NCCAM Interim Applicant Guidance: Product Quality: Biologically Active Agents Used in Complementary and Alternative Medicine (CAM) and Placebo Materials

Notice Number: **NOT-AT-05-004** (See also, NOT-AT-05-003)

Key Dates
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Issued by
National Center for Complementary and Alternative Medicine (NCCAM), (http://nccam.nih.gov/)

I. Introduction

The purpose of this guidance is to provide direction to applicants on the implementation of the NCCAM Interim Policy - NOT-AT-05-003: Biologically Active Agents Used in Complementary and Alternative Medicine (CAM) and Placebo Materials. This guidance is applicable to all Research Grants (R01, R15, R21), Fellowships (Fs), Career Awards (Ks), and Institutional Training Grants (T32, T35). It specifically addresses the product quality policies:

A. Investigators must provide evidence to convince NCCAM that the biologically active test agents and their placebos proposed for investigation are of sufficient quality.

B. Investigators must reserve test agent and placebo samples from each batch for verification at later dates of product quality, stability over time, and comparability from batch to batch. Before grant award, NCCAM will request that the applicant submit a plan for a sampling scheme, storing and analyzing samples, determining tolerable variances, and making the results of the analyses available to NCCAM. NCCAM may request access to the resulting records of these analyses and even aliquots of study materials for independent analyses. Special terms of award will be added to the Notice of Grant Award pursuant to 42 CFR 52.9 and 45 CFR 74.53. These terms require that the grantee be responsible for implementing the proposed and NCCAM-evaluated plan and submitting the requested information to NCCAM. Lack of compliance with the terms may be grounds for termination of the award.

For additional policies on scope of research and IND application, see NCCAM Policy - NOT-AT-05-003: Biologically Active Agents Used in Complementary and Alternative Medicine (CAM) and Placebo Materials.

II. Contacting NCCAM

Investigators are strongly encouraged to contact a Program Officer who can answer questions about the policy or applicant guidance. Contact the appropriate Program Officer for your scientific area of research. The list of Program Officers can be found at http://nccam.nih.gov/research/contact/index.htm.

III. Guidance to Applicants

A. Information in Applications

Applicants should consider the cost of implementing NCCAM policy (including preparation of an IND application, if required by FDA) in the original application budget.

Although just-in-time information will be more comprehensive, sufficient product quality information must be included in the application to allow the reviewers to evaluate the significance, feasibility and scientific strength of the project.

The following information should be included in the Research Plan:

- Name of the product (species, strain, as applicable);

- Parts to be used (e.g., root, stem, leaf) as applicable;
- Description of placebo or vehicle control group;
- Doses or concentrations to be used.

In the Background and Significance section, provide the following:

- Justification/rationale for studying the chosen product;
- Justification for the chosen form of the product (extract, powder, etc.);
- Justification for the proposed doses/concentrations;
- Description of the pharmacokinetics of the product (if known);
- Source of the product (and if not using a commercial source, an explanation of why a product generally available to the public is not being used).

B. Just-in-Time Information

After peer review, applicants with a better likelihood of being supported will be notified by NCCAM to submit product quality information. The information will be evaluated by a working group of the National Advisory Council for Complementary and Alternative Medicine. The working group will be convened by NCCAM after review but before a funding decision is made. Using the applicant guidance as evaluation criteria, the working group will determine if the information is satisfactory or unsatisfactory. Applicants submitting unsatisfactory information will not be funded. However, the applicant will have opportunities to submit additional information in response to a written request. (Applications are “alive” for 3 council cycles.) Applicants will be informed after the working group meeting about the evaluation outcome, funding decision, and opportunity to submit additional information, if necessary.

IV. Guidance on Just-in-Time Information

The following just-in-time information should be provided by the applicant upon NCCAM request. Guidance on five categories of products is provided: Botanicals (IV. A.); Products Derived from Animals (IV. B); Probiotics (IV. C.); Placebos (IV. D.); All Other Agents (IV. E.).

A. Botanicals

For single ingredient botanical preparations, information on the raw material and final preparation is needed. For multiple ingredient botanical preparations, identity and quality information (specifications and Certificates of Analysis for all components and for the finished product) is needed for each individual ingredient, as well as for the mixture as a whole.

1. Identification of each study agent using the scientific taxonomic nomenclature (e.g., genus, species, variety-if applicable) and author citation.
2. The name of the study agent supplier of the final study product. If the supplier is a “middle man,” the provider of the source material(s) to the supplier. This information should extend back to the raw material harvest, if possible.
3. A letter from the supplier stating commitment to provide product and cooperate with the IND application process, if required.
4. Description of where and how an authenticated reference specimen of the source material is reserved.
5. Identification of the specific pharmacopeial monograph (e.g., U.S. Pharmacopeia) with which the material complies, or a description of suitable tests performed that are specific to the proposed botanical study material and that can be compared to results from an authenticated reference. When no pharmacopeial monograph exists for a study ingredient or in cases where the ingredient does not conform to the existing monograph, specifications should be provided that include all of the same tests found in the monograph.
6. Description (macroscopic) of the parts of the plant from which the product is derived.
7. Information on the geographic source of the material, time of harvest, plant part, and credentials of the person who collected and/or identified the material. If this information is not available, explain how future preparation or acquisition of a reasonably comparable raw material and final or finished study agent can be assured.
8. If the source plant is collected from wild populations, evidence that it was collected in compliance with the WHO Guidelines Guidelines on Good Agricultural and Collection Practices for Medicinal Plants or other national or local guidelines.

9. Description of the extraction procedure (e.g., solvent(s) used, ratio of starting material to finished extract, time and temperature employed, type of extraction, whether fresh or dried material was used, whether any excipient materials were added, what percentage of the extract is native extract, and what percentage is composed of excipients). Define the entire composition of the final extract.
10. Information on the formulation of the final or finished product (e.g., ingredients) and matching placebo, if applicable (see guidance for **Placebos, IV. D.**).
11. Information regarding active and/or other relevant marker compound(s) used for standardization.
12. Information on the characterization (e.g., chemical profile or fingerprint) of the agent as thoroughly as the state of the science allows. Describe the methods used.
13. Any other information relevant to the standardization process of assuring reasonably consistent material suitable for scientific study (including process control, as well as chemical and/or biological standardization of ingredients).
14. Information on the analysis of the product for contaminants, such as pesticide residues, heavy metals, toxic elements, mycotoxins, microorganisms, and adulterants.
15. The specifications and Certificate of Analysis to show compliance to specifications for purity and content from the supplier/manufacturer or other supporting manufacturer information, relating to the batches to be used in the study.
16. Description of bioavailability, dissolution, disintegration and release if the information is available.
17. Information on short- and long-term stability.
18. Information on storage conditions appropriate for assuring stability during the life of the study and how you plan to store the test agent.
19. If more than one batch will be used for the project, information on batch-to-batch reproducibility.
20. Plans to reserve and analyze product samples from all batches used during the course of the study. Plans should include how and when the samples are selected, how many samples, how the samples are stored, what analyses are conducted, the methods used, and how frequently and by whom the analyses are done. Plans should include tolerances for variability and what will be done if variability exceeds those limits. Sufficient material must be retained from each batch to allow independent analysis, should NCCAM require it.

B. Products Derived from Animals

For single ingredient preparations derived from animals, information on the raw material and final preparation is needed. For multiple ingredient preparations derived from animals, identity and quality information (specifications and Certificates of Analysis for all components and for the finished product) is needed for each individual ingredient, as well as for the mixture as a whole.

1. Identification of the study agent using the scientific taxonomic nomenclature (e.g., genus, species, variety-if applicable) and author citation.
2. The name of the study agent supplier of the final product. If the supplier is a “middle man,” the provider of the source material(s) to the supplier. This information should extend back to the raw materials (source animal), if possible.
3. A letter from the supplier stating commitment to provide product and cooperate with the IND application process, if required.
4. Description of the parts of the animal from which the product is derived.
5. Identification of the specific pharmacopoeial monograph (e.g., U.S. Pharmacopeia) with which the material complies, or a description of suitable tests performed that are specific to the proposed study material and that can be compared to results from an authenticated reference. When no pharmacopoeial monograph exists for a study ingredient or in cases where the ingredient does not conform to the existing monograph, specifications should be provided that include all of the same tests found in the monograph.
6. If the source animal is collected from the wild, evidence that it is not on an endangered species list and that it was captured and handled in compliance with national or local guidelines.
7. How the source materials for manufacture into test products are derived from animals. Describe the procedures for ensuring that discomfort, distress, pain, and injury will be limited. Describe the use of analgesic, anesthetic, and tranquilizing drugs and/or comfortable restraining devices, where appropriate. Describe any method of euthanasia to be used.
8. Information on the formulation of the final or finished product (e.g., ingredients) and matching placebo, if applicable (see guidance for **Placebos, IV. D.**).
9. Information regarding the active and/or other relevant marker compound(s) used for standardization.

10. Information on the characterization of the agent as thoroughly as the state of the science allows. Describe the methods used.
11. Information on the analysis of the product for contaminants, such as pesticide residues, heavy metals, toxic elements, mycotoxins, microorganisms, and adulterants.
12. How freedom from disease communicable to humans is assured; include documentation from manufacturer if available.
13. The specifications and Certificate of Analysis to show compliance to specifications for purity and content from the supplier/manufacturer or other supporting manufacturer information, relating to the batches to be used in the study.
14. Description of bioavailability, dissolution, disintegration and release if the information is available.
15. Information on short- and long-term stability.
16. Information on storage conditions appropriate for assuring stability during the life of the study and how you plan to store the study agent.
17. If more than one batch will be used for the project, information on batch-to-batch reproducibility.
18. Plans to reserve and analyze product samples from all batches used during the course of the study. Plans should include how and when the samples are selected, how many samples, how the samples are stored, what analyses are conducted, the methods used, and how frequently and by whom the analyses are done. Plans should include tolerances for variability and what will be done if variability exceeds those limits. Sufficient material must be retained from each batch to allow independent analysis, should NCCAM require it.

C. Probiotics

1. Identification of the study agent using the scientific taxonomic nomenclature (e.g., genus, species, strain) and author citation.
2. The name of the study agent supplier of the final product. If the supplier is a “middle man,” the provider of the source material(s) to the supplier.
3. A letter from the supplier, or provider of source material, and compounding company, if appropriate, stating commitment to provide product and cooperate with the IND application process, if required.
4. Information on the final or finished formulation of the product (e.g., ingredients) and matching placebo, if applicable (see guidance for **Placebos, IV. D.**).
5. Information on enteric protection.
6. Information on the analysis of the product for contaminants, such as pesticide residues, heavy metals, toxic elements, mycotoxins, microorganisms, and adulterants.
7. The Certificate of Analysis for purity and content from the supplier/manufacturer or other supporting manufacturer information, relating to the batches to be used in the study.
8. Description of bioavailability, dissolution, disintegration and release if the information is appropriate and available.
9. Information on short- and long-term viability (of live microorganisms) or potency (inactivated microorganisms).
10. Information on the storage conditions appropriate for assuring viability or potency during the life of the study and how you plan to store the test agent.
11. If more than one batch will be used for the project, information on batch-to-batch reproducibility.
12. Plans to reserve and analyze product samples from all batches used during the course of the study. Plans should include how and when the samples are selected, how many samples, how the samples are stored, what analyses are conducted, the methods used, and how frequently and by whom the analyses are done. Plans should include tolerances for variability and what will be done if variability exceeds those limits. Sufficient material must be retained from each batch to allow independent analysis, should NCCAM require it.

D. Placebos

1. A letter from the supplier stating commitment to provide product and cooperate with the IND application process, if required.
2. Information on the formulation of the product (e.g., ingredients).
3. Verification that the product is inactive and matches the active product in form, color, smell, taste, or other relevant sensory or physical characteristics.
4. Information on the analysis of the product for contaminants, such as pesticide residues, heavy metals, toxic elements, mycotoxins, microorganisms, and adulterants.
5. The specifications and Certificate of Analysis to show compliance to specifications for purity and content from the

supplier/manufacturer or other supporting manufacturer information, relating to the batches to be used in the study.
6. Description of bioavailability, dissolution, disintegration and release if the information is available.
7. Information on short- and long-term stability.
8. Information on storage conditions appropriate for assuring stability during the life of the study and how you plan to store the placebo.
9. If more than one batch will be used for the project, information on batch-to-batch reproducibility.
10. Plans to reserve and analyze product samples from all batches used during the course of the study. Plans should include how and when the samples are selected, how many samples, how the samples are stored, what analyses are conducted, the methods used, and how frequently and by whom the analyses are done. Plans should include tolerances for variability and what will be done if variability exceeds those limits. Sufficient material must be retained from each batch to allow independent analysis, should NCCAM require it.

E. All Other Agents (e.g., other dietary supplements, prebiotics, functional foods, essential oils) (Homeopathic medicines are not included in this guidance.)

Information on the formulation of the product (e.g., ingredients) and matching placebo, if applicable (see guidance for **Placebos, IV. D.**).

1. Identification of the specific pharmacopoeial monograph (e.g., U.S. Pharmacopeia) with which the material complies, or a description of suitable tests performed that are specific to the proposed study material and that can be compared to results from an authenticated reference. When no pharmacopoeial monograph exists for a study ingredient or in cases where the ingredient does not conform to the existing monograph, specifications should be provided that include all of the same tests found in the monograph.
2. A letter from the supplier stating commitment to provide product and cooperate with the IND application process, if required.
3. Information on the analysis of the product for contaminants, such as pesticide residues, heavy metals, toxic elements, mycotoxins, microorganisms, and adulterants.
4. The specifications and Certificate of Analysis to show compliance with the specifications for purity and content from the supplier/manufacturer or other supporting manufacturer information, relating to the batches to be used in the study.
5. Description of bioavailability, dissolution, disintegration and release if the information is available.
6. Information on short- and long-term stability.
7. Information on the storage conditions appropriate for assuring stability during the life of the study and how you plan to store the test agent.
8. If more than one batch will be used for the project, information on batch-to-batch reproducibility.
9. Plans to reserve and analyze product samples from all batches used during the course of the study. Plans should include how and when the samples are selected, how many samples, how the samples are stored, what analyses are conducted, the methods used, and how frequently and by whom the analyses are done. Plans should include tolerances for variability and what will be done if variability exceeds those limits. Sufficient material must be retained from each batch to allow independent analysis, should NCCAM require it.

V. Resources

American Herbal Pharmacopoeia
(http://www.herbal-ahp.org/#)

Australian Government: Therapeutic Goods Administration Questions & Answers for the Identification of Herbal Materials and Extracts
(http://www.tga.gov.au/cm/idherbal.htm)

Bergey's Manual of Systematic Bacteriology

Complementary Healthcare Council of Australia: Code of Practice for Ensuring Raw Material Quality and Safety
(http://www.chc.org.au/lib/pdf/rawmat.pdf)

Considerations for NCCAM Clinical Trial Grant Applications

(http://nccam.nih.gov/research/policies/clinical-considerations.htm)

Dietary Supplements Health and Education Act
(http://www.cfsan.fda.gov/~dms/dietsupp.html)

European Medicines Agency (EMEA)
(http://www.emea.eu.int/index/indexh1.htm)

CPMP/QWP/2819/00 (EMEA/CVMP/814/00) Note for Guidance on Quality of Herbal Medicinal Products (CPMP/CVMP adopted July 01)
(http://www.emea.eu.int/pdfs/human/qwp/281900en.pdf)

CPMP/QWP/2820/00 (EMEA/CVMP/815/00) Note for Guidance on Specifications: Test procedures and Acceptance Criteria for Herbal Drugs, Herbal Drug Preparations and Herbal Medicinal Products (CPMP/CVMP adopted July 01)
(http://www.emea.eu.int/pdfs/human/qwp/282000en.pdf)

Food Chemical Codex
(http://www.iom.edu/project.asp?id=4585)

Health Canada Natural Health Products Regulations
(http://www.hc-sc.gc.ca/hpfb-dgpsa/nhpd-dpsn/regs_cg2_tc_e.html)

Herbs of Commerce, 2 nd Edition (2000)
(http://www.herbalgram.org/herbalgram/articleview.asp?a=2222&p=Y)

Homeopathic Pharmacopoeia of the United States
(http://www.hpus.com)

International Code of Botanical Nomenclature (Saint Louis Code) 2000
(http://www.bgbm.fu-berlin.de/iapt/nomenclature/code/SaintLouis/0000St.Luistitle.htm)

NCCAM Terms of Awards for Clinical Trial
(http://nccam.nih.gov/research/policies/terms-of-awards.htm)

Saskatchewan Herb and Spice Association and the National Herb and Spice Coalition: Good Practices for Plant Identification for the Herbal Industry
(http://www.saskherbspice.org/Good%20Practices%20for%20plant%20identification.pdf)

U.S. Food and Drug Administration: Current Good Manufacturing Practice in Manufacturing, Packing, or Holding Dietary Ingredients and Dietary Supplements
(http://www.cfsan.fda.gov/~lrd/fr030313.html

U.S. Food and Drug Administration: Food, Drug & Cosmetic Act
(http://www.access.gpo.gov/uscode/title21/chapter9_.html) (regulates functional foods)

U.S. Food and Drug Administration: Guidance for Industry: Botanical Drug Products
(http://www.fda.gov/cder) (regarding the need for and content of an IND for botanical drugs)

U.S. Pharmacopeia – National Formulary monographs for botanical raw materials and extracts
(http://www.uspverified.org/standards/monographs.html

World Health Organization Guidelines on Good Agriculture and Collection Practices for Medicinal Plants
(http://www.who.int/medicines/library/trm/medicinalplants/agricultural.pdf)

World Health Organization Monographs on Selected Medicinal Plants
(http://www.who.int/bookorders/anglais/home1.jsp?sesslan=1)

Weekly TOC for this Announcement

[NIH Funding Opportunities and Notices]

Office of Extramural Research (OER)

National Institutes of Health (NIH)
9000 Rockville Pike
Bethesda, Maryland 20892

Department of Health and Human Services (HHS)

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