Statement of Work

Analysis of Bulk Drugs & Pharmaceutical Formulations

A. Background

The Pharmaceutical Resources Branch (PRB), Developmental Therapeutics Program (DTP), Division Cancer Treatment and Diagnosis (DCTD), National Cancer Institute (NCI) is seeking services for the analysis of bulk drug substances and formulated drug products. Reports of these analyses will be used as a basis for assessing the suitability of these materials for use for screening, pharmacological studies, toxicological studies, formulation studies, or for clinical trials. Data provided in these analytical reports will be supplied to the Food and Drug Administration (FDA) as part of the Investigational New Drug (IND) filings for new anti-tumor agents. Historical summaries of the data are used in preparing specifications of the various bulk drug substances. These specifications are used in procurement actions as well as for the routine quality control of these materials. The Contractors selected should be experienced in the analytical assessment of bulk drug substances and clinical drug products and will be expected to have operational equipment and capabilities.

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

B. Scope and Tasks

Each Contractor shall complete and deliver approximately 10-15 Requests for Analysis assignments each year. *The actual number of assignments is expected to be variable, dependent upon the approval rate of developmental compounds*. These assignments will involve the following project activities:

1. Complete all work required by typical "Requests for Analysis" on bulk drug substances. Approximately 4-6 bulk drug lots per year are anticipated.

2. Complete all work required by typical "Requests for Analysis" on formulated drug products. Approximately 2-4 lots of formulated drug products per year are anticipated.

3. Develop validated chromatographic methods for bulk drug substances and formulated drug products. Analytical methods development will be required for approximately 2-3 new drug substances per year.

4. Complete assigned work on approximately 2-3 long-term projects (6-12 months in duration) each year, usually involving stability studies on bulk drug substance, according to FDA guidance.

The Contractor shall perform analysis of bulk drug substances and their pharmaceutical formulations. All materials to be analyzed will be assigned and usually supplied by the NCI Project Officer. The Project Officer will transmit with each sample a "Request for Analysis". The "Request for Analysis" will list the Request Number, date, NCI compound designation (NSC Number), chemical name, structure, supplier, lot number, method of preparation (where applicable), specifications (when available), and other pertinent information. Specific analytical tests to be performed by the Contractor will be specified by the Project Officer. The Contractor

shall prepare analytical reports which detail the work performed in response to a specific "Request for Analysis". Each "Request for Analysis" will address various objectives which may include the following:

a) Establish the identity of the drug substance, usually by a combination of spectroscopic and spectrometric studies.

b) Establish the purity of bulk drug substance, usually by the development of a validated chromatographic method according to FDA guidance.

c) Identify and determine the amounts of major impurities present in the bulk drug substance, primarily by a combination of chromatographic and spectroscopic/spectrometric analyses and preferably by LC-MS (liquid chromatography-mass spectrometric analysis).

d) Determine physical and chemical properties of drug substances (e.g., solubility, optical rotation, thermal properties (m.p., DSC, TGA), partition coefficient and pKa's).

e) Determine the stability of the drug substance and drug product under designated storage conditions, in accordance with FDA guidance.

f) Identify and determine the concentration of the active pharmaceutical ingredient in dosage forms.

g) Determine weight variation and content uniformity of dosage forms.

h) Develop dissolution method for solid dosage forms.

i) Adapt bulk drug substance assay methods to allow the determination of drug levels in plasma or other complex matrices.

The Contractor shall consider the chemicals and drugs to be analyzed under the proposed contract as proprietary in nature. Under no circumstances are chemicals or drugs or any information associated with these chemicals or drugs to be released or divulged without prior written approval of the Project Officer.

The Contractor shall maintain laboratory notebooks containing raw data at the contract site. All data generated under the proposed contract are property of the Government and must be supplied to the Government upon request.

The Contractor shall comply with Government drug, health and safety regulations:

a) FDA requirements. Facilities shall meet FDA standards for Laboratory Quality Control unit, in accordance with current Good Manufacturing Practices (cGMP) regulation. If inspections by FDA during the term of the contract cite deficiencies which, in the opinion of the Project Officer and Contracting Officer (C.O.), are judged to disqualify its function as a Laboratory Control unit, such citations could be the basis for termination of the contract unless satisfactory corrective actions are implemented..

b) Occupational Safety and Health Act (OSHA), United States Environmental Protection

Agency (EPA) and United States Department of Transportation (DOT) regulations: The Contractor shall comply with all OSHA and DOT regulations regarding the handling of chemicals. The Contractor shall comply with all EPA regulations regarding the discharge of water and air pollutants and assure that disposal of all chemical residues meets current EPA regulations.

In order to meet the objectives listed above, the Contractor shall be expected to analyze bulk drug substance and formulated drug product. The Contractor shall also develop validated analytical methods to establish the identity and purity of the materials analyzed. The following is a list of approaches for different assignments:

1. Although each "Request for Analysis" for a bulk drug substance will specify the analytical tests required, in most cases those tests will be selected from the following list:

   a) Melting point or DSC (Differential Scanning Calorimetry) determination
   b) Infrared spectroscopy
   c) Ultraviolet spectroscopy
   d) Nuclear magnetic resonance spectroscopy (proton, carbon, fluorine and phosphorus) and 2-D correlated experiments
   e) Mass Spectrometry (low- and high-resolution)
   f) Optical rotation
   g) Thin-layer and/or paper chromatography
   h) High performance liquid chromatography or gas-liquid chromatography
   i) LC-MS (liquid chromatography-mass spectrometric analysis) and LC-MS/MS determinations
   j) Capillary electrophoresis
   k) Karl Fischer water determination
   l) Trace analysis for heavy metals

   Additional tests and procedures may also be required by the Project Officer. These include solubility determinations, bulk and solution stability studies, electrochemical techniques, partition coefficient and pKa measurements, thermogravimetric analyses (TGA), AA, ICP-MS, and other tests as needed.

2. Although each "Request for Analysis" for a formulated drug will specify the analytical tests required, in most cases those tests will be selected from the following list:

   a) Infrared spectroscopy
   b) Ultraviolet spectroscopy
   c) High performance liquid chromatography or gas-liquid chromatography
   d) Any other tests (e.g., dissolution, content uniformity) appropriate to the various dosage forms (tablets, capsules, liquid fills or lyophilized products).

3. "Requests for Analysis" on new drugs may require the development of validated chromatographic methods, in accordance with FDA guidance. The Contractor shall also provide data validating the assay methods developed. These data shall be submitted to the Project Officer in a separate "Validation Report", which will include a detailed description of the assay procedure; appropriate measures of accuracy, specificity, sensitivity, precision; stability-indicating capability and other information as required.

4. It is anticipated that several (2-4) long term projects (i.e., projects of 6-12 months in duration) will be assigned per year. These assignments are not intended to conflict with the more routine "Requests for Analysis". Project assignments will be made by the Project Officer. Examples of long term projects include: identifying impurities, stability assessment, and developing an assay method for drug level determinations in plasma.

It is anticipated that 3 awards of multiple-year, incrementally funded, completion-type contracts will be made for a period of five (5) years. Each increment of funding for these contracts will be for a period not exceeding 12 months. Each Contractor is estimated to provide 3.5 technical staff - years per year with completion and delivery of 10 to 15 reports for approximately 10-15 Request for Analysis assignments. A staff year is 1875 hours of direct labor per year excluding holidays and sick leaves.

It is anticipated that these contracts will commence on approximately June 1, 2012 and end on approximately May 31, 2017.

C. TRAVEL REQUIREMENTS

The Principal Investigator (P.I.) or a designated person, shall be permitted to attend one professional meeting per year with prior approval of the C.O. Any other technical trips to be charged to the contract must also have prior approval by the C.O.. Estimates for any anticipated travel of this type should be shown in the cost section of the Proposal.