

## APPENDIX C

### Exceptions or Modifications to This CRADA

#### Standard Modifications for Extramural Clinical Trial CRADAs

Add the following new sections to the **Article 2. Definitions**:

- 2.12 “*Adverse Drug Experience*” means an adverse clinical experience as defined under 21 C.F.R. 310.305 and 312.32 where applicable.
- 2.13 “*Agent*” means [drug or biologic product].
- 2.14 “*Annual Report*” means the brief report of the progress of an IND associated investigation which the IND sponsor is required to submit to the FDA within 60 days of the anniversary date that the IND went into effect (pursuant to 21 C.F.R. 312.33).
- 2.15 “*Clinical Data and Results*” means all information, data and results developed or obtained in connection with clinical trials conducted within the scope of the CRADA Research Plan whether by intramural research scientists or extramural grantee or contract investigators.
- 2.16 “*Clinical Data and Results and Raw Data in NIH’s Possession and Control*” means all information collected from NIH intramural preclinical or clinical studies performed pursuant to the Research Plan, all data obtained by NIH under contracts with extramural contract investigators for completion of studies within the scope of the CRADA Research Plan, and all information and data in the NCI-sponsored IND for Agent.
- 2.17 “*Contract*” means a funding agreement that is a research and development contract that provides that the contractor perform for the benefit of the Government, with an expectation of completion of the stated research goals and the delivery of a report, data, materials or other product. Generally, Contracts are administered under the Federal Acquisition Regulations (FAR) codified at Title 48 C.F.R., Chapter 1 or the Health Services Acquisition Regulations (HSAR) codified at Title 48 C.F.R., Chapter 3.
- 2.18 “*CTA*” means Clinical Trial Agreement.
- 2.19 “*CTEP*” means the Cancer Therapy Evaluation Program, DCTD, NCI, the program within NCI which plans, assesses and coordinates all aspects of clinical trials including extramural clinical research programs, internal resources, treatment methods and effectiveness, and compilation and exchange of data.
- 2.20 “*DCTD*” means Division of Cancer Treatment and Diagnosis, NCI.
- 2.21 “*FDA*” means US Food and Drug Administration.
- 2.22 “*Grant*” means a funding agreement that is an award of financial assistance which may be provided for support of basic research in a specific field of interest to the funding Federal agency.
- 2.23 “*IND*” means an Investigational New Drug Application submitted to the FDA to receive approval to conduct experimental clinical trials.

- 2.24 “*Multi-Party Data*” means clinical data from clinical studies sponsored by NCI pursuant to CTAs or CRADAs, where such data are collected under protocols involving combinations of investigational agents from more than one CTA or CRADA collaborator.
- 2.25 “*NCI*” means the National Cancer Institute, NIH, PHS, DHHS.
- 2.26 “*Protocol Review Committee*” (or “*PRC*”) means the CTEP/DCTD committee that reviews and approves studies involving NCI investigational agents and/or activities supported by NCI.
- 2.27 “*Raw Data*” means the primary quantitative and empirical data first collected by the intramural and extramural investigators from experiments and clinical trials conducted within the scope of the Research Plan of this CRADA .
- 2.28 “*Steering Committee*” means the joint NCI/Collaborator research and development team whose composition and responsibilities with regard to the clinical experiments performed under this CRADA are described in Article 3.3 of this CRADA.
- 2.29 “*Summary Data*” means a summary of the Raw Data provided to the NCI by the extramural investigators that will either be included by NCI in an Annual Report to an NCI-sponsored IND, or made available by NCI to the Collaborator for submission to the FDA under a Collaborator-sponsored IND. [Add next sentence only when Collaborator sponsors IND:] Said summary data will be made available to the general public upon request.

Amend the first sentence of **Article 3.1 *Principal Investigators*** by removing the first clause so that the first sentence reads as follows:

The PHS Principal Investigator (PI) designated in the RP will be responsible for the scientific and technical conduct of this project on behalf of PHS.

Add a new **Article 3.3** as follows:

- 3.3 *Steering Committee and CRADA Research.* The Parties agree to establish a Steering Committee comprising at least the Principal Investigators designated pursuant to Article 3.1 to conduct and monitor the research of the Agent in accordance with the CRADA Research Plan. Members of the Steering Committee shall continue to remain employed by their respective employers under their respective terms of employment.

Agent's clinical development under the CRADA Research Plan shall be a collaborative undertaking by Collaborator and NCI. Details of this development beyond those set forth in the CRADA Research Plan shall be formulated and/or discussed in Steering Committee meeting(s) before implementation of large-scale or resource intensive studies. The clinical development plans formulated by the Steering Committee shall be implemented either intramurally at the NCI or extramurally under NCI-sponsored funding agreements.

Additional CRADA information, including Steering Committee meeting reports, Protocol Review Committee records, clinical trial protocols, Institutional Review Board approval information, IND and general regulatory information, and preclinical and clinical data in NCI's possession and control shall remain on file with NCI.

The Collaborator has the option to sponsor its own clinical trials and hold its own IND for studies performed which are outside the scope of this CRADA from which all data is proprietary to Collaborator.

Add a new **Article 3.4** as follows:

- 3.4 *Clinical Protocols.* Clinical protocol proposals for each study within the scope of the CRADA Research Plan will be solicited from selected intramural and extramural clinical investigators. Each clinical protocol should describe in detail the research to be conducted at each center and must be submitted to the PRC for approval prior to implementation. Each clinical protocol received by NCI will be forwarded to Collaborator for review and comment approximately two weeks before it is reviewed by the PRC. Comments from Collaborator received by CTEP before the PRC meeting will be discussed by the PRC, will be given due consideration, and will be incorporated into the protocol, absent good cause. Comments from either Collaborator or the CTEP staff that are agreed upon in the PRC meeting will be formatted as a consensus review, which is returned to the investigator for necessary and/or suggested changes before the protocol can be given final approval and submitted to the FDA. A copy of the final approved protocol will be forwarded to Collaborator at the same time as it is submitted to the FDA.

Add a new **Article 3.5** as follows to reflect the IND sponsorship under this CRADA:

- 3.5 *Investigational New Drug Application.* The Parties expect that either NCI or Collaborator will submit an IND which may cross-reference an IND or Drug Master File held by the other. All information in INDs will be fully shared between NCI and Collaborator, except as follows: If NCI files an IND for Agent that is the subject of this CRADA, Collaborator may, at its option, supply information in support of the IND in the form of a Drug Master File directly to the FDA so long as Collaborator grants NIH a right to cross-reference such information in its IND filing. In the event that Collaborator supplies CONFIDENTIAL information directly to NCI in support of an NCI IND, such information will be protected in accordance with the corresponding Confidentiality provisions of Article 8 of this Agreement.

Add a new **Article 3.6** as follows:

- 3.6 *Drug Information and Supply.* Collaborator agrees to provide NCI without charge clinical-grade Agent in sufficient quantity to complete the preclinical studies and clinical trial protocol(s) sponsored by NCI that are within the scope of the CRADA Research Plan. Furthermore, Collaborator agrees to provide without charge Agent or unformulated analytical grade Agent or metabolites, if available, to NCI to supply extramural investigators for the development of mutually agreed upon analytical assays or ancillary correlative studies conducted in conjunction with NCI-sponsored protocols. Collaborator will provide Certificates of Analysis to NCI for each lot of finished product provided.

The contact person for NCI will be Mr. Alfred Fallavollita, Chief, Pharmaceutical Management Branch (Telephone Number 301-496-5725) and the Collaborator contact will be (Telephone Number ).

Add a new **Article 3.7** as follows:

- 3.7 *Protection of Human Subjects and Appropriate Care of Laboratory Animals.* All human clinical trials

performed under this CRADA shall conform to the appropriate Federal law, including, but not limited to all applicable FDA regulations and DHHS regulations relating to the protection of human subjects (see 45 C.F.R. Part 46). NCI and Collaborator also agree to comply with all applicable Federal statutes and Public Health Service policies relating to the use and care of laboratory animals (see 7 U.S.C. 2131 et seq.) Additional information is available from the Office of Protection from Research Risk, Telephone: 301-496-7163.

Add the following to the end of **Article 4.1 *Interim Reports***:

Steering Committee reports or copies of Annual Reports updating the progress of the CRADA research shall satisfy the reporting requirements under this Article 4.1. In addition, copies of the Annual Reports and other pertinent IND data (including, but not limited to, clinical brochure data, and formulation and preclinical data, including toxicology findings) shall be exchanged by the Parties as they become available.

Add a new **Article 4.3** as follows:

4.3 *Adverse Drug Experience Reporting.* DCTD shall report all serious or unexpected adverse events to FDA in accordance with the reporting obligations of 21 CFR 312.32 and will, concurrently, forward all such reports to Collaborator. All other adverse event reports received by DCTD shall be reported to the FDA consistent with 21 CFR 312.32 and 312.33. In addition, copies of the Annual Reports and other pertinent IND data (including, but not limited to, Clinical Brochure data, formulation and preclinical data, including toxicology findings) will be provided to Collaborator as they become available.

In the event that Collaborator informs the FDA of any serious or unexpected adverse events, Collaborator must notify the NCI at the same time. NCI will then notify the investigator(s) conducting studies under NCI-sponsored protocols.

Add a new **Article 4.4** as follows:

4.4 *Annual Reports.* NCI shall provide Collaborator a copy of the Annual Report simultaneously with the submission of the Annual Report to the FDA.

Replace the text under **Article 8.7 *Publication*** with the following:

The Parties are encouraged to make publicly available the results of their research. Except as provided at the end of this paragraph with respect to abstracts, before either Party submits a paper for publication or otherwise intends to publicly disclose information about a Subject Invention, Subject Data, additional Clinical Data and Results and Raw Data in NIH's Possession and Control, or Research Materials, the other Party shall be provided thirty (30) days to review the proposed publication or disclosure to assure that Proprietary/Confidential Information is protected. The publication or other disclosure shall be delayed for up to thirty (30) additional days upon written request by any Party as necessary to preserve U.S. or foreign patent or other IP rights. Abstracts presented by NCI investigators will be sent to NCI's Regulatory Affairs Branch for forwarding to Collaborator after submission but prior to presentation or publication to permit preservation of U.S. and foreign patent rights.

Add a new **Article 8.8** as follows:

- 8.8 *Extramural Research and Data.* In pursuing the development of Agent pursuant to this CRADA, NIH may utilize extramural investigators for part or all of the completion of this Research Plan through either Federal Grants or Federal Contracts. Participation by extramural contract or grantee investigators shall be determined after competitive solicitation and review of study protocols by NIH. However, said extramural contract or grantee investigators are not Parties to this CRADA, and this CRADA does not address rights to intellectual property created by such investigators. Nonetheless:
- a. Subject to the other provisions of Article 8 of this CRADA, NIH shall maintain all IND, Clinical Data and Results, and Raw Data in NIH's Possession and Control as Proprietary and CONFIDENTIAL, and make them available exclusively to the Collaborator for its own use and for use in obtaining FDA approval for the commercial marketing of Subject Inventions and Agent products. Accordingly, said data shall not be transferrable to any third party without the written permission of the NCI.
  - b. NIH shall not execute a Contract for preclinical studies or clinical trials for the development of Agent unless the extramural contract investigator agrees to confidentiality provisions at least as restrictive as provided in this CRADA and to the Collaborator's exclusive use of data, in accordance with Article 8.8 (a), for its own use and for use in obtaining FDA approval for the commercial marketing of Agent.
  - c. NCI shall urge all extramural grantee investigators participating in the studies sponsored by NCI and using Agent to cooperate exclusively with Collaborator in providing Clinical Data and Results and Raw Data for use in obtaining pharmaceutical regulatory approval for the commercial marketing of Agent. However, NCI's urging will not constitute a term or condition for making a grant award to said extramural investigators.
  - d. In seeking direct access to Clinical Data and Results and Raw Data or any other information that is in the possession of extramural contract or grantee investigators working with Agent under the sponsorship of NCI, Collaborator shall first contact the Regulatory Affairs Branch, (RAB) NCI [telephone: 301-496-7912]. Subsequent to authorization by RAB, Collaborator may directly contact the extramural investigators. Costs associated with providing Clinical Data and Results or Raw Data to Collaborator in customized formats shall be borne by Collaborator.
  - e. Collaborator's exclusive access under subsection (a) above to Clinical Data and Results and Raw Data in NIH's Possession and Control is dependent, however, upon Collaborator's continued development and commercialization of the technology. In the event that Collaborator discontinues development or commercialization of the technology without the transfer of its development efforts to another party, NCI retains the right to make the Clinical Data and Results and Raw Data in NIH's Possession and Control available to another collaborator.

Add a new **Article 8.9** as follows:

- 8.9 *Multi-Party Data Rights.* For clinical protocol(s) where Agent is used in combination with another investigational agent supplied to NCI pursuant to a CTA or CRADA between NCI and an entity not a Party to this CRADA [hereinafter referred to as "Third Party"], the access and use of Multi-Party Data by the Collaborator and Third Party shall be co-exclusive as follows:
- a. NCI will provide both Collaborator and Third Party with notice regarding the existence and

nature of the agreements governing their collaborations with NIH, the design of the proposed combination protocol(s), and the existence of any obligations that might restrict NCI's participation in the proposed combination protocols.

- b. Collaborator shall agree to permit use of the Multi-Party Data from these trials by Third Party to the extent necessary to allow Third Party to develop, obtain regulatory approval for, or commercialize its own investigational agent(s). However, this provision will not apply unless Third Party also agrees to Collaborator's reciprocal use of Multi-Party Data.
- c. Collaborator and Third Party must agree in writing prior to the commencement of the combination trials that each will use the Multi-Party Data solely for the development, regulatory approval, and commercialization of its own investigational agent(s).

Add the following sentence to the end of **Article 10.2 *Unilateral Termination***:

However, in the event of unilateral termination or early expiration, Collaborator's obligation under Article 3.6 will survive termination to the extent necessary to complete approved clinical studies under mutually agreed upon protocols.

Add a new **Article 10.6** as follows:

10.6 *Research License and Alternative Sources of Supply in the Event Collaborator Terminates Development of Agent*

- a. Collaborator hereby grants to NCI a nonexclusive, nontransferable, irrevocable, paid-up license to practice or have practiced for or on behalf of the United States any invention which Collaborator may have or obtain on Agent, its manufacture, or on the process for use of Agent, throughout the world, for medical research purposes, including those related to or connected with the therapy of cancer; but this license shall become effective only if and when Collaborator terminates its development of Agent without the transfer of its development efforts to another party, and NCI elects to continue the development of Agent.
- b. If Collaborator elects to terminate its development of Agent without the transfer of its development efforts to another party, and NCI elects to continue its development of Agent, then Collaborator will:
  - (i) allow NCI to purchase at cost said Agent from Collaborator inventory; or
  - (ii) arrange for an independent contractor to manufacture and provide for NCI purchase of said agent at cost; or
  - (iii) provide to NCI all information necessary to allow NCI to contract and manufacture said Agent independent of Collaborator;

for use in preclinical studies and clinical trials. Such obligation shall last until either a date on which an alternate source of equivalent materials, acceptable to NCI, can be obtained by NCI, or two years after the date of notification from Collaborator to NCI that Collaborator elects to terminate its development of Agent, whichever comes first.

Modify the first sentence in **Article 12.3** to read as follows:

The Collaborator agrees to hold the U.S. Government harmless and to indemnify the Government for all liabilities, demands, damages, expenses and losses arising out of the use by the Collaborator for any purpose of the Subject Data, additional Clinical Data and Results and Raw Data in NIH's Possession and Control, Research Materials and/or Subject Inventions produced in whole or part by PHS employees under this CRADA, unless due to the negligence or willful misconduct of PHS, its employees, or agents.

Add a new **Article 13.13** as follows:

13.13 *FDA Meetings*. All meetings with FDA concerning clinical studies for the development of Agent within the scope of the CRADA Research Plan will be discussed by Collaborator and NCI in advance and will be held on mutually agreed upon dates. Collaborator reserves the right to set jointly with NCI the agenda for any such meeting.

Amend **Article 14.2 *Survivability*** by including Articles 4.3 (*Adverse Drug Experience Reporting*) and 10.6 (*Research License and Alternative Sources of Supply in the Event that Collaborator Terminates Development of Agent*) and the last sentence of Article 10.2 (regarding drug supply in the event of collaborator's unilateral termination) as provisions that will survive termination of this CRADA.