

**Testimony of Dr. Willie E. May**

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SUBCOMMITTEE ON TECHNOLOGY AND  
INNOVATION**

**Hearing on**

**The Potential Need for Measurement Standards to  
Facilitate the Research and Development of Biologic  
Drugs**

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Chairman Wu, Ranking Member Smith, and Members of the Subcommittee, thank you for the invitation to testify today. I am Willie E. May, Director of the National Institute of Standards and Technology's (NIST) Chemical Science and Technology Laboratory (CSTL). Additionally, for the past four years, I have been responsible for assessing, developing and coordinating NIST programs in the Biosciences. I am pleased to be offered the opportunity to participate in this morning's discussion regarding the "Potential Need for Measurement Standards to Facilitate Research and Development of Biologic Drugs." My testimony will explain NIST's role in this area and some of the critical measurement challenges that we have identified.

***The Need for Additional Measurement Science and Measurement Standards to Improve the Quality and Efficiency of Healthcare*** The rising cost of healthcare and increased prevalence of chronic diseases, such as heart disease and diabetes, are having a significant impact on the economy and quality of life for many in the United States. The Obama Administration is committed to improving quality and enhancing the efficiency and delivery of healthcare. The provision of the necessary measurement science and standards potentially can drive innovation and make the drug and biologics development process more efficient. NIST's unique mission, core competencies in measurement science and standards, and history of relevantly addressing such needs in other areas, provide strong evidence that NIST can help accelerate this innovation.

#### ***NIST's Historical and Current Role***

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. Over the years, NIST traditionally has focused its research and measurement service activities on the physical science and engineering disciplines – and become internationally renowned in that regard as demonstrated by our world-premier measurement and standards program and many internationally-recognized awards in measurement science, including three Nobel Prizes in Physics since 1997.

In keeping with the spirit of our mission to address the measurement barriers to innovation that are the highest risk to U.S. economic security and quality of life, the biosciences have been identified as a new area for significant emphasis at NIST, with healthcare being our initial area of focus. To help define our efforts, NIST has engaged in extensive outreach to the Food and Drug Administration (FDA), National Institutes of Health (NIH), US Pharmacopeia, and the medical diagnostic and pharmaceutical industries over the last 5 years. The consistent feedback from those efforts have indicated that major improvements are needed in the measurement science and measurement technologies that support efforts to predict, diagnose and manage disease, as well as for those used to discover and develop safe and effective medical therapies. The lack of adequate standards to ensure accurate and comparable measurements is an issue that must be addressed to fully realize the potential impacts of new innovations in healthcare and its delivery, whether it be for *in vitro* diagnostic and medical imaging biomarkers, predictive toxicology for drug safety, medical device materials biocompatibility, genetic testing, or biopharmaceutical manufacturing. Whether quantifying the amount of protein

in a cancer cell or determining which drug will be most efficacious with minimal side-effects on an individual basis, measurements are the foundation for improving our understanding of biological systems. This is critical to guide and support the efficient knowledge-based, development of new tools for meeting next generation of health care needs. NIST's FY 2010 budget request includes \$14 million to support new initiatives in healthcare, including standards and measurement work to address the information technology and medical diagnostic issues mentioned here.

NIST is not a new player in the health care arena. Improvement in measurement science, our foundational role and area of expertise, is and has always been critical to technological innovation in the health sciences. For example, we have:

- a collaborative program with the American Dental Association begun in the late 1920's which has led to, among other things, the development of polymer composite dental fillings and the air-driven turbine drill now found in virtually all dentist offices;
- a program in Radiation Physics begun in the 1920's that is responsible for the standards used in the calibration of X-rays, mammography, and other radiotherapies like those used in the treatment of prostate cancer; and
- a program in Clinical Diagnostics begun in the 1970's that initially focused on high purity primary references for electrolytes (e.g. sodium, potassium, calcium), and metabolites (e.g. cholesterol, creatinine, glucose, uric acid, urea).

NIST's current efforts are focused on improving quality and reducing the cost of healthcare by targeting the measurement and standards needs associated with clinical diagnostics and medical imaging. The typical patient is often unaware of the inaccuracies associated with most medical testing that contribute to the high cost and suboptimal quality of health care. For example, standards exist for only about 10 percent of the 700 most commonly ordered clinical tests, and there are no traceable, quantitative standards for MRIs, CT scans, ultrasounds, and other medical imaging technologies, even though such images account for \$50 billion in annual health-care spending. Lack of traceable measurement references and the resulting lack of demonstrable accuracy and comparability of results in clinical testing and medical imaging contributes to misdiagnosis and/or wasteful repeat testing, and treatment decisions based on inaccurate information.

NIST works closely with industry, academia, and other government agencies to identify the measurement and standards tools required to improve the quality of laboratory medical tests and medical imaging. Our efforts have resulted in significant breakthroughs such as the development of calibrations for radiotherapies and mammography that led to reduced exposure to radiation and made treatments safer; and identification of potential new biomarkers associated with the onset of Type 2 diabetes, metabolic syndrome and cancer. We have also expanded our program in clinical diagnostics to include blood serum-based standards to reduce measurement errors and associated costs of clinical testing to support early cancer diagnosis and treatment.

NIST could potentially impact yet another area associated with the increasing cost of healthcare: the growing use of biologics to treat disease. These therapies can substantially improve patients' health and quality of life, but also can be very expensive. To help bring down costs for both patients and the Federal government, the President has proposed to establish a pathway for FDA approval of "generic" biologics that would provide seven years of data exclusivity for innovator products. We can contribute to the President's proposal by leveraging our expertise in measurement science and measurement standards to:

- improve efficiency and reliability of the manufacturing processes involved in the production of biologics ; and
- put in place the measurement tools to facilitate the approval of such drugs, such as measurement methods or reference materials that would allow the FDA to accurately assess the "sameness" of a biologic made by different manufacturers.

A discussion of the measurement challenges that we have identified in this area will be the focus of the remainder of my testimony.

***Measurement and standards barriers for the efficient manufacturing and characterization of safe and effective biopharmaceuticals***

Based on input from the FDA and biopharmaceutical manufacturers, NIST has identified a number of measurement and standards challenges that, if addressed, will enable:

- a more complete understanding of the biopharmaceutical manufacturing process;
- better control over the chemical, physical, and biological processes involved in manufacturing complex protein pharmaceuticals; and
- improved methods for physical, chemical and biological characterization of the finished product.

A key measurement need, whether for manufacturing process scale-up, process changes or for the regulatory approval of generic biologics (or "biosimilars"), is the ability to measure the "sameness" between different batches of manufactured proteins and to gain a better understanding of the variations that are critical to the efficacy and safety of the drug.

Working with stakeholders, NIST has identified the following critical phenomena and measurement barriers as areas where the development of improved measurement technologies and methods would have great potential to positively impact the biopharmaceutical manufacturing industry and improve the ability of FDA to regulate "generic biologics" as proposed by the President.

**Immunogenicity** - There is currently no measurement infrastructure in place to ensure the accuracy and comparability of the various methods used to measure key attributes of protein biologics that cause immunogenicity. Immunogenicity is the ability of a protein therapeutic to provoke an immune response in a patient. An immune response may range from neutralization of the drug rendering it ineffective to a life-threatening allergic reaction. A key attribute of protein biologics linked to immunogenicity is aggregation.

Aggregation is the process by which one or more proteins may “clump” together to form visible or invisible particles. For regulatory approval, all protein therapeutics must be carefully examined for the presence of aggregates; however, detecting and measuring the wide size range of possible protein aggregates remains difficult. Manufacturers often use different measurement tools and protocols that can lead to contradictory results.

Improving the measurement science for protein aggregates would benefit manufacturers and patients in several ways. For example, development of protein particulate standards would support harmonization of results across different measurement platforms used by manufacturers and provide a better scientific framework for regulatory requirements and decisions. These standards would also facilitate the development and acceptance of improved tools for measuring protein aggregates during manufacturing and in final products. Improved measurement of aggregation would ultimately lead to better understanding and prediction of protein aggregation and immunogenicity. The ability to predict immunogenicity of new biopharmaceuticals would, in turn, increase the probability for their successful development.

**Three-dimensional (3-D) protein structure** - Biopharmaceutical proteins are synthesized in cells as linear chains of amino acids that must be “folded” into a three-dimensional shape that allows them to function as intended. The improper folding of a biopharmaceutical affects several aspects of how it functions as a drug once injected into the patient. Potency, efficacy and safety can all be severely compromised by misfolding events. At present there are no consistently reliable physical or chemical characterization methods for determining the 3-D structure of biologic drugs.

Standards and improved methods for the characterization of 3-D structure would help biopharmaceutical manufacturers and instrument vendors verify the accuracy and comparability of the structures of manufactured biopharmaceuticals. These efforts would help to ensure that the manufacturer is producing the same product from one batch to the next and would also allow for direct structural comparison of the new product to the original product form. Standards would also help determine the relationship between the structure of a biopharmaceutical and its function, which is critical to our understanding of how the biopharmaceutical will act in the body. Standards for protein 3-D structure would make the biopharmaceutical marketplace more efficient in these key areas: authentication of identity, and determining the intercomparability of the drug from batch to batch.

**Post-translational modification (PTM) of manufactured proteins** – The majority of approved protein therapeutics contain post-translational modifications. PTMs are chemical modifications to the protein that occur after it is synthesized such as the addition of sugar molecules, lipids, or biochemical functional groups. Among these, the addition of sugar molecules, or glycosylation, is the most important because over half of all protein therapeutics are glycosylated. PTMs are known to be critical to the safety and efficacy of many biopharmaceuticals and consistent PTM profiles must be maintained for manufactured biologics. There are multiple and varied methods for determining PTMs; however, assessing the accuracy and comparability of results from different methods

remains difficult. In order to evaluate the sameness of protein products, these modifications must be fully understood and characterized. Due to the complex and varied nature of the modifications, methods are currently lacking which quantitatively assess the structure and how it impacts protein stability and functionality.

Improved measurement methods and standards would enable instrument vendors and biopharmaceutical manufacturers to develop measurement systems for determining PTM of products. Characterizing the PTM signature of products would enable more streamlined comparative analysis, could also be used as a basis for the authentication of manufactured products and help safeguard against counterfeit drugs, and would reduce the cost of comparing the PTM of batches of biopharmaceuticals produced by different methods or companies.

**Contaminants in the manufacturing process** – There is currently no measurement infrastructure in place to help ensure the accuracy and comparability of the methods needed by manufacturers, regulators, and investigators to identify and protect the public from the intentional and unintentional introduction of substances in pharmaceuticals and biologic drugs. Chemical contaminants, such as heavy metals or organic chemical compounds, can leach from the manufacturing vessels, containment vials used in producing biologic drugs or packaging materials. These contaminants can alter protein therapeutics in ways that harm patients. For example, a major adverse clinical event occurred when batches of erythropoietin (EPO, a glycoprotein hormone that controls red cell production) were contaminated with leachable chemicals from primary manufacturing containers. The unidentified contamination caused aggregation of EPO, triggering an immune reaction that destroyed the patients' abilities to regenerate red blood cells.<sup>1</sup> Contamination by proteins originating from the host cells used to produce a protein therapeutic is also a concern. Additionally, cellular contamination problems have occurred where the unknown presence of a host cell enzyme destroyed the biopharmaceutical protein once it was packaged, rendering the product useless.

Standards (reference measurement procedures, reference data and certified reference materials) would enable regulators and biopharmaceutical manufacturers to develop and critically evaluate measurement systems for adulterant detection, which would improve the safety of biopharmaceuticals and vaccines. For example, it might be useful to develop certified reference materials for organic leachates found in biopharmaceutical products and/or a reference data base of process and packaging materials and their corresponding leachates. Additionally methods for identifying host cell protein contaminants would facilitate their removal, reducing the possibility of toxic or immunogenic adverse drug events.

**Production cell unpredictability** – Biomanufacturing processes are highly variable and unpredictable due to a lack of tools to measure the internal workings of the cells that synthesize, modify and secrete the desired biopharmaceutical product. Most protein therapeutics are produced in Chinese Hamster Ovary (CHO) cells, but numerous problems are routinely encountered where CHO cells, for unknown reasons, do not perform appropriately. When this occurs, weeks or months of production time are

wasted. Industry has indicated to NIST a strong desire to have available measurement tools to enable a more complete understanding of the CHO cell system to a point where it can better be manipulated and controlled. This would require the ability to identify, quantify and measure the thousands of biomolecules and signaling pathways that govern the inner working of these tiny biopharmaceutical factories.

Industry and academia would be better equipped to understand changes in the cell function and the associated production capacity by using a systems biology-based approach to monitor production cell behavior. However, this would require greatly improved measurement capabilities and a robust measurement infrastructure to support analysis of cell behavior at this level, particularly in a manufacturing environment. With such robust capabilities available, a more fundamental understanding of bioprocessing would be possible, enabling the agile, low cost manufacturing of safe and effective protein- and cell-based products.

**Quality-by-Design (QbD) Implementation** – According to the FDA <sup>2</sup>, under a quality by design paradigm, biopharmaceutical manufacturing will depend on a risk-based approach linking attributes and processes to product performance, safety, and efficacy. QbD relies heavily on the use of process measurement technology and process understanding. Currently, there is no measurement science support in place to help manufacturers develop and validate new process measurement tools and improve biological manufacturing processes. Often when new measurement tools are introduced, each manufacturer must expend considerable effort and expense to validate their performance. As a result, there is much duplication of effort, and manufacturers are often hesitant to accept new tools. In addition, manufacturers are reluctant to adopt process changes that might increase manufacturing efficiency for fear of unpredictable changes to the product.

**Viral clearance** – Removal of potential viral contaminants by filtration is a key operation in the manufacture of biologic drugs. Both filter vendors and biopharmaceutical manufacturers agree that standardized test methods for classifying and identifying virus filters are needed to better assess performance and comparability of different filters. Establishing and understanding uncertainties in the measurements of virus size using different methods, which often give conflicting results, is the key to developing robust filter challenge protocols. In addition, there is well known variability in virus preparations obtained from different contract testing labs used to challenge filters.

Improved viral size measurements and preparation methodologies would enable manufacturers of biopharmaceuticals to better evaluate filter performance and compare different filters. The development of standard materials and methods to support the detection of viral particles present at low levels in biologic drugs would support product safety and quality assurance.

A longer range and broader challenge for the industry is the **unpredictable nature of biopharmaceutical function** –Presently we do not fully understand the interplay between all of the ongoing interactions that take place in our bodies that ultimately define

our health. This incomplete understanding makes it difficult to completely predict the effect of new drugs, as we do not know how the drug will impact other parts of the biological system beyond the part it was designed to address. This lack of understanding poses a challenge to the development of new drugs and biologics because we are not able to confidently measure or predict how effective the products under development will be, or how toxic they might be. Multiple biologics have been subject to market recalls and withdrawals due to unpredicted side effects.

Addressing this challenge will take a significant multidisciplinary approach and a significant amount of fundamental research. Critical to this effort is the development of improved measurement capabilities that are essential to the creation and validation of reliable new functional assays and predictive toxicology tools that would help the biopharmaceutical and drug development industry streamline drug development and approval processes.

### ***NIST's Role in Biopharmaceutical Manufacturing***

NIST has the unique Federal role of providing measurement science and developing the measurement standards needed to help the American economy innovate and compete. The biopharmaceutical industry (Companies that innovate the original products and those that produce generic products) faces many challenges to further grow and succeed in a globally competitive marketplace. Biotechnology drugs, protein and cell-based therapeutics, represent the fastest growing category of therapeutic drugs in the United States. Improved characterization and manufacturing of biologic drugs will support the growth of a new industrial sector that could produce generic biologics eligible for FDA approval, as proposed by the President, which would reduce the cost of healthcare for patients and the Federal government. . We have developed a comprehensive program plan that would broadly address critical measurement and standards issues associated with the manufacturing of both innovator and generic biopharmaceuticals such as:

- The **structural sameness** of the manufactured biopharmaceutical
- The propensity of the biopharmaceutical to induce an **immune response** in patients
- The presence of **contaminants** coming from manufacturing and packaging
- The ability to better **predict safety and efficacy** of candidate biopharmaceuticals
- The comprehensive understanding of **complex inner workings of production cells**

NIST already has begun a pilot intramural effort focused on physico/chemical measurements of protein structure, glycosylation & aggregation.

### ***Summary***

NIST has been, and continues to be, a critical resource for addressing the measurement and standards challenges associated with innovation in healthcare. The cost of developing new

drugs (including biologics) is certainly a contributor to healthcare costs. We look forward to a successful partnership with key stakeholders in industry, government and academia to address the measurement science and measurement standards challenges associated with the cost-effective production of both innovator and generic biologic drugs.

New measurement science and standards for biologic drugs will facilitate fact-based decision-making regarding:

- research and development, manufacturing and the regulatory approval process;
- reduced manufacturing costs and increased safety; and
- the determination of “sameness” in the production of both “innovator” and generic biologic drugs.

Mr. Chairman, thank you for the opportunity to testify today. This completes my statement and I will be happy to entertain questions.

Information Sources Cited:

1. McKoy, J. M., et. al., Epoetin-associated pure red cell aplasia: past, present, and future considerations, *Transfusion*, Vol. 48 (August 2008), pp. 1754-1762.
2. FDA, Submission of Quality Information for Biotechnology Products in the Office of Biotechnology Products; Notice of Pilot, *Federal Register*, Vol. 73, No. 128 (July 2, 2008).



**Dr. Willie E. May** is director of the Chemical Science and Technology Laboratory (CSTL), one of the ten technical operational units within the National Institute of Standards and Technology (NIST) and has ~325 technical staff of and an annual Budget of approximately \$90M. The NIST 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 quality of life. CSTL supports NIST's Mission by addressing customer needs for measurements, standards, and data in the areas broadly encompassed by chemistry, chemical engineering and the biosciences. Areas of growth and/or increased emphasis include bioscience and health, nanometrology, climate change science, and renewable energy technologies. CSTL is organized into six

Divisions along disciplinary lines:

- [Analytical Chemistry](#): Chemical measurements research and services in: inorganic, organic and electroanalytical chemistry; atomic, molecular and mass spectrometry; and microanalytical technologies
- [Biochemical Science](#): DNA chemistry, sequencing; Protein structure, properties, and modeling; Biomaterials; Biocatalysis and bioprocessing measurements
- [Chemical and Biochemical Reference Data](#): Experimental, theoretical, and computational research on the identity and reactivity of chemical species, emphasizing data, information, and protocols for the identification of chemical and biochemical species
- [Process Measurements](#): Research, calibration services, and provision of primary standards for temperature, pressure, vacuum, humidity, fluid flow, air speed, liquid density and volume, and gaseous leak-rate measurements; Sensor research
- [Surface and Microanalysis Science](#): Nanoscale chemical characterization; Particle characterization and standards; Electronic and advanced materials characterization; Surface and interface chemistry; Advanced isotope metrology
- [Thermophysical Properties](#): Experimental, theoretical, and simulation research on the properties of gases, liquids, and solids, emphasizing thermophysical properties

Prior to his current position, Dr. May led NIST's research and measurement service programs in analytical chemistry for more than 20 years. His personal research activities were focused in the area of trace organic analytical chemistry, with special emphasis on the development of liquid chromatographic methods for the determination of individual organic species in complex mixtures and the development of liquid chromatographic methods for the determination of physico-chemical properties such as aqueous solubilities, octanol/water partition coefficients, and vapor pressures of organic compounds. This work is described in more than 100 peer-reviewed publications. During

his 35+-year professional career, he has presented more than 300 invited lectures at U.S. industrial sites, colleges/universities and technical meetings throughout the world.

Dr. May has several leadership responsibilities in addition to those at NIST. He is a member of the 18-person International Committee on Weights and Measures (CIPM), whose principal task is to promote world-wide uniformity in units of measurement and oversee the activities of the International Bureau of Weights and Measures in Paris, France (BIPM); Chairs the CIPM Consultative Committee on Metrology in Chemistry's Organic Analysis Working Group; Chairs the Interamerican System for Metrology's Chemical Metrology Working Group, Co-Chair's the Joint Committee on Traceability in Laboratory Medicine's Working Group on Reference Materials and Reference Procedures; and Chairs the Executive Board for the Hollings Marine Laboratory in Charleston, SC.

**Honors and Awards:** Department of Commerce Bronze Medal Award, 1981; National Bureau of Standards (NBS) Equal Employment Opportunity (EEO) Award, 1982; Department of Commerce Silver Medal Award, 1985; Arthur Flemming Award for Outstanding Federal Service, 1986; NOBCChE Percy Julian Award for Outstanding Research in Organic Analytical Chemistry and Presidential Rank Award of Meritorious Federal Executive, 1992; Department of Commerce Gold Medal, 1992; American Chemical Society Distinguished Service in the Advancement of Analytical Chemistry Award, 2001; Keynote Speaker for the 2002 Winter Commencement Ceremonies, University of Maryland, College of Life Sciences; Council for Chemical Research Diversity Award, the NOBCChE Henry Hill Award for exemplary work and leadership in the field of chemistry, Science Spectrum Magazine Emerald Award, in 2005, and the 2007 Distinguished Alumnus of the Year Award from the College of Chemical and Life Sciences, University of Maryland