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NIST Special Publication 903034

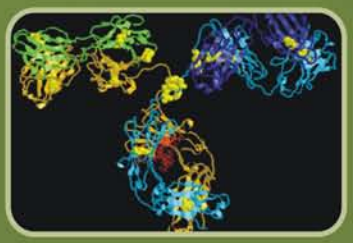
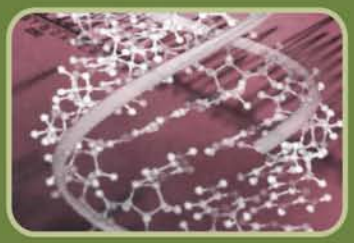
Conference Report

Accelerating Innovation in 21st Century Biosciences: Identifying the Measurement, Standards, and Technological Challenges

October 19-22, 2008
Gaithersburg, Maryland






Acknowledgements

Thanks go to the many sponsors who contributed to this effort.
Sponsor profiles are included in Appendix A.

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Accelerating Innovation in 21st Century Biosciences: Identifying the Measurement, Standards, and Technological Challenges

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Overview

The science of understanding how biological systems operate and interact with one another (the biosciences) is increasingly important to global prosperity and quality of life. As the world's population grows, so will the need for more efficient and sustainable ways to grow food, keep people healthy, produce energy, and manufacture biological drugs, therapeutics, and chemicals. These advances can only be realized by gaining a deeper understanding of how biological systems operate—an understanding that depends on advancing the state of the art in biosciences measurement.

Despite major breakthroughs and discoveries in recent years, our understanding of biological systems still faces many challenges. Biology is an informational science that depends on accurate measurements and standards. Whether quantifying the amount of protein in a cancer cell or the rate at which an organism converts sugar to alcohol, measurements are the foundation for improving our understanding of biological systems.

Exhibit E.1 Conference Focus Areas

Agriculture - increasing yield, quality, and safety in the world's food supply

Bioenergy - obtaining sustainable energy from biological sources

Environment - understanding our planet through linking molecules to ecosystems

Biopharmaceutical Manufacturing - obtaining higher quality products through better bioprocess measurements

Medicine - improving health through measurement of complex biological signatures

Hot Topics - unrecognized, overlooked, underestimated, and often ignored measurement needs in the biosciences, including

- Agriculture viability
- Antibiotic and antiviral drug resistance
- Environmental bioremediation
- Environmental bioterrorism monitoring
- Marine versus terrestrial sources of bioenergy
- Personalized medicine
- Stem cell therapy
- Synthetic biology

To identify measurement challenges in the biosciences, the National Institute of Standards and Technology (NIST) and the University of Maryland Biotechnology Institute (UMBI) co-hosted an international conference, *Accelerating Innovation in 21st Century Biosciences: Identifying the Measurement, Standards, and Technological Challenges*, on October 19-22, 2008, in Gaithersburg, Maryland.

Attended by leading bioscience professionals from all over the world, this landmark event was a first-time opportunity to discuss the global measurement and standards challenges to innovation in key bioscience areas (Exhibit E.1). Bioscience practitioners with diverse backgrounds met to share the views of international policymakers, create opportunities for networking and collaboration, and discuss opportunities and challenges. This report provides an overview of the conference and the important ideas generated by experts in the field.

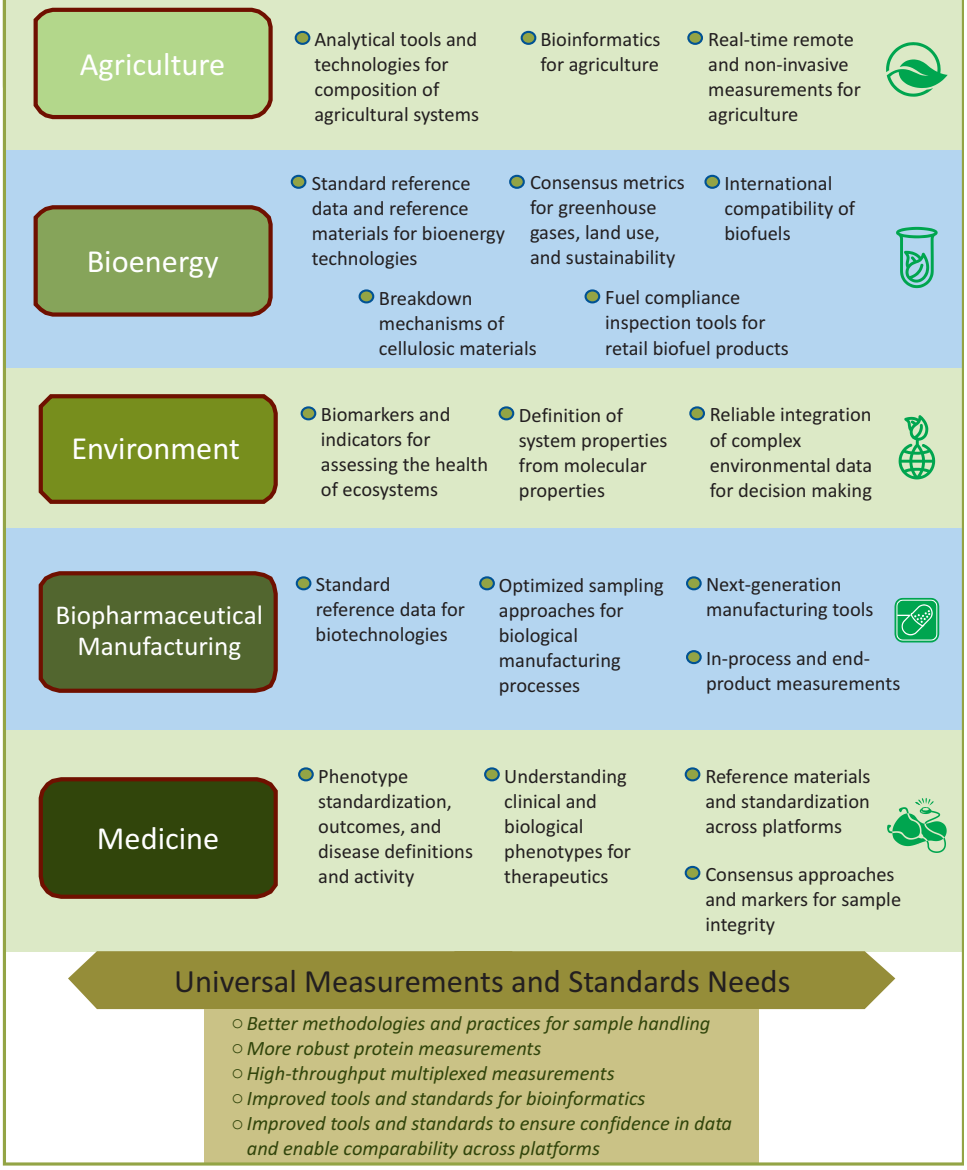
Priority Measurement and Standards Challenges

An important outcome of the conference is a prioritized list of challenges that can be used to guide future research at NIST and the measurement and standards community worldwide. These priorities are summarized in Exhibit E.2.

EXECUTIVE SUMMARY

Agriculture - ***Standards and standardized methods*** *are a priority, as they assure confidence and consistency in biological measurements of plant/animal systems and their ecological and environmental interactions. As markets continue to expand globally, international standards will be important to assure worldwide product acceptance.* ***Improved measurement methods*** *are also needed to achieve greater accuracy, speed of measurements and analysis, and real-time, remote capability. Innovative technologies are needed to measure complex biological system parameters, such as water in plants, structures of microbiota, and reversible interactions in living systems. Assimilation and dissemination of data and accessible* ***bioinformatics systems*** *are critical and remain a significant challenge.* ***Sustainable agriculture*** *will require consensus on how to measure sustainability and life-cycle impacts. Ensuring that sustainable practices are attractive to farmers and livestock operators, and communicating the true cost of sustainability, are both key challenges.*

Exhibit E.2 Priority Measurement and Standards Challenges for Biosciences



Bioenergy - Improved ***characterization methods*** *for various forms of biomass in terms of composition, reliability, quality, and enzyme activity, are needed, particularly for next-generation biofuels. Methods are also needed to monitor the characteristics of biomass in production and harvesting; during conversion processes; and in storage, transport, and delivery. The* ***standardization and sustainability of biofuels*** *is a global challenge that requires nations to work together. Standards are needed to establish the performance and sustainability of biofuels regardless of feedstock. Ensuring consistent measurements and standards across the biofuels supply chain requires an extensive network of measurement methods. While some exist, many others need to be developed, particularly for biomass production. On the production side, characterizing the breakdown mechanisms of and measuring the parameters relevant to the* ***recalcitrance of cellulosic biomass*** *are key challenges to unlocking the energy potential of non-food biomass resources such as perennial grasses, wood energy crops, and agricultural residues.*

Environment - Priority challenges for obtaining ***system properties*** involve defining the critical attributes of ecosystems, determining the measures of system health, and identifying the indicators that provide early warning of changes in ecosystem health that are important to sustaining human well-being. Standardized, validated methods for the development and use of ***biomarkers*** are currently lacking and are critical to effective early warning systems. Issues such as natural variability, specificity of biomarkers, and variability across environmental conditions impede standardization and need to be addressed. The major challenge to incorporating ***broad perspective variables*** (e.g., resource and land use, air and water transport, climate change) will depend on the effective integration of diverse data at different scales, from the molecular to systems level. Effective early warning systems will require an array of measurement technologies ranging from DNA probes to satellites, geographic information systems (GIS), and others. A greater understanding of the links between external drivers and ***stressors affecting ecosystem health, environmental exposures, and system-level responses*** is needed as a foundation for an environmental early warning system. This knowledge is impeded by the growing magnitude and diversity of toxins, chemicals, hazardous compounds, pathogens, diseases, and other stressors released into water, air, land, and living systems. New measurements and standards, including sampling methods, are required for toxins, microbial contaminants, pathogens, and many other threats to a healthy environment.

Biopharmaceutical Manufacturing - ***Controlling and monitoring biological manufacturing processes*** that work with living cells is difficult due to a high degree of uncertainty, both in processing and obtaining desired product attributes. The ability to make measurements in complex matrices in a process environment and ***obtain samples online and in-process*** remains a significant challenge. Without understanding the mechanisms behind product variability, obtaining the desired attributes becomes an iterative process. Finding simpler ways to mimic complex systems (e.g., immune system assay), more accurate bioassays, and measuring *in vivo* changes could improve pathways to reliable product attributes. ***Tools for measuring system parameters*** such as structural properties, aggregation, oxidation, and others, will ultimately pave the way for predictive biotechnology and product development. The high cost of measurement remains a significant impediment in today's biomanufacturing environment.

Medicine - Developing ***sampling standards and protocols*** for the proper processing, handling, and treatment of cells, tissues, and other biological samples is a high priority. Without standard methods, the result is questionable sample integrity, poor reproducibility of results, and difficulty in performing credible analysis. Definitions and ***standards for phenotype data*** are also critical; these are needed to help identify, characterize, and predict disease pathways, activity, and disease and treatment outcomes. ***Standardization of data and assays across biological platforms*** is a priority, but is hindered by the diversity of platforms and a lack of interoperability and comparability among platforms. There is a need for clear ***definition of reference points***, and improved traceability of measurements to reference points. ***Information exchange*** and ensuring consistency of information continues to be a major challenge.

Universal Ideas and Observations

The universal, crosscutting needs identified across all biosciences are:

- Better methodologies and practices for sample handling
- More robust protein measurements
- High-throughput multiplexed measurements
- Improved tools and standards for bioinformatics
- Improved tools and standards to ensure confidence in data and enable comparability across platforms

EXECUTIVE SUMMARY

Observations that emerged from the conference include the following:

- Improvements in the biosciences are key to global economic security and quality of life in the future
- A much deeper understanding of complex biological systems is needed
- Highly sophisticated measurements are needed in order to study the relevant changes that occur in complex biomolecular networks
- Major measurement challenges exist that are stifling innovation in the biosciences
- Current technology is inadequate due to a very limited measurement infrastructure that allows scientists to have confidence in only a very small percentage of the biomeasurements being conducted
- New multiplex, multiparametric measurement technologies must be invented and developed
- These new measurement systems will rely heavily on the accuracy and comparability of the data obtained from current technologies as a basis upon which to build the new systems
- Standardization of current measurement technologies will be needed to enable next-generation systems
- Standardization of next-generation biomeasurement systems that bridge historical and new data will be needed as new methods emerge

1.0 INTRODUCTION

Importance of Measurement to the Biosciences

The science of understanding how biological systems operate and interact with one another (the biosciences) is increasingly important to global prosperity and quality of life. As the world's population grows, so will the need for more efficient and sustainable ways to grow food, keep people healthy, produce energy, and manufacture biological drugs, therapeutics, and chemicals. These advances can only be realized by gaining a deeper understanding of how biological systems operate—an understanding that depends on advancing the state of the art in biosciences measurement.

Despite major breakthroughs and discoveries in recent years, our understanding of biological systems still faces many challenges. Biology is an informational science that depends on accurate measurements and standards. Whether quantifying the amount of protein in a cancer cell or the rate at which an organism converts sugar to alcohol, measurements are the foundation for improving our understanding of biological systems. Future progress depends on our ability to measure key features, including the complex interplay of thousands of biochemicals that control living systems.

Conference Overview

Given the importance of measurement to the biosciences, the National Institute of Standards and Technology (NIST) and the University of Maryland Biotechnology Institute (UMBI) co-hosted an international conference, *Accelerating Innovation in 21st Century Biosciences: Identifying the Measurement Standards and Technological Challenges*, on October 19-22, 2008, in Gaithersburg, Maryland. This landmark event drew attendance of leading bioscience professionals from all over the world.

Speakers from industry, government, and national metrology institutes as well as academic scholars and researchers from the biosciences arena presented and discussed global measurement, standards, and technology concerns for 21st century biosciences. The conference was a first-time opportunity to identify and discuss the global measurement and standards challenges to biosciences innovation in a number of important areas (see Exhibit 1.1). If left unresolved, these impediments could prevent the realization of the benefits of important new discoveries in the biosciences.

Exhibit 1.1 Conference Focus Areas

Agriculture - increasing yield, quality, and safety in the world's food supply

Bioenergy - obtaining sustainable energy from biological sources

Environment - understanding our planet through linking molecules to ecosystems

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Medicine - improving health through measurement of complex biological signatures

Hot Topics - unrecognized, overlooked, underestimated, and often ignored measurement needs in the biosciences, including

- Agriculture viability
- Antibiotic and antiviral drug resistance
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- Environmental bioterrorism monitoring
- Marine versus terrestrial sources of bioenergy
- Personalized medicine
- Stem cell therapy
- Synthetic biology

INTRODUCTION

The conference provided an excellent venue for participants to meet with bioscience practitioners from all over the world, share the views of international policy makers, network, collaborate, exchange technical information, and build international relationships. The design and content of the conference was developed by a dedicated Biosciences Steering and Organizing Committee comprised of stakeholders from different areas of the biosciences and measurement communities (see Exhibit 1.2). The committee worked together to develop a broad-based conference format that would encourage information exchange and allow for the free flow of ideas. The conference format included an international plenary symposium with roundtable discussions, followed by visionary topical speakers in the primary conference focus areas. Two days were then devoted to technical panel sessions to identify and prioritize the critical measurement and standards challenges to innovation in biosciences.

Exhibit 1.2 Conference Steering and Organizing Committee

Conference Co-Chairs

Willie E. May, National Institute of Standards and Technology (NIST)

Jennie Hunter-Cevera, University of Maryland Biotechnology Institute (UMBI)

Steering and Organizing Committee

Clare Allocca, NIST

Michael Amos, NIST

Jason Boehm, NIST

Judy Britz, Principal at Britz Consulting

Gary Brooker, Johns Hopkins University (JHU)

William Heetderks, National Institutes of Health (NIH)

Fred Holland, Hollings Marine Laboratory, National Oceanic and Atmospheric Administration (NOAA)

Craig Jackson, Consultant

Robert Kaarls, Secretary of International Committee for Weights and Measures (CIPM)

George Klee, Mayo Clinic

Helen Parkes, Laboratory of the Government Chemist, UK (LGC)

Jerry Parrott, Human Genome Sciences, Inc.

Terry Purkable, Applied Physics Lab (APL), JHU

Sara Radcliffe, Biotechnology Industry Organization (BIO)

Fred Razzaghi, Consultant

Theodore Roumel, UMBI

James Serum, Scitek Ventures

Tamas Torok, Lawrence Berkeley National Laboratory (LBNL)

Keith Webber, Food and Drug Administration (FDA)

Science Policy Roundtable

During the opening plenary session, a roundtable discussion was held to gain a global understanding of the challenges facing the biosciences and to exchange information on advances and opportunities. In a moderated format, forward-thinking leaders in different fields of the biosciences discussed their focus with respect to investments in biosciences and related policy. Roundtable participants are listed in Exhibit 1.3.

Exhibit 1.3
Science Policy Roundtable

Moderated by Mitch Waldrop, *Nature*

- Laurence Besley, Department of Innovation, Industry, Science and Research, Australia
- Chavonda Jacobs-Young, White House Office of Science and Technology Policy, USA
- Timothy Hall, Directorate General for Research, European Commission
- João Alziro Herz da Jornada, Department of Development, Industry and Exterior Commerce, Brazil

National Metrology Institutes Directors' Roundtable

Directors from National Metrology Institutes (NMIs) around the world responded to topic questions of interest to the biosciences community and discussed the unique challenges facing their countries. They gave a brief summary of the history of their institution and what they are currently working on in the biosciences, including funding levels for measurement and standards activities. Roundtable participants are listed in Exhibit 1.4.

Exhibit 1.4 National Metrology Institutes Directors' Roundtable

Moderated by Robert Kaarls, Secretary of CIPM

- Kwang Hwa Chung, Korea Research Institute of Standards and Science (KRISS), Korea
- Patrick Gallagher, NIST, USA
- Alejandro Herrero Molina, Joint Research Centre, Institute for Reference Materials and Measurements (JRC-IRMM), European Commission (EC)
- Anna Hills, National Physical Laboratory (NPL), UK
- James McLaren, National Research Council, Institute for National Measurement Standards (NRC- INMS), Canada
- Marc Pieksma, Nederlands Meetinstituut (NMi), The Netherlands

Plenary Topical Presentations

Following the roundtable discussions, leaders in each of the conference focus areas provided their views on the opportunities and challenges to innovation. Each plenary talk included a sector overview; importance of the area to society and the economy; the vision for the future, i.e., the future promise of biosciences and the industry; major technological impediments to innovation; and the impacts of failing to address challenges. Plenary speakers are shown in Exhibit 1.5. Presentations are available online at http://www.cstl.nist.gov/Bioscience%20Conference/Material.html

Exhibit 1.5
Plenary Symposium Speakers

Agriculture - Pamela Ronald and Raoul Adamchak, University of California at Davis, USA

Bioenergy - Anna Palmisano, U.S. Department of Energy (U.S. DOE), USA

Environment - Stephen Weisberg, Southern California Coastal Water Research Project Authority, USA

Biopharmaceutical Manufacturing - James Thomas, Amgen, USA

Medicine - Lee Hood, Institute for Systems Biology (ISB), USA

Technical Panels

Two days of the conference were devoted to technical panel sessions covering each of the conference focus areas. Each technical panel was co-chaired by a Steering Committee member and an outside subject matter expert (see Exhibit 1.6). The technical panel members were chosen based on their expertise in the field of interest and ability to provide a broad perspective on future challenges. A complete list of technical panel members is provided in Appendix B.

In the facilitated sessions for each focus area, panel members worked to identify and prioritize the measurement and standards challenges that significantly impede innovation. A series of questions was asked in each session, relevant to each focus topic, as follows:

- What are the characteristics and vision of the future?
- What are the broad challenges to achieving the vision?
- What do we need to measure to achieve the promise of biosciences, and why is it important?
- What are the measurement and standards challenges limiting the potential technological innovations?

The results of these discussions provide an excellent perspective on future potential and the challenges to be faced. A particularly important outcome is a prioritized list of challenges that could be used to guide future work at NIST and the measurement and standards community worldwide.

The hot topics session diverged from the facilitated format and included short talks from industry, government, and academic experts in strategically important bioscience areas. Following the presentations, participants were permitted to submit questions for discussion and response by the panel members. Presentations are available online at http://www.cstl.nist.gov/Bioscience%20Conference/Material.html.

Exhibit 1.6 Technical Panel Co-Leaders

Agriculture (1) Tamas Torok, Lawrence Berkeley National Laboratory; (2) Steven Britz, U.S. Department of Agriculture

Bioenergy (1) Terry Purkable, Johns Hopkins University Applied Physics Laboratory; (2) Hratch Semerjian, Council for Chemical Research

Environment (1) Fred Holland, Hollings Marine Laboratory; (2) Hendrik Emons, European Commission Joint Research Center Institute for Reference Materials and Measurements (EC-JRC-IRMM); (3) Kevin Summers, U.S. Environmental Protection Agency

Biopharmaceutical Manufacturing (1) Fred Razzaghi, Consultant; (2) William Koch, U.S. Pharmacopeia; (3) Larry Mahan, MD Department of Business and Economic Development

Medicine (1) Judy Britz, Britz Consulting; (2) Paul J. Utz, Stanford School of Medicine

Hot Topics (1) Jennie Hunter-Cevera, University of Maryland Biotechnology Institute; (2) Craig Jackson, Consultant

Organization of the Report

The remainder of this report is organized around the outcomes of the technical panel sessions for the five primary focus areas: agriculture, energy, environment, manufacturing, and medicine, as well as the hot topics section. To clarify that this report focuses on the biological aspects of these fields, in some cases the word "bio" is added to the titles of tables and charts (e.g., bioenergy, biomanufacturing).

Each of the following chapters summarizes the responses of the technical panel to the topical questions that were posed, including a vision of the future, broad technological and non-technological challenges, the role of measurement in technological innovation, the measurements and standards challenges, and priority measurement topics to guide future decision making.

The appendices provide supporting information for the conference, including sponsor profiles, a list of technical panel participants, and a compilation of the acronyms used throughout this report.

2.0 AGRICULTURE

As world population continues to increase, thousands of acres of arable land are lost to development each year. As a result, there is increased pressure on agriculture and aquaculture to provide affordable, safe, and nutritious foods. New and innovative technologies are being developed to improve crop productivity, enhance crop protection, and increase environmental stress tolerance to help meet growing demands on the agricultural/aquaculture industry. Developing and testing these technologies involves sophisticated measurements on complex biological systems, including plants, animals, and microorganisms.

Technical Panel on Agriculture

Increasing yield, quality, and safety in the world's food supply

Technical Panel Co-Leaders: (1) Tamas Torok, Lawrence Berkeley National Laboratory; (2) Steven Britz, U.S. Department of Agriculture

Plenary Speakers: Pamela Ronald and Raoul Adamchak, University of California, Davis

The agriculture technical panel and plenary focused on future opportunities and challenges facing this important sector of the biosciences. These discussions produced a potential vision of the future and the broad challenges to be addressed. An important outcome was identification and prioritization of the critical measurement and standards challenges to technology innovation in this field. Overcoming these challenges is critical to increasing the yield, quality, and safety of the world's food supply.

Vision of the Future

In the future, technological advances could lead to significant improvements in the way we grow, produce, and protect our food supply. These will affect more than just the quantity and quality of food supplied. Improvements will be achieved in the nutritional makeup of food (healthier and safer food), the sustainability of food systems (ecological, societal, and environmental), and the scientific ability to design foods that are personalized for individual consumption.

Exhibit 2.1 illustrates the concepts put forth to describe some of the future characteristics of agriculture and the food supply. These characteristics embody what could potentially be attained with continued and sustained progress in technological innovation.

Exhibit 2.1 Characteristics of the Vision of the Future for Agriculture

Technological Advances

- Systems are in place for more rapid plant breeding (predation-free and disease-free crops, moisture- and salt-resistant crops)
- Rapid, accurate, complete phytochemical composition analysis is possible, from farm to fork
- Genetically engineered (GE) agricultural products and crops are readily available
- Food is engineered for particular nutrients or profiles of nutrients; nutrient intakes are personalized based on genomics, proteomics, lipidomics, and metabolomics
- Multiparameter measurements in complex biological systems are possible
- Unmanned aerial vehicles (UAVs) with remote sensing of crop stressors have the ability to monitor potentially dangerous products
- Leaf pigments/protein: remote monitoring of photosynthetic capacity and nutrient limitation; precision agriculture; production capacity

Societal Aspects

- Technical advancements provide food for 10 billion people in 20, 30, 40 years
- By 2030, education is available to the public, including farmers and breeders, on the environmental, social, and economic impacts of sustainable agriculture
- Use of antibiotics in animal agriculture is significantly reduced or eliminated

Global Markets and Products

- Multi-country standards are in use
- Value of crops is based on compositional characteristics; agriculture becomes more than just a commodity market

Sustainability

- Efficient, safe nutrients and pesticides are used
- Real-time monitoring and modeling on the ecosystem scale is possible
- Crops are available to cope with climate change and rising emissions of CO_2
- Sustainable animal production systems are in use
- Social and environmental costs (economic, other) of production are considered in design and operation of agricultural systems
- Solar energy is used as an energy resource for farm systems
- Carbohydrate profile, structural (i.e., fiber) and non-structural: important to defining nutritionally available energy in human foods and animals feeds; important to biofuel applications

Broad Challenges

The broad technological challenges identified for agriculture are shown in Exhibit 2.2. These illustrate the importance of better understanding the biology of plants and animals, their interactions with the environment, and their value as sources of food. To improve the quality of the food supply, clarification and consensus is needed on the constituents that are most nutritious and valuable to human health. Other challenges arise in expanding the food supply through aquaculture, which will require a much greater understanding and control of aquatic resources. Promoting a sustainable food supply is a key thread throughout. Future challenges arise in the use of fertilizers, pesticides, and water resources, as well as reducing the carbon footprint and other impacts on air, land, and water.

Exhibit 2.2 Broad Technological Challenges for Agriculture

Understanding Plants and Their Environments	
HIGH PRIORITY	▪ Bioinformatics bottlenecks (communication, controlling vocabulary, data integration, storage analysis, and access to information) ▪ Insufficient knowledge of plant biology and ecosystems at the molecular level ▪ Inefficient water use
MEDIUM PRIORITY	▪ Need to increase "effective" yield: move from valuing mass to target components (how to measure effective yield) ▪ Dynamic, non-invasive, *in situ* measurements capable of detecting/monitoring reversible, temporal, and spatial interactions ➤ Unintended consequences of GE food or increased yield, such as food safety issues (toxins and microbes) ▪ Establishing "best" targets for plant breeders to focus on
Understanding Animals and Their Environments	
MEDIUM PRIORITY	▪ Improved status of animal production efficiency, health, and environmental impact ▪ Replacing antibiotics and antimicrobials in animal feed
Post Harvest (Identity Preservation)	
MEDIUM PRIORITY	▪ Packaging food in safer ways (fewer contaminants such as heavy metals and toxins)
Improved Nutritional Quality	
HIGH PRIORITY	▪ Lack of agreement on valuable nutrients (beyond proteins, carbohydrates, fats, vitamins)
MEDIUM PRIORITY	▪ Improved methods for measuring phytochemical composition ▪ Need to clarify and agree on meat and egg nutritional quality ➤ Essential fatty acid (EFA) status altered by limited food intake
Expanded Aquaculture Capabilities	
MEDIUM PRIORITY	▪ Improvement of fish nutrition and disease control ▪ Need to develop algae that satisfy nutrient needs while minimizing water, soil effects (i.e., fewer pesticides, minimized environmental damage) ▪ Accounting for problems with invasive species
Sustainability	
HIGH PRIORITY	▪ Enabling and encouraging precision agricultural practices ▪ Lack of comprehensive monitoring and modeling: water and agricultural chemistry ▪ Need to reduce the carbon footprint of agriculture
MEDIUM PRIORITY	▪ Better understanding of diseases for the development of "selective" pesticides ▪ Need to quantify "local" hydrology (atmosphere, surface, subsurface) ▪ Addressing air quality associated with animal production facilities

Exhibit 2.3 illustrates the broad non-technological challenges that can impede technological advances to improve the food supply. Appropriate policies, incentives, standards, and regulation can help accelerate and encourage technological advances as appropriate.

Communication to promote dissemination of accurate information to the public is a broad challenge that must be addressed. A better understanding of land allocation (and the various benefits and disadvantages) is a key aspect. Consumers need to be better informed about what constitutes a healthy diet, the risks associated with the food supply, and future challenges.

Education is an important element. To expand and continue rapid breeding programs, for example, will require rebuilding the plant breeding work force. Due to breakthroughs in nanotechnology and other areas, agriculture and food are increasingly multi-disciplinary and will require greater input from disciplines not traditionally involved in this field.

Exhibit 2.3 Broad Non-Technological Challenges for Agriculture

Policies/Regulations	

HIGH PRIORITY	▪ Policies needed for rapid plant and animal breeding:
	  ► Smart regulation
	  ► Consistent international policies
	  ► Government incentives to reduce cost
	▪ Clarify/identify appropriate standards

MEDIUM PRIORITY	▪ Addressing identified concerns about achieving national food security ▪ Internalizing environmental costs
Communication	
MEDIUM PRIORITY	▪ Lack of public participation in allocating land ► Competing considerations for food, energy, "nature", living space ▪ Public perception of risk ▪ Need for improved diet education ▪ Increasing population and its implications ▪ Inability of consumers to make fully informed decisions about food consumption ▪ Inadequate education and information about products
Education	
MEDIUM PRIORITY	▪ Need to rebuild plant breeding work force ▪ Multi-disciplinary educational requirements for new technology

Role of Measurement

Measurements and standards play a key role in the agricultural sector, from plant genetics to production and harvest. Exhibit 2.4 illustrates the measurement parameters of interest and why they are important to better understanding and improving agricultural systems.

Exhibit 2.4 Key Measurements to Support Technological Innovation in Agriculture

Understanding Plants and Their Environment

- *Gene expression*: important part of expanding necessary information on biological systems
- *Stomatal conductance*: supports primary production and remote monitoring of photosynthesis and water supply
- *Genome plus environment, which equates to phenotype*: relation between plant and environment, to predict plant response and pathogen geography (timely, effective, efficient treatment)
- *Photosynthetic partitioning and yield, genetics, CO_2, environment*: biotic/abiotic stress
- *Microbial community structure/activities*: space and time, intimate part of plant environment, safety
- *Environmental microbial baseline*: finding human pathogens among background microbiota
- *Reversible short-time interactions of living systems (massively parallel)*: understand multi-tasking
- *Remote sensing*: sensors for quantifying specific stressors (nutrient, disease, weeds, etc.); ecosystem health assessment larger-scale linkage
- *Leaf pigments/protein*: remote monitoring of photosynthetic capacity and nutrient limitation; precision agriculture; production capacity

Understanding Animals and Their Environment

- *Fertility and reproduction in animals*: improved food supply
- *Antibiotic resistance*: safety and health of animals

Post Harvest (Identity Preservation)

- *GE protein in food*: analysis of food components
- *Standardized database of food components (baseline, seasonal, geography)*: compare GE and traditional plants
- *Toxicity of biomaterial*: ensure food safety
- *Microbiota*: interactions between food-borne microbes and consumer
- *Traceability of food, with rapid track back to origin of problems*: food safety, quality
- *Rapid mycotoxin analysis*: critical to food safety

Improved Nutritional Quality

- *Phytochemical composition in foodstuffs*: relation to genetics, environmental impacts
- *Effects of phytochemicals on humans*: impacts on cells, organisms
- *Lipid composition*: fats and oils are approximately 1/3 of energy intake; nutritional quality/absorption is related to lipid class and fatty acid content
- *Amino acid profile rapid analysis*: building blocks of protein critical to growth and therefore important to formulating animal production feeds
- *Seed composition*: more details will enhance crop quality
- *Blood proteins for efficacy*: what's good/bad, most non-invasive, multiple proteins
- *Natural antioxidants*: foods contain a host of antioxidants important for food stability; many are undefined, qualitative analysis is needed
- *Carbohydrate profile, structural (i.e., fiber) and non-structural*: important to defining nutritionally available energy in human foods and animal feeds; important to biofuel applications

Expanded Aquaculture Capabilities

- *Metagenomics of water environment*: proteomics
- *Environmental sensitivities*: viability of aquaculture

Exhibit 2.5 illustrates some of the measurements that are important to sustainable agriculture and particularly to reducing or mitigating pollution from farms. In general, this area was recognized as a high priority for measurements. Sustainability is becoming a key challenge as the industry looks to increase yields, quality, and nutrients without increasing environmental and other detrimental impacts.

Measurement also plays a role in policy and regulation. For example, to assure the biosafety and acceptance of GE crops, relevant functional assays are needed to support regulation. The challenges to accomplishing this are very complex.

Measurement is also essential to communication of information about the food supply to the public. Confidence in food-related measurement helps assuage public concerns about food safety and enables consumers to make well-informed decisions.

Exhibit 2.5 Key Measurements to Support Sustainability in Agriculture

Mitigating Environmental Impacts from Farms

- *Sustainability measurements*: recognition of good practices in the marketplace and promotion of sustainable practices
- *Carbon and greenhouse gas (GHG) emissions associated with organic and conventional production practices*: accessible database for carbon offsets
- *Preferential fluid dynamics*: although active only a fraction of the time, this process is responsible for up to 90% of pesticides reaching ground water
- *Rapid analysis of phytate phosphorous*: animal nutrition and environmental effects
- *Fast analysis of potential human pathogens in waste used for fertilizer or compost*: safety of raw produce
- *Manure nutrient profile*: animal waste profiles and environmental impacts
- *Animal feed conversion ratio*: improved precision of feed formulations (less waste)

Land Use and Soil Sustainability

- *Indirect land use change*: assessment of environmental/societal/economic externalities
- *Degraded land*: identification of where and how improved land use is possible
- *Rapid soil nutrient analysis*: soil nutrient mapping and fertilizer application as part of a precision agriculture system
- *Soil-water dynamics (surface and subsurface hydrology)*: water drives plant growth and chemical transport and behavior

Measurements and Standards Challenges

The key challenges related to measurements and standards for agriculture are illustrated in Exhibit 2.6. While these are not comprehensive lists of the measurement needs facing agriculture, they provide a starting point for some of the key challenges from a biosciences perspective.

Standards and Standardized Methods. A central theme is assuring confidence and consistency in biological measurements of plant/animal systems and their ecological and environmental interactions. Consensus among users of measurements and analytical tools is a critical aspect. Current methodologies have considerable variability and inconsistency among laboratories and within the user community. As the global aspects of markets continue to increase, international standards will be important to assure worldwide product acceptance and understanding of key parameters.

Exhibit 2.6 Measurement and Standards Challenges for Agriculture

Standards and Standardized Methods	
HIGH PRIORITY	▪ Better sampling methods and sample processing methods robust enough for complex samples (environmental, food, animal) ▪ Reference materials for field testing devices ▪ Acceptance of standard method, if developed, by those using independent or in-house methods ▪ International standards for compounds: protein, microbe analysis (threshold, standard method)
MEDIUM PRIORITY	▪ Resolution of analytical variation (actual lab-to-lab and within a lab), with practical value ▪ Achieving consensus among those who use analytical tools and make decisions based on the values ▪ Lack of knowledge of where to "sense" an agricultural environment (where to sample and reflect environmental risk)
Technological Improvements to Measurements/Methods	
HIGH PRIORITY	▪ Fertility tests and standards, with knowledge transfer to industry to improve animal and plant science ▪ "Shotgun" lipidomics as a quantitative tool ▸ Requires an array of stable-isotope labeled standards for various lipid class, molecular species ▪ Ineffective existing methods for chemical composition—time consuming and often require extraction, which may generate errors ▪ Methods to assess carbon flux in plants—real-time (e.g., carbon-11) ▪ High-throughput molecular breeding technology ▪ Classification and enumeration of high-complexity microbial communities
MEDIUM PRIORITY	▪ Remote estimates of soil moisture/chemistry are too uncertain to use for optimizing irrigation ▪ Prion screening ▪ Identification and classification of microorganisms; species concept and lateral gene transfer ▪ Robust remote quantitative sensor for canopy photosynthetic capacity (not normalized difference vegetation index [NDVI]) to identify stress ▪ Quantified uncertainty and representative measurements that monitor the environment (soil water dynamics, flow processes, etc.) ▪ Detection of multiple proteins in complex mixtures (cheap, rapid, sensitive) ▪ High-throughput fatty acid analysis including robotic derivatization (transmethylation), columns/methods for ultra-fast gas chromatography (GC) analysis, and software for automated data analysis
Measurement Innovation	
HIGH PRIORITY	▪ Remote quantitative sensor for plant water status ▪ Nanotechnology devices for rapid detection (field devices)
MEDIUM PRIORITY	▪ *In vivo*, real-time measurements in an intact system ▪ Measurement of reversible interactions in multi-tasking living systems ▪ Measurement of microbiota structure and function ▪ Quantification of subsoil stratigraphy

Exhibit 2.6 Measurement and Standards Challenges (cont.)

Sustainable Agriculture	
HIGH PRIORITY	▪ Identification of minimal metadata collection requirements ▪ Understanding cost of sustainability: time, capital vs. value realized, economic/commercial value, social value ▪ Promoting sustainable agricultural applications: ► Ease of use ► Level of required training ► Repeatability
MEDIUM PRIORITY	▪ Complexities of measurements for carbon footprint ▪ Limited accessibility of remote sensing data from federal and military sources ▪ Lack of agreement/establishment of variables to include in life-cycle analysis (LCA) and sustainability assessment

Technological Improvements to Measurement Methods. Primary challenges appear to be the need for greater accuracy, broader capabilities, speed of measurements and analysis, and the ability to take measurements both in real time and remotely. Improvements to measurement methods could provide new insights on plant and animal breeding, the value and use of lipids and fats, and the complexities of microbial communities. Enhanced monitoring of the environmental interactions among plant and animal systems could increase the capability to identify stresses on the environment and produce new knowledge to enhance plant and animal science and engineering.

Measurement Innovation. The complexity of the biological systems involved creates a unique challenge that will require innovation in measurement methods, particularly for measuring water in plants, structures of microbiota, and reversible interactions occurring among living systems. New technologies such as nanotechnology could potentially be applied to develop new measurement methods that may help answer some of the key questions pertaining to plant and animal systems.

Sustainable Agriculture. Exhibit 2.7 illustrates some of the key measurement challenges related to developing and promoting the use of sustainable agricultural practices. One of the major challenges is identifying and coming to consensus on the minimal set of data that is needed to define and monitor sustainability, as well as to examine the life-cycle impacts. There are also significant challenges in understanding and communicating the true costs of sustainability (as well as non-sustainability), and ensuring that sustainable practices are practical for farmers and livestock operators. This means sustainable practices must be easy to implement and use, require a low level of training, and give reproducible results.

Priority Measurement Topics

The measurement challenges illustrated in Exhibit 2.6 provide the foundation for a set of three priority measurement focus areas for agriculture that aim to address these challenges. Collectively, panel members determined: the importance of the focus area, objectives in addressing it, a potential approach, and stakeholder roles. They also rated the technological and commercial risks and the impacts of action in five categories. Their findings are reflected in Exhibits 2.7–2.9.

These focus areas address some of the most critical challenges that have been identified for agriculture. Many focus on improved data processing and analysis, making accurate measurement and information accessibility essential to overcoming these challenges. The priorities also reflect a need for new measurement technologies and standards to support a new level of quality and functionality in next-generation agriculture.

Exhibit 2.7 Priority Measurement Topic

Analytical Tools and Technologies for Composition of Agricultural Systems

PRIORITY MEASUREMENT AND STANDARDS CHALLENGE

Adequate analytical tools and technologies are not available for effectively and accurately measuring chemical and biochemical composition in plants, animals, soils, water, and waste streams.

RATIONALE

- Improved food quality and safety
- Improved and efficient utilization of resources
- Assurance of public confidence in food supply and agriculture

OBJECTIVES

- Robust tools for composition measurement
  - Increased capability for metabolomics, proteomics, etc.
  - Increased speed, sensitivity, specificity, and ease of use
  - Decreased cost and size
- Clearly defined standards for public health
- Accessible information for all stakeholders

ELEMENTS OF APPROACH

- Encourage joint or collaborative efforts of laboratories
- Involve multiple government agencies and state agricultural groups

STAKEHOLDERS AND ROLES

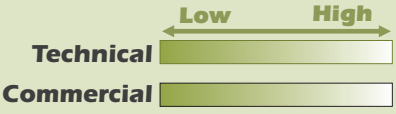
Government: USDA and NIST in a leadership role; EPA and FDA in supporting roles

National laboratories: National laboratories as appropriate

Industry: Consumer and producer stakeholder groups

Other: State and regional agricultural groups

RISK



The cost of improving analytical technologies may be high, but the long-term payoff will be positive.

RELATIVE IMPACTS

Accelerates innovation	***	New instrumentation and data analysis
Enhances competitiveness	***	Improved markets
Provides societal benefits	***	Improved food safety and quality
Supports environmental protection	***	Increased detection of contaminants
Preserves/enhances energy security	**	Potential improvements to bioenergy crops

*** (High)

Exhibit 2.8 Priority Measurement Topic

Bioinformatics for Agriculture

PRIORITY MEASUREMENT AND STANDARDS CHALLENGE

Management of data generation, handling, processing, and dissemination is not effective enough to maximize the benefit of bioinformatics.

RATIONALE

- Bioinformatics are the foundation for biology-based technology innovation
- Better computational tools are essential to cope with the complexity of data analysis, management, representation, and visualization

OBJECTIVES

- Rapid and accurate analysis of data
- Integration of data into relational models that answer biological questions with high confidence
- Enhanced data-sharing capacity

ELEMENTS OF APPROACH

- Encourage joint or collaborative efforts by laboratories
- Involve multiple government agencies and state agricultural groups

STAKEHOLDERS AND ROLES

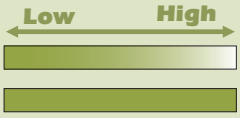
Government: USDA, NIST

National laboratories: As appropriate

Academia: Development of tools

Industry: Data inputs

RISK



Complexity of data handling and coordination among many users creates high commercial risk.

RELATIVE IMPACTS

Accelerates innovation	***	Allows for modeling, validation, and testing; describes system inter-relationships
Enhances competitiveness	***	Faster, confident data analysis supports accurate models and rapid innovation
Provides societal benefits	***	Improved food supply for global populations
Supports environmental protection	***	Decreased environmental impact, optimized agricultural activities
Preserves/enhances energy security	**	Optimized energy use and resources

*** (High)

Exhibit 2.9 Priority Measurement Topic

Real-Time Remote and Non-Invasive Measurements for Agriculture

PRIORITY MEASUREMENT AND STANDARDS CHALLENGE

Real-time technologies are not adequate for the remote/non-invasive measurement of required state variables for agriculture.

RATIONALE

- Improved resource use efficiency
- Reduced biotic stress
- Environmental protection
- Improved productivity/cost efficiency

OBJECTIVES

- Sensors for water and nutrient status, weeds, pathogens, pests, temperature, pesticide volatilization, and air quality
- Data processing systems for raw data
- Data processing systems for analysis and decision making

ELEMENTS OF APPROACH

- Encourage joint or collaborative efforts of laboratories
- Involve multiple government agencies and state agricultural groups

STAKEHOLDERS AND ROLES

Government: USDA research centers, NIST

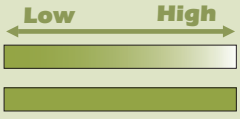
National laboratories: As appropriate

Academia: Data collection and testing

Industry: Technology development, validation

Private research institutes: Data validation

RISK



Time and cost associated with new technology development creates high risk.

RELATIVE IMPACTS

Accelerates innovation	***	New technology developed
Enhances competitiveness	***	Increased quality and productivity and reduce cost
Provides societal benefits	***	Reduced unneeded inputs, pollution, run-off
Supports environmental protection	***	See above
Preserves/enhances energy security	**	Increased biomass of energy crops

*** (High)

3.0 BIOENERGY

Recent scientific scenarios and possible contributions to rising food prices have raised some questions about the sustainability of first-generation biofuels produced from food crops (e.g., corn-based ethanol) or using resources (land and water) necessary for growing food for humans and farm animals. The production of alternative fuels from renewable, non-food biological feedstocks, therefore remains an important component of any future alternative energy strategy, and offers potential for addressing greenhouse gas (GHG) emissions. Biodiesel produced from oil-rich algae or the recombinant or synthetic biology-based production of next-generation biofuels are examples of more sustainable sources of bioenergy currently under development. Measurements and standards are a critical aspect of biofuels at every stage of development, from basic research in plant science and genetics, to the distribution and delivery of biofuels to consumers.

Technical Panel on Bioenergy

Obtaining sustainable energy from biological sources

Technical Panel Co-Leaders: (1) Terry Purkable, Johns Hopkins University Applied Physics Laboratory; (2) Hratch Semerjian, Council for Chemical Research

Plenary Speakers: Anna Palmisano, U.S. Department of Energy

The energy technical panel and plenary focused on future opportunities and challenges for sustainable production of non-food-based biofuels. Group discussions produced a potential vision of the future and the broad challenges to be addressed. They then identified and prioritized the critical measurement and standards challenges to the development and use of next-generation biofuels. Overcoming these challenges will be critical to establishing and maintaining the feedstock production, conversion, and delivery infrastructure needed to ensure that renewable biomass is a viable energy supply option.

Vision of the Future

It is expected that bioenergy, and particularly biofuels, will increasingly become an established part of the energy infrastructure. While today most biofuels are made from corn (ethanol) and soy beans (biodiesel), next-generation biofuels produced from non-food sources will dominate in the future. While biofuels will not be the only alternative transportation energy option, they will be an important component along with electric vehicles, hydrogen fuel-cell vehicles, and others.

Exhibit 3.1 illustrates the concepts and characteristics of the vision of the future for biofuels. Attaining this vision will depend highly on the development and deployment of new biochemical and thermochemical technologies to convert non-food biomass resources (e.g., cellulosic biomass, algae) into viable fuels, chemicals, and materials. It is envisioned that integrated biorefineries of the future will routinely produce a wide slate of products from a diversity of feedstocks such as perennial grasses, woody energy crops, agricultural and forestry residues, and even industrial and consumer wastes.

Exhibit 3.1 Characteristics of the Vision of the Future for Bioenergy

Energy Security and Infrastructure

- A significant portion of transportation fuels are derived from sustainable, domestically produced biofuels
- 75% of fossil fuels are replaced with bio-based sources via a variety of fuels and blends
- Biofuels provide a significant source of clean, long-distance, and heavy-duty transportation fuels
- A robust national infrastructure promotes expanded use of biofuels (and flex-fuel engines)

Technological Advances

- Engines have been modified to make better use of biofuels
- Oil/hydrocarbons are produced directly from plants
- Direct conversion of sunlight to bio-based energy is possible (e.g., via genetic engineering)
- Biocatalysis provides new routes to chemicals
- Integrated biorefineries use proven biochemical and thermochemical technologies and diverse feedstocks to produce a variety of products

Global Market and Products

- Advances in biomanufacturing and co-products create new markets and products
- Enzymes and bacteria for biochemical production of biofuels are traded as commodities; clear standards and certified reference materials (CRMs) are available to assess organism potency for production of biofuels
- Global biodiesel/ethanol standards independent of feedstock are in use
- Global production and use of liquid biofuels from optimized bio-refineries increase, and such refineries are responsive to regionally appropriate standards
- The cost of energy from renewable biomass is less than the cost of energy from oil and coal
- National laws on fuel quality and testing assure marketability

Societal Aspects

- Long-term public commitment to biofuels beyond economics is a primary driver of development and deployment
- Consumers have a wider choice of economic transportation fuels

Sustainability

- Life-cycle analyses are available for expanded uses and types of biofuels
- Bioenergy is integrated with other sectors (e.g., buildings) on a local basis to improve sustainability (e.g., lawn clippings into fuel)

Broad Challenges

The broad challenges identified for biofuels are shown in Exhibit 3.2. The most critical challenges relate to technology development, specifically solving the recalcitrance problems of cellulosic biomass. Effective, economical pretreatment and conversion technologies, both biochemical and thermochemical, will be needed to successfully use non-food biomass such as perennial grasses, crop residues, and wood.

Exhibit 3.2 Broad Technological Challenges for Bioenergy

Technology Development	
HIGH PRIORITY	▪ Economical conversion technologies (enzymes, gasification, products) for processing cellulosic biomass ▪ Better catalysts for cellulosic biofuels ▪ Genetic engineering for more efficient production ▪ Catalysts for chemical production from biomass residues ▪ Optimized, integrated biorefining systems
MEDIUM PRIORITY	▪ New biology for more efficient use of solar energy and acreage (microbes and algae)
LOWER PRIORITY	▪ Addressing the energy-water nexus (water and biomass sources, biorefining) ▪ Optimizing energy inputs into process (e.g., fertilizer, process heat) ▪ Efficient separation technology for end products
Feedstock Production, Storage and Transport	
MEDIUM PRIORITY	▪ Land use—optimizing fuel/acre efficiency ▪ Multi-feedstock plants
LOWER PRIORITY	▪ Assurance of feedstock supply and storage
Distribution and Delivery Infrastructure	
HIGH PRIORITY	▪ Infrastructure to deploy biofuels (transporting, storing, blending, dispensing)
MEDIUM PRIORITY	▪ Fleet availability (engine development)
LOWER PRIORITY	▪ Standards and regulations (logistics) ▪ Optimization of infrastructure, i.e., supplies, production, distribution, and utilization; including byproducts
Methods and Standards Infrastructure	
MEDIUM PRIORITY	▪ Local production/utilization, transport costs, point-source pollution ▪ Global standards addressing regional and other barriers ▪ Need for rapid, precise, and inexpensive methods and certified reference materials
LOWER PRIORITY	▪ Harmonization of standards for different feedstocks
Sustainability	
HIGH PRIORITY	▪ Sustainability of bio-feedstocks, from dirt to delivery ▪ Robust LCA methodology to enable fair comparison with oil, agriculture, and cattle
MEDIUM PRIORITY	▪ Defining and measuring sustainability across all relevant areas ▪ Yield sustainability—biomass replacement, water use, other resources ▪ Effects of urbanization on farmland and other indirect impacts on land ▪ Limits of recyclability of materials on manufacturing options for bioproducts

Distribution and delivery infrastructure also presents a critical issue, particularly as the volume of biofuels begins to increase. The current infrastructure needs to be expanded and improved to handle large volumes of next-generation biofuels. The infrastructure for transporting and storing biomass feedstocks is also insufficient and needs to be upgraded. Standards are needed both upstream to identify the quality and specifications of perishable biomass feedstocks from production through transport and storage, and downstream to specify fuel quality from the plant gate to vehicle use.

Exhibit 3.3 illustrates the broad non-technological challenges to achieving the promise of next-generation biofuels. Public perception is a key issue; strong science and education are needed to increase public understanding and dispel misperceptions about biofuels. Market push and pull continue to be a challenge for biofuels. Next-generation biofuels based on non-food biomass are not cost effective given today's technology, and capital and operating costs are high. Price-enabled products are needed to trigger demand and ensure continued investments from the commercial sector. Loan guarantees and other incentives may help to push biofuels forward until new technology becomes more mature.

For the industry to become established, stable development infrastructure must be created and sustained over the long term. The presence of a stable, educated workforce; funding to support long-term R&D as well as near-term demonstration projects; and coordination of information and other efforts at the federal, state, and local levels are all important elements of the needed infrastructure.

Even though substantial investments have already been made, continued investment by the public and private sectors will be needed to move next-generation technologies into the marketplace. While cellulosic ethanol technologies are on the immediate horizon, there will be a significant lag between construction and operation of the first-generation plants and optimized operation of integrated biorefineries.

Exhibit 3.3 Broad Non-Technological Challenges for Bioenergy

Public Acceptance	
HIGH PRIORITY	▪ Improvement of public awareness of key issues through strong science
MEDIUM PRIORITY	▪ Distribution of the correct message to a wide audience via multimedia
Economics	
HIGH PRIORITY	▪ Price-enabled products (trigger demand and sustain interest and production)
MEDIUM PRIORITY	▪ Large up-front capital costs ▪ Uncertainties in the price of oil and other economic factors (economic growth, commodities markets, cost of raw materials and resources)
LOWER PRIORITY	▪ Identification of value-added components in feedstock and process
Development Infrastructure	
HIGH PRIORITY	▪ Basic infrastructure (stable workforce, adequate funding, coordination)
MEDIUM PRIORITY	▪ Educated workforce (scientists, engineers, multi-disciplinary researchers)
Public and Private Investment	
HIGH PRIORITY	▪ Long-term commitment to biofuels and funding for technology and infrastructure ▪ Long-term public and private commitment and funding for R&D and next-generation technologies
MEDIUM PRIORITY	▪ Stronger national coordination of effort ▪ Economic incentives for farmers and technology originators

Role of Measurement

Measurements and standards are vital to development and deployment of next-generation biofuels on a large scale. As illustrated in Exhibit 3.4, metrology is needed to support all aspects of the supply chain, from feedstock production and harvesting, to biomass conversion processes and eventual consumer use in vehicles.

Exhibit 3.4 Key Measurements to Support Technological Innovation in Bioenergy

Sustainability

- *Input variables that comprise sustainability*: land/water, infrastructure, demand, costs
- *Consensus on sustainability and GHGs from land use*: methods and standards for all alternate inputs related to current production and future production required by renewable fuel standards (RFS)
- *Sustainability of biomass resources*: available biomass resources compared to traditional sources they replace
- *Land use carbon and change*: land use change parameters will be important to land use class (LUC) values

Finished Fuel Properties

- *Characterization of biofuels/material interactions*: corrosion, surface friction
  - Inexpensive and accurate methods to work in the field, and assurance of biofuels quality, especially ethanol and biodiesel, at customer levels
  - Internationally accepted standards, certified reference materials, and methods to facilitate use in global market are fundamental for robust use
- *Renewable content*: retail enforcement of mandates, regulations
- *Toxicity of byproducts and biofuels*: impacts on health and safety
- *Characterization of combustion products*: characterization of next-generation biofuel engines

Thermochemical and Physical Properties

- *Feedstock and fuel properties*: critical to quality control
- *Properties of critical substances and reactions*: alcohol, structure, thermodynamics, reaction kinetics and transport properties (equilibrium constants), enzyme activity; certified reference materials and analytical methods, standard reference data
  - Enables process design and process optimization; measurement/monitoring of process variables; supports computation and modeling
- *Fundamental thermophysical properties*: heat of combustion, vapor pressure, vapor-liquid equilibrium (VLE), liquid-liquid equilibrium (LLE), and viscosity to enable rational design and optimization
- *Energy efficiency*: energy inputs, process energy, energy outputs to enable technology comparison

Process Monitoring

- *Feedstocks characteristics*: impact of feedstocks on processes
- *Chemical composition of feedstocks*: enable process parameter modification/feedback in biorefineries
- *Online/automated analysis of complex process streams*: better control, optimization, ultimately higher yield, efficiency, and profit
- *Online chemical composition of bioproduct and co-products*: enable tight quality control
- *Conversion of biomass to sugar*: better understanding of a critical process step, assessment of phases
- *Metabolic "traffic monitor" in organisms*: understand mechanisms of industrial organisms
- *Quality assurance*: new measurement methods, procedures, and CRMs to support high quality in biofuels production, especially second-generation enzymes
- *Remote sensing of crop readiness and water use*: enable large-scale production planning

Measurement and Standards Challenges

The key challenges related to measurements and standards for bioenergy are illustrated in Exhibit 3.5. These are not intended to be all-inclusive of the measurement needs that must be addressed for bioenergy. However, they provide a starting point for identifying some of the key challenges facing the emerging biofuels industry.

Exhibit 3.5 Measurement and Standards Challenges for Bioenergy

Analytical Measurements	
HIGH PRIORITY	▪ Characterization of various forms of biomass and fundamental biochemical substances (e.g., xylose, cellulose) ▪ Fast test methods and devices for field enforcement; faster, simpler, cheaper field techniques to measure product characteristics ▪ Lack of understanding and inadequate measurement of future biofuels (e.g., biodiesel, other next-generation fuels)
MEDIUM PRIORITY	▪ Carbon dating to identify renewable fraction of biofuels ▪ Robust, sound methods for monitoring production of next-generation biofuels, especially enzymatic processes ▪ Method to determine origin of biofuels (e.g., feedstock source) ▪ Difficulty in testing toxicity in humans
LOWER PRIORITY	▪ Lack of measurement technology to address thermal instability of long-chain compounds
Documentary Standards	
HIGH PRIORITY	▪ Standards based on performance measurements that are independent of feedstock ▪ Consensus metrics for greenhouse gases, definition of sustainability of biofuels production
MEDIUM PRIORITY	▪ Standards to enable stable, quantifiable fluorescence (biomarkers, microarray, gene chip) for online sampling/monitoring ▪ Standardization of highly complex feedstocks (e.g., oils composed of many types of triglycerides)
Harmonization of Measurements and Standards	
HIGH PRIORITY	▪ Extensive infrastructure of measurements and associated techniques: reference materials, cheap field methods; accredited laboratories; certification schemes ▪ Harmonized test methods and units between countries to enable comparison of results
MEDIUM PRIORITY	▪ International harmonization of measurements of key parameters; involvement of national metrology institutes for CRM, protocols, and sustainability measurements ▪ Preemptive federal laws covering various biofuels metrics
LOWER PRIORITY	▪ Alignment of state/local standards with national standards

Analytical Measurements. *There is an immediate need to improve characterization methods for various forms of biomass in terms of composition, reliability, quality, and enzyme activity, particularly for next-generation biofuels. Methods are needed to monitor the characteristics of biomass in production and harvesting; during conversion processes; and after storage, transport, and delivery. In the long term, it would be desirable to be able to understand and monitor issues related to toxicity, reliably identify the renewable fraction of a biofuel in situ, and identify the originating feedstock.*

Documentary Standards. *Standards are needed to establish the performance and sustainability of biofuels, regardless of the type of feedstock used. Sustainability is an issue that should be addressed in the near term, particularly by defining sustainability parameters. Defining sustainability for both the biofuels already in the marketplace and next-generation biofuels continues to be a challenge worldwide. The standardization of highly complex mixtures, such as oils containing a variety of triglycerides, is problematic because of the many combinations possible, although this could potentially be addressed via development of standards using surrogate mixtures.*

Harmonization of Measurements and Standards. *Ensuring consistent measurements and standards across the biofuels supply chain requires an extensive network of measurement methods and techniques. While portions of this network are already in place, new components will need to be developed, particularly for biomass production and quality assurance. The measurement infrastructure also needs to accommodate next-generation biofuels as they begin to enter the market. With the global market for biofuels steadily increasing, a high priority is to establish a measurement and standards framework and infrastructure that are harmonious across nations. This will ensure that the United States can potentially export and import biofuels and bioproducts as well as biomass feedstocks.*

Priority Measurement Topics

The measurement challenges illustrated in Exhibit 3.5 provide the foundation for a set of five priority measurement focus areas for bioenergy that aim to address these challenges. Collectively, panel members determined: the importance of the focus area, objectives in addressing it, a potential approach, and stakeholder roles. They also rated the technological and commercial risks and the impacts of action in five categories. Their findings are reflected in Exhibits 3.6–3.10.

These focus areas address some of the most critical challenges that have been identified for bioenergy. Many concentrate on standards and references, making compatibility and consensus essential to overcoming these challenges. The priorities also reflect a need for new measurement technologies to support a new level of quality and functionality in next-generation bioenergy.

Exhibit 3.6 Priority Measurement Topic

Standard Reference Data and Certified Reference Materials for Bioenergy Technologies

PRIORITY MEASUREMENT AND STANDARDS CHALLENGE

The lack of standard reference data for bioenergy process design, optimization, and policy is slowing development of these technologies. Without certified reference materials as the basis for reliable measures, bioenergy technology cannot achieve its full potential.

RATIONALE

- Improved effectiveness of process design, optimization, and policy
- Fundamental for measurements and biofuels infrastructure
- Enabled understanding of biotechnological processes

OBJECTIVES

- Acceptance and comparability of measurement results
  - ➤ Customer bases for acceptance
  - ➤ Legal bases for commerce
  - ➤ Quality assurance (e.g., proficiency of performance)
- Comprehensive and reliable tables of biofuels property data
  - ➤ Consensus data of importance

ELEMENTS OF APPROACH

- Coordination on a global scale
- Skilled people to evaluate data
- Adequate and long-term funding for efforts
- Find data gaps, fill with new experiments and computations
- Involve full production chain
- Gain user inputs on priorities

STAKEHOLDERS AND ROLES

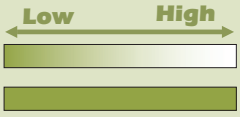
Government: Funding support; NIST (leadership on measurement infrastructure)

Industry: Trade groups

Private research institutes: Test and validation

Standardization bodies: Standards

RISK



Good data is necessary at an early stage for commercial development. The reference material may be obsolete by the time it reaches the market, posing some commercial risk.

RELATIVE IMPACTS

Accelerates innovation	***	New bioenergy technologies
Enhances competitiveness	***	Lowered cost, proven performance and quality, enhanced global marketability
Provides societal benefits	***	Accelerated use of renewable energy options
Supports environmental protection	**	Optimized energy requirements for processing and distribution
Preserves/enhances energy security	***	Commercial use of biofuels as alternatives to oil

*** (High)

Exhibit 3.7 Priority Measurement Topic

Consensus Metrics for Greenhouse Gases, Land Use, and Sustainability

PRIORITY MEASUREMENT AND STANDARDS CHALLENGE

A gap exists between emerging definitions of sustainability and the potential to move toward sustainable practices; consensus metrics and documentary standards will enable a consistent approach to sustainability.

RATIONALE

- An objective approach allows for marketplace acceptance, business and development planning, land management decisions, and public policy development

OBJECTIVES

- Objective, measurable approach to sustainability to help improve the process
- Utilization of consensus metrics in the development of biofuels

ELEMENTS OF APPROACH

- U.S. government works with other governments to create a standards framework
- Focus on regionally appropriate, measurable sustainability standards

STAKEHOLDERS AND ROLES

Government: Open process with many research initiatives and stakeholders, including agriculture, biofuel producers, international agricultural research groups, and non-governmental organizations

RISK

	Low ← → High
Technical	
Commercial	

The cost of improving analytical technologies may be high, but the payoff will be positive in the long term.

RELATIVE IMPACTS

Accelerates innovation	**	Better understanding of sustainability of new biofuels products
Enhances competitiveness	***	Helps demonstrate balance of sustainability and performance, enables global marketability
Provides societal benefits	***	Ensures greater sustainability in product development and use
Supports environmental protection	***	Provides consistent approach to sustainability with fewer environmental impacts
Preserves/enhances energy security	***	Sustainable alternative to imported fuels

*** (High)

Exhibit 3.8 Priority Measurement Topic

Breakdown Mechanisms of Cellulosic Materials

PRIORITY MEASUREMENT AND STANDARDS CHALLENGE

Molecular events associated with the breakdown of cellulosic materials to sugars (an extremely difficult process that is key to the conversion and use of cellulosic biomass) are not well understood.

RATIONALE

- Enhanced production of biofuels from cellulosic materials
- Improved processes that are more cost effective and faster (potentially increasing yield)

OBJECTIVES

- Improved understanding of the various mechanisms and interactions of lignocellulose with enzymes
- Better model of lignocellulosic structure
  - Computational chemistry

ELEMENTS OF APPROACH

- Industry partnership with NIST
- Set up benchmarks for plant material science
- Enable determination of
  - The structure of cellulose and hemicellulose in different types of feedstocks and the impact of different types on pre-treatment of structure
  - How enzymes interact with pretreatment products/ individual trial enzymes

STAKEHOLDERS AND ROLES

Government: Policy, standards support, funding

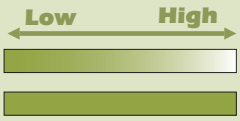
National laboratories: Techniques/fundamental data or materials

Academia: Basic research/engineering

Industry: Validator feedback

Private research institutes: Basic research/engineering

RISK



Technical and commercial risk is relatively high until the technology is proven.

RELATIVE IMPACTS

Accelerates innovation	***	Accelerated technology development for use of cellulosic materials for biofuels
Enhances competitiveness	**	Cost-effective pathways for biomass pretreatment and conversion
Provides societal benefits	**	Use of non-food biomass resources
Supports environmental protection	**	Fewer environmental impacts and greenhouse gases from cellulosic biofuels
Preserves/enhances energy security	***	Use of abundant, domestic biomass as fuel source

*** (High)

Exhibit 3.9 Priority Measurement Topic

Fuel Compliance Inspection Tools for Retail Products

PRIORITY MEASUREMENT AND STANDARDS CHALLENGE

Lack of field inspection test kits that are accurate, affordable, and accompanied by timely lab results increases product cost and decreases consumer protection.

RATIONALE

- More timely inspection for compliance will improve consumer protection and economics

OBJECTIVES

- A screening device that is faster, simpler, and cheaper
- Results within minutes that would test for compliance with ASTM standards

ELEMENTS OF APPROACH

- Develop
  - The device, (sensitivity of test, test methods for content, firmly established tolerance limits)
  - Reference materials (accuracy/ reliability)
  - ASTM standards for emerging biomass and finished fuel
- Technology transfer to manufacturer/distributors

STAKEHOLDERS AND ROLES

Industry (including trade groups and standards organizations): Form a task force of automotive engineers, consumers, developers, regulators, manufacturers, and the fuel industry to address issues

RISK

Near-term, inexpensive technology with low technical and commercial risk and high probability for acceptance.

RELATIVE IMPACTS

Accelerates innovation	*	Indirect advanced fuels development
Enhances competitiveness	*	Increased consumer confidence and marketability
Provides societal benefits	***	Consumer protection with new fuels, enables cheaper fuels
Supports environmental protection	**	More consistent fuels, inspection tests to reduce environmental impacts
Preserves/enhances energy security	***	Confident use of new renewable energy resource

*** (High)

Exhibit 3.10 Priority Measurement Topic

International Compatibility of Biofuels

PRIORITY MEASUREMENT AND STANDARDS CHALLENGE

Lack of compatible test methods and units between countries increases cost and hampers biofuels development, use, and global trading.

RATIONALE

- Trade facilitation
- Comparison of fuel technologies
- Guaranteed quality and fuel performance

OBJECTIVES

- Comparability of fuel properties to support international trade (export and import)
- Compatible infrastructure design
- Assurance of engine compatibility

ELEMENTS OF APPROACH

- Utilize and work with existing international consortia/ organizations
- Identify criteria for comparison that is globally acceptable

STAKEHOLDERS AND ROLES

Government: U.S. and other countries, NIST and other NMIs

Academia: Data collection

Industry: Test and validation

Trade groups: International trade and standards organizations

RISK

Low technical and commercial risk for standards and test methods; global support for new methods.

RELATIVE IMPACTS

Accelerates innovation	*	Indirect support for new, advanced biofuels
Enhances competitiveness	***	International trade and marketability support
Provides societal benefits	**	Consumer confidence in renewable transportation fuels
Supports environmental protection	***	Global comparability and acceptance for sustainability
Preserves/enhances energy security	***	Global acceptance, use of biofuels

*** (High)

4.0 ENVIRONMENT

Technological advances in commerce, healthcare, agriculture, and energy production in the 21st century will profoundly affect the condition of the environment and the ecosystems that compose it in many unanticipated ways. For example, introduction of "new" pollutants (e.g., prescription drugs and metabolites, new-generation pesticides, and flame retardants) may impair natural processes and degrade environmental quality. These unintended consequences of environmental alterations on global ecosystems have the potential to adversely affect human well-being, including public health, economic sustainability, and the resilience of communities and cultures. It is critical that early warning systems to assess the status and trends of the environment and identify potential threats to ecosystems and human well-being be established at local, regional, national, and global scales before irreparable harm ensues. To mitigate these risks, identification of environmental quality and public health indicators, and development of new measurement and testing technologies and methods, including sampling procedures and sensor systems, will be required.

Technical Panel on Environment

Understanding our planet through linking molecules to ecosystems

Technical Panel Co-Leaders: (1) Fred Holland, Former Director, Hollings Marine Laboratory; and (2) Hendrik Emons, Head of Reference Materials Unit, Institute for Reference Materials and Measurements (IRMM)/JRC European Commission

Plenary Speakers: Stephen Weisberg, Southern California Coastal Water Research Project Authority, USA

The environment technical panel and plenary focused on exploring the potential measurement, standards, and technological challenges that must be overcome to establish and implement the required early warning systems. The panel identified the technological advances required to distinguish natural environmental changes from those resulting from anthropogenic activities. The following sections describe the results of the technical panel discussions, including a potential vision of the future and broad challenges that need to be addressed. The prioritized critical measurement and standards challenges to technology innovation identified by the committee must be overcome to create and sustain environmental early warning systems that contribute to sustaining healthy ecosystems and human well-being.

Vision of the Future

In the future, it is envisioned that systems for monitoring and tracking the state of the environment will quantitatively measure ecosystem health in near real time through advances in technology and measurement methods. Interoperable and networked information management systems and models will translate the complex data obtained into information valued by other sectors and environmental decision makers. It is possible that a "P4 medicine" approach, described by Dr. Leroy Hood in his Medicine plenary lecture, could be achieved for the environment (predictive, preventive, place-specific, and participatory) where information from environmental early warning systems is combined with the prognosis and treatment of potentially endangered ecosystems.

Exhibit 4.1 illustrates some of the characteristics of the future of the environment that could help sustain early warning systems. Measurement technologies—new and improved—play a key role in all of the concepts shown.

Exhibit 4.1 Characteristics of the Vision of the Future for Environment

Measurement Science and Technology

- Analytical methods for assessing environmental health that are quantitative, specific, and standardized are available for application for a range of spatial and temporal scales
- Broadly applicable, rapid molecular biology tools are used to measure toxins, pathogens, biodiversity (microbes to communities), and organism health
- Networked real-time sensors feed information about toxins, pathogens, biodiversity, and ecosystem processes into web-based databases where reliable models convert the complex data into information useful for environmental decision-making
- Advanced databases and IT systems support for centralized knowledge and information exchange

Predictive Modeling and Simulation

- Models that describe structure-property-function relations and connectivity from molecules and ecosystems are developed and used to identify key environmental quality indicators and measurements
- New modeling approaches improve capabilities for forecasting and hindcasting changes in environmental conditions

Ecosystem Health Services and Products

- Rapid, accurate, qualitative, objective measures of ecosystems enable P4 (predictive, preventive, place-specific, participatory) management of ecosystems
- The connectivity between a healthy environment and human well-being and quality of life is understood and valued by society

Broad Challenges

The broad challenges identified for environment are shown in Exhibit 4.2. Some of the greatest challenges relate to our lack of a mechanistic understanding of the linkages between human activities, environmental threat, ecosystem processes, and human well-being. Currently, there is little agreement on what to measure and how to measure it to characterize environmental health. New tools and methods are needed to increase knowledge and understanding of complex ecosystems and how they interact to sustain human well-being. The impacts of anthropogenic activity on the environment can be significant, and ideally should be predicted and understood in advance, rather than addressed retrospectively. Another critical challenge is effectively assimilating and integrating the large amounts of multi-disciplinary data required for a reliable early warning system. The complexity of ecosystems and resulting information presents considerable challenges if the data are to be used for decision-making in a timely way. Communication of information in general is an issue, particularly among different disciplines, scientific communities, and with the public and private sectors. Overall, the non-linear, dynamic state of the environment and ecosystems represents an overarching challenge that adds to the complexity of forecasting potential issues and impacts before they occur.

Exhibit 4.2 Broad Technological Challenges for Environment

Defining Complex Ecosystems and Health	
HIGH PRIORITY	▪ Rapid and reliable real-time results for key environmental quality indicators that bridge historical and new measurement approaches ▪ Lack of reference materials for key environmental quality indicators (toxins, strains, genetic sequences) ▪ Difficulties in making new technologies user-friendly (kits, dipsticks, indices) from local to global scales ▪ Lack of reliable and rapid methods for assessing pathogen risks and virulence
MEDIUM PRIORITY	▪ Accepted and standardized procedure for validation of new measurement methods at multiple spatial and temporal scales with fewer false positives ▪ Standardized sample processing (concentrating, extracting, purifying) for molecular level indicators
LOWER PRIORITY	▪ Lack of fast, cheap approaches or tools for measuring ecosystem health, including biodiversity
Impacts of Commercial Activity	
HIGH PRIORITY	▪ Technology transfer to client communities (commerce, government, management, public at large) ▪ Prevention/prediction of environmental problems before they occur ▪ Non-linearity/dynamic state of ecosystems
MEDIUM PRIORITY	▪ Addressing potential issues early on, during development stages (research to application); enacting regulations in advance using forecasting tools ▪ Adoption of new approaches and methods at local scales/field level
LOWER PRIORITY	▪ Understanding of new product performance and prediction of unintended impact on environment ▪ Forecasting and addressing climate change (highest priority in Organisation for Economic Cooperation and Development/Working Party on Biotechnology [OECD/WPB])
Complex Data Integration/Processing	
HIGH PRIORITY	▪ Interdisciplinary environmental measurements represent multiple spatial and temporal scales and are difficult to integrate ▪ Reliable forecasting tools and predictive models for environmental stresses do not exist and modes of action are poorly understood for many stressors
MEDIUM PRIORITY	▪ Difficulty measuring the non-linearity and dynamic nature of ecosystems
Communications	
HIGH PRIORITY	▪ The perception that environmental health is not important and is antithetical to the economy and human well-being ▪ Inadequate mechanisms and systems for communicating environmental data across sectors and disciplines
MEDIUM PRIORITY	▪ Engagement of the commercial sector to become proactive in protecting ecosystem health and services
LOWER PRIORITY	▪ Interdisciplinary communications require a common language/terminology

Role of Measurement

Exhibit 4.3 illustrates the measurements that are important to building early warning systems for the environment, particularly those relevant to system properties and ecosystem health. Important measurement areas include (1) explanatory variables and external drivers that provide information about the environmental setting and the external environmental and socio-economic factors that affect ecosystem characteristics (climate change, land and resource use, extreme events such as hurricanes, and the degree and type of pollution); (2) biomarkers, diagnostics, and exposure measures that provide information about threats or factors that affect environmental condition and health; and (3) broader system properties (biodiversity, food, and biomass/fiber production) that are critical to sustaining ecosystem functions and services and support human well-being. Identification of system properties was particularly problematic because no generally accepted definition of ecosystem health exists and many ecosystem services are undervalued by society (waste processing, food and biomass/fiber production, climate and flood control).

Exhibit 4.3 Key Ecosystem Measurements for Environmental Early Warning Systems

Explanatory Variables and External Drivers

- *Identification and characterization of stressors:* resource and land use, pollution, extreme events, invasive species, and climate change
- *External drivers and inputs:* atmospheric and hydrographic processes, inputs of key materials
- *Bulk physical and chemical properties:* temperature, oxygen levels, and other environmental quality parameters
- *Full life-cycle carbon budget:* cradle-to-grave understanding of interactions with climate
- *Historical and current data:* retrospective analysis, evaluation of trends

Biomarkers/Diagnostics/Exposure Measures

- *Degree of environmental contamination and stress*: levels of chemical pollutants, toxins, and pathogens in the environment
- *Contaminant fate and effects*: threshold values for new and emerging pollutants, mixtures of pollutants, pathogen abundance and virulence
- *Identification of threshold values and limits for exposures*: pollutant concentrations that affect critical biological functions
- *Abundance and genetic profiles of key pathogens and other toxin-producing organisms*: improved assessment of risk and virulence, genetic markets of toxicity and virulence
- *Species identification and organism identity*: microbes to higher taxa (group in class of organisms)
- *Genetic profiles of pathogens and other microbes*: presence of virulence or toxin-producing genes
- *Extreme and unanticipated occurrences or events*: extreme wildlife mortalities, persistent toxic algae blooms, and presence of invasive organisms
- *Human exposures and health effects*: contaminant levels in food products and recreational waters

System Properties

- *Biodiversity at multiple levels*: community, specific taxa, and molecular
- *Health of sentinel organisms*: population and disease status, physiological state, metabolic signatures, and reproductive condition
- *Rates of key processes*: food and fiber production, material transformations and processing
- *Change in ecosystem services that affects human well-being*: flood control, food or fiber harvest levels, and human illness and disease

Supporting or explanatory measurements provide important ancillary information for developing preventive and remediation strategies and identify external drivers and factors that affect ecosystem health that are well beyond the immediate system boundaries and sphere of influence. Biomarkers and other diagnostic indicators are important to identification, characterization, prevention, and treatment of adverse environmental changes. For example, biomarkers can be used to identify potential for disease, determine the virulence and fate of harmful organisms or pathogens, and assess the potential for toxic releases. Exposure measurements provide information about the actual degree of contamination and other stresses the biological components of an ecosystem experience. Evaluating system responses to multiple stressors, such as complex mixtures of chemical pollutants, is important because synergistic interactions often result in effects which far exceed the additive effects of the substances composing the mixture. Information about the effects of multiple stressors provides input to models that improve predictions of potential impacts on health, safety, and environmental condition. Overall system measurements are those ecosystem attributes that are most directly connected to ecosystem attributes and services that affect human health and well-being. For example, the health of sentinel species, like fish and marine mammals, may provide early warning and better understanding of potential threats to human health and well-being.

Measurements and Standards Challenges

The key challenges related to measurements and standards for environmental early warning systems are illustrated in Exhibits 4.4 and 4.5. These are not intended to be all-inclusive for the measurement needs that must be addressed for this important field. However, they provide a starting point for identifying and prioritizing some of the key challenges that must be addressed.

Explanatory Variables. The major challenge to incorporating broad perspective variables (e.g., resource and land use, air and water transport, global patterns) will depend on effective integration of a diversity of data at different scales, from the molecular to ecosystem levels. This will require an array of measurement technologies ranging from DNA probes to satellites, geographic information systems, and others. Collecting and integrating multi-disciplinary data at these scales will require a significant investment for research, development, demonstration and deployment of new technologies, data gathering, and modeling.

Exposures and Stressors. Greater understanding of the linkages among external drivers and stressors affecting ecosystem health, environmental exposures, and system-level responses is needed as an underlying foundation for an environmental early warning system. Gaining this knowledge is impeded by the growing magnitude and diversity of toxins, chemicals, hazardous compounds, pathogens, diseases, and other stressors released into water, air, land, and living systems. The impacts of multiple stressors and complex mixtures is particularly problematic and must be measured and understood to forecast and effectively remediate system responses and sustain ecosystem services critical to human well-being. New measurements and standards, including sampling methods, could be required for toxins, pathogens, and other stressors.

Biomarkers. Standardized, validated methods for the development and use of biomarkers are currently lacking and are critical for the proper incorporation of biosciences into early warning systems. Issues such as natural variability, specificity of biomarkers, variability across environmental conditions, accountability for regional differences within and among species, and other challenges which impede standardization have to be addressed.

System Indicators and Properties. Priority challenges for obtaining system properties involve first defining what constitutes the ecosystem, determining the measures of system health, and identifying the indicators that provide early warning of changes in ecosystem health, or services that are important to sustaining ecosystem health and human well-being. Once defined, a variety of challenges remain in obtaining the system-level measurements needed, such as characterization of biodiversity at the molecular level, assessment of the health status of sentinel organisms, effective utilization of remote sensing systems,

Exhibit 4.4 Measurement and Standards Challenges for Environment Early Warning Systems

System Properties	
HIGH PRIORITY	▪ Definition of the components and indicators of ecosystem health and services ▪ Species definition from a molecular perspective: appropriate level of similarity ▪ Assurance of temporal/geographic stability of indicator or diagnostic responses
MEDIUM PRIORITY	▪ The non-steady state, non-linear aspects of ecosystems and environment ▪ Remote-sensing technology to provide molecular- to system-scale measurements—requires technology development and ability to interpret hyperspectral signatures ▪ Availability of repositories for cells, tissues, and cultures ▪ Reproducibility of measurement results across researchers, platforms, and users ▪ Establishment of a standard and supplemental catalog for biologic component identification at all levels (molecular-ecosystem/biomedical) ▪ Difficulty with biological sample stability and archiving when compared to chemicals ▪ Handling natural bio-variability in protein characterization and single nucleotide polymorphisms (SNP)/ post-translational modifications (PTM)
System Indicators	
HIGH PRIORITY	▪ Characterization and quantification of a "healthy" ecosystem, community, or organism ▪ Lack of accepted measures of sentinel organism health ▪ Difficulty validating metagenomic analysis ▪ Identification of crucial system-level parameter(s)
MEDIUM PRIORITY	▪ Net carbon sequestration or emissions by natural or managed ecosystems ▪ Availability of inexpensive, reliable, non-satellite-based remote sensing technologies
LOWER PRIORITY	▪ Effective method for identifying reliable sentinel organisms
Biomarkers	
HIGH PRIORITY	▪ Difficulties with biomarkers (e.g., some are species-specific; current standards and reference materials may not apply; regional differences may exist within species) ▪ Validated methods for multiple biomarkers (metabolite patterns) for stress and disease
MEDIUM PRIORITY	▪ Poor comparability of proteomics measurements ▪ Missing reference materials for quality assurance/calibration ▪ Lack of reliable generic biomarkers for organism "stress", including disease
Explanatory Variables	
MEDIUM PRIORITY	▪ Data integration from molecular to system level—technology ranging from DNA probe to satellite imagery ▪ Sufficient investment in technology
Exposures and Stressors	
LOWER PRIORITY	▪ Availability of more certified toxin standards ▪ Pathogen concentration/extraction from environmental samples ▪ Validation of cell-line culture viability/virulence during archival for use in later response studies ▪ Predicting emerging pathogens arising from climate change ▪ Methods for measuring emerging contaminants/metabolites in water, sediment, and tissues, given a continuously changing compound list ▪ Limited data and methods for toxicity of mixed and new chemicals ▪ Lack of methods/standards for many harmful algal bloom (HAB)-related toxins

attainment of accurate measurements, and assurance of the integrity and fitness-for-purpose of biological samples. Development of system-scale indicators and property measurements will be a mid- to long-term endeavor due to the complexity of ecosystems.

As Exhibit 4.5 illustrates, there are a number of critical crosscutting measurement and standards challenges that should be addressed to enable the development of environmental early warning systems. Standardization of methods and measurements is a key aspect. One of the most important issues to be resolved is reconciling differences between old and new measurements and developing new standards where they are needed. Other key challenges involve handling the large amounts of information required at different scales, ensuring validity of data, coordinating with existing efforts in different disciplines/agencies, and building a foundation of widely applicable molecular-level measurement tools such as biomarkers, genetic probes, and microarrays. Other challenges arise in the comparability of measurement results, and the effective linking of different environmental parameters to enable appropriate decision-making.

Exhibit 4.5 Crosscutting Measurement and Standards Challenges for Environmental Early Warning Systems

HIGH PRIORITY	▪ Reconciling differences between new and old measurements and developing additional standards and methods where needed ▪ Identification of appropriate genetic markers for biological groups of interest ▪ Securing the needed resources for personnel, funding, and technological advances ▪ Building/maintenance of a repository of certified reference genetic probes for species, certified nucleic acid probes, polymerase chain reaction (PCR) primers ▪ Greater coordination/synergy among bioinformatics initiatives and related efforts ▪ Reliability and consistency of measurement results over broad spatial and temporal scales: from pipette to biome, from microseconds to centuries
MEDIUM PRIORITY	▪ Comparability of measurement results for toxins, pathogens, diseases, and molecular tools ▪ Measurement bias—amplification and inhibition of specific properties ▪ Education/training on measurement data quality from local to global scales ▪ Understanding linkages of environmental parameters: pathogen presence, appropriate genotype and virulence, risk of disease ▪ Failure to exploit advances in other fields (weather, climate) and apply to environmental measurements and forecasting (leveraging IT advances, intelligence/knowledge sharing)
LOWER PRIORITY	▪ Lack of disease definitions/descriptions and ways to disseminate disease data ▪ Building/sharing of authenticated sequence libraries ▪ Large number of anthropogenic chemicals being recognized as "emerging contaminants" ▪ Economical methods for bulk toxin production and purification

Priority Measurement Topics

The measurement challenges illustrated in Exhibits 4.4 and 4.5 provide the foundation for a set of three priority measurement focus areas for environmental early warning systems that aim to address these challenges. Collectively, panel members determined: the importance of the focus area, objectives in addressing it, a potential approach, and stakeholder roles. They also rated the technological and commercial risks and the impacts of action in five categories. Their findings are reflected in Exhibits 4.6–4.8.

These focus areas address some of the most critical challenges that have been identified for environmental early warning systems. They cover a spectrum of measurements needed to support the availability of ecosystem health indicators and the quantification and integration of complex environmental data. The priorities also reflect a need for new measurement technologies and standards to support a new level of quality and functionality in next-generation environmental early warning systems.

Exhibit 4.6 Priority Measurement Topic

Biomarkers and Indicators for Assessing the Health of Ecosystems

PRIORITY MEASUREMENT AND STANDARDS CHALLENGE

Validated biomarkers are lacking for evaluation of the status of earth's ecosystems; appropriate biomarkers could provide important diagnostic information on ecosystem health and system indicators, and could help identify and remediate possible threats.

RATIONALE

- Early warning and forecasting to improve public health and well-being, food safety, environmental protection and remediation, and to determine safety of actions
- Better diagnostic tools and therapies: rapid assay development, enhanced bioremediation, preventive technologies

OBJECTIVES

- Robust tools for composition measurement
  - Increased capability for metabolomics, proteomics, etc.
  - Increased speed, sensitivity, specificity, and ease of use
  - Decreased cost and size
- Clearly defined standards for public health
- Accessible information for all stakeholders

ELEMENTS OF APPROACH

- Encourage joint or collaborative efforts of laboratories
- Involve multiple government agencies from local to international level

STAKEHOLDERS AND ROLES

Government: Steering/coordination, funding, international collaboration, use of system, public information, research support; EPA, NOAA, USGS, NIST (reference materials), CDC, NASA, DOE, DOI, NSF, NIH

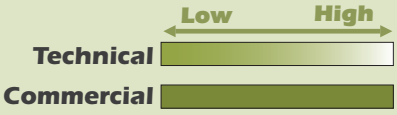
National laboratories: Reference laboratories as appropriate

Academia: Discovery, integration, measurements, and tools; research universities

Industry (vendors, suppliers, etc.): Tools, supplies; biotechnology, food, environmental, NGOs

Trade groups: Acceptance, public awareness, communication

RISK



Near-term risk is moderate in early stages; risk is high over the long term, as systems development become more costly and complex.

RELATIVE IMPACTS

Accelerates innovation	**	Development of early warning systems
Enhances competitiveness	***	Enhancements in food safety, human health, and ecosystem health
Provides societal benefits	***	Safer environment, better health, industrial protection; sustains critical ecosystem services
Supports environmental protection	***	Rapid detection of perturbation and trends for ecosystem assessment and risks
Preserves/enhances energy security	***	Sustainable alternative energy development

*** (High)

Exhibit 4.7 Priority Measurement Topic

Definition of System Properties from Molecular Properties

PRIORITY MEASUREMENT AND STANDARDS CHALLENGE

Identifying, understanding, and quantifying what to measure is difficult. Challenges arise in translating traditional versus molecular definitions, and determining operational definitions of species.

RATIONALE

- Tools for management of populations
- A standardized measurement of biodiversity
- Identification of accidental releases/invasive species

OBJECTIVES

- Protocols for quantitative assessment of similarity: roadmap to reference methods and standards that answer specific questions
- Standard for what constitutes a biological species from a molecular perspective (context-dependent) and selection of metrics for quantification
- Process for determining the definition of a molecular species

ELEMENTS OF APPROACH

- Use a coordinating entity to spearhead activity
- Select six target groups/taxa representing the diversity of life
- Reference combining and traditional taxonomy; determine standardized genes of target groups/taxa
- Compare across the six groups/taxa to identify shared and unique markers

STAKEHOLDERS AND ROLES

Government: Steering/coordination, funding, international collaboration, use of system, public information, research support; EPA, NOAA, USGS, NIST (reference materials), CDC, NASA, DOE, DOI, NSF, NIH

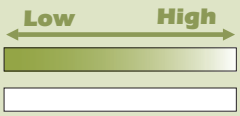
National laboratories: Reference laboratories

Academia: Discovery, integration, measurements, and tools; research universities

Industry (vendors, suppliers, etc.): Tools, supplies; biotechnology, food, environmental, NGOs

Trade groups: Acceptance, public awareness, communication

RISK



Technical risk is moderate. Commercial risk is uncertain until development work begins to yield results.

RELATIVE IMPACTS

Accelerates innovation	***	Foundation for creation of early warning systems
Enhances competitiveness	***	Reduced cost of environment, health, and safety
Provides societal benefits	***	Enhanced quality of life
Supports environmental protection	***	Advanced systems for protecting environment, health, and safety
Preserves/enhances energy security	***	Adaptation of biofuels based on properties

***** (High)**

Exhibit 4.8 Priority Measurement Topic

Reliable Integration of Complex Environmental Data for Decision Making

PRIORITY MEASUREMENT AND STANDARDS CHALLENGE

Challenges include data interoperability, biological/biomedical ontologies, bioinformatics (analytical models performance and comparability), and lack of an environmental registry/ontology (species, awareness, concepts).

RATIONALE

- More reliable information for timely decision making on complex environmental problems
- Standardized repository of information promotes data comparability and quality, enhances synthesis, and reduces uncertainties

OBJECTIVES

- An enterprise architecture that enables timely and efficient data integration and analysis with results of known quality
- Greater coordination of data and tools among bioinformatics initiatives and other efforts

ELEMENTS OF APPROACH

- Include systems biology/complex systems analysis and data interoperability standards
- Integrate with GEOSS

STAKEHOLDERS AND ROLES

Government: Steering/coordination, funding, international collaboration, use of system, public information, research support; EPA, NOAA, USGS, NIST (reference materials), CDC, NASA, DOE, DOI, NSF, NIH

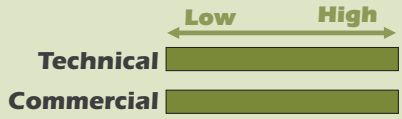
National laboratories: Reference laboratories

Academia: Discovery, integration, measurements, and tools; research universities

Industry (vendors, suppliers, etc.): Tools, supplies; biotechnology, food, environmental, NGOs

Trade groups: Acceptance, public awareness, communication

RISK

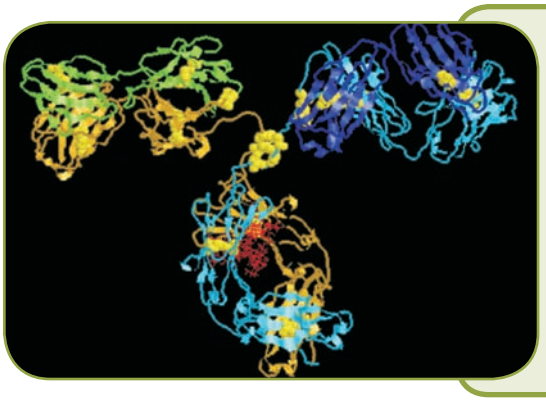


High technical and commercial risk associated with developing and managing highly diverse, complex data frameworks.

RELATIVE IMPACTS

Accelerates innovation	***	Foundation for creation of early warning systems
Enhances competitiveness	***	Cost reduction of decision making
Provides societal benefits	***	Enhanced protection of health and safety
Supports environmental protection	***	Better understanding and mitigation of environmental impacts, adverse incidents
Preserves/enhances energy security	**	Understanding of environmental impacts of biofuels

*** (High)



5.0 BIOPHARMACEUTICAL MANUFACTURING

As the world enters the 21st century, biological manufacturing science is touching on nearly every aspect of human life—from processing starting materials into finished products, to processing waste into energy—and is creating economic value at each step along the way. While technological advances and scientific discoveries are accelerating change and driving innovation in the commercial biomanufacturing sector, the manufacture of many biological products depends on technologies that have remained the same for years. Keeping pace with societal demands for therapeutics, energy, and other biobased goods and services will require innovative approaches that in turn depend on the availability of transformative tools for product characterization and measurement, manufacturing engineering, and knowledge management.

Technical Panel on Biopharmaceutical Manufacturing

Obtaining higher quality products through better bioprocess measurements

Technical Panel Co-Leaders: (1) Fred Razzaghi, Consultant; (2) William Koch, U.S. Pharmacopeia; (3) Larry Mahan, MD DBED

Plenary Speakers: James Thomas, Amgen

The biopharmaceutical manufacturing technical panel and plenary focused on identifying critical capabilities for biomanufacturing. Participants sought to highlight where new or novel metrology methods, standards, and technologies are needed to help blaze the path to 21st century biomanufacturing systems that are risk-based, efficient, agile (high-throughput), flexible, and focused on quality.

Panel discussions produced a potential vision of the future and the broad challenges to be addressed. An important outcome was identification and prioritization of the critical measurement and standards challenges to technology innovation in this field. Overcoming these challenges will be critical to ensuring that measurement technology is available to keep pace with and support technological innovations in biomanufacturing.

Vision of the Future

In the future, it is envisioned that technological advances could lead to a range of improvements in biomanufacturing and enable production of biological products more cost effectively and reliably. Greater understanding of biological properties, the manufacturing process, and product variables will enable greater process control, the use of standardized platforms, and more flexibility in processing and products. Innovations such as cell-free manufacturing, seamless scale-up of new product lines, standardized platform technologies (bioreactors, cell lines), and new methods for manufacturing regenerative medicine products (e.g., stem cell therapies) will enable faster realization of emerging concepts such as personalized/niche drugs and customized biotherapies.

Exhibit 5.1 Characteristics of the Vision of the Future for Biopharmaceutical Manufacturing

Technological Advances

- Stem cells are differentiated into cellular, tissue, or organ-based regenerative therapies
- Manufacturing processes using and/or producing biological materials are well-controlled to maximize yield of the most desired molecular or cellular product forms
- Standardized platform technologies are in place for perfusion systems in biopharmaceutical production: bioreactors, cell lines and expression construction, and control systems
- Scale-up is seamless: yield, purity, identity, and ability to scale up readily
- Process and product are transparent
- Manufacturing, safety, and protective response to vaccines are known and incorporated into design
- Sampling of bioreactors is possible
- Cell-free manufacturing enables:
  - Proof of measurements to support characteristics—design input and process control
  - Controlling/understanding variations—quality, systems biology for the future
  - Design control of available characteristics
- Long-term product-process correlation prediction enables the understanding of:
  - Impacts of raw materials
  - How to model product and process
  - Quality
  - Structure-function relationships
  - Each stage and end-size
  - Performance
  - Knowledge-based design

Societal Aspects

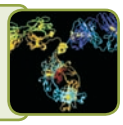
- Biotherapeutics are personalized in terms of design, development, and delivery
- Customized niche drugs can be made for individual patients in small quantities
- Products are manufactured in safer, more environmentally-friendly ways using "green" biological methods
- New, more predictable manufacturing methods will facilitate "follow-on biologics," making expensive drugs more affordable and available

Global Markets and Products

- Biomanufactured products are cost-competitive
- Product/process modifications both in development and licensed manufacture are faster
- Companies can cooperate on all but profit centers
- Flexible, continuous bioprocessing has a short-turnaround demand flow process
- Building universal platforms for cell manufacturing is well-understood
- Systemic methods are available for process, product, and evaluation

Sustainability

- Standardized cleanup process is possible for biofuels/biorefineries
- More green processes are possible



Broad Challenges

The broad technological challenges identified for biomanufacturing are shown in Exhibit 5.2. These illustrate the need for better understanding of the manufacturing process. Today this is largely an iterative, slow process that involves trial and error and then feedback to incorporate improvements. The inherent uncertainty of biological processes sometimes makes it difficult to predict or control processing outcomes and product quality, and to scaleup new processes.

The quality-assurance tools available to other types of manufacturing (e.g., chemicals, food) are practically nonexistent for biological manufacturing processes. Tools that measure performance, diagnose quality issues, and evaluate products are needed to enable better, more cost-effective biological manufacturing.

Another critical challenge is knowledge-based and stems from a generally limited understanding of systems biology and end-use pathways, *in vivo* mechanisms, and the variability and/or relevance of material attributes. Better understanding of these technical areas could provide the knowledge to improve biomanufacturing reliability and reduce some of the uncertainties in today's processes.

Exhibit 5.2 Broad Technological Challenges for Biopharmaceutical Manufacturing

Manufacturing Innovation Drivers	
HIGH PRIORITY	▪ Lack of understanding of the manufacturing process; slow steps to understanding what works (analytics, clinical trials, feedback to implement changes)
MEDIUM PRIORITY	▪ Difficulty of biomanufacturing process ▸ Uncertainty (e.g., cells can mutate) ▸ Scale-up sometimes not possible or changes product ▸ The biologic produces a desired product in low concentration ▪ Requirement for biological system to produce a product, not just chemistry
Enabling Technologies	
HIGH PRIORITY	▪ Insufficient in-process and end-product measurements (e.g., functionality)
MEDIUM PRIORITY	▪ Insufficient measurement tools ▸ Inadequate tools to predict performance ▸ Diagnostic tools are not sharp enough for robust point stratification
LOWER PRIORITY	▪ Availability of rapid protein and carbohydrate analyses to support process analytical technology (PAT) ▪ Improved pre-clinical models to enable better clinical predictability
Fundamental Systems Biology	
HIGH PRIORITY	▪ Inadequate systems biology knowledge and end-use pathways ▸ Difficulty of bio-processes, e.g., *in vivo* mechanisms of action are not well understood ▸ Understanding the impact or relevance of the variability of material attributes, e.g., if one pathway is altered, what effects occur downstream on multiple organ systems and the organism?
MEDIUM PRIORITY	▪ Lack of manufacturing science knowledge, especially for industrial pharmacy, pushes biomanufacturing down the value chain

Exhibit 5.3 illustrates the broad non-technological challenges for biomanufacturing. A key challenge is the high cost and risk of R&D. Current investments in R&D, education, and other infrastructure are insufficient to keep pace with the increasing size and global nature of biomanufacturing. Solving some of the challenges requires an interdisciplinary approach, which can be impeded by an inability to communicate in the same technical "language". Conflicts in collaboration can lead to a fracturing of effort between industry and academia, taking longer or making it difficult to find solutions.

Policy and regulation are other key areas that can inadvertently impede progress in some cases. Biological systems are inherently uncertain. As a result, biologics must often undergo continuous process improvement and change in an iterative manner, with efficacy being determined after the product has been manufactured (since the outcome cannot always be predicted).

Exhibit 5.3 Broad Non-Technological Challenges for Biopharmaceutical Manufacturing

Costs, Culture, Communications	
HIGH PRIORITY	▪ Costs to implement new technology and cost of high-risk research ▸ Risk of contamination requires sterile production ▸ Multiple complex products increase risk and cost ▪ Insufficient investment, education/research, regulatory structure, and capacity given the size and global nature of the challenge ▪ Problems of interdisciplinary communication
MEDIUM PRIORITY	▪ Pros and cons of fractured efforts involving industry, academia, and others ▪ Communication of the value proposition ▸ Concerns over regulatory and approval process ▸ Certain obstacles to making changes
Education and Fundamental Knowledge	
MEDIUM PRIORITY	▪ Lack of experienced bioengineers with broad training ▪ Field is cutting edge and lacks historical knowledge base
Policies/Regulation	
HIGH PRIORITY	▪ Lack of guaranteed continuous improvement ▸ Conflicting paradigm—once a product is made, it is perfect ▸ Flexibility to learn and improve/understand risk ▪ Variability in personalized products (cell therapies, bioreactors) ▸ Poor understanding of test methods and limitations ▪ Poorly understood boundaries of complex biological products ▸ Iterative process in producing and improving products
MEDIUM PRIORITY	▪ Difficulty of standardization for cutting edge technology ▸ Gaps in basic knowledge ▸ Lack of standards for emerging technologies

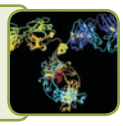


Exhibit 5.4 Key Measurements to Support Technological Innovation in Biopharmaceutical Manufacturing

Biopharmaceutical Production

- *Properties*: biochemical composition, biophysical attributes, biologic attributes, and material attributes to provide data on functionality, reliability, and performance
- *Identification of product attributes*: purity, quality, safety (rapid microbiology, molecular biology), efficacy/strength, formulation, stability, and use assurance indices to provide measures of product quality assurance
- *Characterization of raw materials*: optimization of materials use through measures of impact of feedstock variation on organism growth, feedstock components, product impurities, and ancillary products (e.g., catalysts)
- *Protein identification measures*: simple, low-cost, rapid measures enable process understanding through data on specific proteins and concentrations
- *Protein aggregation and causes*: better measurements enable process understanding and optimization
- *Online potency*: enables process development and manufacturing
- *Material process*: measurement and data analysis to provide feedback on processing
- *Limits of variability*: understanding of all acceptable limits
- *Complex profiles or spectra/consistency*: enable comparison when data sets have changed

Biopharmaceutical Safety and Use

- *Biological state of patient*: treatment efficacy
- *Function*: fitness for use, safety, and potency
- *Function in man*: immunogenicity (+/-), protection

Enabling Regulatory Decisions

- *Consensus standards for product definitions/quality*: economic impact of availability of information
- *Production (and nutrient) level in the bioreactor*: process and quality control
- *Genotypic/phenotype drift of manufacturing platform (e.g., microbe, algae, etc.)*: product reliability and control
- *Rapid glycol profiling of therapeutic proteins*: safety and effectiveness
- *Product purification characteristics*: efficiency of purification/cleanup and impact on molecule of interest
- *Purity/concentration of feed streams*: control and understanding
- *Production attributes*: understanding of starting material and process
- *In-process measurement without negative effect*: control/monitoring of cell growth/viability and tissue engineering structure
- *Scale-up parameters (bioreactor parameters, chemical, physical, thermochemical)*: effective scale-up of medical material transfer system (MMTS) from lab- to large-scale
- *Bio-process mass balance*: decrease of reactants and/or increase in products (in-line with feedback)

Lifecycle Sustainability

- *Measurands*: better understand what to measure
- *Process byproducts/wastes*: fate of solid and liquid wastes and waste gases
- *Reproducible quality*: better control of quality and product
- *Lifecycle economics*: determination of cost-benefits and profit-benefits
- *Real-time measurements*: acceleration, improvement, and optimization of process; create continuity; improve models

Role of Measurement

Measurements and standards play an important role in biomanufacturing in biopharmaceutical production processes, to ensure safety during processing and use, and from a lifecycle perspective (sustainability). Measurements and standards are also critical to support the regulatory process, particularly as it pertains to approval of new biological products and innovations, as well as the environmental impacts of biological processes. Exhibit 5.4 illustrates the key measurements in this field and why they are important.

Measurement and Standards Challenges

The key challenges related to measurements and standards for biomanufacturing are illustrated in Exhibit 5.5. These challenges represent the measurement needs that must be addressed in this field, but are not all-inclusive. They provide a good starting point for understanding some of the urgent measurement challenges facing this unique and rapidly growing industry.

Biomanufacturing Processes. Biological manufacturing processes, which work with living cells, have a high degree of uncertainty in both processing methods and in reliably obtaining the desired product attributes; they are difficult to control and monitor. The ability to make measurements in complex matrices in a process environment, and obtaining samples online and in-process, remains a significant challenge. When data is available, it is difficult to determine how that data can be used to improve the process. The variability in different product platforms creates a barrier in a number of ways, but particularly in designing generic processing tools and methods that can be applied across platforms.

Products. Variability in biological products is difficult both to measure and predict with any reliability (e.g., what creates variability?), mostly due to the inherently dynamic nature of living systems. Without understanding the mechanisms behind product variability, obtaining the desired attributes becomes an iterative rather than straightforward process. In many cases, measurements of product attributes are driven by the need to meet regulatory requirements or approvals. Such measurements do not necessarily provide any useful information about manufacturing performance or other factors that impact product attributes and functionality. Finding simpler ways to mimic complex systems (e.g., immune system assay), more accurate bioassays, and how to measure product changes *in vivo* could provide tools for understanding and improving pathways to reliable product attributes.

Lack of Fundamental Knowledge. Developing a better understanding and analysis of the risk factors for product efficacy is a high priority. The lack of efficacy is often determined by different processes and procedures in use. These are not necessarily matched to criteria of acceptability within the manufacturing process. As a result, risk analysis is not rational, but rather drug-related or tied to doctor error.

Tools/Methods. New tools are needed to measure proteins/biomarkers in complex fluids, particularly alternatives to mass spectrometry. An enhanced understanding of structure-function relationships, for example, could enable improved quality, consistency, safety, effectiveness, and yield of biological products. Tools for measuring structural properties, aggregation, oxidation, and other system properties will ultimately pave the way for predictive biotechnology and product development. A key issue is the current level of sensitivity, specificity, and objectivity of measurements for biological systems in the manufacturing environment.

Other. The high cost of measurement is an impediment in today's biomanufacturing environment. Cost decisions are complicated by whether tools are permanent or disposable technology, and if processes must be retrofitted. Add-on technologies can require process redesign at significant cost, and the ultimate cost-benefit ratios must be demonstrated to justify the investment. Another challenge in developing and implementing new measurement technology is the sometimes diverse nature of the user and desired outcomes, which can range from physicians to regulators to equipment suppliers.

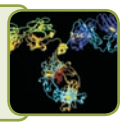


Exhibit 5.5 Measurement and Standards Challenges for Biopharmaceutical Manufacturing

Biomanufacturing Processes	
HIGH PRIORITY	▪ Specific measurements in complex matrices, compounded by interference in in-process environments ▪ Lack of cross-platform compatibility and comparable methodologies ▪ Lack of clarity on how to use the data to improve the process ▪ Obtaining representative samples online
Products	
MEDIUM PRIORITY	▪ Inadequate understanding of sources of product variability ▪ Mimicking complex systems (e.g., immune system assay) in simpler ways ▪ Prevalence of regulatory-driven measurements versus those driven by characteristics for manufacturing performance and function
LOWER PRIORITY	▪ Accurate bioassays (potency) in the face of inherent variability of biological systems ▪ Measuring product changes *in vivo* (difficult to measure function *ex vivo*)
Lack of Fundamental Knowledge	
HIGH PRIORITY	▪ Irrational risk analysis caused by determination of efficacy by different processes and procedures that are not necessarily matched to criteria of acceptability within manufacturing process
Tools/Methods	
HIGH PRIORITY	▪ Lack of alternatives to mass spectrometry (MS) as a measurement tool for proteins/biomarkers in complex fluids ▪ Sensitivity, specificity, and objectivity of measurements
MEDIUM PRIORITY	▪ Lack of generally applicable data pre-processing tools to incorporate more information into models
Other	
HIGH PRIORITY	▪ Cost of measurement ▸ Permanent versus disposable technology ▸ Add-on technology and redesign implications
MEDIUM PRIORITY	▪ Measurement challenges created by diverse users ▸ Innovator/copier ▸ Regulatory (U.S. vs. other country) ▸ End-user (physician/patient/hospital/NGO) ▪ High level of skill required to install the equipment in-process

Priority Measurement Topics

The measurement challenges illustrated in Exhibit 5.5 provide the foundation for a set of four priority measurement focus areas for biomanufacturing that aim to address these challenges. Collectively, panel members determined: the importance of the focus area, objectives in addressing it, a potential approach, and stakeholder roles. They also rated the technological and commercial risks and the impacts of action in a set of categories. Their findings are reflected in Exhibits 5.6–5.9.

These focus areas address some of the most critical challenges that have been identified for biomanufacturing. Many are data- and knowledge-based, making improved data-gathering and analytical tools essential to overcoming these challenges. The priorities also reflect a need for new measurement technologies and standards to support a new level of quality and functionality in next-generation manufacturing and bioproducts.

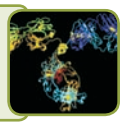
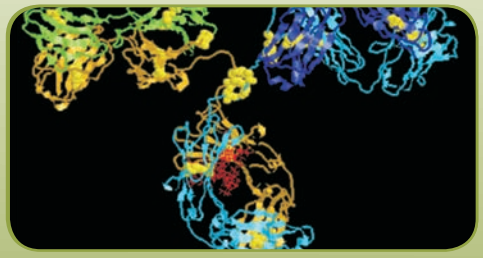


Exhibit 5.6 Priority Measurement Topic



Standard Reference Data for Biotechnologies

PRIORITY MEASUREMENT AND STANDARDS CHALLENGE

A lack of comparable measurements inhibits understanding of process/product correlation. Written standards for process performance, final products, and input materials are lacking; these standards also require industry acceptance.

RATIONALE

- Enhanced, predictable, biological manufacturing processes will enable lower costs and greater user benefits

OBJECTIVES

- Standards to improve processes that accelerate delivery of good medical products to end-users
- Reduced measurement uncertainty resulting in reduced manufacturing cost, higher product consistency and manufacturing predictability, reduced manufacturing failures, and better product safety

ELEMENTS OF APPROACH

- Increase cross-disciplinary collaboration with USP, PDA/ regulators worldwide, MBSC, industry (instrument and product manufacturers), academia, and NIH/other funding agencies
- Obtain stakeholder input (regulators, standard-setters, industry, general interest/industry) into prioritization of needs leading to infrastructure development, partnerships

STAKEHOLDERS AND ROLES

Government: FDA, funding agencies, NIST and international equivalents, intergovernmental agencies (e.g., WHO)

Academia: Collaborators, innovators, independent evaluators

Industry: Involved

Standards developers: USP and others in a coordination role—forum or similar mechanism

RISK

Low — High

Technical

Standards development is low-risk, but applicability may be too late.

Commercial

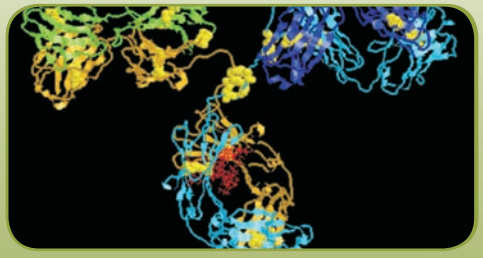
Inappropriate standards can slow biopharmaceutical manufacturing and undermine standard-setter credibility; lack of standards is costly and limiting.

RELATIVE IMPACTS

Accelerates innovation	***	Easier path for new products
Enhances competitiveness	**	Enhances global/regional market acceptability
Provides societal benefits	***	Better medicines faster
Supports environmental protection	***	Better prediction of outcomes
Preserves/enhances energy security	*	Support for bioenergy products

***** (High)**

Exhibit 5.7 Priority Measurement Topic



Optimized Sampling Approaches for Biological Manufacturing Processes

PRIORITY MEASUREMENT AND STANDARDS CHALLENGE

Obtaining representative samples without negatively impacting the biological process is difficult; *in situ* sampling is ideal, but appropriate sensors are lacking.

RATIONALE

- Improved quality assurance
- Optimization provides enhanced flexibility
- Greater process control

OBJECTIVES

- Full characterization of reactor performance
- Optimized design criteria
  - Representative sample size
  - Sample presentation
  - Sterility requirements
  - Utility considerations
  - Disposal considerations
  - Liquid versus vapor

ELEMENTS OF APPROACH

- Develop pre-competitive sampling approaches where possible
- Conduct R&D for *in situ* approaches, such as non-fouling sensing, inferential sensing, stable systems for measurements
- Pursue collaborative approaches

STAKEHOLDERS AND ROLES

Government: Broad government consortia; supporting roles for all stakeholders; NIST (measurement infrastructure)

Industry: Involved

RISK

Technical risk is high for *in situ* methods, low for sampling; adoption of technology may be slow.

RELATIVE IMPACTS

Accelerates innovation	**	High impact on in-process development, low impact on manufacturing
Enhances competitiveness	**	High impact if data used for optimization, low impact if used for monitoring quality

*** (High)

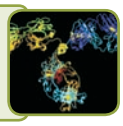
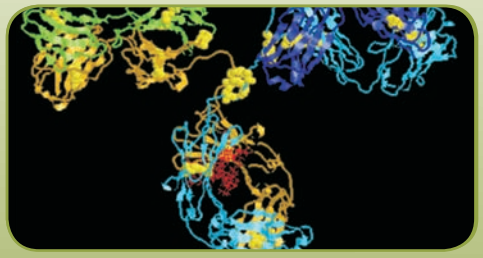


Exhibit 5.8 Priority Measurement Topic



Next-Generation Biomanufacturing Tools

PRIORITY MEASUREMENT AND STANDARDS CHALLENGE

Complexity with content management systems (CMS); stability (comparability, portability) of existing tools; understanding of system biology.

RATIONALE

- Enables predictive biotechnology
- Improved quality, consistency, safety, effectiveness, and yield of biological products

OBJECTIVES

- An orthogonal method for determination and characterization of glycosylation, aggregation, oxidation, and other relevant aspects
- Understanding of structure-function relationships in biological systems
- Tools to determine what aspects are relevant
- Comparability of methods and determination of what to measure
- Data and multivariant analysis for performance: sensitivity, specificity, and objectivity

ELEMENTS OF APPROACH

- Develop academia/industry/NIST/measurement community partnerships
- Research infrastructure, conduct other basic research
- Establish pilot plant
- Develop new funding models, information exchange

STAKEHOLDERS AND ROLES

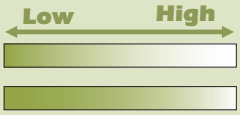
Government: Collaborative partnerships, NIST (measurement infrastructure)

National laboratories: As appropriate

Academia: Research infrastructure

Industry: Collaborative partnerships

RISK



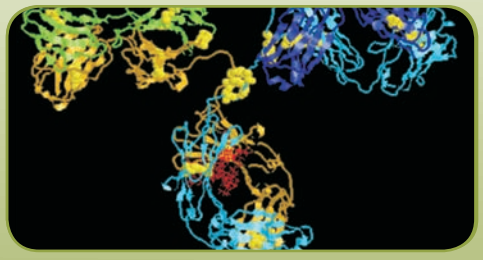
Natural development so technical risk is low; low return on investment increases commercial risk.

RELATIVE IMPACTS

Accelerates innovation	***	Better prediction of performance
Enhances competitiveness	***	Cost-effective manufacturing
Provides societal benefits	***	Safer, more effective products
Supports environmental protection	**	Understanding potential byproducts, wastes

*** (High)

Exhibit 5.9 Priority Measurement Topic



In-Process and End-Product Measurements

PRIORITY MEASUREMENT AND STANDARDS CHALLENGE

There are a lack of accepted process and production cell-culture standards in which to test systems and biology characterizations, which are needed to enable development of effective measurement methods.

RATIONALE

- Ability to assess the relevance and process risk of new measurement tools and enable identification of sources and effects of variability
- Enhanced fundamental understanding of the systems biology of production platforms, leading to better predictive outcomes and product quality assurance

OBJECTIVES

- A commonly available, fully described set of cell-culture reference systems to allow development of measurement tools, standards, criteria, and objectives

ELEMENTS OF APPROACH

- Establish industry/NIST/FDA/NGO partners (UMBI CARB, ATCC, USP, etc.) consortium for consensus platforms and production methods of "standard" products
- Identify site(s) of R&D activities (the UL labs) and repositories for cells, standards, etc.
- Convene a NIST-driven conference to initiate working committee(s) and gain buy-in

STAKEHOLDERS AND ROLES

Government: NIST, FDA, NIH

National laboratories: Various

Academia: University biotechnology centers

Industry: Biopharma

Private research institutes: ATCC, USP

Trade groups: BIO, PhRMA (supportive role)

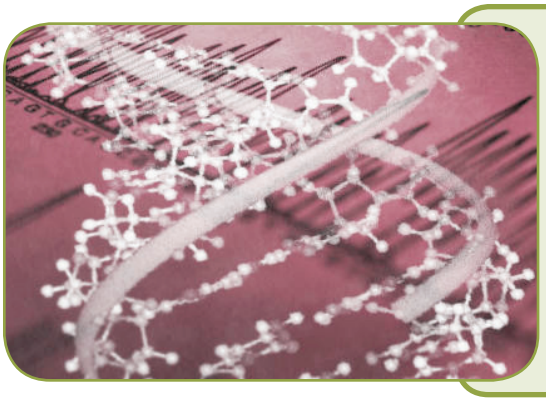
RISK

Low risk to develop with positive benefits to many stakeholders.

RELATIVE IMPACTS

Accelerates innovation	***	UL concept for biomanufacturing; common standard platform lowers variability, increases potential acceptance by end-user
Enhances competitiveness	**	High impact on new technologies in manufacturing; medium impact on product acceptance
Provides societal benefits	***	Expedited process, lower development and production cost, understanding of product quality
Supports environmental protection	**	Increased production efficiencies (less waste, contaminants, etc.)
Preserves/enhances energy security	**	Increased potential to incorporate "given technologies" in manufacturing; increased sustainability

*** (High)



6.0 MEDICINE

Technical Panel on Medicine

Improving health through measurement of complex biological signatures

Technical Panel Co-Leaders: (1) Judy Britz, Britz Consulting; (2) Paul J. Utz, Stanford School of Medicine

Plenary Speaker: Lee Hood, Institute for Systems Biology

The future of biology and medicine depends on the development of technologies and research approaches that embrace the high degree of complexity in biological systems. Therapeutic or preventative interventions will be based on "disease signatures"—unique descriptors that are definitive markers of health status. These signatures will be derived from the integration of quantitative and qualitative measurements (biochemical, biophysical, and bioelectronic) of hundreds to thousands of biomolecules and/or intermolecular and cellular interactions. Likewise, the next generation of health assessment diagnostic tests will be based on multiplex determinations constituting a unique complex signature, rather than single markers of biological activities. The shift to signature analysis in diagnostics will help enable routine health status monitoring that uses each person's own signatures of wellness and disease as the controls against which to detect pathologic changes. This new focus will enable a comprehensive, integrated approach to wellness that includes prevention of disease, early detection of disease risk, and individualized treatment plans for each patient. In turn, this new approach to wellness may help control the rising cost of healthcare, for which spending now consumes nearly one-fifth of the U.S. gross national product.

The medicine technical panel and plenary focused on the current needs and future opportunities related to innovative areas of medicine. These discussions emphasized identifying potential challenges impeding innovation in biomeasurements, clinical trial design, and the information processing and visualization technologies required to make disease signature analysis translatable into clinical practice. Panel participants identified a potential vision for the future, the broad technological challenges that need to be addressed, and the critical measurement and standards challenges that must be overcome to achieve technology innovation in the field of medicine.

Vision of the Future

In the future, it is envisioned that revolutions in medicine will dramatically change the way patients are diagnosed and treated. As shown in Exhibit 6.1, technological advances, greater understanding of the correlation of disease to phenotype, ability to test the underlying etiology, and more sophisticated tests and assays will all contribute to improving diagnoses. Biomarkers will be well developed and more robust, enabling their use in guiding treatment decisions. Increased knowledge in many areas, combined with new predictive tools, will allow for the better identification and understanding of the characteristics and pathways of disease, enabling more effective therapies to be developed more quickly.

Standardization will play an important role in optimizing sample and data collection, improving the understanding and mining of information from journals worldwide, and providing the infrastructure for new medical tools, such as the use of disease signatures. Modeling capabilities will improve with a greater range of capabilities for assessing current status as well as future disease risks. These advances will support the movement toward health-based and preventive medicine, in addition to providing support for improved diagnosis and treatment.

Exhibit 6.1 Characteristics of the Vision of the Future for Medicine: Technological Advances Supporting Treatment and Diagnosis

Diagnosis

- More accurate diagnoses translate to more efficacious treatments; physicians can order multiplexed assays for disease groups (e.g., autoimmunity) and obtain readily interpretable, numerical scores defining relative risk
- Normal pathway correlation to phenotype is understood; measurement of aberrant signaling to identify therapeutic responses that correlate with genomic/protein expression profiles is possible
- Evidence-based lab medicine replaces intuitive test interpretation
- Underlying disease etiology is evaluated, rather than a complex array of symptoms and pathways
- Standards guide collection of samples and data, as well as how disease signatures are characterized

Treatment

- The major cellular/molecular subtypes of disease can be identified, with robust biomarkers used in guiding treatment decisions
- Therapies are developed faster, based on more comprehensive understanding of biomolecular systems and more powerful tools for molecular engineering, and guided by companion diagnostics

Fundamental Knowledge

- Biomarkers and diagnostic clinical trials are integrated, and diagnostic clinical trials exist—sensitivity, specificity, predictive values are assessed
- Standard language and terminology enable harvesting the full benefit from published research literature
- Modeling capabilities range from proactive to reactive, and optimize treatment based on assessment of current status as well as risk for future events
- Statistical interpretations as well as mechanistic models are used as complementary information

Personalized medicine, where diagnosis, prevention, and treatment are tailored to individuals, is envisioned as a future reality. The groundwork for customized medicine is now being laid, although significant challenges must first be overcome. As Exhibit 6.2 illustrates, substantial advances in our knowledge of the genome and genotypes, phenotypes, and establishment of disease signatures will contribute to the creation of truly personalized medicine. These will enable the connection of diagnosis and treatment, as well as the identification of potentially risky outcomes with individual patient characteristics.

In the future, preventing disease and poor health, rather than reactively diagnosing and treating disease, will become the greater focus of medical practice. Emphasis will be placed on maintaining and improving good health, enabled by better, less-invasive health testing and monitoring methods, as well as safer therapies.

The business of healthcare will evolve to keep pace with the new demands placed on it by the move toward personalization and preventive, health-based medicine. This will require a substantial change and improvement in the way medical records and data are collected, stored, updated, and used. Medical records will need to be easily updatable in real time and transferable across different medical disciplines. Massive sets of patient information with many layers of detail will need to be combined with data on the etiology and genetics of disease to enable interpretation of health conditions as well as identification of preventive measures.

Exhibit 6.2 Characteristics of the Vision of the Future for Medicine: Personalized, Health-Based Medicine and New Business Models

Personalized Medicine

- Personalized medicine is a reality—physicians are able to integrate the individual's genotype, phenotype, diagnosis, and disease based on a signature; develop a patient profile; and select type, drug, and monitoring needs accordingly. Treatment is predictive and personalized:
  - Whole genome sequence is known per person
  - Therapy is targeted based on genome, gene expression, and pathways
  - Success of treatment is precisely monitored
  - Individuals at risk for poor outcomes are identified through screening tests (blood, imaging, etc.)
  - Shared databases enable characterization of a patient against the larger population
  - Massive datasets/patient information (longitudinal and heterogeneous) are available; genetic data is essential for interpretation—together leading to health/disease signatures and P4 medicine (predictive, preventive, personalized, participatory)
  - Medical records are useful to and usable by all practitioners; patient records are available and can be updated in real time with point-of-contact measurements, enabling monitoring of patient health/wellness

Health-Based Medicine

- Prevention is the focus: reactive medicine is transformed into proactive medicine
  - Prevention/early treatment are enabled by testing multiple biomarkers and pathways
  - Non-invasive and less-invasive methods make it easier to profile and monitor health
  - Public policy/government resources are directed to available, preventive medicine
  - Insurance pays for preventive screenings; this is more cost-effective than treating disease
- Medicine is more focused on wellness
  - Intervention is targeted for maximum therapeutic efficacy with minimal toxicity
  - The heterogeneity of disease is recognized, enabling new terminology to differenciate between healthy and unhealthy
  - Markers to define health, rather than disease, are identified

Broad Challenges

The broad technological challenges to achieving the vision for medicine are shown in Exhibit 6.3. These reflect the growing movement toward revolutionary new ways of practicing medicine that are based on a deeper understanding of disease, the susceptibility of individuals to disease, and the efficacy and safety of treatments. Critical challenges are evident in a lack of adequate standards and measures; handling and effectively using massive amounts of information related to patient care and disease; and building the necessary science, technology, and knowledge foundation to support a new level of customized medicine tools.

The current regulatory environment, policies impacting privacy, lack of economic incentives, and inadequate communication all constitute broad, non-technological challenges to personalized medicine and advanced medical practices, as shown in Exhibit 6.4. The regulatory process will have to adjust to accommodate the changes inherent in personalized treatment where the patient has greater control over treatment options. New paradigms in diagnostics may require new regulatory approaches.

Privacy issues will also arise, due to the larger and more detailed quantities of personal information needed for customized medical practice. As the sharing and transfer of information across practitioners and medical disciplines becomes more automated and routine, more complex issues related to the protection of patient information could emerge.

Exhibit 6.3 Broad Technological Challenges for Medicine

Information/Data Management	
HIGH PRIORITY	▪ Management challenges resulting from computational barriers created by massive quantities of non-comparable data ▪ Phenotype data entry and categorization ▪ Standardization of clinical information ▪ Effective and useful collection and storage of data
LOWER PRIORITY	▪ Flow of research data from journals to databases and IT resources
Products	
HIGH PRIORITY	▪ Lack of standardized units of measure ("gold standard") for comparing, compiling, and analyzing across interface structures and input technologies, platforms, etc. ▪ Lack of standardized testing across different technologies ▪ Portable standards/reference materials for all medical tests ▪ Technical/reference standards for samples, assays, protocols, data, validating assays ▪ Lack of standards to compare results of measurements on animal models (e.g., enzyme activity, structural and functional difference detection) by different laboratories and instrument manufacturers ▪ Need for derived reference standards for many assays
MEDIUM PRIORITY	▪ Standard method for sample acquisition and processing of blood cells, tissue, and biopsy specimens; internal controls to monitor proper sample handling ▪ Standardization of assays for proactive tests and methodology
Lack of Fundamental Knowledge	
HIGH PRIORITY	▪ Lack of accepted "standard phenotypic" description of disease and normal populations ▸ Disease subtype and heterogeneity ▸ Clinical trial outcomes ▸ Histology/pathology ▪ Establishment of reliable clinical diagnoses (eliminating diagnostic inaccuracy) ▪ Identifying assays for testing health or disease and salient differences (i.e., what are the irrelevant parameters and changes) ▪ Biological validation of biomarkers in clinical trials ▪ Lack of data linking personalized medicine test results to improved patient outcomes (defining disease outcomes)
MEDIUM PRIORITY	▪ Lack of predictive tools to guide molecular-level engineering to develop new therapies and expand/accelerate the therapy/drug pipeline ▪ Barriers created by heterogeneity make it difficult to develop drugs and diagnoses
LOWER PRIORITY	▪ Protein measurements: poor capture agents and sample uniformity ▪ Computation challenges: analysis of heterogeneity

Exhibit 6.4 Broad Non-Technological Challenges for Medicine

Regulatory	
MEDIUM PRIORITY	▪ Validation and regulatory challenge inherent in "patient as own control" and expense of outcomes research
LOWER PRIORITY	▪ Lack of clinical understanding in regulatory bodies (ability to prioritize parameters) ▪ Regulatory classification of diagnostic tests
Health Care Policy	
HIGH PRIORITY	▪ Privacy issues and consensus, public and private
LOWER PRIORITY	▪ Ways to evaluate and improve practices with real patients
Economics and Incentives	
HIGH PRIORITY	▪ Lack of funding/funding prioritization and the existence of competing priorities, such as science, economics, and social objectives
MEDIUM PRIORITY	▪ Rising healthcare costs (imaging, high costs of customized therapies, overall costs) ▪ High cost of diagnostic trials ▪ Economic incentives for preventative and predictive medicine ▸ Competing business incentives in personalized medicine/companion diagnostics
Economics and Incentives	
HIGH PRIORITY	▪ Cultural attitudes around sharing (work toward common standards and goals) ▪ Lack of collaboration between industry and academia overall ▪ Communication/collaboration between industry, academia, and government agencies
MEDIUM PRIORITY	▪ Education for: ▸ Patients (pros/cons) ▸ Providers (interpret pros/cons) ▸ Payers (preventive and proactive, bulk versus niche) ▸ Individuals (participate as own control)

Additionally, the cost of healthcare is high and continues to increase. Personalized therapeutics could increase costs further in the short term, particularly in the early phases of development and use. Economic incentives may be needed to induce greater investments in preventive and predictive or health-based medical practice.

Role of Measurement

Measurements have played an important role in medicine from its earliest beginnings, and today are an integral foundation of medical research, diagnostics, and treatment. Exhibit 6.5 illustrates the key measurements needed to support continued technological innovations in this crucial field and why they are necessary.

MEDICINE

Measurement is a key enabler of improved diagnostics. Genetic measurements aid in the understanding of disease pathways and signatures, are critical to the use of biomarkers and genetic markers for disease, and can provide information for early treatment and disease recognition.

Measurements are also crucial to understanding and subsequently improving the outcomes of medical treatments, as illustrated in Exhibit 6.5. Measures of morbidity, mortality, and quality-of-life parameters can reveal a lot about the efficacy of treatments and their long-term impacts. Outcome measures that evaluate how well new treatment paradigms are working compared with traditional approaches can be invaluable in guiding and refining innovative medical procedures or therapies.

Exhibit 6.5 Key Measurements to Support Technological Innovation in Medicine

Diagnostics

- *Scatter, absorption, and fluorescence of single cells with different metabolites*: impact on cell functionality
- *Interoperable data features for complete phenotype descriptions (physical, labs); robust, reproducible, platform-independent, and implementable with minimal training*: standardization and best practices
- *Relationships between measurement and phenotype*: disease pathways
- *All "-omics" (genomics, proteomics, glycomics, metabolomics, cellomics, lipomics)*: standards and reference materials needed for all potential biomarkers
- *Concentrations (free and bound) of low-abundance gene products, metabolites, etc., in biological specimens*: enables new diagnostics
- *Antibodies*: measurement of epitopes
- *Intact proteins in biological sample*: accurate, reproducible measures are essential; intact proteins are important to understanding sample
- *Post-translational modifications*: changes in activity
- *Rare- and single-cell state analysis of circulation, surface markers in circulatory blood cells, circulating microRNA*: diagnosis and treatment, circulation of medications
- *Single nucleotide polymorphism (SNP) studies, all genetic variations, epigenetics*: disease signatures, early treatment, and disease recognition
- *Antibody/antigen expression (protein expression)*: understanding disease pathways
- *Living cell assays (antigen-specific, X-ray/MRI/CT/imaging)*: vaccines and infection, clinical outcomes
- *Genotype and eliminating interference pattern (EIP)-genetic DNA, RNA (expression and regulatory species, protein, form and structure of cell, organ, and organism)*: understanding disease pathways, genetic markers for disease
- *Carbohydrate analysis*: relationships to changes in half-life and detection

Biomarkers

- *Biomarkers of pharmacodynamics (proteins, peptides, pharmacogenomics [PGx])*: prediction or establishment of drug efficacy
- *Biomarkers of pharmacokinetics (drug levels, PGx)*: guide to dosing
- *Circulating antibodies*: markers of disease exposure and presence of autoimmune disease
- *Tissue markers and measures of tissue at the cellular level, via molecular imaging:* inclusion of normal and pathological states
- *Biologically validated markers*: aid decision making

Dynamic Measurements Over Time (longitudinal)

- *Longitudinal data (biomarkers and clinical information)*: better characterization of patient populations
- *Platform-specific standards*: comparability of results over space and time
- *Snapshot of serum/plasma protein, transcription, and serum versus tissue*: non-invasive samples of disease phenotype
- *Molecular structure and dynamics at resolutions beyond current technologies*: enable molecular engineering of new therapeutics

Exhibit 6.5 Key Measurements to Support Technological Innovation in Medicine (cont.)

Measuring Outcomes and Effectiveness

- *Morbidity/mortality, quality of life*: measure of outcomes based on comparable inputs
- *Histology—disease phenotype (gold standard)*: early detection and prediction of disease
- *Quantitative measures of clinical phenotypes*: ensure efficacy and utility of diagnostic test
- *Detailed clinical phenotype and medication history, effects of medications*: impacts effectiveness of diagnosis and treatment
- *Clinical phenotype/outcome measures versus biology and imaging*: disease treatment paradigms
- *Disease definitions, indices, outcome measures*: disease treatment paradigms
- *Long-term outcomes of defined phenotypes with accompanying sample banks*: validation of biomarkers
- *Biomarkers and outcomes data*: better links with actual patient symptoms

Validation/Standardization of Measurement

- *Common quantitative units across measurement platforms*: consistency in measurement
- *Defined measurement(s) that best distinguish disease from health (stable, unique, platform- and antibody-independent measurements)*: based on forms that are optimal discriminators or predictors, rather than what is available or easy to measure
- *Consistency measures for input information*: patient history, phenotypes (age, race, sex), social factors, diet, environment provide data for retrospective analysis
- *Sample integrity measures*: ensures quality of sample banks
- *Process integrity and quality*: informs best-practice decisions
- *Statistical international standards*: enable correct inferences, global consensus
- *Variables that are not machine-dependent*: markers that are stable over time
- *Standard reference particles with defined refractive index, size, concentration, and fluorescence load*: objective, device-independent standard
- *Positron emission tomography with fluoride tracers (F-PET) sample integrity, suitability for immunohistochemistry (IHC), gene expression, other analysis*: lowering of cost and time and improvement of data integrity
- *Extension of CDISC standards to biomarkers and platform-independent data standards*: enables integration and comparison of data across platforms

Consistent, accurate, validated information is crucial today but will be even more so in a personalized medicine environment. Common, standardized ways of reporting and making measurements, as well as consistency in the type of patient data that is entered into the medical information system, are essential for effective diagnosis and treatment. In some cases, simply defining the attributes that must be measured (i.e., measurands) to assess disease and health is important. Standards, which specify how measurements should be made, are necessary to ensure that physicians are consistently informed about critical medical variables, tests, treatments, and protocols.

Measurement and Standards Challenges

The key challenges related to measurements and standards that were identified for medicine are illustrated in Exhibit 6.6. These are not intended to be all-inclusive of the measurement needs in medicine, but rather describe some of the challenges that need to be addressed to support personalized, health-based medicine. Standardization is a key theme that runs throughout the challenges shown here; it impacts the effective collection and handling of samples, is critical to the use of clinical phenotypes, and plays a key role in diagnostics and treatment.

Exhibit 6.6 Measurement and Standards Challenges for Medicine

Sample Integrity and Preparation	
HIGH PRIORITY	▪ Standards and protocols for proper handling and treatment of samples ▸ Cells: Lack of validated method for processing, freezing/thawing cells; poor reproducibility of samples, lack of standards for fluorescence-activated cell sorting (FACS) ▸ Variation in formalin-fixed, paraffin-embedded tissue with positron emission tomography (FFPET) preparation; lack of standardization, standard integrity tests ▸ Similar initial samples for consistent analysis ▸ Lack of solid tissue standards and consensus on standard procedures ▸ Lack of standards for labeled measurands—synthetic standards are feasible but not adequate, and there are no means to determine sample integrity ▪ Collection of relevant samples in a manner that provides meaningful results in real-world settings ▪ Standardization of diverse instrument platforms ▸ Reconciling different types of assays used for the same measurand; technology exists, but impetus to accomplish may not be strong ▸ Data and assay interoperability/comparability ▸ Comparability between technologies and technology-independent standards ▪ Sharing of best practices and creating standard processes and methods requires better communication and process integrity ▸ Limited number of technologies to measure process integrity ▪ Traceability of biological measurements to an absolute or relative reference (functionality, dynamics, definition of environmental information) ▪ Intact stabilized cellular standards—characterized, qualitative cell lines for all signal pathways, NCI cell lines
MEDIUM PRIORITY	▪ Definition of a "normal," "healthy" reference value and range when patient is in control
LOWER PRIORITY	▪ Standardization of data collection and quality controls to ensure data and sample integrity ▸ Inadequate technology and sample collection methods ▸ Collection sites that are poorly equipped and have poorly trained personnel ▪ Fluorochrome reference standards for all relevant detection systems are needed but require funding and dedicated expertise (e.g., FITC RM8640, SRM1932) ▸ Standardization of methods for small molecules (near-term) is hindered by various combinations of pre-analytical and analytical components, although technology exists to solve this ▪ Standards for rate measurements are lacking and not a priority for standards organizations; must be developed and validated independently ▪ Standardization of PGx results (e.g., warfarin) and lack of agreement on what clinical scenarios and equations to use ▸ Outcome endpoint definitions have prevented agreement ▸ Data for equation development is limited

Exhibit 6.6 Measurement and Standards Challenges for Medicine (cont.)

Clinical Phenotype and Outcomes	
HIGH PRIORITY	▪ Different standards/definitions for phenotype data ▸ Lack of agreement, complexity, subjective data ▸ Outcomes and phenotypes (e.g., disease activity indices) ▸ Inhibitive information-sharing and policies ▸ Phenotype inconsistency and lack of consensus ▸ Definition of disease categories; tie to treatment plan, models, causes and outcomes, pathway perturbation
LOWER PRIORITY	▪ Standards for dynamic disease symptoms/characteristics (rather than approximation): looking at changes over time (active point) and underlying mechanisms ▪ Lack of models to generate and test hypotheses (now and to improve future processes) ▪ Information standards for encoding patient outcomes ▸ Cost challenges, limited incentives, few dedicated efforts ▸ Availability of natural language processing technologies to encode free text ▸ Need for well-characterized patient records to train and evaluate technologies ▪ Lack of agreement on metadata structure relevant to interchange of image and associated metadata ▪ Information management standards for biomarkers data
Simplifying Technologies	
MEDIUM PRIORITY	▪ Point-of-care device—reference material and control, robustness, operational/logistical issues

Sample Integrity and Preparation. Developing standards and protocols for the proper processing, handling, and treatment of cells, tissues, and other biological samples is a priority challenge. Without standard methods, the result is questionable sample integrity, poor reproducibility of results, and difficulty performing credible analysis. One objective is the ability to collect relevant samples in a way that is reproducible, accurate, and provides meaningful results in practical, real-world settings.

Clinical Phenotype and Outcomes. Definitions and standards for phenotype data are a high-priority challenge and are needed to help identify, characterize, and predict disease pathways and activity levels, and understand disease and treatment outcomes. The standardization of phenotypes is impeded by their inherent complexity, data that is mostly subjective in nature, and a lack of agreement on how to best characterize the data.

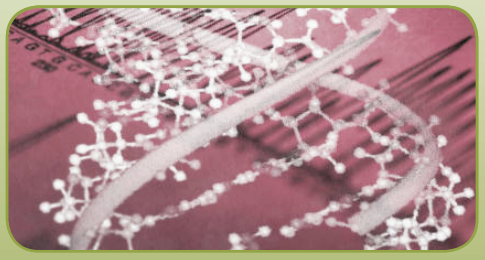
Standards and Preferences. The standardization of data and assays across a large number of biological platforms is a major challenge in medicine. Existing platforms are diverse and lack interoperability and comparability, and the technology needed to address these issues is not available. The inconsistencies inherent in tracing biological measurements to a well-defined reference point also make standardization challenging, as do a number of non-technical issues, including a lack of information-sharing and an unwillingness to undertake potentially costly efforts to develop cross-platform standards.

Priority Measurement Topics

The measurement challenges illustrated in Exhibit 6.6 provide the foundation for a set of four priority measurement focus areas for medicine that aim to address these challenges. Collectively, panel members determined: the importance of the focus area, objectives in addressing it, a potential approach, and stakeholder roles. They also rated the technological and commercial risks and the impacts of action in a set of categories. Their findings are reflected in Exhibits 6.7–6.10.

These focus areas address some of the most critical challenges that have been identified for emerging innovations in medicine. Many are related to the development of new standards and protocols that are essential to overcoming these challenges. Standardization will be critical to developing consistent frameworks for clinical data that can be used to better understand, monitor, predict, and control next-generation treatment and disease outcomes.

Exhibit 6.7 Priority Measurement Topic



Consensus Approaches and Markers for Sample Integrity

PRIORITY MEASUREMENT AND STANDARDS CHALLENGE

A lack of consensus regarding the best approach(es) to sample preparation as well as a lack of markers of sample integrity are impeding progress toward the goal of personalized medicine. Sample integrity is key to reproducibility of results and credible analysis.

RATIONALE

- Quality results to help achieve long-term benefits of personalized medicine
  - Integrity markers
  - Automated annotation of time, temperature, etc.
  - Clinical data integration tools

OBJECTIVES

- Consistent sample collection and storage to provide samples that:
  - Can be used across platforms
  - Maintain integrity over time
  - Provide for traceability
  - Provide meaningful results

ELEMENTS OF APPROACH

- Identify markers of sample integrity for different sample types
- Improve methods of sample preparation for various applications
- Define guidelines and the regulatory environment and provide training (government-sponsored consortium)

STAKEHOLDERS AND ROLES

Government: Broad consortium; NIST (reference materials)

National laboratories: As appropriate

Academia: Supporting role

Industry: Involved

Professional associations: AACC, IFCC, others

Private research groups: Supporting role

RISK

Technical risks include identification of sample integrity markers for different sample types and improving methods of sample preparation.

RELATIVE IMPACTS

Accelerates innovation	***	Supports goals for personalized medicine
Enhances competitiveness	***	More cost-effective sampling
Provides societal benefits	***	Prevention and control of disease

*** (High)

Exhibit 6.8 Priority Measurement Topic

Understanding Clinical and Biological Phenotypes for Therapeutics

PRIORITY MEASUREMENT AND STANDARDS CHALLENGE

There is a lack of understanding of clinical and biological phenotypes needed to achieve the goal of personalized medicine.

RATIONALE

- Understanding phenotypes is essential to achieve the long-term goal of personalized medicine

OBJECTIVES

- Better understanding of pathobiology
- Identification of targets for therapy
- Improved trial design, endpoints, and outcomes
- Improved marketability: cheaper, tastes better, etc.

ELEMENTS OF APPROACH

- Identify path forward for establishing and working in consortia
- Develop relevant pre-clinical models (animal, *in vitro*, and *in silico* models)
- Facilitate collaborations between government, industry, and academia (national and international)

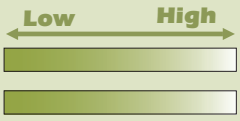
STAKEHOLDERS AND ROLES

Government: NIST (involved)

National laboratories: As appropriate

Professional associations: Medical profession; broad consensus on phenotype nomenclature

RISK



Moderate technical and commercial risk associated with paths to improve understanding of phenotypes, with positive outcomes for personalized medicine.

RELATIVE IMPACTS

Accelerates innovation	***	Supports goals for personalized medicine
Enhances competitiveness	***	Cost-effective therapies
Provides societal benefits	***	Enhanced human health

*** (High)

Exhibit 6.9 Priority Measurement Topic

Phenotype Standardization, Outcomes, Disease Definitions, and Disease Activity

PRIORITY MEASUREMENT AND STANDARDS CHALLENGE

Standardization of phenotypes is lacking; different standards and definitions result in disagreement on outcomes, phenotype inconsistency, and other limiting factors.

RATIONALE

- Correlation between phenotype and underlying pathways and biological mechanisms
- Improved disease identification and management

OBJECTIVES

- Definition of what the phenotype means
  - Disease signature or indices
  - Perturbed or normal pathways
  - Biologic correlates of descriptive characteristics
  - Severity
  - Changes over time in disease activity
  - Environmental or therapeutic outcomes in phenotypes

ELEMENTS OF APPROACH

- Develop informatics infrastructure, biorepositories, provision of standards
- Create new communication networks
- Consider impact on U.S. and foreign policy and regulation
- Improve interactions between FDA, NIST, NIH, IFCC, DARPA, DOD, and professional societies

STAKEHOLDERS AND ROLES

Government: FDA, DOD, DARPA, NIST

National laboratories: As appropriate

Academia: Input to approach

Industry: Biotech, pharmaceuticals

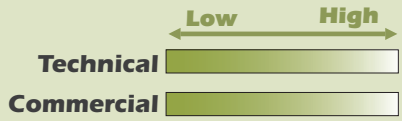
Professional associations: Medical

Private research institutes: ISB, others

Trade groups: BIO, PhRMA

Other: Insurers, health maintenance organizations (HMOs)

RISK



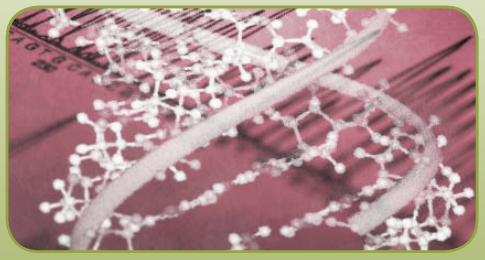
Standardization provides consistency and improves understanding with moderate technical and commercial risk.

RELATIVE IMPACTS

Accelerates innovation	***	New paradigms in treatment of disease
Enhances competitiveness	***	Economic benefits of better disease management
Provides societal benefits	***	Prevention and control of disease

*** (High)

Exhibit 6.10 Priority Measurement Topic



Reference Materials and Standardization Across Platforms

PRIORITY MEASUREMENT AND STANDARDS CHALLENGE

Measurement is not standardized across platforms, which can produce misleading results and interpretation.

RATIONALE

- Cross-validation of methods and platforms
- Confidence in biological measurements
- Process-based standard aids in process management, assay characterization

OBJECTIVES

- Comparison of data across platforms using platform-independent reference material with
  - Equivalency of data interpretation across technologies and platforms
  - Relative unit of measure with traceability to an independent standard

ELEMENTS OF APPROACH

- Develop independent reference material, which is not changed and cannot change, as a surrogate for biological parameters

STAKEHOLDERS AND ROLES

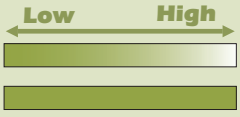
Government: NIST

National laboratories: Various

Professional associations: AACC, CAP, IFCC

Standards organizations: Supporting role

RISK

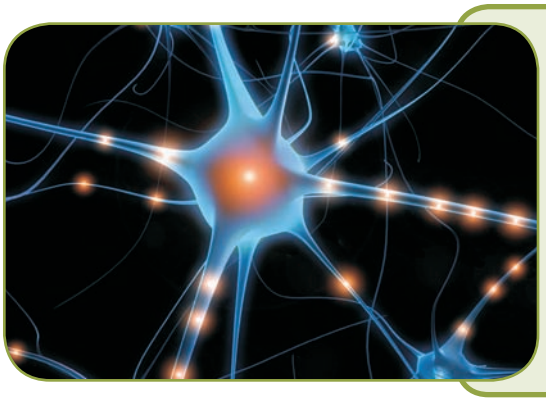


Commercial risk is high as standardization across platforms may be difficult, but outcomes would improve confidence.

RELATIVE IMPACTS

Accelerates innovation	***	Facilitates medical innovations
Enhances competitiveness	***	Global compatibility, marketability
Provides societal benefits	***	Confidence in test results

*** (High)



7.0 HOT TOPICS

Science today tends to be driven by what is considered "fundable" according to popularity in the field, sometimes leading scientists down a path before they question the value of the topic and the validity of their methodology. However, there are less "popular" bioscience areas and programs that should be considered hot topics by the measurement community. The Hot Topics technical panel session identified these overlooked areas that require better measurement technologies and standards to advance R&D in the biosciences.

Technical Panel on Hot Topics

Addressing Unrecognized, Overlooked, Underestimated, and Ignored Measurement Needs in the Biosciences

Technical Panel Co-Leaders: (1) Jennie Hunter-Cevera, UMBI; (2) Craig Jackson, Consultant

Session Speakers (in order of presentations)

Keith R. Yamamoto, UCSF: "*Quantification and Integration in Biomedical Research: Measurements and Standards—Emerging, Needed, Overlooked, Resisted*"

Kathy Hudson, Johns Hopkins University: "*Genetic Testing: Measurement Standards & Technological Challenges*"

Ann Reid, The National Academies: "*Measuring the Microbial World*"

Renee A. Reijo Pera, Stanford University School of Medicine: "*Stem Cells and Therapies*"

Gregory Petsko, Brandeis University: "*Unintended Consequences in Biological Systems*"

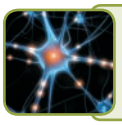
George E. Pierce, Georgia State University: "*Environment—Drinking Water, Drinking Water Disinfection, and Bioremediation*" and "*Biomanufacturing—Scale-up of Vaccines and Biologics*"

Feng Chen, University of Maryland Biotechnology Institute: "*Algae for Biofuels and Clean Coal*"

Bob Wall, USDA: "*Closing the Gap: Unrecognized, Overlooked, Underestimated, and Ignored Challenges*"

Joe Spence, USDA: "*Food and Agriculture Detection and Measurement*"

The hot topics panel session followed a different format than the technical panel sessions, with short presentations by industry, academic, and government experts in the fields of medicine, energy, agriculture, environment, and homeland security/forensics. The focus of presentations was on questions and challenges that may have been unrecognized, overlooked, underestimated, or ignored. Emphasis was placed on challenges not addressed during plenary discussions or technical panel sessions. Attendees with insights and personal experience in relevant areas were encouraged to submit questions for the panel. Topics included:



HOT TOPICS

Agriculture Viability. *What is the hard evidence for risk of transgenic plants? What systems are we employing technically in assuring that transgenic plants can become more acceptable? What are the quality assurance measures for animals that are being used to produce pharmaceuticals today? What is the downside to use of antibiotics and steroids in animal production with respect to their own metabolism and cost savings? How can metagenomics play a role in improving crop yield through bio-inoculants? Are certain crops better for addressing the mitigation of global climate change than others and how does one measure this over time with respect to soil nutrient depletion?*

Antibiotic and Antiviral Drug Resistance. *Is the evidence compelling that resistance stems from using antibiotics as growth stimulants? What will it take to find a new class of antibiotics—or, better yet, a really broad class of antibiotics that would even work against "trojan horses" with respect to biothreats? What new technologies and paradigms are needed to predict, detect, and manage emerging antibiotic-resistant strains that might result in epidemics?*

Environmental Bioremediation. *How cost-effective is bioremediation? Does the benefit of bioremediation differ depending upon the pollutant being remediated? How should resources be allocated for bioremediation when benefits are not definable? Are there biotechnologies or nanotechnologies being developed to deal with "cleaning up" nuclear contamination?*

Environmental Bioterrorism Monitoring. *Do we now have the right tools to distinguish environmental terrorism from natural phenomena? How sensitive is "sensitive enough" for finding biothreats released into the environment?*

Marine Versus Terrestrial Sources of Bioenergy. *What are the advantages and disadvantages of tapping these sources? Can we engineer optimal enzyme functions within various organisms that are envisioned as energy producers? What are the anticipated limits that will constrain the use of bioenergy? What advances have been made that improve production rates from various forms of bioenergy to make the cost economical without subsidizing the operation? Are there predictive measurements and or models for prediction of conservation and sustainability issues?*

Personalized Medicine. *What do we need if we are to realize the benefits of comparing changes within an individual rather than with respect to assumed "healthy" populations? How might personalized medicine balance genomic information with phenotypic information? Are our technologies, analytical methods, and standards adequate for making the long-term comparisons implied by personalized medicine and making inferences from changes? Will population comparisons become irrelevant to personalized medicine or require better definitions of populations and sub-populations?*

Stem Cell Therapy. *What barriers do we still face in understanding potential tumor formation? How do you stop the cells from proliferating once inserted into the patient? When stem cells become therapeutics, do we have the capability, capacity, and know-how required to produce them in the quantities necessary? Will therapeutic stem cells originate from the patient in whom they will be transplanted to a different tissue?*

Synthetic Biology. How far have we come and how far do we still have to go? Can engineered pathways in these new life forms really survive and function as they were "created" to? What are the concerns regarding alterations in the biosphere that should be considered when practicing synthetic biology? More simply put, could new life forms thrive at the expense of unrecognizably important life forms in the biosphere?

Common Measurement Challenges in Biological Science Investigation and Application

A number of measurement challenges that cut across different sectors of the biosciences were identified. These are summarized below.

Information and Data Exchange. Inadequacies in our ability to conveniently share information across disciplines resulting from database structural incompatibilities were commonly cited as serious challenges to information exchange. The absence of interoperability in respect to data transfer between instrument platforms is one example of such inadequacy. Another example is the inflexibility of data structures to accommodate new information or previously overlooked information that needs to be incorporated into existing databases. Inadequacies in data and information availability and in the formats in which the data are stored pose serious, even threatening, risks when the data are intended to be used for making decisions.

Education in Principles of Measurement. A general lack of familiarity of the importance of measurement science for the quality assurance of laboratory measurement results was observed, indicating a need for education in the principles of measurement. Some measurement concepts and fundamentals are relatively unknown outside the metrology community.

Quality Assurance of Data and Tests. The absence of reference materials suitable for use in biological measurements limits confidence in the quality of data upon which decisions and recommendations can be made. This issue is wide ranging, extending from assessment of water quality to genetic markers for disease. Quality assurance procedures outside the current regulatory structure for genetic marker tests used in medical diagnosis, for example, create a situation that does not provide confidence in the comparability or accuracy of these tests. Test quality has not kept pace with new developments to the extent that confidence in measurement results can be deemed satisfactory.

***In Situ* Measurement.** Measurements that ignore the environment or milieu in which biological processes and reactions occur can provide data that mislead rather than inform. This is a consequence of the need for measurements that can be made *in situ* with the same accuracy of measurements previously made only after preparation of samples which destroy the information that is only available *in situ*.

Non-Invasive Measurement. The need for non-invasive measurements, particularly for cells, was noted in several contexts. MRI, CAT, and PET scanning are technologies that might be adaptable to measurements of single cells. Examples of applicability are in embryogenesis and single-cell toxicology studies. A lack of technologies suitable for non-invasive measurement of embryonic systems and development severely impede progress in assessing the likelihood of successful *in vitro* fertilization. Similarly, technologies capable of acting like global positioning systems for intracellular structures could provide advantages for evaluating the effects

of both toxic substances and potential therapeutic drugs on cells. If such technologies were to be developed, many of the impediments now identified with animal testing and limited traditional methods could potentially be overcome.

Cross-Discipline Transfer of Technology. Technologies that have been developed and are currently used in medical diagnostic testing environments need to be made available to laboratories in which more routine biological testing is employed; examples are water quality and soils testing. Some of the impediments are economic, but others result from the absence of methods and reference materials suitable for use in these application areas. Testing for microbial contamination of water is too frequently performed by methods that are not usable in real time (e.g., the water may have been safe when it was tested, but the test was two days ago).

Ineffective Animal Models for Drug Testing. The traditional uses of animal models for assessment of risk and efficacy in the evaluation of new drugs are unsatisfactory, particularly when more specifically targeted therapeutic agents are being evaluated. Misleading results may arise from inadequate specificity of conventional methods and may result in risks not being identified or efficacy missed. Single-cell procedures that can be more suitable are hampered by inadequate sensitivity or the absence of calibration materials to assure the validity of such measurements.

Understanding Measurement Needs. Technological advances are limited conceptually by measurement of what we know how to measure, rather than what we believe could be more informative. The challenge is being able to measure the attribute with the specificity and accuracy needed to form a sound basis for recommendations and decisions.

8.0 UNIVERSAL IDEAS AND OBSERVATIONS

Universal Ideas

As the preceding sections have illustrated, measurement challenges have been identified that are relevant to the unique requirements of individual sectors (e.g., agriculture, medicine). However, a number of critical measurement needs have emerged that are common to many areas of the biosciences. This is notable because solutions for these common measurement problems could thus have wide applicability and support innovation in more than one area. The universal, crosscutting needs identified for the biosciences are:

- Better methodologies and practices for sample handling (ensures sample integrity, reproducibility of results, and traceability)
- More robust protein measurements (enables broader understanding of disease and treatment)
- High-throughput multiplexed measurements (enables rapid analysis of performance and functionality, and supports an accelerated discovery process)
- Improved tools and standards for bioinformatics (enhances the reliability, accessibility, and utility of critical information exchange systems)
- Improved measurement tools and standards (ensures confidence in data and enables comparability across platforms)

Observations

Based on the roundtable and plenary presentations, and discussions among the various technical panels, a number of overarching observations emerged. These emphasize the importance of biosciences to our economic future and quality of life, as well as the importance of measurement to achieving the future promise of biosciences. It is clear that, more sophisticated, highly reliable, and standardized measurement methods will be necessary to support and accelerate technological innovation in this important field. As rapid advances in the biosciences continue to emerge, measurements and standards will need to advance as well. Failure to do so could not only stifle innovation and discovery, but impede some of the new concepts that will be critical to our future economic security and quality of life.

Overarching observations about the biosciences include the following:

- Improvements in the biosciences are a key to global economic security and quality of life in the future.
- A much deeper understanding of complex biological systems is needed.
- Highly sophisticated measurements are needed in order to study the relevant changes that occur in complex biomolecular networks.
- Major measurement challenges exist that are stifling innovation in the biosciences.
- Current technology is inadequate due to a very limited measurement infrastructure that allows scientists to have confidence in only a very small percentage of the biomeasurements being conducted.

UNIVERSAL IDEAS AND OBSERVATIONS

- New multiplex, multiparametric measurement technologies will need to be invented and developed.
- These new measurement systems will heavily rely upon the accuracy and comparability of the data obtained from current technologies to build the new systems.
- Standardization of current measurement technologies will be needed to enable next-generation systems.
- Standardization of next-generation biomeasurement systems that bridge historical and new data will be needed as new methods emerge.

APPENDIX A: SPONSOR PROFILES

The National Institute of Standards and Technology (NIST)

www.nist.gov

From automated teller machines and atomic clocks to mammograms and semiconductors, innumerable products and services rely in some way on technology, measurement, and standards provided by the National Institute of Standards and Technology.

Founded in 1901, NIST is a non-regulatory federal agency within the U.S. Department of Commerce. NIST's mission is to promote U.S. innovation and industrial competitiveness by advancing measurement science, standards, and technology in ways that enhance economic security and improve our quality of life. NIST carries out its mission in four cooperative programs:

- The NIST Laboratories, conducting research that advances the nation's technology infrastructure and is needed by U.S. industry to continually improve products and services
- The Baldrige National Quality Program, which promotes performance excellence among U.S. manufacturers, service companies, educational institutions, healthcare providers, and non-profit organizations; conducts outreach programs; and manages the annual Malcolm Baldridge National Quality Award, which recognizes performance excellence and quality achievement
- The Hollings Manufacturing Extension Partnership, a nationwide network of local centers offering technical and business assistance to smaller manufacturers
- The Technology Innovation Program, which provides cost-shared awards to industry, universities, and consortia for research on potentially revolutionary technologies that address critical national and societal needs.

The University of Maryland Biotechnology Institute (UMBI)

www.umbi.org

The University of Maryland Biotechnology Institute is a hub of intensive study into the applied science of biotechnology and its application to human health, the marine environment, agriculture, and protein engineering/structural biology.

Established in 1985 by the state of Maryland, UMBI's four centers conduct research and training that provide a core of expertise and facilities to advance the state's scientific and economic development.

UMBI emphasizes collaboration with industry, other research institutions, and federal laboratories and sponsors training workshops, short courses, symposia, and seminars throughout the year.

UMBI's mission is to conduct groundbreaking research in key areas of biotechnology, make fundamental discoveries, generate innovative solutions to practical problems, and develop new technologies for commercial application. UMBI is committed to providing an exceptional environment for specialized training and mentoring tomorrow's biotechnology workforce while promoting economic growth.

American Autoimmune Related Diseases Association, Inc. (AARDA)

www.aarda.org

The American Autoimmune Related Diseases Association is dedicated to the eradication of autoimmune diseases and the alleviation of suffering and the socioeconomic impact of autoimmunity through fostering and facilitating collaboration in the areas of education, public awareness, research, and patient services in an effective, ethical, and efficient manner. The AARDA is the only national non-profit health agency dedicated to bringing a national focus to autoimmunity, the major cause of serious chronic diseases. Approximately 50 million Americans—20% of the population, or one in five people—suffer from autoimmune diseases. Women are more likely than men to be affected; some estimates say that 75% of those affected—some 30 million people—are women. Still, with these statistics, autoimmunity is rarely discussed as a women's health issue.

Aspen Technology, Inc. (AspenTech)

www.aspentech.com

AspenTech is the world's leading supplier of software that optimizes process manufacturing. From our MIT and U.S. Department of Energy roots in the early 1980s, to the groundbreaking release of aspenONE V7 in 2008, AspenTech has always been at the forefront of innovation in the process industries.

With integrated AspenTech solutions, process manufacturers can implement best practices for optimizing their engineering, manufacturing, and supply chains. As a result, AspenTech customers are better able to achieve their operational excellence goals—increasing capacity, improving margins, reducing costs, and becoming more energy efficient.

Today, AspenTech solutions are used by virtually every leading company in the process manufacturing industry. More than 75,000 users at over 1,500 companies rely on AspenTech. For more than 25 years, AspenTech customers have achieved hundreds of millions of dollars in cost savings and performance improvements.

The culmination of that industry leadership and experience was manifested in the release of aspenONE V7 in 2008. It represents best practices for process optimization. It redefines ease-of-use in software for the process industries. It makes operational excellence achievable and—even in the face of today's market challenges—easier than you think.

Energetics Incorporated

www.energetics.com

Energetics, Incorporated is a full-service technical and management consulting company.

We provide our clients with support to help research, develop, and commercialize new technologies to meet the nation's need for cost-effective, efficient, and environmentally-friendly sources of energy. In addition, we provide technical and management support to clients responsible for the protection of the U.S. infrastructure related to energy assurance and homeland security.

Our special strengths include an in-depth knowledge of:

- Energy supply and generation technologies
- Electric utility industry/technologies

- Federal energy and environmental regulation
- Advanced transportation and industrial technologies
- Process and manufacturing industries
- Building energy technology
- Energy assurance and security

IEEE-USA

www.ieeeusa.org

IEEE-USA is an organizational unit of the Institute of Electrical and Electronics Engineers, Inc. created in 1973 to support the career and public policy interests of IEEE's U.S. members. IEEE-USA is primarily supported by an annual assessment paid by U.S. IEEE members.

IEEE-USA's mission as outlined in the IEEE bylaws is to recommend policies and implement programs specifically intended to serve and benefit the members, the profession, and the public in the United States in appropriate professional areas of economic, ethical, legislative, social, and technology policy concern.

Our vision is to serve IEEE U.S. members by being the technical professional's best resource for achieving lifelong career vitality and by providing an effective voice on policies that promote U.S. prosperity.

Johns Hopkins University (JHU)

www.jhu.edu

The mission of The Johns Hopkins University is to educate its students and cultivate their capacity for life-long learning, to foster independent and original research, and to bring the benefits of discovery to the world.

Further, JHU strives to create an interactive community of educators, students, researchers, corporations, and government representatives whose collaborative thinking and discovery expand academic and technological boundaries and advance economic development.

Human Genome Sciences (HGS)

www.hgsi.com

The mission of Human Genome Sciences is to apply great science and great medicine to bring innovative drugs to patients with unmet medical needs.

We are poised for the market with a clinical pipeline that includes three novel products in late-stage development: Albuferon in Phase 3 trials for hepatitis C, LymphoStat-B in Phase 3 trials for systemic lupus, and ABthrax in late-stage development for inhalation anthrax.

Both Albuferon and LymphoStat-B have the therapeutic potential to change and save lives and the commercial potential to become blockbusters in the marketplace. Each is being co-developed and commercialized in collaboration with a world leader in the pharmaceutical industry—Novartis for Albuferon and GlaxoSmithKline for LymphoStat-B.

ABthrax is being developed under a contract with the U.S. Government and represents a new way to address the threat of inhalation anthrax. The pivotal efficacy studies have demonstrated a dramatic and significant

survival benefit. In January 2009, HGS began the delivery of 20,000 doses of ABthrax to the U.S. Strategic National Stockpile. Right behind these three late-stage products is a high-potential mid-stage pipeline led by our TRAIL receptor antibodies for cancer—and including a number of products to which HGS has substantial financial rights in the GSK pipeline.

Our manufacturing capability represents a significant strategic advantage. HGS is able to produce and purify multiple protein and antibody drugs in two state-of-the-art process development and manufacturing facilities—totaling approximately 400,000 square feet and offering both small-scale and large-scale production.

HGS has built a strong cash position that allows us to focus on advancing our lead products toward commercialization as rapidly as possible, while at the same time investing in our early- and mid-stage pipeline.

U.S. Pharmacopeia (USP)

www.usp.org

The United States Pharmacopeia (USP) is an official public standards-setting authority for all prescription and over-the-counter medicines and other healthcare products manufactured or sold in the United States. USP also sets widely recognized standards for food ingredients and dietary supplements. USP sets standards for the quality, purity, strength, and consistency of these products—critical to the public health.

USP's standards are recognized and used in more than 130 countries around the globe. These standards have helped to ensure public health throughout the world for close to 200 years.

USP is a non-governmental, not-for-profit public health organization whose independent, volunteer experts work under strict conflict-of-interest rules to set its scientific standards. USP's contributions to public health are enriched by the participation and oversight of volunteers representing pharmacy, medicine, and other health care professions as well as academia, government, the pharmaceutical and food industries, health plans, and consumer organizations.

USP's mission is to improve the health of people around the world through public standards and related programs that help ensure the quality, safety, and benefit of medicines and foods.

Waters Corporation

www.waters.com

For fifty years, Waters Corporation has developed innovative analytical science solutions to support customer discoveries, operations, performance, and regulatory compliance.

Waters holds worldwide leading positions in complementary analytical technologies—liquid chromatography, mass spectrometry, rheometry, and microcalorimetry. These markets account for approximately $5 billion of the estimated $20-$25 billion worldwide analytical instrumentation market.

Specifically, the company designs, manufactures, sells, and services ultra-performance liquid chromatography (UPLC), high-performance liquid chromatography (HPLC), chromatography columns and chemistry products, mass spectrometry (MS) systems, thermal analysis, and rheometry instruments. Waters operates in two divisions: Waters Division and TA Instruments.

Montgomery County Department of Economic Development

www.montgomerycountymd.gov

Montgomery County, Maryland, is your gateway to the Mid-Atlantic's robust business community. Centrally located at the epicenter of the region's federal and advanced technology marketplace, it is next door to the nation's capital and home to:

- More than 200 biotech companies
- The highest concentration of PhDs in the nation
- More than 100,000 advanced technology workers
- 19 federal research and regulatory agencies
- More entrepreneurs than any other jurisdiction in the nation
- The largest number of woman- and Asian-owned businesses in Maryland
- Half of all Hispanic-owned businesses in Maryland
- The second largest and fastest growing number of African American-owned businesses in Maryland

Federal agencies including the NIH, FDA, and NIST are all located in Montgomery County. Industry leaders are also located here, including Discovery Communications, Hughes Network Systems, Human Genome Sciences, Lockheed Martin, Marriott International, and MedImmune.

Montgomery County encourages business and economic development in a number of ways. The highly-successful Business Innovation Network nurtures and grows young entrepreneurs into thriving county employers. Its nationally renowned 93,000-acre Agricultural Reserve helps protect, promote, and support diverse agribusinesses. The award-winning Small Business Mentorship Program pairs new business owners with successful business leaders. A Local Small Business Reserve Program helps ensure that local businesses get their share of county procurement contracts.

APPENDIX B: TECHNICAL PANEL PARTICIPANTS

**See glossary for list of acronyms*

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APPENDIX C: LIST OF ACRONYMS

AACC	American Association for Clinical Chemistry
AARDA	American Autoimmune Related Diseases Association, Inc.
APL	Applied Physics Lab
ASTM	American Society for Testing and Materials, now ASTM International
ATCC	Association Tunisienne de lutte contre le Cancer (Tunisian Association for Fighting Against Cancer)
BIO	Biotechnology Industry Organization
CAP	College of American Pathologists
CARB	Center for Advanced Research in Biotechnology
CAT	computerized axial tomography
CCQM	Consultative Committee for Amount of Substance, Bureau International des Poids et Mesures
CCR	Council for Chemical Research
CDC	Centers for Disease Control and Prevention
CDISC	Clinical Data Interchange Standards Consortium
CDRH/FDA	Center for Devices and Radiological Health/Food and Drug Administration
CIPM	International Committee for Weights and Measures (Comité International des Poids et Mesures)
CMS	Centers for Medicare & Medicaid Services
CO_2	carbon dioxide
CPAC	Center for Process Analytical Chemistry
CRM	certified reference material
CT	computed tomography
DARPA	Defense Advanced Research Projects Agency
DBED	Department of Business and Economic Development

LIST OF ACRONYMS

DNA	deoxyribonucleic acid
DOD	U.S. Department of Defense
DOE	U.S. Department of Energy
DOI	U.S. Department of the Interior
EC	European Commission
EC-JRC-IRMM	European Commission, Joint Research Center Institute for Reference Materials and Measurements
EFA	essential fatty acid
EIP	eliminating interference pattern
EPA	U.S. Environmental Protection Agency
EPI	epigenetic
FACE	Free Air CO_2 Enrichment
FACS	fluorescence-activated cell sorting
FDA	Food and Drug Administration
FDA-CDER-OPS	Food and Drug Administration, Center for Drug Evaluation and Research Office of Pharmaceutical Science
FDA-CDRH	Food and Drug Administration, Center for Devices and Radiological Health
FITC	fluorescein conjugation of antibodies
F-PET	positron emission tomography with fluoride tracers
FFPET	formalin-fixed, paraffin-embedded tissue with positron emission tomography
GC	gas chromatography
GE	General Electric
GE	genetic engineering
GEOSS	Global Earth Observation System of Systems
GHG	greenhouse gas
GIS	geographic information system
GSK	Glaxo SmithKline
HAB	harmful algal bloom
HGS	Human Genome Sciences
HMO	health maintenance organization

IEAA	Institute of Electrical and Electronics Engineers
IFCC	International Federation of Clinical Chemistry and Laboratory Medicine
IHC	immunohistochemistry
INMETRO	National Institute of Metrology, Standardization, and Industrial Quality (Instituto Nacional de Metrologia, Normalização e Qualidade Industrial)
INMS	Institute for National Measurement Standards (Canada)
ISB	Institute for Systems Biology
IT	information technology
ITRI	Industrial Technologies Research Institute
JBA	Japan Bioindustry Association
JCVI	J. Craig Venter Institute
JGI	Joint Genome Institute
JHU	Johns Hopkins University
JHU-APL	Johns Hopkins University, Applied Physics Laboratory
KRISS	Korea Research Institute of Standards and Science
LBNL	Lawrence Berkeley National Laboratory
LCA	life-cycle analysis
LGC	UK designated national measurement institute for chemical and biochemical analysis
LLE	liquid-liquid equilibrium
LT	long-term
LUC	land use class
MBSC	Medical Board of the State of California
MD DBED	Maryland Department of Business and Economic Development
MMTS	medical material transfer system
MRI	magnetic resonance imaging
MS	mass spectroscopy
MT	mid-term
NASA	National Aeronautics and Space Administration
NCI	National Cancer Institute
NDVI	normalized difference vegetation index

LIST OF ACRONYMS

NGOs	non-government organizations
NIBIB	National Institutes of Health, National Institute of Biomedical Imaging and BioEngineering
NIBSC	National Institute for Biological Standards and Control
NIH	National Institutes of Health
NIH-NIAMS	National Institutes of Health, National Institute of Arthritis, Musculoskeletal and Skin Diseases
NIST	National Institute of Standards and Technology
NIST-TIP	National Institute of Standards and Technology, Technology Innovation Program
NMI	National Metrology Institute
NMi	Nederlands Meetinstituut
NOAA	National Oceanic and Atmospheric Administration
NOAA-NCCOS	National Oceanic and Atmospheric Administration, National Centers for Coastal Ocean Science
NOAA-NMFS	National Oceanic and Atmospheric Administration, National Marine Fisheries Service
NOAA-NOS	National Oceanic and Atmospheric Administration, National Ocean Service
NPL	National Physical Laboratory
NRC	National Research Council, USA
NRC-INMS	National Research Council, Institute for National Measurement Standards (Canada)
NSF	National Science Foundation
NT	near-term
OECD	Organisation for Economic Co-operation and Development
OECD/WPB	OECD, Working Party on Biotechnology
-omics	general term for a broad discipline of science and engineering for analyzing the interactions of biological information objects in various omes, such as genome, proteome, metabolome, expressome, and interactome.
FDA-OPS-CDER	Food and Drug Administration, Office of Pharmaceutical Science, Center for Drug Evaluation and Research
OSTP	Office of Science and Technology Policy
P4	predictive, preventive, personalized, and participatory
PAT	process analytical technology
PCR	polymerase chain reaction

PDA	Parenteral Drug Association
PET	positron emission tomography
PGx	Pharmacogenomics (an individual's genetic variation effects on therapeutic responses or adverse events)
PhRMA	Pharmaceutical Research and Manufacturers of America
PLT	platelet count
PTM	post-translational modifications
PURMA	Public Utilities Risk Management Association
R&D	research and development
RBC	red blood cell
RFS	renewable fuels standard
RNA	ribonucleic acid
SCCWRP	Southern California Coastal Water Research Project
SNP	single nucleotide polymorphism
SRM	Standard Reference Material®
UAV	unmanned aerial vehicle or unmanned aircraft vehicle systems (UAVs)
UCSC	University of California, Santa Cruz
UCSF	University of California, San Francisco
UK	United Kingdom
UL	Underwriters Laboratory
UMBI	University of Maryland, Biotechnology Institute
UNC-CH	University of North Carolina at Chapel Hill
USDA	U.S. Department of Agriculture
USDA-ARS	U.S. Department of Agriculture, Agricultural Research Service
USDA-WRRC	U.S. Department of Agriculture, Western Regional Research Center
USGS	U.S. Geological Survey
USP	United States Pharmacopeia
VLE	vapor-liquid equilibrium
WBC	white blood cell
WHO	World Health Organization

XDx	Molecular diagnostics company

The Steering Committee wishes to thank the following members of the
NIST Biovision Executive Team who contributed to the planning of this conference:

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