National Toxicology Program

Board of Scientific Counselors

December 15, 2022

National Institute of Environmental Health Sciences
Research Triangle Park, NC

Summary Minutes

Table of Contents

1. Location of Background Materials and Presentations

Background materials and presentations for the Board of Scientific Counselors meeting on December 15, 2022, are available on the National Toxicology Program (NTP) Past BSC Meetings page (https://ntp.niehs.nih.gov/go/meeting)

2. Abbreviations and Acronyms

ADME	absorption, distribution, metabolism, and excretion
AI	artificial intelligence
BSC	Board of Scientific Counselors
CEBS	Chemical Effects in Biological Systems
COR	Contracting Officer's Representative
CT	Computed Tomography
DIR	Division of Intramural Research
DNTP	Division of the National Toxicology Program
DTT	Division of Translational Toxicology
MHTS	medium- to high-throughput screening
MRI	Magnetic Resonance Imaging
OPO	Office of Program Operations
RFP	Request for Proposal
TK	toxicokinetics

3. Attendees[1]

Board of Scientific Counselors

Chair: David Eaton, PhD, DABT, ATS, University of Washington (emeritus) and University of Arizona

David Berube, PhD, North Carolina State University

Eric Blomme, DVM, PhD, DACVP, AbbVie

Susan Felter, PhD, Procter & Gamble

David Michaels, PhD, George Washington University

Devon Payne-Sturges, DrPH, University of Maryland, College Park

Mark Russi, MD, Yale University

Anne Ryan, DVM, PhD, DACVP, FIATP, Act 5 Ventures, LLC

Veena Singla, PhD, Natural Resources Defense Council

National Institute of Environmental Health Sciences/Division of Translational Toxicology (NIEHS/DTT) Staff

Danica Andrews

Julie Bardo

Brian Berridge

Milene Brownlow

Mark Cesta

Ronald Herbert

Michelle Hooth

Georgia Roberts

Robert Sills

Matthew Stout

Suramya Waidyanatha

Mary Wolfe

Other Federal Agency Staff

Gonçalo Gamboa da Costa, U.S. Food and Drug Administration (BSC liaison)

Christina Lawson, National Institute for Occupational Safety and Health (BSC liaison)

[1]The meeting was webcast with the listed individuals attending by Zoom. NIEHS/NTP staff are limited to those with a role in the meeting. Public attendees are not listed.

Contract Support Staff

Ernie Hood, Bridport Services

4. Introductions and Welcome

The National Toxicology Program (NTP) Board of Scientific Counselors (BSC) convened on December 15, 2022, via Zoom for identified attendees noted above and by webcast for public attendees. Dr. David Eaton served as chair. Dr. Milene Brownlow served as the Designated Federal Official.

Dr. Eaton called the meeting to order at 1:30 p.m., welcomed everyone to the meeting, and asked all attendees to introduce themselves. BSC members Drs. Weihsueh Chiu, Kathleen Gray, Pamela Lein, Matthew Martin, and Susan Tilton were absent.

Dr. Berridge addressed brief comments to attendees. He thanked the outgoing board members for their contributions: Drs. Chiu, Eaton, Berube, Felter, Michaels, Ryan, and Tilton. He also noted that BSC member Dr. Pamela Lein recently received the Excellence in Research Award from the American Association of Veterinary Medical Colleges. Dr. Eaton added his thanks to the outgoing board members and thanked Dr. Berridge for his leadership of the NTP and NIEHS/DTT over the last several years.

Dr. Brownlow read the conflict-of-interest policy statement and briefed the attendees on meeting logistics. Dr. Eaton noted that no written or oral public comments were received prior to the meeting. One of the roles of the board is to review and approve external contracts, which was the purpose of the meeting, during which three contract concepts would be presented and voted upon.

5. NIEHS Contract Concept Introduction

Dr. Matthew Stout from the DTT Office of Program Operations (OPO) provided background information about NIEHS contract concepts. The BSC is asked to review research and development (R&D) contracts requiring external peer review, including new contracts, recompetitions with changes in the statements of work, and those ongoing for five or more years since last review. The latter two apply to the contract concepts to be reviewed in this meeting. The review is required prior to the issuance of a Request for Proposal (RFP). A single contract concept may encompass multiple statements of work, solicitations, and/or contracts. The resulting contracts will support NIEHS and/or NTP projects.

NIEHS/DTT funding encompasses intramural funding (22%), which covers salaries and fringe benefits, operating expenses, and travel, and R&D funds, which cover contracts and Interagency Agreements (78%). DTT relies upon contract support in a wide variety of areas, including those to be addressed in this meeting: Chemistry, Toxicology, and Pathology. They represent NIEHS/DTT's primary "wet-lab" capabilities. There are many interconnectivities among NIEHS/DTT contracts and relationships among capabilities such that outputs of one contract may become inputs for another. Dr. Stout provided an example of such interconnectivities. He described the role of a Contracting Officer's Representative (COR) and the DTT OPO in contract award and management. Other mechanisms include the NIEHS Office of Technology Transfer

and the NIEHS Division of Extramural Research and Training. Concept discussions can take place in a meeting open to the public, where discussions are limited to review of the general project purposes, scopes, goals, and various optional approaches to pursue the overall objectives. If a discussion turns to the development or selection of details of the projects or RFPs, it must take place in a meeting closed to the public.

The BSC members are asked to review the contract concepts for overall value and scientific relevance as well as for fulfilling the program goal of protecting public health. Specific areas should include:

- The significance from a scientific or technical standpoint of the goals of the proposed research or development activity
- The availability of the technology and other resources necessary to achieve those goals
- The extent to which there are identified, practical uses for the anticipated results of the activity
- Where the review includes the project approach, the adequacy of the methodology to be utilized in carrying out the activity

Julie Bardo from the NIEHS Office of Acquisitions provided further information from her office's perspective.

6. Contract Concept Review for Chemistry Support Services for the DTT, NIEHS

Chemistry and ADME Resources Group Leader Dr. Suramya Waidyanatha briefed the board on the contact concept for Chemistry Support Services. Chemistry support is essential for NIEHS/DTT research activities, many of which are in support of the NTP. The scope and breadth of the support needed exceeds the resources available at NIEHS. Therefore, chemistry support has been obtained through contract resources for over 40 years.

Chemistry support falls under nine broad functional areas:

- Logistics & Handling
- Characterization
- Formulation
- Biosample Analysis
- Animal Studies
- Special Studies
- Omics
- *In Vitro* Assays
- MHTS Activities

Broad chemistry support is required across the NIEHS/DTT pipeline, including both *in vitro* and *in vivo* toxicology studies, and *in vitro* and *in vivo* ADME and TK study types.

Dr. Waidyanatha noted that chemistry support is typically obtained on a per test article basis, which allows support to be applied to multiple studies conducted at different times and at different research facilities. The anticipated support varies per functional area.

She related the charge to the BSC:

- The BSC members are asked to review the contract concept for overall value and scientific relevance, as well as for fulfilling NIEHS' goal of protecting public health. Consideration should be given to:
    - The significance of the goals of the proposed research activity
    - The availability of the technology and other resources necessary to achieve those goals
    - The extent to which there are practical scientific or clinical uses for the expected results
    - The adequacy of the proposed mechanism
- The NIEHS/DTT seeks approval from the BSC to continue this type of activity using a contract mechanism.

Clarifying Questions

Dr. Eaton asked two clarifying questions. First, he asked whether all the contract activities for laboratory services must comply with Good Laboratory Practices. Dr. Waidyanatha said that it depends on the type of study. Dr. Eaton's second question centered on the seventh functional area, omics. He noted that the description had not included genomics. Dr. Waidyanatha said that omics endpoints supported under chemistry support contracts are analytical chemistry-based and a separate contract covers genomics.

6.1 BSC Discussion

Lead discussant Dr. Ryan asked whether the contract concept was a recompete or a contract that was more than five years old. Dr. Waidyanatha replied that it was a recompete. Dr. Ryan asked whether it was fair to say that the newer areas are the omics and the *in vitro* work. Dr. Waidyanatha noted that nothing had changed since the previous statement of work. Dr. Ryan asked Dr. Waidyanatha to explain the interface between the omics piece in the proposed contract concept and the bioinformatics concept that the board approved in April 2022, as well as the interface between the *in vitro* work in the chemistry concept versus what is covered in the toxicology concept. Dr. Waidyanatha replied that the omics techniques mentioned in this concept are more focused on use of analytical chemistry approaches. She noted that the *in vitro* assays mentioned in the concept are focused on understanding ADME/TK properties. Dr. Ryan said that the support received per test article basis is very efficient. She felt that high-level technology is being leveraged to achieve program goals, and there are also practical uses for the anticipated results of the activity. She said that adequacy of the methodology seemed appropriate.

Second discussant Dr. Blomme asked how the group is thinking about the generation of data using tools such as artificial intelligence, and how it would fit in the context of data streams. He observed that it would be important to think about how the data could be collected in a way that

would accommodate leveraging of artificial intelligence to accomplish better science going forward. Dr. Waidyanatha said that discussion is beyond the scope of the contract being considered, and asked Dr. Berridge to comment. He reiterated that it should be considered how to more effectively transfer the data captured in several different platforms to help fulfill long-term goals of leveraging the many data sets. Dr. Berridge replied that it is a timely question. He noted that the NIEHS/DTT and NTP have a history of transparently sharing data, particularly in the CEBS database. As novel kinds of data are increasingly being generated, NIEHS/DTT is actively developing pipelines that allow collection of data efficiently into a central location. The government and NIH, in particular, have articulated the expectation that all programs do so, and NIEHS/DTT has been actively working to ensure that all data are available and accessible, he noted.

6.2 BSC Action

Dr. Eaton called for a motion on whether a contract mechanism is the appropriate mechanism to support the proposed activities. Dr. Ryan so moved; Dr. Berube seconded the motion.

The Board voted unanimously in favor of the motion to approve the contract concept.

7. Contract Concept Review for Toxicology Support for the DTT, NIEHS

Health Science Evaluator Dr. Georgia Roberts briefed the board on the contract concept for Toxicology Support. She provided a history and overview of the requirement, which has existed for more than 40 years. Toxicology research consist of areas such as general toxicology, carcinogenicity, developmental and reproductive toxicology, neurobehavior and neurotoxicology, immunotoxicology, and molecular toxicology.

Support over the years has included:

- Implementation of in-house capabilities
    - Utilization of contract resources to implement and scale technologies and testing approaches developed in-house
        - Evaluation of reliability and reproducibility, iterative refinement
        - Determination of the potential for routine use
        - Implementation as appropriate in on-going evaluations
        - Adoption of newer approaches within the toxicology research community
        - Engagement with regulatory partners to facilitate use of new data streams
- Problem formulation
    - Utilization of highly qualified, skilled, and knowledgeable contract staff
    - Support for the development of research questions to address broad objectives
- On-test chemistry

    - Inhalation
        - Bulk chemical characterization
        - Development/validation of generation and monitoring systems
    - Non-inhalation
        - Confirmation of identity and purity
        - Formulation preparation and analysis
- Conduct of *in chemico* and *in vitro* studies
    - For *in vitro* studies, using immortal or primary cells, cell suspensions, cells grown at the air-liquid interface, or 3D complex tissue models with multiple cell types, including microphysiological systems
- Conduct of *in vivo* animal studies
    - Various life stages, multiple routes of exposure
    - Capacity for simultaneous conduct of multiple studies
    - Wide variety of in-life and post-life assessments

Dr. Roberts related the charge to the BSC:

- The BSC members are asked to review the contract concept for overall value and scientific relevance, as well as for fulfilling NIEHS' goal of protecting public health. Consideration should be given to:
    - The significance of the goals of the proposed research activity
    - The availability of the technology and other resources necessary to achieve those goals
    - The extent to which there are practical scientific or clinical uses for the expected results
    - The adequacy of the proposed mechanism
- The NIEHS/DTT seeks approval from the BSC to continue this type of activity using a contract mechanism.

Clarifying Question

Dr. Eaton said that NIEHS is well-known in academia as a source of grants. He noted that Dr. Roberts had listed microphysiological systems, which have mainly been developed in academic institutions. He asked whether there are contracts that could go to academic institutions. Dr. Stout replied that there is no reason an academic institution would not be eligible to bid on a contract. He said that NIEHS puts out requirements based on needs, and issues solicitations based on getting the best technical expertise to perform the work.

7.1 BSC Discussion

Dr. Felter, as the lead BSC discussant, asked several questions. First, she asked Dr. Roberts about problem formulation. She said it was unclear what is being done in-house versus what NIEHS/DTT is looking to contract support to do. She asked whether problem formulation referred to what research would help answer the questions that NIEHS/DTT has established, or whether it refers to the questions themselves. Dr. Roberts replied that Dr. Felter had captured all the possibilities well, but that the answer fell outside the scope of the meeting. Dr. Felter observed that in the last many years, she had seen significant evolution in toxicology, with the research questions evolving along with development of newer methods to answer them. She mentioned that she fully supported continued use of contract work for NIEHS/DTT toxicology research. In terms of the areas that are changing, such as the increased use of *in vitro* work, she asked about research to better understand the relationship between *in vitro* concentrations and *in vivo* scenarios, and whether that is being done in-house by NIEHS/DIR or by contractors. Dr. Roberts replied that the specific approach for how work is accomplished is handled on a case-by-case basis based on the circumstances for a specific program. Dr. Felter encouraged NIEHS/DTT to think carefully about the protocols being used with methods that are still under development. With the newer methods, it would be important as part of protocol development to consider the time points and organs to be measured, and she asked whether those issues were developed in-house or by contractors with specific expertise. Dr. Roberts reiterated that it would be determined on a case-by-case basis, by surveying the available expertise. Dr. Eaton commented that the question boils down to how NIEHS/DTT can facilitate through these contracts, better correlation or associations between *in vitro* concentrations and their relevance to *in vivo* NTP and NIEHS/DTT studies. Dr. Roberts said that in most cases NIEHS/DTT uses expertise across a wide range of contracts as well as across the division, and across NIEHS and external stakeholders.

Dr. Berube asked Dr. Roberts how the preferred approach is determined while trying to control bias toward certain types of methods. Dr. Roberts said there is not an unsupervised method in use to address that, and that many of the tools selected are a compromise among several aspects. Technical capability is always one, but it must be balanced with logistical considerations and funding opportunities. Dr. Berube asked if there had been any attempt to establish protocols on how the process could be formalized to reduce bias. Dr. Roberts said that some testing approaches are well-established and well-known, but they are flexible to accommodate customization as appropriate for a given problem. She added that there is effort to bring in a group of people with disparate scientific expertise, even within the division, to help inform the approach(es) needed. Dr. Berube said that the inclusion of many voices does not necessarily prevent a bad decision. Dr. Eaton agreed that whenever there is a complex issue in which an expert judgement is involved, individual biases will contribute to the decision, and more voices will not necessarily solve the problem.

Dr. Felter made the point that once a protocol or regulatory guideline has been published, it can be very difficult to move away from it, even though the science has advanced. As NIEHS/DTT takes on challenging questions as to what is relevant for human safety, it will be important to find a way to conduct key research that might involve having deviations from protocols that have been used for generations or decades. Thus, moving forward may involve challenging the status quos. Dr. Berube added that the most important consideration for protocols is transparency. Dr.

Roberts noted that there is typically a buffet of ways to approach a question, particularly when animal studies are involved, and so the approach can be tailored.

7.2 BSC Action

Dr. Eaton called for a motion on whether a contract mechanism is the appropriate mechanism to support the proposed activities. Dr. Felter so moved; Dr. Berube seconded the motion.

The Board voted unanimously in favor of the motion to approve the contract concept.

8. Contract Concept Review for Pathology Support for the DTT, NIEHS

Pathology Coordinator Ms. Danica Andrews briefed the board on the contract concept for Pathology Support. The purpose of the contract concept is to provide a variety of pathology support for NIEHS (DTT and DIR) research programs. Pathology support contracts have been in place for nearly 40 years, having initially provided support to NIEHS/DTT for NTP Pathology Review processes and evolving to support NIEHS/DIR research as well. The support contracts include histopathology and pathology peer review, necropsy and histology, personnel support, imaging technologies, investigative/mechanistic studies, scientific publication support, and emerging technology and needs.

Histology and pathology peer review encompasses primary pathology evaluations for NIEHS/DTT and NIEHS/DIR studies and pathology peer review for NIEHS/DTT and NTP studies. A wide range of organ systems expertise is needed to support histopathology.

Necropsy and histology support is provided for NIEHS/DTT and NIEHS/DIR studies. The support includes immunohistochemistry/immunofluorescence, *in situ* hybridization, frozen sections, and electron microscopy.

Under personnel support, professional and technical support is used for several groups and core laboratories, including pathologists for NIEHS/DTT studies, technicians, specialists, and pathologists for NIEHS/DTT labs as well as others within NIEHS/DTT including the Laboratory Animal Medicine Group, and omics/bioinformatics and *in vitro* culture systems support for the Molecular Pathology Group.

Imaging sciences support incorporated increased and the expanding use of new imaging technologies such as artificial intelligence and specialized technologies such as MRI and CT.

Investigative/mechanistic studies include *in vitro* culture systems, *in vivo* studies (animal models), molecular biology techniques, and omics/bioinformatics support.

Scientific publication support is provided for technical writing, publication support, and online content updates, including

- Scientific manuscripts, online content
- Non-Neoplastic Lesion Atlas
- Electron Microscopy (Ultrastructural) Atlas

- Global Toxicologic Pathway Training Program

Under emerging technology and needs, the pathology support contracts have expanded over time, with recent needs calling for including new technologies and addressing current issues such as:

- Increasing mechanistic studies
- Addressing emerging public health issues
- Increasing need for new capabilities to modernize laboratory animal medicine practices
- Increasing need for specialized pathology expertise

Ms. Andrews related the charge to the BSC:

- The BSC members are asked to review the contract concept for overall value and scientific relevance, as well as for fulfilling NIEHS' goal of protecting public health. Consideration should be given to:
    - The significance of the goals of the proposed research activity
    - The availability of the technology and other resources necessary to achieve those goals
    - The extent to which there are practical scientific or clinical uses for the expected results
    - The adequacy of the proposed mechanism
- The NIEHS/DTT seeks approval from the BSC to continue this type of activity using a contract mechanism.

Clarifying Question

Dr. Eaton said he was surprised at the mention of *in vitro* support. He described a service he had heard about recently that involved imaging of Ames assays involving high-throughput mutagenesis screening done by computer imaging of 384-well plates. He asked Ms. Andrews if that type of service would fall under the contract. Ms. Andrews replied that support for that type of screening platform could be considered, although they were thinking more about organs-on-a-chip and similar methods, where what is happening can be seen more functionally. She said they would be open to incorporating, investigating, and providing support for any of the approaches such as those described by Dr. Eaton. Dr. Stout described an example of a use case for pathology in an *in vitro* environment.

8.1 BSC Discussion

Lead discussant Dr. Ryan asked whether this contract was five years since the last review or a change in the statement of work due to new capabilities. Dr. Andrews said it is a recompetition, and that it has been 10 years since the last iteration. Dr. Ryan asked whether the new capabilities comprise the expansion in digital imaging and the global training program. Dr. Andrews replied that work has already been going on in those areas, with more emphasis on them moving

forward. Dr. Ryan asked about the nature of the NIEHS/DIR support in the concept. Dr. Sills replied that NIEHS/DIR is more principal-investigator-based than NIEHS/DTT, so core laboratory expertise is provided on that basis to those colleagues. Dr. Mark Cesta added the group does read slides for NIEHS/DIR scientists, on a collaborative basis. Dr. Stout said that across the contract portfolio, any or all the contracted activities may support NIEHS/DIR collaborations or projects. The contracts are NIEHS contracts, so there is no barrier to supporting other divisions.

Dr. Blomme asked whether the contract would include resources to develop artificial intelligence/machine learning algorithms to address evaluation of slides in a more routine manner, or whether that would be part of another contract. Dr. Andrews said that would be part of this contract. Dr. Ronald Herbert said that expertise in AI has been accessed through the contract mechanism, with the use of an AI scientist to help develop AI capabilities at NIEHS. The hope is to expand core AI capabilities in pathology services at NIEHS for both DTT and DIR. He added that initially the work will be primarily in diagnostics, and it is hoped that in the future AI applications will be research oriented.

Regarding the contract support for publications, Dr. Payne-Sturges asked if that had been part of the scope of the contract previously, and how attribution has been given. Ms. Andrews replied that it has been part of the contracts for the past several iterations. Dr. Stout said that across the NIEHS/DTT contract portfolio, there are many examples of publications that include both contract and government staff. There is also a mechanism under U.S. government reports by which there are acknowledged groups of collaborators and contributors. Dr. Sills mentioned the Non-Neoplastic Lesion Atlas as an example in which all authors are acknowledged in each section.

Regarding the proposed Global Toxicologic Pathology Training Program, Dr. Payne-Sturges asked how it would be implemented and whether NIEHS staff would oversee the trainees. Dr. Sills replied that there is an established NIEHS/DTT training program, and that the Global Toxicologic Pathology Training Program is virtual through a website with training modules. Dr. Wolfe said the link would be sent to board members.

8.2 BSC Action

Dr. Eaton called for a motion on whether a contract mechanism is the appropriate mechanism to support the proposed activities. Dr. Ryan so moved; Dr. Berube seconded the motion.

The Board voted unanimously in favor of the motion to approve the contract concept.

9. Adjournment

Dr. Eaton noted the importance of contract support to both NIEHS and NTP, as they represent opportunities to seek the best expertise from a variety of different groups. He noted that Dr. Berridge had to step away from the meeting and asked Dr. Hooth to provide closing remarks on his behalf.

Dr. Hooth thanked the Board members for their thoughtful considerations of the contract concepts. She thanked Dr. Eaton for his leadership in chairing the meeting, and the presenters

and NIEHS/DTT staff, as well as their partners in the Office of Acquisitions. She thanked Drs. Wolfe and Brownlow for their contributions to the meeting, along with the AV support staff for their navigation of the technological challenge presented by the virtual meeting. She thanked the departing board members.

Dr. Wolfe echoed Dr. Hooth's comments and thanked the team who handled logistics for the meeting as well as the board members, including those rotating off because their terms had ended. She thanked Dr. Eaton for his close collaboration in planning the board meetings.

Dr. Brownlow added her gratitude to everyone for their contributions and her appreciation to the board members for their patience and flexibility as the meeting's schedule and agenda were planned.

Dr. Eaton noted that it was his final meeting as chair but was confident he would be back at BSC meetings in 2023 in some capacity. He adjourned the meeting at 3:31 pm, December 15, 2021.

10. Approval of the Summary Minutes by the NTP BSC Chair

These summary minutes for the NTP Board of Scientific Counselors meeting on December 15, 2022, have been read and approved by the chair.

Signed

David L. Eaton, PhD, DABT, FATS

Professor Emeritus, University of Washington

NTP BSC Chair