Memorandum of Understanding

Between

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES (HHS)
NATIONAL INSTITUTES OF HEALTH (NIH)
National Institute of Environmental Health Sciences (NIEHS)
National Toxicology Program (NTP)

And

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES (HHS)
NATIONAL INSTITUTES OF HEALTH (NIH)
National Center for Advancing Translational Sciences (NCATS)
Division of Pre-Clinical Innovation (DPI)

And

U.S. ENVIRONMENTAL PROTECTION AGENCY (EPA)
Office of Research and Development (ORD)

And

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES (HHS)
U.S. Food and Drug Administration (FDA)

Concerning

High Throughput Screening, Toxicity Pathway Profiling, and Biological Interpretation of Findings

I. PURPOSE/OBJECTIVES/GOALS

This four-party Memorandum of Understanding (MOU) sets in place the mechanism to renew and strengthen the existing collaborations between the NIEHS/NTP, the NCATS/DPI, the Office of Research and Development (ORD) of the EPA, and the FDA in the research, development, validation, and translation of new and innovative test methods that characterize key steps in toxicity pathways. A central component of this MOU is the exploration of high throughput screening (HTS) assays and tests using cell culture systems, phylogenetically lower animal species (e.g., fish, worms), together with high throughput whole genome analytical methods, to evaluate mechanisms of toxicity. Ultimately, the data generated by these new tools is to be provided to risk assessors to use in the protection of human health and the environment.

The goals of this MOU are to investigate the use of these new tools to (1) identify mechanisms of chemically-induced biological activity; (2) prioritize chemicals for more extensive toxicological evaluation: and (3) develop more predictive models of *in vivo* biological response. Success in achieving these goals is expected to result in test methods for toxicity testing that are more scientifically and economically efficient and models for risk assessment that are more biologically based. As a consequence, a reduction or replacement of animals in regulatory testing is anticipated to occur in parallel with an increased ability to evaluate the large numbers of chemicals that currently lack adequate toxicological evaluation.

II. BACKGROUND

For more than a decade, EPA and NIEHS have recognized the need to modify the scientific basis for hazard identification and risk assessment by working toward partially or fully replacing current test methods with higher throughput, mechanism-based test methods. This recognition led both organizations to initiate programs to evaluate using *in vitro* biochemical- and cell-based assays and non-rodent animal models for toxicological testing. In 2004, the NTP released its Vision and Roadmap for the 21st Century (http://ntp.niehs.nih.gov/go/vision) which established an HTS initiative to focus on integrating HTS and non-rodent screening assays into its testing program. In 2005, the EPA established the National Center for Computational Toxicology (NCCT) within ORD to bring innovative molecular biological and computational tools to the evaluation of hazards and risks of environmental chemicals. To accomplish its mission, the NCCT works closely with ORD's National Health and Environmental Effects Research Laboratory (NHEERL), which conducts related laboratory, clinical, and epidemiological research. The NTP Vision for the 21st Century and the goal of the ORD are to support the evolution of toxicology from a predominantly observational science at the level of disease-specific models to a predominantly predictive science focused upon a broad inclusion of target-specific, mechanism-based, biological observations. The NIH Chemical Genomics Center (NCGC), one of the centers of the Molecular Libraries Screening Centers Network (MLSCN) within the NIH Roadmap for Medical Research Molecular Libraries Initiative, has been a key collaborator with both the NTP and EPA in this process. The NIH established the NCGC in 2004 as a national resource for chemical probe development and compound profiling using industrial-scale HTS assays, informatics, and chemistry. In late 2011, the NCGC was incorporated into the Division of Pre-Clinical Innovation (DPI) of the newly established NCATS, a center within NIH.

In 2005, the EPA with support from the NTP funded a project at the National Research Council (NRC) to develop a long-range vision for toxicity testing and a strategic plan for implementing the vision. The impetus for this project was a strong commitment by both agencies that future toxicity testing and assessment paradigms meet evolving regulatory needs (e.g., that the paradigms readily accommodate the increasingly large numbers of substances that need to be tested); incorporate the recent advances in molecular toxicology, computational sciences, and information technology; and offer increased efficiency in design, costs, and animal usage. In response, the NRC Committee on Toxicity Testing and Assessment of Environmental Agents released in 2007 a report entitled Toxicity Testing in the Twenty-first Century: A Vision and a Strategy (NRC 2007) (http://www.nap.edu/catalog/11970/toxicity-testing-in-the-21st-century-a-vision-and-a). This report was a powerful catalyst for a focused and collaborative effort across

the research community to (1) develop a more robust scientific basis for assessing potential adverse health effects of environmental agents; (2) provide broad coverage of chemicals, chemical mixtures, outcomes, and life stages; (3) use population-based and human exposure data to inform decisions regarding chemical selection and environmentally relevant testing conditions; (4) reduce the cost and time of toxicity testing; and (5) use laboratory animals in targeted testing where essential data are needed and cannot be appropriately obtained *in vitro* or using phylogenetically lower animal species.

During this same time period, the FDA recognized that advancements in basic and translational research were not efficiently yielding new products needed to benefit consumers. In 2011, FDA developed an Advancing Regulatory Science Plan to help address this problem and to encourage innovation. A key element of this plan is to develop more predicative models for safety testing (http://www.fda.gov/downloads/ScienceResearch/SpecialTopics/RegulatoryScience/UCM268225.pdf). FDA contributes to the development of these methods through its own research programs and additionally concentrates on validation, and translation of these new and innovative test methods into the regulatory paradigm.

The convergence of science, technology, regulatory need, and public opinion has produced an historic opportunity to transform toxicology and risk assessment into more accurate, rapid, and cost-effective sciences. In recognition of the need for a long-term, multiple Federal agency commitment, this MOU is being renewed to guide the construction and governance of a detailed research strategy to make the NRC Committee's vision a reality. This MOU builds on a number of separate and joint efforts among our four organizations that are very much aligned with the NRC Committee's vision. Building on the strengths of the individual organizations is intended to facilitate the advancements necessary to move toxicology to a more predictive science-based on the most relevant and meaningful tools of modern molecular biology and chemistry.

III. AUTHORITIES

EPA enters into this MOU pursuant to Section 103 of the Clean Air Act [42 U.S.C. §7403 (a) and (b)]; Section 104 of the Clean Water Act; [33 U.S.C. § 1254 (a) and (b)]; Section 300 j-l of the Safe Drinking Water Act (42 U.S.C. §1442); Section 10 of the Toxic Substances Control Act [15 U.S.C. § 2609 (a)]; and Section 20 of the Federal Insecticide, Fungicide, and Rodenticide Act [7 U.S.C. § 136r (a)].

NIEHS enters into this MOU pursuant to Sections 301, 401, and 463 of the Public Health Service Act [42 U.S.C. § 241, 281, and 285l].

NCATS enters into this MOU pursuant to Section 301 of the Public Health Service Act [42 U.S.C. § 241].

FDA enters this MOU pursuant to Section 301 of the Public Health Service Act [42 U.S.C. § 241].

IV. ROLES AND RESPONSIBILITIES

Each participant intends to implement the following provisions of this MOU, under the responsibility of the Assistant Administrator for ORD, the Directors of the NTP and the NCATS, and the Commissioner of Food and Drugs.

A. Toxicity Pathways: A shared focus of all participants is to identify and/or develop HTS assays that investigate "toxicity" pathways. The member organizations agree to collaborate to identify toxicity pathways that contribute to a variety of adverse health outcomes (e.g., from acute oral toxicity to long-term effects like cancer) and assays that provide information on key steps in those pathways. All participants agree that this aim will best be accomplished through regular joint meetings as well as combining experimental investigation with external stakeholder engagement, seeking advice from acknowledged experts in different disciplines in the international scientific community. The member organizations agree to identify data gaps where research and development are needed to modify existing assays (e.g., incorporation of metabolic competency) and/or to develop new assays designed to allow a more comprehensive evaluation of how compounds interact with key steps in critical toxicity pathways.

Chemical Selection: The member organizations agree that large numbers of compounds with existing toxicological data need to be identified and tested in the identified HTS assays and alternative animal models. The NTP and the EPA have databases of toxicological information on a large number of compounds. FDA also holds a significant amount of toxicological information, some of which is confidential or trade secret information of entities regulated by FDA but some of which is publicly available. The EPA also has models and databases for determining whether exposures are likely to occur, at what level, and by what route. The member organizations agree, where appropriate, to collaborate on identifying compounds for testing and to share toxicity and exposure information on compounds selected for testing. The member organizations also plan to make appropriate efforts to ensure, as a means for evaluating endpoint reproducibility, appropriate levels of redundancy within and between the chemical libraries under study. The FDA agrees to share toxicological information that may be useful to the joint effort but that is not confidential or trade secret. The member organizations agree to jointly determine appropriate quality assurance/quality control procedures for the compounds chosen for testing.

Analysis and Bioinformatics: Analysis of individual HTS assay results (i.e., identifying active and inactive compounds for a particular assay) and bioinformatics (i.e., evaluating sets of data from multiple *in vitro* and *in vivo* assays while taking into account chemico-physical properties for significant relationships) are critical to the success of the joint initiative. As a result, the member organizations agree to (1) collaborate on the development of the most appropriate tools for the analysis of HTS data; (2) share non-confidential data (both HTS as well as that generated using traditional test methods); (3) employ computational approaches to evaluate the information from HTS studies, and (4) work to make all the data publicly accessible. The NTP, EPA, and FDA agree to undertake targeted *in vivo* follow-up studies when appropriate. The member organizations also agree to consider the use of extramural mechanisms to support these activities. Proof-of-concept studies will be important to demonstrate the feasibility of new approaches and their undertaking will require a critical level of effort across institutions. It is envisioned that these efforts will evolve towards a systems-biology approach as a foundation for constructing

and using biologically based dose-response models in risk assessment. Regulatory acceptance of these new approaches will take considerable thought and effort. Therefore, an important consideration will be the translation of the results of this joint research program into testing strategies that provide data useful to risk assessors.

B. Outreach: Effective and open communication about this research program, its findings and their use is important to its acceptance and ultimate success. The member organizations agree to conduct joint outreach activities related to the development and use of HTS and other innovative approaches for assessing toxicity. Such activities might include:

- Sponsoring relevant workshops (e.g., to identify the key toxicity pathways for various organ systems or to develop best practices for analysis of the new data streams).
- Organizing symposia that focus on advances in the area of HTS for toxicity testing and systems-biology models for integration and interpretation of the data.
- Co-sponsoring a seminar series that addresses key advancements in HTS or translation of HTS data into phenotypic outcomes that would form the basis for more mechanism-based risk assessment practices.
- Contributing via presentations and posters to national and international meetings.
- Co-authoring articles to keep the scientific community informed of progress and advances in this research program.
- Continuing to interact via joint meetings of the EPA Chemical Prioritization Community of Practice (CPCP), the NCATS, the NTP, and the FDA.
- Promoting the regulatory acceptance of alternative approaches when deemed scientifically defensible.

C. Governance: The activities identified in this MOU are to be managed by a Governance Board (GB) composed of the Scientific Director of the DPI, NCATS, the Director of the EPA/ORD National Center for Computational Toxicology, the Chief of the NTP Biomolecular Screening Branch, and the Senior Advisor for Toxicology in the Office of the Center Director of the FDA Center for Food Safety and Applied Nutrition. The members of the GB, with advice from their management, are to be responsible for developing and implementing a cross-organizational research strategy, promoting cross-organization interactions, identifying and recommending actions to overcome barriers to success, ensuring minimal redundancy of activities, serving as spokespersons for the quadripartite effort within and outside their respective organizations, and reporting on the overall progress of the program to their respective organizations at periodic intervals. The GB is expected to meet by teleconference or in person at least once every two months.

D. Scientific Review: The activities carried out by the member organizations in support of this MOU will be reviewed at regular intervals by their respective review panels. For the NCATS, the NTP, and the EPA, this is their respective Board of Scientific Counselors. For the FDA, this is FDA's Agency Toxicology Working Group, the FDA Food Advisory Committee and the FDA Science Advisory Board.

V. LIMITATIONS

All commitments made in this MOU are subject to the availability of appropriated funds and each party's research priorities. Nothing in this MOU, in and of itself, obligates any participant to expend appropriations or to enter into any contract, assistance agreement, interagency agreement, or other financial obligation.

This MOU is neither a fiscal nor a funds obligation document. Any endeavor involving reimbursement or contribution of funds between the participants to this MOU will be handled in accordance with applicable laws, regulations, and procedures and will be subject to separate subsidiary agreements that will be effected in writing by representatives of the participants.

Except as provided in this Section (Section V, LIMITATION) and Section VII, INTELLECTUAL PROPERTY, this MOU is not legally binding and does not create any right or benefit, substantive or procedural, enforceable by law or equity against the NIH/NIEHS/NTP, the NIH/NCATS/DPI, the EPA, or the FDA.

VI. PROPRIETARY INFORMATION

Not applicable as all participants are Federal agencies. Note, however, that no sharing by FDA with other parties to this MOU of information that is confidential or trade secret is contemplated by this MOU.

VII. INTELLECTUAL PROPERTY

The parties agree that inventorship of any patentable matter, created by any of the participants pursuant to the terms of this MOU, will be determined in accordance with U.S. patent laws. Ownership will follow inventorship and vest in the inventors or their employers as determined by contract or law.

The participants agree to notify each other when joint-authoring a journal article that includes a non-government employee as a co-author. In such cases, the participants should ensure that all necessary rights under copyright are acquired to the satisfaction of all parties.

VIII. CONFIDENTIAL INFORMATION

FDA is the custodian of information, including toxicological information that is owned by entities that FDA regulates. FDA will not, as part of the activities covered by this MOU, share with other parties to the MOU any information that is confidential or trade secret.

IX. POINTS OF CONTACT

The following individuals are designated points of contact for the MOU:

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X. MODIFICATION/DURATION/TERMINATION

This MOU is to take effect upon signature of all participants and remain in effect for a period of five years, unless the participants decide otherwise in writing. This MOU may be amended at any time by the mutual written consent of the participants. A participant may terminate its participation in this MOU by providing written notice to the other participants at least thirty (30) days in advance of the desired termination date.

The participants anticipate that other parties may seek to join this effort in the future. If that occurs, a new MOU may be prepared and will, when signed by each of the parties to this MOU, supersede this MOU.

XI. APPROVAL

National Toxicology Program

[redacted]

5-11-15
Date

Linda S. Birnbaum, Ph.D., DABT, ATS
Director
National Institute of Environmental Health Sciences
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National Center for Advancing Translational Sciences

[redacted]

5/20/2015
Date

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6/16/15
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