An extraordinary standard: New NIST protein could spur biopharmaceutical innovation

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EXTRAORDINARY STANDARD

NIST'S **MONOCLONAL ANTIBODY** REFERENCE MATERIAL

Monoclonal antibodies are a class of therapeutic compounds accounting for **five of the 10 top-selling drugs** and more than **$75 billion in annual sales** worldwide.

What are **MONOCLONAL ANTIBODIES?**

The body tailor-makes antibodies to combat specific foreign substances, such as **viruses and bacteria.**

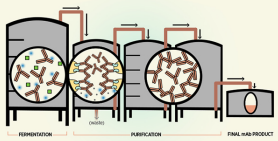
Therapeutic monoclonal antibodies are highly specific protein molecules designed to mimic the human body's immune response.

They also can act like **guided missiles** that precisely deliver **therapeutic payloads** of chemicals or radiation to cancer tumors.

How are **MONOCLONAL ANTIBODIES** made?

Monoclonal antibodies are **nearly identical copies of a single type of antibody** produced by living systems, typically **mammalian cells**.

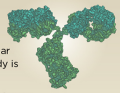
Mass producing these complex molecules requires building a "**biological factory**."



It entails developing processes and scaling them up—from research to manufacturing. Tests and assays are built into each step.

Why did NIST develop a **MONOCLONAL ANTIBODY REFERENCE MATERIAL?**

Manufacturers rely on many different **chemical and biochemical assays** to determine that each batch of their particular therapeutic monoclonal antibody is safe and effective.



The **NISTmAb** will **help manufacturers** know that their assays are working properly.

The **NISTmAb IgG1** (*aka* NIST RM 8671)

is a **first-of-its-kind measurement tool** for the biopharmaceutical industry;

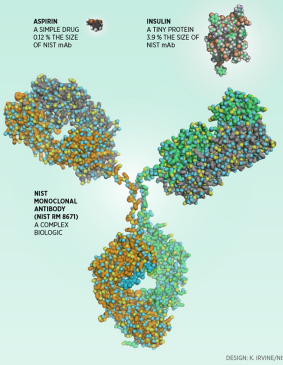
provides a **standard reference** for everyone;

will **aid the development, quality control, and testing of biological drugs**.

Biological drugs are **BIG**

"In terms of size and rough complexity, **if an aspirin were a bicycle**, a small biologic would be a Toyota Prius, and **a large biologic would be an F-16 fighter jet.**"

—W. Nicholson Price II and Arti K. Rai, "Manufacturing Barriers to Biologics Competition and Innovation."



DESIGN: K. IRVINE/NIST

NIST National Institute of Standards and Technology U.S. Department of Commerce

www.nist.gov

NIST's monoclonal antibody reference material is a standard benchmark for all. With it, manufacturers and regulators can better assess methods for analyzing and assuring the quality of complex biological drugs. Credit: Irvine/NIST

The National Institute of Standards and Technology (NIST) has issued one of the world's most intricate measurement standards: an exhaustively analyzed antibody protein that the biopharmaceutical industry will use to help ensure the quality of treatments across a widening range of health conditions, including cancers, autoimmune disorders and infectious diseases.

The standard is an antibody protein—consisting of more than 20,000 atoms—analyzed so thoroughly that the material can be used by organizations around the globe to verify and improve their analytical methods for quality control.

Donated by MedImmune, the global biologics research and development arm of AstraZeneca, and then characterized by NIST and collaborators, the new reference material (RM)—NIST RM 8671—is a monoclonal antibody, or mAb. This class of therapeutic compounds is produced in the lab by living cells, usually from mouse or hamster cell lines.

Uniform in composition and structure, mAbs account for five of the 10 top-selling drugs and over $75 billion in annual sales worldwide. According to one estimate, about 300 monoclonal-antibody-based therapeutics are being evaluated for safety and effectiveness in clinical trials.

Antibodies work by binding to and inactivating proteins involved in

disease pathways. mAbs also can act like guided missiles that precisely deliver therapeutic payloads of chemicals or radiation.

Chosen for development in consultation with industry, NIST RM 8671 is an important addition to the toolkits of biological drug manufacturers and their suppliers and regulators. It serves as a representative molecule that can be used to determine that methods for assessing product quality are working properly and to evaluate new methods or technologies.

It also provides an industry very mindful of intellectual property concerns with a standard benchmark for everyone, from aspiring startup to multinational firm to regulator.

As such, "it can serve as a common benchmark for future innovation," explained NIST research chemist John Schiel, who led an international effort that explored and demonstrated uses of the reference mAb. "The material has many anticipated applications—in establishing industry-recognized best practices, for example—and we are hoping that there will be many future uses that we can't predict from the current state of practice in biopharmaceutical research and production."

NIST's new monoclonal antibody reference material -- NIST RM 8671 -- is shipped in cryovials packaged in dry ice. It should be stored in a frozen state at ?80 °C (-112 °F). Shown is a sample that underwent extensive round-robin testing by more than 100 collaborators before the biological material, donated by MedImmune, was certified as a NIST RM. Credit: Matthew DeLorme

A Useful Tool

Industry experts have indicated that a universally available 'public' mAb, characterized and distributed by NIST, will allow better assessment of existing analytical methods and potentially faster adoption of new technologies.

In fact, the utility of the reference material already has been demonstrated by more than 100 collaborators from companies, regulatory agencies and universities around the world. As documented in a three-volume book set published by the American Chemical Society (ACS), the partners engaged in a "crowdsourcing" exercise. Research teams used current and emerging analytical methods to, in effect, take measure of the mAb from many different vantage points before NIST formally released it as a standard.

"NISTmAb, will act as a shared catalyst for developing, troubleshooting, adapting and bridging analytical technologies," explained Oleg Borisov, director of analytical development at Novavax. "The book from ACS demonstrates this. It presents extensive information and data on a single monoclonal antibody, and describes the methodologies that enabled this state-of-the-art characterization. The result is a comprehensive characterization dossier that should serve as a valuable reference to researchers."

Schiel, Borisov and Darryl Davis, associate director of biologics research at Janssen R&D, LLC, Pharmaceutical Companies of Johnson & Johnson, are editors of the set, State-of-the-Art and Emerging Technologies for Therapeutic Monoclonal Antibody Characterization.

Each vial of NIST RM 8671 will contain 800 microliters of the NISTmAb at a concentration of 10 milligrams per milliliter. The standard comes with the results of NIST measurements that provide a

thorough profile of the standard protein, Schiel said, providing details on size, concentration, composition, structure, purity, stability and other attributes.

Kurt Brorson, a research biologist in the Office of Biotechnology Products at the Food and Drug Administration (FDA), said the new standard can be used as a "universal system suitability test" for many of the assays and test methods used to assure the quality of mAbs. "The biotech industry can more efficiently cross-validate (measurement) methods at different sites or more efficiently develop platform analytics for related molecules," he explained.

"The NISTmAb should help in answering a simple, yet critical, question that can consume a disproportionate amount of time when deviations arise with testing; is it the sample or the method that is varying?" said Michael Tarlov, chief of NIST's Biomolecular Measurement Division and leader of the NIST-wide Biomanufacturing Program.

During the NISTmAb's meticulously recorded audition, NIST and its collaborators developed data comparable to that found in a Biologics License Application submitted to the FDA when a company seeks approval for a new mAb-based therapeutic. These data are available online, along with results of analyses done with still-experimental tools, providing a historical record of NIST RM 8671 that will be updated as more analyses are done and as questions arise and spawn new studies.

Combined with the three-volume book set, the reference material and data repository provide a comprehensive—yet updateable—picture of the state-of-practice in the fastest-growing area of biopharmaceuticals.

"We hope that this compilation serves as a baseline for many years of future collaboration, continued development and ultimately a routine analytical pipeline for rapid time-to-market for mAb therapeutics,"

Schiel, Davis and Borisov state in the preface of their book set.

More information: For technical details on NIST RM 8671, go to: www-s.nist.gov/srmors/view_detail.cfm?srm=8671

Provided by National Institute of Standards and Technology (NIST)