Research-Grade Cranberry Product Development
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STATEMENT OF WORK

PURPOSE

This Contractor shall support the preparation, characterization, standardization, and maintenance of a supply of cranberry products and matching placebos with concomitant quality control and quality assurance. These products will be used in NIH-supported research, specifically (but not exclusively) for basic and clinical research on the role of cranberry (*Vaccinium macrocarpon*) in the prevention and treatment of urinary tract infections (UTI), other infections, and other conditions for which there is credible evidence of efficacy. Products of primary interest are (1) cranberry juice cocktail, (2) concentrate, and (3) encapsulated powders, and their matching placebos.

BACKGROUND

Significance

UTIs are a serious health problem affecting millions of people each year. Infections of the urinary tract are common – only respiratory infections occur more often. Each year, UTIs account for about 9.6 million doctor visits. One woman in five develops a UTI during her lifetime; UTIs in men are not so common. Nearly 20% of women who have a UTI will have another, and 30% of those will have yet another. Pregnant women seem no more prone to UTIs than other women.

Most infections arise from one type of bacteria, *Escherichia coli*, which normally live in the colon. Usually, the latest infection stems from a strain or type of bacteria that is different from the infection before it, indicating a separate infection. (Even when several UTIs in a row are due to *E. coli*, slight differences in the bacterial strains indicate distinct infections.)

NIH-funded research suggests that one factor behind recurrent UTIs may be the ability of bacteria to attach to cells lining the urinary tract.

Cranberry Use

Traditionally UTIs are treated with antibacterial drugs, but these are expensive, can have side effects, and may promote the emergence of drug-resistant bacteria. Therefore, physicians suggest additional steps that patients can take on their own to avoid infection, including drinking cranberry juice (http://www.niddk.nih.gov/health/urolog/pubs/utiadult/utiadult.htm).

Although cranberry juice is the form of cranberries most widely used, other cranberry products include cranberry powder in hard or soft gelatin capsules. A market report in HerbalGram 49 (Blumenthal 2000) ranked cranberry as number 10 among top-selling herbs in the U.S. in 1999. This represents a 1.7% dollar share of the herb market. In the year ending January 7, 2001, cranberry did not appear on the list of 20 top-selling herbal supplements (Blumenthal 2001).

Efficacy

The use of cranberry among individuals to prevent or treat UTI is a common practice. The accumulating evidence from small, non-controlled and controlled clinical trials suggests that cranberry may relieve symptoms associated

with UTI and may reduce the need for antibiotics. The findings from the preliminary research provide convincing reasons to support the conduct of small-scale, focused clinical studies.
In 1998 (updated 2001), the Cochrane Library conducted separate reviews of cranberry for the prevention (Jepson , The Cochrane Library, Issue 2, 2001) and treatment (Jepson , The Cochrane Library, Issue 2, 2001) of UTI. Each review used similar search strategies and selection criteria. These included all randomized or quasi-randomized controlled trials. Trials of at least one month and at least five days were included for prevention and treatment respectively. For prevention, four trials met the inclusion criteria (Avorn 1994, Haverkorn 1994, Foda 1995, Walker 1997). For treatment, no trials meeting the inclusion criteria were found; only a few uncontrolled trials were found (Papas 1966; Rogers 1991). They concluded that there was no good quality or reliable evidence of the effectiveness of cranberry juice or other cranberry products for the prevention or treatment of UTI and that more research is needed.

Three crossover studies (not included in either review) investigated the effect of cranberry on urine pH but did not attempt to assess activity in UTI. Two of these demonstrated a decrease in pH (Kinney 1979; Jackson 1997) whereas another did not (Nahata 1981, 1982).

Finally, other studies not cited in the reviews show different results. One of these did not support the efficacy of cranberry in UTI in children with neurogenic bladder (Schlager 1999). A study of adults with spinal cord injury demonstrated a reduction in biofilm load (Reid 2001), but the importance of this effect for frank UTI was not determined. A small study of urostomy patients found equivocal results (Tsukada 1994).

Many of the clinical studies reported in the literature suffer from major limitations, as acknowledged in the Cochrane Library reviews. Many trials have not been controlled or randomized, and randomization procedures have not always been described. Crossover designs used in some studies may not be appropriate for studies of UTI. Other limitations include no blinding or failed blinding, lack of controlled diets or dietary assessment, use of convenience samples, and small numbers of subjects. Sample sizes have ranged from as few as 10 to as many as 192. Trials have been faulted for the large number of dropouts/withdrawals which may be indicative that cranberry juice is not acceptable over the longer periods. Intention-to-treat analyses were not often applied. Most studies have been conducted in older or elderly patients. Very few have been in younger patients, with or without comorbidities. Primary outcomes have differed and have often been urinary pH, as well as rate of bacteriuria, biofilm load, and urinary white and red blood cells, rather than UTI.

Safety

Cranberry taken orally in food amounts appears safe, although ingesting large amounts may result in diarrhea and other gastrointestinal symptoms. Safety of amounts greater than that consumed in foods is unknown. One study of cranberry tablets suggests caution for patients at risk for nephrolithiasis until safety of cranberry is confirmed (Terris 2001). Currently, there is insufficient reliable information available to assess the interaction of cranberry with dietary supplements, medications, foods or laboratory tests.

Mechanism of Action

The potential mechanism of action of cranberry has not been clearly elucidated.

High levels of benzoic acid have been reported in cranberry juice, and until recently, a possible mechanism for the bacteriostatic effect of cranberry juice was suggested to be due to acidification of the urine (Blatherwick 1914, 1923; Bodel 1959; Kinney 1979). Several studies, however, have cast doubt on this mechansim (Kahn 1967; McLeod 1978; Nahata 1981, 1982; Avorn 1994).

Current belief is that the prevention of UTI is achieved by inhibiting the infecting bacteria, *E. coli*, from adhering to uroepithelial cells (Sobota 1984; Schmidt and Sobota 1988; Zafriri 1989; Ofek 1991; Howell 1998). Bacterial adherence to these cells is a critical step in the development of infection. It is facilitated by fimbriae (proteinaceous fibers on the bacterial cell well). Fimbriae produce adhesions which attach to receptors on uroepithelial cells. It is hypothesized that cranberry constituents act by preventing adhesion. Thus, the causative bacteria are flushed, preventing their colonization of the urinary tract. In addition, there has been a report of the potential of cranberry

juice to weaken attachment of *E. coli* to inert (nonliving) surfaces for control of biofilm formation on urinary catheters (Allison 2000).

Two components of cranberry juice have been shown to inhibit the adherence of *E. coli* to uroepithelial cells in vitro. The first is fructose which may not survive absorption and metabolism intact to reach the urinary bladder. The second is a group of polymeric proanthocyanidins (Howell 1998); the chemical structures of three have been elucidated (Foo 2000). Fructose inhibits the adherence of type-1 fimbriated *E. coli* and proanthocyanidins inhibit the adherence of P-fimbriated *E. coli* to uroepithelial cells (Zafriri 1989; Ahuja 1998).

Cranberry Product

The appropriate cranberry product, dose and duration of intervention for prevention or treatment of UTI are unknown. While cranberry juice cocktail is the most studied product, concentrates and encapsulated powders have also been used. Some sources suggest six capsules of dried cranberry powder are equivalent to 2 oz. cranberry juice cocktail. The chemical composition of the study agents, in general, has not been described in the published literature, nor has the equivalence of the active constituents or markers among cocktails, concentrates, and capsules/tablets been described. Therefore, comparison among study agents or trial results has not been possible.

The single-strength juice is highly acidic and astringent which makes the juice unpalatable at full strength. Accordingly, the juice drink, i.e., cranberry juice cocktail, is a mixture of single-strength cranberry juice, sweetener, water, and vitamin C (Kuzminski 1996). Cocktails have been sweetened with fructose or artificially sweetened. The percent concentrate used in the cocktails has ranged from about 25% to 80%, although cocktail with 33% pure juice is common.

Cranberries contain about 88% water. Among the other organic constituents are flavonoids, anthocyanins, catechin, triterpinoids, B-hydroxybutyric acid, citric, malic, glucuronic, quinic and benzoic acids, ellagic acid, and vitamin C (Siciliano 1998). Quinic acid and the ratio of quinic acid to malic acid are reasonably constant and are used to calculate percentage of cranberry juice content in juice drinks and to assess cranberry juice authenticity (Kuzminski1996). Although anthocyanins change and degrade with processing and storage, the anthocyanin profile is unique to cranberry, and its qualitative pattern is characteristic.

Doses of the cocktails have ranged from 160 to 750 ml a day, usually in divided doses at meals. Intervention duration has also ranged, from 5 days to 6 months (longer trials for prevention). The rationale behind the amount and concentrate of cranberry juice given to participants and the duration of intervention is usually not provided.

PROJECT DESCRIPTION

The purpose of the Contract shall be to develop standardized products for cranberry (*Vaccinium macrocarpon*) (1) juice cocktail, (2) concentrate, and (3) encapsulated powders, and their matching placebos. The Contractor shall provide adequate information about the source, collection, storage, processing, extraction and purification process, formulation, stability, and safety of the products in order to meet Food and Drug Administration (FDA) requirements for the filing of Investigational New Drug (IND) applications (http://www.fda.gov/cder/guidance/phase1.pdf).

It is important that the cranberry products for NIH-supported research be of a high quality. The NCCAM plans for research on cranberry include award of (1) this Contract for development and production of cranberry research-grade products and placebos and (2) subsequent grants for basic and clinical research on the role of cranberry in the prevention and treatment of UTI, other infections, and other conditions for which there is credible evidence of efficacy. Award of the Contract for cranberry product development is the first step in the overall program. Year 1 of the contract shall include collecting and generating the data appropriate for developing standardized cranberry products and a Drug Master File (DMF) (http://www.fda.gov/cder/guidance/dmf.htm); some of these activities will continue into Year 2. [Only the Contractor, its subcontractors (as applicable), and the NIH will be involved during Year 1.]

During Year 2, NIH will award grants for basic and clinical research to multiple institutions. These grantees will be required to use the cranberry products developed and provided by the Contractor. Grantees will finalize their

protocols independent of the Contractor with the exception of product provision. Grantees and the NIH shall determine type of products, doses, and quantities needed for a variety of research projects. In addition, packaging of products, labeling, and delivery schedules shall be determined. IND applications with reference to the DMF will be filed during Year 2 by the grantees. The Contractor shall have submitted the DMF earlier in Year 2. Finally in Year 2, the Contractor shall be responsible for producing, labeling, packaging, storing, inventorying and distributing one batch of the cranberry products and placebos to the grantees. Provision of products to grantees means that during Year 2, the Contractor shall scale up from developing research-grade materials to the manufacture of larger quantities of the product. This activity shall require the development of detailed operating procedures for the raw materials, as well as the final research-grade products. Stability testing on the products in the first batch will begin.

In the final year of the Contract, Year 3, the Contractor shall provide a second batch of cranberry products and placebos to the grantees. It is likely that some grants awarded in the second year of the Contract will have project periods that extend beyond the life of the Contract. Therefore, all study materials shall be provided to the grantees before the end of the Contract. In addition, stability testing shall continue and comparison of the two batches of products shall occur. Preparation for publication of manuscripts on the standardized product shall be finalized and submitted by the Contractor.

Timeline

The following timeline is tentative and for planning purposes only.

[Offerors shall address the appropriateness and feasibility of the proposed timeline, to include Paragraphs 1 - 17 below, in their proposals.]

Year	**Periods**
Year 1	**09/30/02-09/29/03**

Establish contacts at FDA regarding preparation of the Drug Master File.
Begin cranberry product and placebo development.
Begin to develop the Drug Master File, including collecting and generating data as necessary.

Year 2	**09/30/03-09/29/04**

Continue product development.
Finalize Standard Operating Procedures for raw cranberry material by December 1, 2003.
[**]Clinical and basic research grants awarded December 1, 2003.
[**]Grantee protocols finalized.
[**]Grantees determine product dosing and form requirements, as well as quantity of study agents;
Finalize Standard Operating Procedures for standardized dosage forms of cranberry products and placebos by February 1, 2004.
Complete placebo evaluation by February 1, 2004.
Submit Drug Master File to FDA by February 1, 2004.
[**]Grantees submit IND's to FDA by March/April 2004.
Manufacture of cranberry and placebo products.
Begin stability testing on batch #1
Provide batch #1 of standardized cranberry product and placebo to grantees by June 1, 2004.

[**] Starred items are not the Contractor's responsibility but influence Contractor's activities.

Year 3	**09/30/04-09/29/05**

Continue stability testing on batch #1 and start testing on batch #2.
Provide batch #2 of standardized cranberry product and placebo to grantees June 1, 2005.
Demonstrate batch-to-batch consistency based on chemical, physical, biological tests.
Prepare publications.

KEY ACTIVITIES

The Contractor shall have the capability to develop six products simultaneously: three cranberry products (e.g., juice, concentrate, encapsulated powder) and their matching placebos.

Some proposed activities are subject to change during finalization of the grantee's protocols. (For proposal purposes, assumptions are made in this RFP about timeline and types and amounts of cranberry product needed.)

STATEMENT OF WORK

Independently, and not as an agent of the Government, the Contractor shall furnish all the necessary services, qualified personnel, material, equipment, and facilities not otherwise provided by the Government as needed to perform the work below.

Product Development

1. Develop three cranberry products. Many of the activities related to characterization and standardization of the three active preparations and preparation of the Drug Master Files may be the same or overlap; however, many may not be.

    a. Accurately identify *Vaccinium macrocarpon*, and determine the macro- and microscopic and other physical characteristics (e.g., DNA fingerprinting, color, etc.) necessary for accurate identification of plant source and the respective products.

    b. Identify and provide a consistent, high-quality source of the raw cranberry material. This activity includes identification of the sources of cranberry and assurance that the supply has not been placed on the FDA alert list.

    c. Develop and document validated, qualitative and quantitative analytical methods for the determination of marker compounds in crude materials.

    d. Use the methods developed in Paragraph 1c above to identify the chemical profile for active constituents and inactive marker compounds for purposes of plant identification. Determine their variability for purposes of defining acceptance criteria for identification of the test article(s).

    e. Establish acceptable ranges for content of marker compounds (biologically active and inactive constituents) for application to production of standardized research-grade cranberry products.

    f. Identify and describe the cultivar(s) from which the standardized cranberry fruit product is derived, how it is processed (or extracted), and the form in which it is provided.

    g. Describe the Good Agricultural Practices (GAP) plan (cultivation methods, harvesting, processing, storage practices, integrated pest management, etc.) that shall be used to assure uniformity of active and inactive markers in the raw material.

    h. Identify, describe, and control production methods (raw materials specifications, in-process controls, finished product testing) that assure batch-to-batch consistency of active and inactive marker content in the research-grade cranberry products.

2. Develop three placebos that match each of the three cranberry products. The Contractor shall develop inactive products with sensory (color, feel, smell, taste) and physical characteristics similar to those of the cranberry products with which they will be matched. *(As part of their proposal, Offerors shall describe the method(s) by which success of the matching will be evaluated.)*

3. Establish stability-indicating analytical methods (using markers if necessary) and conduct stability studies of the cranberry products. The stability of the cranberry products should not be based entirely on the assay of the active constituents, assay of the markers, or biological assay, because degradants formed during storage from other chemical constituents in the products should also be controlled. Analytical methods capable of detecting degradants (e.g., chromatographic fingerprint) should be established through exploratory experiments using accepted protocols for performance of accelerated stability studies.

4. Develop quality control/quality assurance procedures as part of an integrated Good Manufacturing Practices (GMP) plan. The Contractor shall determine (and describe in the Standard Operating Procedures) the control checks performed at various stages of the cultivation, harvest, production, manufacture, processing, storage, and packaging of the cranberry products and placebos. Specifications and analytical methods necessary to assure the identity, strength, quality, purity, and homogeneity of the test article throughout the shelf-life of the product shall be established. The methods and standards of acceptance should be sufficiently detailed to permit duplication and verification by other laboratories. Quality control units for the raw source material and research-grade product shall check or test that specifications are met and quality systems are maintained.

5. Establish standard operating procedures (SOPs) for production of the raw cranberry materials, three final cranberry products, and matching placebos. (Grantees will not be involved in development of these SOPs.) The Government Project Officer will review and approve the final SOPs. These SOPs may contain proprietary information, the confidentiality of which the Contractor will take steps to safeguard (see Paragraph 16 below). One month prior to the expected completion of the SOPs, the Contractor shall submit the SOPs to the Project Officer. Within one week, the Project Officer will provide comment to the Contractor. For proposal purposes, assume that the Contractor shall deliver to the Project Officer the final SOPs for raw materials on December 1, 2003 and for the standardized dosage forms on February 1, 2004.

    a. Establish SOPs, under GAP and GMP, for the production/manufacture of the standardized raw cranberry test articles. These shall specify the growth and harvest conditions and procedures (including pesticides used); harvest location; harvest time; storage/preservation of the fruit prior to processing; processing of the fruit to produce bulk quantities of juice, concentrate and powder; conditions of shipment to (or storage awaiting) the manufacture of the study agents; raw product safety; quality control; and facilities. The SOPs shall specify equipment and quantity of material/product used, temperature employed, processing time, in-process controls (testing performed during production to monitor and, if necessary, to adjust the process), and yield. The quality control shall include botanical identification, chemical identification for active constituents and markers, assay for active constituent, biological assay (if available), heavy metals, microbial limits, residual pesticides, adventitious toxins, and foreign materials and adulterants.

    b. Establish SOPs for manufacture, under GMP, of the standardized dosage forms of the cranberry and placebo products. These shall include a detailed flow diagram and address the manufacturing facilities, process, in-process controls, characterization, and testing. They shall specify the acceptable limits and analytical methods used to assure the identity, strength, quality, and purity of the cranberry products. This may include a combination of tests (e.g., spectroscopic or chromatographic fingerprints, chemical assay of characteristic markers, and biological assay), controls (e.g., strict quality controls of the botanical raw materials and adequate in-process controls), and process validation (documented evidence that provides a high degree of assurance that a specific process will consistently produce a product of predetermined specification and quality characteristics). The details shall include the quantity of botanical raw materials, equipment, reagents, solvents, catalysts, temperature/time for mixing, grinding, extraction and/or drying, yield, and in-process controls. The yield of the process, expressed as the amount of the

extract relative to the amount of the original botanical raw material, shall also be indicated. The quality control tests shall include, but not be limited to, appearance, chemical identification for active constituents and markers, chemical assay for active constituents and markers, biological assay, strength by weight, water content, residual solvents, heavy metals, microbial limits, residual pesticides, and adventitious and endogenous toxins. SOPs for maintenance and cleaning of all test article contact surfaces shall be provided as part of the GMP plan.

6. Develop, submit, and maintain a DMF: http://www.fda.gov/cder/guidance/dmf.htm. A DMF is a submission to the FDA that may be used to provide confidential detailed information about facilities, processes, or articles used in the manufacturing, processing, packaging, and storing of one or more human drugs. The information contained in the DMF may be used to support an IND application (http://www.fda.gov/cder/guidance/phase1.pdf).

   Preparation of the DMF shall be ongoing from Year 1 but shall be submitted to the FDA during Year 2. For proposal purposes, the Contractor shall assume the submission of the original DMF cover letter and the DMF to the FDA and a copy of the cover letter to the Project Officer by February 1, 2004. (The holder of the DMF need not be the Contractor, but could be a subcontractor to the Contractor.)

7. For purposes of this Contract, the Contractor shall not be required to file IND applications. Grantees will be expected to file IND applications. The Contractor, however, shall be responsible for assisting the grantees by completing sections of the IND application.

   [NOTE: Under current regulations, any use in the United States of a drug product (e.g., well-characterized, therapeutic, biotechnology-derived products) not previously authorized for marketing in the United States first requires submission of an IND to the FDA. NIH grantees are required in the PHS 398 application to name the test article and state whether the 30-day interval between submission of applicant certification to the FDA and its response has elapsed or has been waived and/or whether use of the test article has been withheld or restricted by the FDA.]

   It shall be the responsibility of the Contractor to provide the following sections of the IND applications (referencing the DMF may be appropriate) to the grantees and Project Officer by January 1, 2004:

   a. Investigator's Brochures for the cranberry products. This includes safety information, published studies of cranberry and a list of published studies conducted with the products.

   b. Chemistry, manufacturing, and control information on the cranberry products. This includes physical, chemical and biological characteristics; stability data; method of preparation. In addition brief descriptions of the composition, manufacture, and control of the placebos shall be required, as well as copy of all labels and labeling to be provided to the grantees.

   c. Pharmacology and toxicology data, if available.

   d. Previous human experience, including a list of the countries where the products are in clinical testing or have been approved or marketed, if appropriate.

   [NOTE: FDA's draft guidance document, Guidance for Industry, Botanical Drug Products (http://www.fda.gov/cder/guidance/1221dft.pdf) may not be finalized and published until after award of the Contract; but it will provide guidance on submitting IND applications.]

8. Retain a voucher specimen of the plant or plant parts, as well as the three cranberry products for every batch. These shall be retained as the reference standard for use in identification, fingerprinting, future chemical and/or pharmacological/toxicological testing, and other comparative and noncomparative tests. The Offeror shall describe how these specimens will be preserved. For proposal purposes, assume that these voucher specimens and cranberry products shall be delivered to an NIH repository upon completion of the Contract.

9. Demonstrate batch-to-batch consistency for the cranberry products based on results from chemical, physical, biological tests on all relevant batches. All measured chemical constituents present in the products should be qualitatively and quantitatively comparable based on spectroscopic and/or chromatographic fingerprinting.

Provision of Product to Grantees

10. Provide (e.g., label, package, store, inventory, and distribute) in two batches the standardized cranberry products to the NIH-sponsored grantees. Grant investigators and study participants will be blinded to study agents. The Contractor shall develop and implement a system for distribution of the study agents. The system shall involve all aspects of acquisition, distribution, and accountability and shall comply, at a minimum, with Federal, state, and local regulations. The Contractor shall collaborate with the manufacturer (if they are distinct) to provide the grantees with information about the proper dispensing, handling, and administration of the study agents. This information shall include instructions for use (e.g., ingestion before, during or after meals), interactions with concomitant medications and any known adverse experiences.

The Contractor must be able to supply a sufficient quantity of the formulated cranberry and matching placebo within the to-be-determined specifications for the duration of the grantee research. During Year 2, the Contractor shall meet with subcontractors, grantees and the NIH staff to determine capsule size and other physical state needs, number of capsules or milliliters per dose and number of doses per person required for duration of treatment for each of the grants. Information on the product packaging (number of capsules or milliliters per vial/container and product label) will also be determined during Year 2. These products shall be provided in NIH-approved packaging with labeling suitable for human double-blinded clinical trials. They shall be shipped to the grantee pharmacists in one or two batches.

For proposal purposes, assume that the Contractor shall provide cranberry products to 4 grantees whose project length is 4 years and 6 grantees whose project length is only 2 years. Awards to these grantees will be made during Year 2 of the contract, on or about December 1, 2003. Assume all grantees will be ready to receive product 6 months into their grant periods. The 4 grantees whose project periods extend 4 years will require a second batch of product about half way through their grant period. Some grantees may be studying more than one type of product.

For the first delivery (on or about June 1, 2004), consider provision of cranberry juice cocktail and placebo to 5 grantees, cranberry concentrate and placebo to 4 grantees, and encapsulated cranberry powder and placebo to 5 grantees. The amounts for the first batch of juice and placebo are estimated at 33,750 liters each of juice cocktail and placebo; 72,000 fluid ounces each of concentrate and placebo; 135,000 capsules each of 400 mg concentrated cranberry and placebo.

For the second delivery, consider provision of cranberry juice cocktail and placebo to 3 grantees, cranberry concentrate and placebo to 2 grantees, and encapsulated cranberry powder and placebo to 3 grantees on or about June 1, 2005. The amounts for the second batch of juice and placebo are estimated at 20,250 liters each of juice cocktail and placebo; 36,000 fluid ounces each of concentrate and placebo; 81,000 capsules each of cranberry and placebo.

Juice shall be packaged in single-serving containers (250 ml; 3/day); concentrate in 16 fl oz containers (2 oz/day); and capsules in child-proof bottles of a hundred 400 mg capsules (one 3 times a day). For the first batch, there would be 135,000 single-serving containers of cranberry juice; 135,000 containers of placebo juice; 4,500 containers of cranberry concentrate; 4,500 containers of concentrate placebo; 1,350 bottles of 100 cranberry capsules; and 1,350 bottles of 100 placebo capsules. For the second batch, there would be 81,000 single-serving containers of cranberry juice; 81,000 containers of placebo juice; 2,250 containers of cranberry concentrate; 2,250 containers of concentrate placebo; 810 bottles of 100 cranberry capsules; and 810 bottles of 100 placebo capsules. Containers/bottles shall be labeled to preserve the blind for each grantee's study.
[NOTE: All quantities indicated are estimates only and may need to be modified as work on the contract

progresses.]

The Contractor, or its subcontractor (as applicable), shall have a GMP-compliant packaging and labeling facility. The Contractor shall have the capability to print a variety of label products, count capsules, accurately measure 250 ml portions into single-serving containers, cap and seal vials/containers, and shrink-wrap final packaged product (if needed). The Contractor shall have label stocks to address different storage and shipping conditions and that meet all FDA regulatory requirements. Other packaging and labeling services provided by the Contractor shall include patient kit design and assembly.

The Contractor, or its subcontractor (as applicable), shall distribute the study agents efficiently and safely. These services shall include generating a detailed packaging slip for each order for inclusion in the package and a pulling, packing, and checking system to ensure that the proper product and batch number are pulled and packaged for shipment. The Contractor shall ship products in insulated shipping containers to ensure that the packages will maintain a designated temperature during transit and shall be responsible for tracking shipments to confirm receipt of all packages sent. The Contractor shall use overnight delivery services.

Administration/Organization

11. Develop an administrative structure responsible for directing all of the activities of the project and for cooperative interactions with other institutions. This shall include working and contracting with suppliers, when it is necessary to obtain the raw source material or any product thereof (*V. macrocarpon*) from a supplier other than itself.

12. Prepare and submit all technical reports and products as described in Reporting Requirements and Deliverables.

13. Coordinate, arrange, participate in, and provide any information necessary for all meetings related to cranberry product development, production and distribution. Assume for purposes of the proposal:

    a. During Years 1, 2 and 3, monthly conference calls of the Contractor, its subcontractors (as applicable) and the NIH will be held to determine progress, discuss issues, and plan for next phase, as well as for future provision to investigators of research-grade cranberry product and placebo (see Paragraph 17 below).

    b. During Years 1, 2 and 3, the Contractor shall schedule site visits for planning and quality control purposes to the agricultural field and product manufacture facilities: two trips in Year 1, two trips in Year 2 and one trip in Year 3.

    c. During Year 2 and Year 3, the Contractor shall meet once in the Washington DC metropolitan area in January 2004 and conduct monthly conference calls (December 2003 through September 2004) with new clinical and basic science grantees and the NIH to determine study agent needs (agent type, dosing, quantities, labeling, packaging and delivery) and production/delivery schedules. The grantees are responsible for their own travel costs. The Contractor shall be responsible for its own and its subcontractors' travel, as well as preparation of meeting and conference call minutes. Minutes shall include participants, decisions and action items, as well as major issues debated in reaching decisions. Draft minutes are due within 7 days of the call or meeting, and final minutes are due within 14 days and are to be distributed to the grantees and the Government's Contracting and Project Officers.

    d. Early in Year 1, the Contractor shall meet once with the NIH and its subcontractors (as applicable) for one two-day meeting at its own facility for planning purposes.

Technical Provisions

14. Prepare findings (e.g., on chemical constituents, variability of markers, etc. in the standardized product) for publication in peer-reviewed scientific journals. The NCCAM shall have exclusive rights to all data and

reports generated under this contract. No data will be released or published without the approval of the Project Officer. The Contractor shall not have access to the data generated by the grantees to whom the cranberry products are provided.

15. Provide reports, data, standard operating procedures or product to an independent site. The Project Officer may require that reports, data, standard operating procedures or product be transferred directly from the Contractor (or as applicable from a subcontractor's site) to an independent site for analysis and/or review.

16. Establish procedures to safeguard the confidentiality of any proprietary information. Proprietary information is considered confidential and shall only be released in accordance with the terms of clause HHSAR 352.224-70, CONFIDENTIALITY OF INFORMATION (April 1984) (refer to Section H of the contract for the full test of this clause). The following may contain proprietary information and therefore (as applicable) shall be handled in a confidential manner: (1) the operating procedures for the standardized cranberry raw materials and the standardized dosage forms; and (2) data on cranberry study agent constituents (e.g., their quantity, variation, stability).

17. Develop a plan for providing additional supplies of standardized research-grade cranberry product and placebo to researchers after the period of performance of this Contract.