Procter and Gamble – EPA CRADA #1055-19

COOPERATIVE RESEARCH AND DEVELOPMENT AGREEMENT WITH THE UNITED STATES ENVIRONMENTAL PROTECTION AGENCY AND PROCTER AND GAMBLE CORPORATION

This Cooperative Research and Development Agreement ("CRADA" or "Agreement") is entered into by and between Procter and Gamble Corporation which has its principal place of business at 1 P&G Plaza, Cincinnati, Ohio 45202 ("the Cooperator"), and the National Center for Computational Toxicology of the U.S. Environmental Protection Agency ("EPA") under the authority of Title 15, United States Code ' ' 3710a-3710d (commonly known as the Federal Technology Transfer Act of 1986).

WITNESSETH:

A. WHEREAS, the Congress, in enacting the Federal Technology Transfer Act of 1986 (the "FTTA"), has found that Federal laboratories' developments should be made accessible to private industry, state and local governments, and has declared that one of the purposes of such Act is to improve the economic, environmental and social well-being of the United States by stimulating the utilization of Federally-funded technology developments by such parties;

B. WHEREAS, the FTTA provides each Federal agency with the authority to permit the Directors of Government-operated laboratories to enter into cooperative research and development agreements with Federal or non-Federal entities, including private firms and organizations for the purpose of providing to, or obtaining from, collaborating parties, personnel, services, property, facilities, equipment, intellectual property or other resources toward the conduct of specified research and development efforts, which may include the disposition of patent or other intellectual property rights in the inventions resulting from such collaboration;

C. WHEREAS, the Laboratory has performed and sponsored substantial research and development with respect to metabolic scientific approaches for integration of metabolic competence into high-throughput *in vitro* assays, and its translation of the results into risk assessment for use by private and public entities.

D. WHEREAS, the Laboratory possesses certain advanced scientific skills, facilities, special equipment, information, computer software, and know-how pertaining to metabolic competencies into new chemical testing approaches for integration of metabolic

competence into high-throughput *in vitro* assays, and its translation of the results into risk assessment for use by private and public entities.

NCCT does not own any patents or patent applications on the technology.

E. WHEREAS, the Cooperator possesses certain protocols that will help evaluate and extend the use of a new technology developed by NCCT to incorporate metabolic competency into new chemical testing approaches such as high-throughput screening.

F. WHEREAS, the Laboratory and the Cooperator are interested in the further research and development of the metabolic competency technology and its utilization by private and public entities;

G. WHEREAS, the Cooperator desires to provide resources for the Laboratory's development and/or evaluation of the metabolic competency technology; and

H. WHEREAS, the Laboratory views its collaboration with the Cooperator to develop/evaluate the metabolic competency technology to be in the furtherance of the public interest.

NOW, THEREFORE, the parties hereto agree as follows:

Article 1. Definitions

As used in this CRADA, the following terms shall have the following meanings and such meanings should be equally applicable to both the singular and plural forms of the terms defined:

1.1 "CRADA" or "Agreement" means this Cooperative Research and Development Agreement entered into by the Laboratory pursuant to 15 U.S.C. ' 3710a.

1.2 "Computer Software" means computer software, computer programs, computer data bases, and documentation thereof developed, in whole or in part, under this Agreement.

1.3 "Government" means the Government of the United States of America.

1.4 "Invention" means any invention or discovery which is or may be patentable or otherwise protectable under the intellectual property laws of this or any foreign country.

1.5 "Made" in relation to any Invention means the conception or first actual reduction to practice of such Invention.

1.6 "Proprietary Information" means information which embodies trade secrets developed at private expense, or which is confidential scientific, business or financial information, provided that such information:

(a) Is not generally known or available from other sources without obligation concerning its confidentiality;

(b) Has not been made available by the owners to others without obligation concerning its confidentiality; and

(c) Is not already available to the Government without obligation concerning its confidentiality.

1.7 "Subject Data" means all recorded information first produced in the performance of this Agreement. This term includes Computer Software.

1.8 "Subject Invention" means any Invention conceived or first actually reduced to practice in the performance of work under this Agreement.

1.9 "Technology" means materials and methods pertaining to integration of metabolic competence into high-throughput screening assays, and translation of the results into risk assessment applications for use by private and public entities.

1.10 "Works" means any Computer Software or subject matter that is copyrightable.

Article 2. Cooperative Research

2.1 Statement of Work. Cooperative research and development work performed under this Agreement shall be performed in accordance with the Statement of Work ("SOW") attached hereto as Attachment A. The SOW sets forth a "period of performance." The Laboratory and the Cooperator agree to perform the cooperative research and development work and to utilize such personnel, resources, facilities, equipment, skills, know-how and information as is reasonably necessary.

2.2 Review of Work. Periodic conferences shall be held between Laboratory and Cooperator personnel for the purpose of reviewing the progress of the work to be accomplished under this Agreement. The Laboratory shall have exclusive control and supervision over the conduct of all cooperative research and development work conducted at the Laboratory facilities. The Cooperator shall have exclusive control and supervision over the conduct of all cooperative research and development work conducted at Cooperator facilities. It is understood that the nature of this cooperative research and development work is such that completion within the period of performance specified in the SOW or within the limits of financial support allocated, cannot necessarily be guaranteed. Accordingly, it is agreed that all cooperative research is to be performed on a best efforts basis.

2.3 Assigned Personnel. Each party to this Agreement shall perform its respective obligations under this Agreement under the direction of a "Project Manager" and a "Principal Investigator." Project Managers shall be responsible for the overall direction of the work, establishing budgets and providing such approvals and consents as are required hereunder. Principal Investigators shall be responsible for the scientific and technical conduct of the work, including the exchange of Subject Data and other information. The parties designate the following individuals as their respective representatives:

	Laboratory	Cooperator
Project Manager	Sandra Roberts	Catherine Mahony (Strategic Lead) Karen Vandermolen (Project Leader)
Principal Investigator	Chad Deisenroth	Kevin Kennedy

2.4 Scope Change. If at any time the Project Managers or Principal Investigators determine that the research data justify a substantial change in the direction of the work, the parties shall make a good faith effort to agree on any necessary changes to the SOW.

Article 3. Reports

3.1 Final Report. The Laboratory shall submit a final report to the Cooperator of the Laboratory's results within 120 calendar days after (a) completing the SOW or (b) the termination of this Agreement.

Article 4. Financial Obligations. This Article does not apply.

Article 5. Invention, Computer Software, and Patent Rights

5.1 Reporting. The Laboratory shall promptly report to the Cooperator each Subject Invention reported to the Laboratory by its employees. The Cooperator shall promptly report to the Laboratory each Subject Invention reported to the Cooperator by any of its employees.

5.2 Government's Minimum Rights. All assignments made by the Laboratory under this Article 5 and all licenses granted by the Laboratory to the Cooperator are subject to the reservation of statutorily required licenses in favor of the Government as described in this paragraph 5.2. In accordance with 15 U.S.C. ' ' 3710a(b)(2) and (b)(3)(D), the Cooperator grants to the Laboratory a nonexclusive, nontransferable, irrevocable, paid-up license to practice all Cooperator Subject Inventions or have all Cooperator Subject Inventions practiced throughout the world on behalf of the Government. Also, in accordance with 15 U.S.C. ' 3710a(b)(1) the Laboratory retains a nonexclusive, nontransferable, irrevocable, paid-up license to practice all the Laboratory and joint Subject Inventions or have the Laboratory and joint Subject Inventions practiced, throughout the world by or on behalf of the Government.

5.3 Cooperator Employee Inventions. The Cooperator shall obtain from each of its employees and each of the employees of its subcontractors who will, or is likely to perform work under this Agreement, an agreement to assign to the Cooperator his or her rights to Subject Inventions. Regardless of whether such a prospective agreement has been obtained, the Cooperator shall obtain from any of its employees or its subcontractor's employees that is a sole inventor or a co-inventor of a Subject Invention, an assignment of all domestic and foreign right, title and interest in said Subject Invention. The Cooperator shall retain its intellectual property rights to any Subject Invention made by Cooperator employees or the employees of the Cooperator's subcontractor. If the Cooperator decides to not retain its rights, the Cooperator shall offer to assign its rights to the Subject Invention to the Laboratory, subject to a paid-up license to practice the assigned Subject Invention throughout the world. If the Laboratory declines such assignment, the Cooperator may release its right to employee inventors, subject to the reservation of patent licenses in favor of the Government as required in paragraph 5.2 above.

5.4 Laboratory Employee Inventions. The Laboratory shall obtain from each of its employees that is a sole inventor or a co-inventor of a Subject Invention an assignment to the Government, as represented by the Administrator of EPA, of all domestic and foreign right, title and interest in said Subject Invention. If the Laboratory decides not to retain its rights to a Subject Invention, the Laboratory shall offer to assign its rights to the Subject Invention to the Cooperator, subject to the reservation of patent licenses in favor of the Government as required in paragraph 5.2 above. If the Cooperator declines such assignment, the Laboratory may release its rights to its employee inventors.

5.5 Inventions by the Laboratory's Contractors. The Cooperator agrees that the Laboratory may contract with a contractor to perform all or part of the work required under the SOW. The Laboratory shall, in any new contract or work assignment supporting the Agreement, include alternate paragraph (b) in the basic patent rights clause at 37 C.F.R. 401.14(c), under which the Laboratory may require the contractor to negotiate a license with the Cooperator for rights to the subject invention. If EPA obtains an assignment of rights to a subject invention developed by a contractor during the performance of a contract for work supporting the Agreement, the EPA shall grant the Cooperator a license in accordance with Section 5.10.1 of this Agreement.

In the case of a Laboratory contract or work assignment awarded prior to the effective date of this Agreement, which contains one or more provisions that prevent acquisition of a license or title to Subject Inventions by the Cooperator, Laboratory or EPA, the Laboratory and EPA agree that they will exert a good faith effort to amend the contract or work assignment in a way consistent with the preceding paragraph; provided however, that if the Laboratory or EPA should fail to bring about the necessary amendment or assignment of rights, the Laboratory and EPA shall not be liable for a breach of this Agreement, nor shall such failure be a basis for termination of this Agreement by the Cooperator.

5.6 Filing of Patent Applications. The party retaining title to a Subject Invention shall file patent applications in a timely manner; the Cooperator shall be responsible for filing patent applications for joint Subject Inventions between the Cooperator and the Laboratory in a timely manner. The filing party may elect not to file a patent application in any particular country or

countries provided it so advises the other party ninety (90) calendar days prior to the expiration of any applicable filing deadline, priority period, or statutory bar date. The party electing not to file shall assign its intellectual property right, title, and interest in such country or countries to the Subject Invention to the other party and shall cooperate in the preparation and filing of patent applications, provided the other party agrees to file a patent application in such country or countries. Any license or assignment by the Government to the Cooperator shall be subject to reservation of patent licenses in favor of the Government as required in paragraph 5.2. Any license or assignment by the Cooperator to the Government shall be subject to reservation of a paid-up license in favor of the Cooperator to practice the assigned Subject Invention throughout the world.

5.7 Patent Expenses. All of the expenses attendant to the filing of patent applications shall promptly be paid by the party filing such application. Any post filing and post patent fees shall also be borne by the same party. If the Cooperator obtains an exclusive license of the Government's interest in a patent or patent application filed by the Laboratory, the Cooperator shall reimburse the Laboratory for all such patent filing, post filing and post patent expenses paid by the Laboratory. If the Cooperator obtains a nonexclusive license of the Government's interest in a patent or patent application filed by the Laboratory, the Cooperator shall reimburse the Laboratory for one-half of all such filing and other patent expenses.

5.8 Prosecution of Patent Applications. Each party to this Agreement shall promptly provide the other party with copies of any patent application it files on any Subject Invention, and a copy of each action received from a patent office and each item of correspondence with a patent office. The parties agree to consult and cooperate with each other in obtaining and maintaining protection for Subject Inventions. In addition, on request, each party that has filed a patent application shall issue to the other party a "Power to Inspect and Make Copies" in any patent office of any identified patent application.

5.9 Cooperator and Laboratory Employee Rights. In the event that the Cooperator and the Laboratory decide that a patent application on a particular Subject Invention need not be filed in a particular country, either or both (if there are co-inventors from each party) may, at their sole discretion and subject to reasonable conditions, allow the inventor(s) to retain title to that Invention and release to them the right to file. Such conditions shall include nonexclusive, irrevocable, paid-up licenses to the Cooperator and the Government to practice, or have practiced, that Subject Invention throughout the world. Said licenses shall be evidenced by a confirmatory license in a form acceptable to the Cooperator and the Government.

5.10 Exclusive License

5.10.1 Grant. The Laboratory, on behalf of the Government, hereby grants to the Cooperator a first option to an exclusive license of the Government's interest in each Subject Invention and in any resulting patents issued on such Subject Invention. This option may be exercised not later than six (6) months following the filing of a patent application on the Subject Invention in the U.S. Patent and Trademark Office pursuant to paragraph 5.6, above.

5.10.2 Exclusive License Agreement.. Upon notice received by the Laboratory from the Cooperator that it wishes to exercise the option referred to in paragraph 5.10.1 above, the terms of the exclusive license will be negotiated promptly by the Laboratory and the Cooperator. Any exclusive license will be subject to the reservation by the Government of a non-exclusive, irrevocable, paid-up license to practice or have practiced on its behalf the Subject Invention throughout the world.

5.11 Computer Software and Copyrightable Works

5.11.1 Reporting. The Laboratory shall promptly report to the Cooperator any Computer Software or subject matter that is copyrightable ("Works") created by its employees and, to the extent it has the right to do so, Works made by any of its contractors. The Cooperator shall promptly report to the Laboratory any Works created by any of its employees or contractors.

On request from the Laboratory, the Cooperator shall deliver to the Laboratory a copy of such Works in a form mutually agreed to by the Laboratory and the Cooperator.

5.11.2 Laboratory Employee Developed Works. In view of the provisions of 17 U.S.C. ' 105, any Works developed solely by one or more employees of the U.S. Government, as part of their official duties, cannot be protected by copyright in the U.S.

5.11.3 Cooperator Developed Works. In the case of Works developed solely by (an) employee(s) of the Cooperator, the Cooperator shall advise the Laboratory, within six (6) months of reporting such Works, pursuant to paragraph 5.11.1 above, whether it wishes to retain title thereto.

If the Cooperator elects to not retain title to its Works, on written request from the Laboratory, it will assign its rights, including any copyright, to the Laboratory. The Laboratory shall provide the Cooperator with an appropriate document for the conveyance of such rights.

If the Cooperator elects to retain title to its Works, it may assert copyright thereto and/or patent rights, if applicable. If the Cooperator asserts copyright to said Works, it hereby grants to the U.S. Government and others acting on its behalf a nonexclusive, irrevocable, paid-up worldwide license in such copyrighted Works to use, reproduce. distribute, prepare derivative works, perform publicly and display publicly the Work.

5.11.4 Laboratory and Cooperator Jointly Developed Works. If the Cooperator wishes to retain ownership of its copyright interest in the Works, and wishes to rely on copyright protection, it may do so, subject to the Government license in 5.11.3 above, and subject to the provisions of Title 17, U.S. Code, Section 105.

5.11.5 Patenting of Computer Software. In the event the Cooperator seeks patent protection for Computer Software developed either solely by its employees or jointly with Laboratory employees, the foregoing provisions applicable to Subject Inventions shall also apply to such Computer Software.

5.11.6 Patent and Copyright Protection for Computer Software. If the Cooperator seeks both patent protection and copyright protection, the rights of the Government shall be those applicable to Subject Inventions and Copyrightable Subject Matter.

5.11.7 Works Produced by Laboratory Contractors or EPA Contractors. The Laboratory, to the extent permitted by law and/or the Federal Acquisition Regulations at Title 48, C.F.R., shall include FAR clause 52.227-17 in any contract awarded after the effective date of this Agreement, which provides that any rights to copyrights for data first produced under the contract may be assigned to EPA by the contractor. If EPA obtains such rights to Computer Software developed by the contractor while performing work designated by the Laboratory as work under this Agreement, the Laboratory agrees that it will provide the Cooperator a non-exclusive, irrevocable, paid-up worldwide license to the copyrighted work, including the right to reproduce, distribute, prepare derivative works, perform publicly and display publicly the Work.

In the case of a Laboratory contract awarded prior to the effective date of this Agreement, which contains one or more provisions that prevent acquisition of title to computer software by the Laboratory or EPA, the Laboratory and EPA agree that they will exert a good faith effort to amend the contract in such a way as to obtain an assignment of the copyright; provided however, that if the Laboratory or EPA should fail to bring about the necessary amendment, the Laboratory and EPA shall not be liable for a breach of this Agreement, nor shall such failure be a basis for termination of this Agreement by the Cooperator.

Article 6. Data and Publication

6.1 Proprietary Information. The Cooperator shall place a proprietary notice on all information it delivers to the Laboratory under this Agreement which it asserts is Proprietary Information of the Cooperator The Laboratory agrees that: 1) any information designated as Proprietary Information which is furnished by the Cooperator to the Laboratory under this Agreement; 2) any information obtained by either party during the performance of this CRADA that would be claimed as Proprietary Information had it been submitted by the Cooperator; or 3) any information furnished by the Cooperator in contemplation of this Agreement; shall be treated as Proprietary Information and will be used by the Laboratory only for the purpose of carrying out this Agreement or for Government purposes. Information designated as Proprietary Information shall not be disclosed, copied, reproduced or otherwise made available in any form whatsoever to any other person, firm, corporation, partnership, association or other entity without consent of the Cooperator except as such information may be subject to disclosure under the Freedom of Information Act (5 U.S.C. ' 552), and EPA's regulations at 40 C.F.R.
Part 2, or as required to be disclosed by other statutes. The Laboratory agrees to use its best efforts to protect the information designated as Proprietary Information from unauthorized disclosure. The Cooperator agrees that the Laboratory is not liable for the disclosure of Proprietary Information which, after notice to and consultation with the Cooperator, EPA determines may not lawfully be withheld or which a court of competent jurisdiction requires to be disclosed. If no claim of confidentiality accompanies information at the time of submittal and a reasonable person would not have reason to believe such information was proprietary or of a confidential nature, then the information may be made public with no further notice to the Cooperator.

6.2 Release Restrictions. The Laboratory shall have the right to use all Subject Data for any Governmental purpose; provided, however, that the Laboratory shall not release such Subject Data publicly or provide such Subject Data to any Government regulatory body or agency other than the EPA except:

(a) the Laboratory in reporting the results of cooperative research may publish Subject Data, subject to the provisions of paragraph 6.3 below, and provided the Cooperator is given 45 days to review the manuscript and provide suggestions before publication; and

(b) the Laboratory may release such Subject Data where such release is required pursuant to a request under the Freedom of Information Act (5 U.S.C. ' 552) and the EPA regulations at 40 C.F.R. Part 2 or as required to be disclosed by other statutes.

(c) The Cooperator agrees to not release any Subject Data without obtaining prior written consent from the Laboratory.

(d) Pursuant to 35 U.S.C. ' 205, neither the Laboratory nor the Cooperator shall release to the public any Subject Data or other data that discloses or enables an invention if a patent application is to be filed, until the party having the right to file a patent application or provisional patent application has had a reasonable time to file.

6.3 Publication. The Laboratory and the Cooperator agree to confer and consult prior to the publication of Subject Data to ensure that no Proprietary Information is released and that patent rights are not jeopardized. Prior to submitting a manuscript for outside review which contains the results of the research under this Agreement, or prior to publication if no such review is made, each party shall be offered at least 45 calendar days to review such proposed publication and to file patent applications in a timely manner, if it is so entitled or required under this Agreement.

Article 7. Representations and Warranties

7.1 Representation and Warranties of the Laboratory. The Laboratory hereby represents and warrants to the Cooperator as follows:

7.1.1 Organization. The Laboratory is a Federal laboratory of the EPA and is wholly owned by the Government. The Laboratory's substantial purpose is the performance of research or development.

7.1.2 Mission. The performance of the activities specified by this Agreement is consistent with the mission of the Laboratory.

7.1.3 Authority. All prior reviews and approvals required by Federal regulations and laws have been obtained by the Laboratory prior to the execution of this Agreement. The Laboratory official executing this Agreement has the requisite authority to do so.

7.2 Representations and Warranties of the Cooperator. The Cooperator hereby represents and warrants to the Laboratory as follows:

7.2.1 Corporate Organization. The Cooperator, as of the date hereof, is a corporation duly organized, validly existing and in good standing under the laws of the State of Ohio.

7.2.2 Power and Authority. The Cooperator has the requisite power and authority to enter into this Agreement and to perform according to the terms thereof.

7.2.3 Due Authorization. The Board of Directors and stockholders of the Cooperator have taken all actions, if any, required to be taken by law, the Cooperator's Certificate or Articles of Incorporation, its bylaws or otherwise, to authorize the execution and delivery of this Agreement.

7.2.4 No Violation. The execution and delivery of this Agreement do not contravene any material provision of, or constitute a material default under, any material agreement binding on the Cooperator or any valid order of any court, or any regulatory agency or other body having authority to which the Cooperator is subject, nor, to the best of its knowledge, is the Cooperator the subject of any adversarial proceeding by any regulatory governmental agency.

Article 8. Termination

8.1 Termination by Mutual Consent. The Laboratory and the Cooperator may elect to terminate this Agreement, or portions thereof, at any time by mutual consent. In such event the parties shall specify the disposition of all property, patents, unexpended or unobligated funds, and the results arising from the work completed or in progress under this Agreement. Upon termination by mutual consent, the Laboratory, as of the termination date, shall make no new commitments, and as soon after the termination date as feasible, shall cancel all outstanding commitments that relate to those portions of this Agreement that have been mutually terminated.

8.2 Termination by Unilateral Action. Either party may unilaterally terminate this entire Agreement at any time by giving the other party written notice not less than 30 calendar days prior to the desired termination date [The time period is negotiable, but typically has been about 90 calendar days]. The Laboratory shall make no new commitments after receipt of a written termination notice from the Cooperator and shall to the extent possible, by the termination date, cancel all outstanding commitments and contracts that were entered into as a consequence of the requirements of the SOW in Attachment A. However, the Laboratory may, at its own expense, continue said commitments beyond said termination date without liability on the part of the Cooperator.

8.3 Termination Costs. Each party shall pay its own termination costs out of its own funds. Any funds furnished by the Cooperator which are unexpended or unobligated as of the date of termination will be returned to the Cooperator. In no event shall either party be liable for the direct and indirect termination costs of the other party or said other party's expenses caused by or related to the termination.

8.4 Survival. To the extent rights and obligations hereunder have accrued as of the date of expiration or termination, the following Articles of this Agreement shall survive any expiration or termination hereof: 5, 6, and 10, and any expiration or termination hereof shall not affect any license granted hereunder.

Article 9. Disputes

9.1 Settlement. Any dispute arising under this Agreement which cannot be readily resolved shall be submitted jointly to the signatories of this Agreement. A joint decision of the signatories or their designees shall be the disposition of such dispute. If the signatories are unable to jointly resolve a dispute within a reasonable period of time after submission of the dispute for resolution, the matter shall be submitted to the Administrator of EPA or the Administrator's designee for resolution.

9.2 Continuation of Work. Pending the resolution of any dispute or claim pursuant to this Article, the parties agree that performance of all obligations shall be pursued diligently in accordance with the direction of the Laboratory signatory.

Article 10. Liability

10.1 EPA. EPA's responsibility for the payment of claims to the Cooperator or its employees for loss of property, personal injury or death caused by the negligence or the wrongful act or omission of employees of EPA, while acting within the scope of their employment, is in accordance with the provisions of the Federal Tort Claims Act, 28 U.S.C. '' 2671-80 and 40 C.F.R. Part 10.

10.2 No Warranty. Except as specifically stated in Article 7, neither party makes any express or implied warranty as to any matter whatsoever, including the conditions of the research or as to any Invention made or product developed, or the ownership, merchantability, or fitness for a particular purpose, of the research or any such Invention or product.

10.3 Indemnification. The Cooperator agrees to hold the Government harmless and to defend and indemnify the Government for all liabilities, demands, damages, expenses and losses arising out of the use by the Cooperator, its employees or any party acting on the Cooperator's behalf or with its authorization, of the Laboratory's research and technical developments, the Laboratory's facilities or equipment, or out of any use, sale or other disposition by the Cooperator, its employees or others acting on its behalf or with its authorization, of products made by the use of the Laboratory's technical developments. This provision shall survive the termination of this Agreement.

10.4 Force Majeure. Neither party shall be liable for any event or circumstance beyond its reasonable control not caused by the fault or negligence of such party, which causes such party to be unable to perform its obligations under this Agreement (and which it has been unable to overcome by the exercise of due diligence), including but not limited to flood, drought, earthquake, storm, fire, pestilence, lightning and other natural catastrophes, epidemic, war, riot, civil disturbance or disobedience, strikes, labor dispute, sabotage of the Laboratory facilities, or

any order or injunction made by a court or public agency. In the event of the occurrence of such a force majeure event, the party unable to perform shall promptly notify the other party. It shall further use its best efforts to resume performance as quickly as possible and shall suspend performance only for such period of time as is necessary as a result of the force majeure event.

10.5 Cooperator. The Cooperator agrees that during the term of this Agreement it will carry liability insurance in the amount set forth on the attached certificate of insurance to cover any liability to the Government or to Government employees and private individuals that may arise as a result of negligent acts or omissions of any of the Cooperator's employees or agents while they are performing work under this Agreement including any work which such employee or agent may be performing at the Laboratory.

Article 11. Miscellaneous

11.1 No Benefits. No member of, or delegate to the United States Congress, or resident commissioner, shall be admitted to any share or part of this Agreement, nor to any benefit that may arise therefrom. This provision shall not be construed to extend to this Agreement if the Agreement is made with the Cooperator for the Cooperator's general benefit.

11.2 Governing Law. The construction, interpretation, validity, performance and effect of this Agreement for all purposes shall be governed by the laws applicable to the federal government.

11.3 Headings. Titles and headings of the Sections and Subsections of this Agreement are for the convenience of references only and do not form a part of this Agreement and shall in no way affect the interpretation thereof.

11.4 Waivers. None of the provisions of this Agreement shall be considered waived by any party hereto unless such waiver is given in writing to all other parties. The failure of any party to insist upon strict performance of any of the terms and conditions hereof, or failure or delay to exercise any rights provided herein or by law, shall not be deemed a waiver of any rights of any party hereto.

11.5 Severability. The illegality or invalidity of any provisions of this Agreement shall not impair, affect or invalidate the other provisions of this Agreement.

11.6 Amendments. If either party desires a modification to this Agreement, the parties shall, upon reasonable notice of the proposed modification by the party desiring the change, confer in good faith to determine the desirability of such modification. Such modification shall not be effective until a written amendment is signed by all the parties hereto by their representatives duly authorized to execute such amendments.

11.7 Assignment. Except as otherwise permitted herein, neither this Agreement nor any rights or obligations of any party hereunder shall be assigned or otherwise transferred by either party without the prior written consent of the other party. However, the Cooperator may assign

this Agreement to the successors or assignees of a substantial portion of the Cooperator's business interests to which this Agreement directly pertains.

11.8 Notices. All notices pertaining to or required by this Agreement shall be in writing and shall be signed by an authorized representative and shall be delivered by hand or sent by certified mail, return receipt requested, with postage prepaid, addressed as follows:

If to the Cooperator:
Matthew J. Doyle, Director of Central Product Safety
1 P&G Plaza, Cincinnati, Ohio 45202
513-983-1100
Doyle.m@pg.com

If to the Laboratory:
Russell Thomas, Director, National Center for Computational Toxicology
109 T.W. Alexander Dr., Durham, NC 27711
919-541-5776
Thomas.russell@epa.gov

Any party may change such address by notice given to the other party in the manner set forth above.

11.9 Independent Parties. The relationship of the Laboratory and the Cooperator is that of independent parties and not as agents of each other or as joint venturers or partners. The Laboratory shall maintain sole and exclusive control over its personnel and operations. The Cooperator shall maintain sole and exclusive control over its personnel and operations.

11.10 Use of Name or Endorsements. The Cooperator shall not use the name of the Laboratory or EPA, on any product or service which is directly or indirectly related to either this Agreement or any patent license or assignment agreement which implements this Agreement, without the prior approval of the Laboratory. By entering into this Agreement the Laboratory does not directly or indirectly endorse any product or service provided, or to be provided, by the Cooperator, its successors, assignees, or licensees. The Cooperator shall not in any way imply that this Agreement is an endorsement of any such product or service. This section in no way prohibits the publication of any EPA indication or statement regarding the efficacy of any Subject Invention and/or any other results of this Agreement.

11.11 No Approval. Nothing in this Agreement shall be deemed to constitute regulatory or scientific approval of the use of any particular product or technology. The Cooperator agrees that (a) nothing in this Agreement relieves it of any obligation to comply with applicable federal, state, or local laws, regulations, or requirements, and (b) possession or acquisition by the Laboratory of Subject Data, or other information generated or otherwise acquired pursuant to performance of work under this Agreement, does not constitute knowledge of or possession or receipt of such data or information by or on behalf of the Administrator of the Environmental

Global Director of Product Safety, Safety Surveillance, Environmental Science & Sustainability

Statement of Work ("SOW") Annex A

Cooperative Research and Development Agreement ("CRADA")

between U.S Environmental Protection Agency ("EPA")

and the Procter and Gamble (P&G)

I. Goal

EPA's National Center for Computational Toxicology (NCCT) and the Procter and Gamble (Cooperator) are interested in the further development and application of the Alginate Immobilization of Metabolic Enzymes (AIME) technology for integration of metabolic competence into high-throughput *in vitro* assays, and its translation of the results into risk assessment for use by private and public entities. The Cooperator desires to evaluate, optimize, and implement the technology developed by NCCT using chemicals (including botanical substances) of scientific interest to the Cooperator.

II. Research Plan

The research performed under this SOW will be performed over the course of three years:

Phase 1 – The S9 cell fraction has been used historically to recapitulate metabolism from liver for in vitro assays such as the Ames mutagenicity assay. However, S9 cannot readily be used in many cell-based assays due the cytotoxic lipid peroxides formed by CYP metabolism of microsomal lipids, or in biochemical assays where S9 may interfere with protein binding dynamics. To circumvent the technical limitations associated with direct S9 addition to biochemical and cell-based assays, NCCT has developed a method called Alginate Immobilization of Metabolic Enzymes (AIME). The method involves the encapsulation of rat S9 fractions in an alginate solid matrix that allows for passive diffusion of low molecular weight chemicals but retains molecules larger than the polymer network pores that may contribute to assay interference. The encapsulated S9 fraction can be incubated with chemically-treated cells or proteins in multi-well format or used to pre-treat chemical-stock solutions that would be subsequently added to cells or proteins in multi-well plates. The method has been characterized for functional activity across a panel of CYP-dependent substrates and deployed in an estrogen receptor (ER) transactivation assay (VM7Luc4E2) using a reference compound with verified estrogenic metabolites.

To expand the adoption of the AIME method, EPA will provide the Cooperator the established standard operating protocols (SOPs) and customized microtiter plate lids necessary to perform the method. The Cooperator will send an end user representative from a designated contract research organization (CRO) [1] to EPA for requisite training on

1 The CRO referenced in this SOW is Eurofins, which is a sub-contractor accessed through prime contractor Research Triangle Institute (RTI) via STREAMS III (EP-C-16-016). Eurofins has a large cohort of in vitro toxicity assays that the EPA and P&G can use.

the method. Training their scientists with our method, it benefits P&G by complementing the work they have already performed, and benefits NCCT by giving the availability to a wide variety of assays we currently do not perform. The cost of this above training and any travel will be covered by the CRO. The end user will conduct an initial method transfer study at the CRO laboratory facility using the provided SOPs and materials to evaluate the performance of the assay. Performance will be benchmarked by analytical liquid chromatography-mass spectrometry (LC-MS) using a defined set of reference chemical substrates to 4-6 CYPs previously used for AIME method development by EPA.

Assuming successful transfer of the AIME method by the CRO laboratory, the Cooperator will initiate appropriate modifications to the method to align with previous SOPs using S9 fractions in suspension. Modifications may include substitution of reaction buffer, timing of metabolic reactions, lyophilization of reaction components, and reconstitution of reaction components in assay buffer or medium suitable for downstream applications. In exchange, the Cooperator will provide EPA with all optimized SOPs to conduct the method using the alternative approach, as well as any generated LC-MS results used in method validation and modification.

Phase 2 – If the method transfer study is successful, EPA and the Cooperator will proceed with a proof of concept study based on two reference substances for which interference was seen previously using S9 fraction in suspension (inclusive of appropriate assay positive and negative controls). The test samples pre- and post-incubation will first be analyzed using a LC-ESI combined with charged-aerosol detection (CAD), full-scan MS in positive and negative ionization mode and diode array (UV) detection. This approach is an effective way to observe the variety of compounds in the extracts and can be used to qualitatively compare the complexity or "cleanliness" provided by up to three metabolism strategies being pursued. As a follow on, the generated reaction components with the chosen metabolism strategy, containing primary and/or secondary metabolite products, will be run in a suite of targeted assays with emphasis on assays where interference or differences due to metabolism has been observed previously. The assays that would most likely benefit from biotransformation will be focused on molecular targets for developmental and reproductive toxicity where interference has been observed previously as well those where differences due to biotransformation have previously been detected. Assays will be conducted in screening mode using single concentration formats, at a multiple of the predicted/measured serum exposure or in the case of reference substrates as appropriate for the specific assay platform. The Cooperator will provide EPA with all assay data and LC-MS results generated from the proof of concept study.

Phase 3 – If the AIME approach is successful, the Cooperator and EPA may deploy the assay in a larger set of assays and/or using an expanded set of chemicals. Assays will be conducted by the designated CRO in either single-concentration screening format or multiple concentration-response format as appropriate for the specific assay platform. For single-concentration format, all positive compound-assay combinations will be followed up in multiple concentration-response format. If the experimental development is not successful, the EPA and the Cooperator will decide on the best path forward.

III. Milestones

Phase 1

1) EPA provides training, SOPs, and microtiter plate lids necessary to conduct the AIME assay.
2) Designated end user performs method transfer study of the AIME method with EPA SOPs at the designated CRO laboratory facility.
3) Cooperator provides resultant LC-MS results of method transfer study to EPA to evaluate assay performance.

Phase 2

1) EPA and the Cooperator select at least two reference substrates for the AIME assay.
2) EPA provides plated reference chemicals and provides blinded samples to designee.
3) EPA and the Cooperator select appropriate assay suite to perform the alternative AIME method.
4) The Cooperator performs analytical characterization of the reference substrates in metabolically active and inactive modes (starting with 3 different metabolism strategies, i) protein precipitation with organic solvent; ii) solid-phase extraction; iii) Liver S9 encapsulation).
5) The Cooperator selects appropriate metabolism strategy based on a qualitative analytical comparison of the "cleanliness" provided by each strategy.
6) If the AIME method is deemed a suitable strategy, the Cooperator designated CRO performs screening in a targeted set of assays using AIME in both metabolically active and inactive modes.
7) Cooperator provides to EPA SOPs for the modified AIME method, and all LC-MS results and assay data.
8) The Cooperator publishes results with support from designated CRO and EPA.

Phase 3

1) EPA and the Cooperator evaluate expansion of reference chemical set and/or targeted assay suite.
2) The Cooperator designated CRO performs screening in a targeted set of assays using AIME in both metabolically active and inactive modes.
3) Cooperator provides to EPA all assay data on the expanded test substance set and/or assay suite using the modified method.

Throughout the program of work regular discussions (ideally 3 monthly by video- or tele-conference) will be held between scientists from both parties to review progress and build productive connections to facilitate scientific discussion and knowledge sharing. Visits by the Cooperator to EPA and vice versa may be undertaken. All data and SOPs from the studies described above will be made wholly available by the Cooperator to the EPA upon completion of the work and before publication.

IV. Estimated Value and Benefits

A. Value of Contributions
1. Estimated value of EPA contributions (in-kind): Personnel in-kind over the three years is approximately $79, 201. Plated reference chemicals and supplies for project $109,201 over the three-year period of this CRADA.

2. Value of the Cooperator's estimated contribution (in-kind):
SOPs, LC-MS data, non-proprietary assay data is approximately $50,000

B. Benefits of Cooperative Effort
1. For EPA: To the extent set forth in this Agreement and in accordance with the terms hereof, the Cooperator and designated CRO will evaluate, optimize, and deploy the AIME technology to incorporate metabolic activity into high-throughput *in vitro* screening assays. The lack of metabolic activity has been a significant limitation for using the *in vitro* assays to predict toxicity of bioactivated toxicants. The Cooperator will provide the EPA with modified methods for running the AIME assay, and all non-proprietary LC-MS and assay data generated from the work. This will allow EPA to perform metabolism of higher volumes of chemicals in the future to provide to outside CROs for screening.

2. For the Cooperator: The work will address the lack of metabolic capacity in existing HT screening tools and transfer of AIME technology to the Cooperator's metabolism experimental capability to address current technical limitations. In addition, the Cooperator's people will visit the EPA to receive training on the method and have the opportunity to speak with EPA scientists developing the method to further enhance optimization and application efforts. There will be opportunity to build a truly collaborative relationship with a world leading organization (EPA) on multiple levels (theoretical, experimental, thought leadership) to positively impact the development of the Cooperator's scientists and contracting partners.

Catherine Mahony (Strategic Lead), Karen Vandermolen (Project Leader) and Kevin Kennedy (Principal Investigator) will be the primary representatives for the Cooperator in order to manage/effect the collaboration with the EPA.

V. General Provisions for the Conduct of the SOW

The Center shall:

(a) use best efforts to complete the SOW (including provide all agreed deliverables) under and in accordance with the terms of the CRADA;

(b) commence the SOW on the dates as indicated in this CRADA or, if no date is prescribed, not later than two (2) months after the effective date of the CRADA unless the Cooperator shall have agreed in

writing to a request from the Center for an extension to said period to permit a later commencement date, such request not to be unreasonably refused. For clarity, any extensions under this clause shall be agreed in writing by the Cooperator signed by its officer having authority therefor;

(c) all parties are responsible to carry out the SOW, good administration in the form of complete records of all work carried out as part of any SOW (including all activities undertaken, and the results thereof). The foregoing shall include the making of contemporaneous records in notebooks (that may include electronic notebooks) which shall in all instances be in accordance with good research procedures. Furthermore, all of said records shall be maintained confidentially and securely at the Center's address first above written (or such other address(es) as the Center shall notify the Cooperator from time to time) for the Term and five (5) years thereafter. At the Cooperator's request and reasonable cost, the Center shall provide copies of the said records to the Cooperator as soon as practicable;

(d) keep the Cooperator fully informed of all Subject Data, Subject Inventions, Technology and other information arising from the SOW by means of reports or otherwise as requested by the Project Manager of the Cooperator;

(e) in its conduct of SOWs, use all reasonable endeavors to not infringe third party intellectual property rights;

The Cooperator shall:

(a) use best efforts to complete the SOW (including provide all agreed deliverables) under and in accordance with the terms of the CRADA;

(b) commence the SOW on the dates as indicated in this CRADA or, if no date is prescribed, not later than two (2) months after the effective date of the CRADA;

(c) keep the EPA fully informed of all Subject Data, Subject Inventions, Technology and other information arising from the SOW as requested by the Project Manager of the Centre;

(d) in its conduct of SOWs, use all reasonable endeavors to not infringe third party intellectual property rights;