the analysis should be supplied for one variable, with cross references to tabulated results. For example, data analyzed by analysis of variance techniques should include summaries of means and variances by appropriate subgroups, an analysis of variance table with appropriate decompositions of the sums of squares, test statistics, validity checks, etc. Listings of programs used for data analysis are also convenient for quick and easy verification of statistical procedures.

8. STATISTICAL/ANALYTICAL ISSUES

8.1 Adjustments for covariates

8.1.1 Selection of, and adjustment for, demographic or baseline measures, concomitant treatments, or any other covariate or prognostic factor should be explained in the report. The methods of adjustment (e.g. ANCOVA, Cox regression), results of analyses and supportive information (e.g. adjusted means, covariate effects) should be included.

8.2 Handling of dropouts and missing data

8.2.1 The results of the clinical trial should be assessed both for the subset of subjects who completed the trial and for the entire population randomized (intent-to-treat population). Those who do not complete the trial may be either "dropouts" or "non-compliers". "Dropouts" are people who may have dropped out due to illness related to the test fibre or other factors that may or may not be important for the evaluation of the test fibre, protocol, etc. Non-compliers are those who were simply not complying with the protocol. All the data must be provided including dropouts and non-compliers which must be identified. However, the data from non-compliers must not be used in the primary analysis whereas that from dropouts could be.

Several factors need to be considered in analyzing the effects of dropouts, including the reasons for the dropouts, the time to dropout and the proportion of dropouts in the different treatment periods. Ignoring the effects of dropouts can be misleading or introduce bias into the study results. Procedures for dealing with missing data (e.g. imputation) should be described. Details of procedures, imputed values and underlying assumptions should be provided.

8.3 Multicentre studies

8.3.1 A study can be planned to be carried out in several centres using a common protocol with the intention that the data will be pooled for analysis. Results for individual centres and tests for homogeneity across centres (i.e. test for treatment x centre interaction) should also be provided. The combined analysis should be consistent with the study design. These multicentre studies are distinct from separate studies which are sometimes combined through a meta-analysis. Combination of results from separate studies requires careful consideration of patient populations, study designs, study conduct, efficacy criteria, availability of positive and negative test results, etc.

9. REGULATORY INTERPRETATION

9.1 A finding of efficacy in laxation studies for a given novel fibre source (see section 1), subject to its meeting safety criteria as outlined in the "Guidelines Concerning the Safety and Physiological Effects of Novel Fibre Sources and Food Products Containing Them", would permit the inclusion of the fibre contributed by that source in the declaration of dietary fibre on the label of a food product. This would also permit that source to contribute to claims with respect to the fibre content of the product, e.g. "source", "high source" or "very high source" of dietary fibre.

9.2 If the efficacy of a particular novel source of fibre has been shown for a specific food product or class of food products following the present Guideline, then similar food products which use the same fibre source may qualify for the above claims without further clinical investigation, provided that the physical characteristics and properties of fibre in the foods are equivalent and macronutrient profiles of the foods are similar.

9.3 This study protocol may also be used to demonstrate the efficacy with respect to laxation of a reasonable daily intake of a specific product, such as a bread or a breakfast cereal, in support of a claim for "promotes regularity" or "promotes laxation" on the label or in the advertising of that product.

REFERENCES

Acceptable Dietary Fibre Analytical Methods

Mongeau, R. and R. Brassard, Enzymatic gravimetric determination in foods of dietary fiber as the sum of insoluble and soluble fiber fractions: summary of collaborative study. J. AOAC Int. 76:923-925, 1993.
(Note: This method is the AOAC method # 992.16. A detailed version of the method is available from the Health Protection Branch under the following identification: HPB-FC-12, January, 1992.)

Prosky, L., N-G. Asp, I. Furda, J.W. Devries, T.F. Schweizer, B.F. Harland, Determination of total dietary fiber in foods and food products: Collaborative study. J. AOAC 68(4):677-679, 1985 or later revisions thereof.
(Note: The method of Prosky et al. will overestimate the fibre content of dried legumes other than soybean, unless the samples are analyzed uncooked or after autoclaving.)

Englyst, H., M.E. Quigley, G.J. Hudson and J.H. Cummings, Determination of dietary fibre as non-starch polysaccharides by gas-liquid chromatography. Analyst 117:1707-1714, 1992.
(Note: This method plus permanganate lignin produces results comparable to the other two methods although in some cases the results are lower in spite of the latter adjustment.)

Particle size

Mongeau, R. and R. Brassard, Insoluble dietary fibre from breakfast cereals and brans: bile salt binding and water-holding capacity in relation to particle size, Cereal Chem. 59(5):413-417, 1982.

General

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- Terms of Reference
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Guidelines Concerning the Safety and Physiological Effects of Novel Fibre Sources and Food Products Containing Them, Health Protection Branch, February, 1988.

Health and Welfare Canada, Report of the Expert Advisory Committee on Dietary Fibre, Ottawa: Supply and Services Canada, 1985.

Health Protection Branch, Information Letter No. 700, Report of the Expert Committee on Dietary Fibre, December 6, 1985.

Health Protection Branch, Information Letter No. 736, Dietary Fibre, February 5, 1988.

Copies of the above Health Protection Branch publications and reports are available from the Nutrition Evaluation Division, Food Directorate, Health Protection Branch, Tunney's Pasture, Ottawa, Ontario, K1A 0L2, Telephone (613) 957-0352, Fax: (613) 941-6636.