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NIST Gives a Measured Response To the Medical Device Industry's Technology Challenges

History holds a telling lesson on the importance of measurement accuracy to makers of healthcare products. In the early 1900s, U.S.-made clinical thermometers were notorious for errors—about 40 percent did not perform within accepted tolerances. Not surprisingly, German competitors were feasting on the U.S. market.

Enter a young federal laboratory established, quite literally, to make correct measures. The organization, now known as the National Institute of Standards and Technology (NIST), established a standard temperature scale, providing manufacturers with a fixed and reliable reference for checking the performance of their thermometers. Industrywide, the failure rate dropped to about 5 percent.

"So great has been the improvement in American-made thermometers," a University of Michigan professor wrote in 1911, "that the German makers are complaining more and more of the loss of American trade in thermometers."

Today, measurements and standards are even more fundamental to the performance—and success—of manufacturers of healthcare products and their parts and materials suppliers. To keep up with the growing need, NIST is ramping up its efforts to develop and deliver measurement tools and standards for makers of orthopedic implants and biomedical devices, surgical tools, diagnostic and therapeutic equipment, pharmaceuticals, clinical assays, and other products among the mammoth industry's diverse offerings.

"Several converging forces—from technology advances on many fronts, to more demanding regulatory and quality requirements—drive demand not only for higher levels of accuracy and precision, but also for new types of measurements," says NIST Director Arden Bement. As an example, Bement points to the burgeoning area of tissue engineering, where the vastness of the "parameter space" may be exceeded only by the field's enormous potential to deliver biomedically useful products and new diagnostic and treatment capabilities.

Already, according to estimates, measurement-related tasks—from calibrating x-ray machines and lasers, to testing for levels of cholesterol or lead—account for about 13 percent of the more than $1 trillion that Americans spend on health care.

"Measurement support for the healthcare industry, broadly defined, is an area of strategic focus for NIST over this decade," Bement says.

Snapshot of NIST's Four Programs
Part of the U.S. Commerce Department's Technology Administration, NIST tends to the health of our nation's technology infrastructure—a platform of enabling tools and other resources that manufacturers and others use to accomplish their technical aims. These aims range from incorporating new discoveries and innovations into future products, to controlling processes so that they can assure customers that their products are within agreed-upon tolerances. NIST has four programs that serve as resources for the orthopedic industry and the broader healthcare sector.

1) NIST's Laboratories (seven in all) are direct descendants of the National Bureau of Standards and serve as the nation's measurement authority. The laboratories have counterparts in nearly every other nation. Together, these "national metrology institutes" are the custodians of the international measurement system and the primary means to harmonizing measurement-related requirements—whether embodied in regulations, standards, or customer specifications. (To learn more about NIST laboratories, visit: http://www.nist.gov/public_affairs/labs2.htm)

2) NIST's Advanced Technology Program (http://www.atp.nist.gov/) provides cost-shared funding to industry-led teams (which can include non-profit organizations and universities) to accelerate the development and broad dissemination of challenging, high-risk technologies that promise commercial pay-offs and widespread benefits to the Nation. Since its inception in 1989, the ATP has awarded 602 research projects in a wide variety of technology areas, a third of which were joint ventures involving

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two or more companies, and over 60% were led by small businesses. The investment in high-risk research totals $3.7 billion, split almost evenly between government and industry. ATP investment exceeds $470 million for projects focused on healthcare applications. Technology areas range from microfluidic devices, to plants as bioreactors, to scaffolding for bone regeneration. By definition, ATP projects are high-risk endeavors, so success is not assured. Yet, most have borne fruit, and several projects have delivered valuable new healthcare technologies. For example, the ATP is widely credited as being a critical force in the development of the diagnostic "gene chip" industry, providing funding when the technology's prospects were too hazy to attract adequate private sector capital. Another example is Integra LifeSciences, a New Jersey firm that used its 1993 award for research that ultimately yielded new biocompatible polymers. These new bioabsorbable polymers have been fashioned into prototype pins, screws, and other devices envisioned for cartilage, meniscal, and tendon repairs, as well as other applications, potentially eliminating the need for subsequent surgeries to remove implants, such as pins and screws.

3) The Manufacturing Extension Partnership (http://www.mep.nist.gov/), another NIST program, helps to disseminate technology among smaller manufacturers. The MEP is a nationwide network of more than 400 centers and field offices that deliver advice and technical services to businesses aiming to improve their performance—operationally and in the market. Last year, the network's field engineers provided assistance to more than 21,000 firms, aiding their efforts to upgrade business practices and systems, improve processes, develop products and markets, implement new training programs, and accomplish other objectives.

Centers and offices use the NIST-coordinated MEP network to access industrial resources, services, and expertise tailored to their customers' needs. Focused programs in the areas of lean manufacturing and "e-business" are helping suppliers to meet ever-more-demanding customer requirements and to increase productivity—a counter to cost pressures that can erode profit margins.

4) U.S. manufacturers also leverage the tools and resources of the NIST-managed **Malcolm Baldrige National Quality Award** (http://www.quality.nist.gov/), viewed by many as one of the best examples of an effective partnership between government and the private sector. Funded by Congress and endowed with contributions from business, the quality award program has been both motivator and coach to companies striving to continuously improve the quality of their products and services and to raise their levels of performance, month after month, year after year.

"The award is invaluable because it comprehensively lays out a set of ideas that most companies agree they should strive for, but most, in fact, do not," explained the chief executive officer of ADAC Laboratories when the Silicon Valley-based maker of diagnostic imaging equipment won the 1996 Baldrige Award. "Those companies that adhere to the criteria ... have a sustainable competitive advantage over those that do not."

Over the five-year span leading up to the award, productivity at ADAC jumped 65 percent, and its market share increased at home and in Europe, Asia, and Latin America. In 2000, ADAC Laboratories was acquired by Royal Philips Electronics.

A Closer Look: The NIST Laboratories

For decades, the semiconductor industry has stepped to the cadence of "smaller, faster, cheaper." But, now, nearly every industry is following the chipmakers' beat. Manufacturers of implanted medical devices confront the challenge of reducing tolerances to minuscule dimensions, building in more capability, and capitalizing on advances in the many fields of science and technology that are converging on the domain of atoms and molecules. These developments are occurring against the backdrop of changing market demographics. An aging population introduces more demanding requirements for prosthetic devices. Tomorrow's elderly are likely to be more active, placing an even higher premium on the performance, durability, and longevity of implanted products.

NIST's laboratories supply tools and services designed to support innovation, improve process control, and promote trade unfettered by seemingly duplicative regulatory and technical requirements. Ranging from an array of materials databases, to measurement references, to assistance in satisfying standards-related requirements in export markets, the laboratories help U.S. businesses compete today, while ongoing or planned research anticipates future needs. Some examples follow.

Reference Biomaterials. Ultrahigh molecular weight polyethylene (UHMWPE), used in combination with cobalt and chromium

alloy, is the material of choice for artificial joint replacements. Yet, material performance is a moving target, always a candidate for improvement. The challenge of enhancing measurement technology and test methods for assessing the wear of UHMPWE was met by a collaboration involving NIST researchers and their counterparts from Biomet, Inc., Zimmer, Inc., Johnson & Johnson Professional, Inc., and Stryker Howmedica Osteonics Corp.

The team confirmed that the orientation of polyethylene molecules was directly related to wear-resistance. Cross-linking of the polymer's molecular components resulted in the lowest levels of wear. The team also determined that rubbing the surface layer in one direction promotes an aligned state that resists wear along that direction but that rubbing across the aligned direction causes increased wear because resistance is lower in the nonaligned direction. The wear results themselves were consistent with measurements of wear as reported in the literature. (For more information, contact Stephen Hsu; stephen.hsu@nist.gov, (301) 975-6120 or John A. Tesk; john.tesk@nist.gov, (301) 975-6799.)

As part of this work, NIST produced Reference Material (RM) 8456, an orthopedic-grade bar of UHMWPE, as requested by industrial partners. The need arose when supplies from the original source of this reference—the Hospital for Special Surgery in New York City—became limited. The NIST reference enables direct comparison of results from mechanical tests of material properties, reducing measurement uncertainty and ambiguity in the interpretation of results. The UHMPWE reference also should increase confidence in the results of simulations designed to assess the material's long-term performance in joint replacement implants. The material used to prepare RM 8456 was donated by the MediTECH Division of Poly Hi Solidur, Inc. (To purchase or to learn more about RM 8456, contact Joylene Thomas; joylene.thomas@nist.gov, (301) 975-5542.)

Later this year, NIST intends to introduce a companion UHMPWE reference material, RM 8457, which is intended for evaluations of crosslinking induced by radiation exposure. A set of UHMPWE cubes measuring 0.5 centimeter on a side, the reference was used in an ASTM-sponsored interlaboratory evaluation of a new test to measure parameters of crosslinked UHMWPE. RM 8457 supports a new ASTM standard test procedure determining the network parameters of crosslinked UHMPWE. (For more information, contact Joylene Thomas; joylene.thomas@nist.gov, (301) 975-5542.)

In all, NIST produces 90 different health-related Standard Reference Materials—the equivalents of rulers used to check the accuracy of measurement equipment, mostly in clinical laboratories. In addition to UHMPWE, examples are SRMs for tests of nutritional status, measurements of radioactivity, and DNA profiling. Under development are SRMs for prostate-specific antigen (an indicator of prostate cancer), homocysteine (risk of heart disease), folic acid vitamers (neural tube defects), and health status indicators. (For more information, contact Joylene Thomas, joylene.thomas@nist.gov, (301) 975-5542.)

Calibrations and Special Tests. NIST also provides calibration services that assess the performance of equipment used for a variety of health care procedures, such as mammography and laser eye surgery. These services can be key to the acceptance of new technologies in clinics and hospitals, as illustrated by emergence of a growing number of brachytherapy treatments. Such therapies either use rice-sized radioactive seeds that can be implanted in, or near, tumors, or they provide radiation in conjunction with balloon angioplasty in clogged arteries. Doctors are using them in lieu of external radiation sources for prostate cancer patients and to prevent restenosis, or reclosing, of heart arteries following angioplasty. NIST is helping advance these new therapies by calibrating radiation doses that are delivered from the radioactive seeds or other radiation sources. (For more information, contact Dr. Lisa Karam; lisa.karam@nist.gov, (301) 975-5561.)

NIST is the only laboratory in the world to offer calibrations of radioactive seed sources for prostate cancer. The American Association of Physicists in Medicine, the Food and Drug Administration, and the Nuclear Regulatory Commission require that manufacturers trace the accuracy of their prostate seeds to brachytherapy radiation standards at NIST.

A newly begun project, undertaken at the request of the FDA, is developing measurements and standards to reduce the risk that magnetic fields generated by metal detectors will interfere with pacemakers, defibrillators, and other implanted devices that incorporate "on board" electronics. NIST scientists and engineers are building a system that emulates magnetic fields produced by commercially available detectors, which are becoming nearly ubiquitous. Medical device makers may be able to use the system to test their products before release, providing a high level of assurance that passing through a metal detector will not disrupt performance.

High-Nitrogen Stainless Steel. A project to develop sensors to characterize advanced methods for processing highly uniform, ultrafine metal powders yielded an unanticipated dividend: a technique for making highly nitrogenated stainless steel alloys with enhanced strength, ductility, and corrosion resistance. Initial tests indicate that NIST's new microengineered alloys are more resistant to corrosion than 316L, the stainless steel widely used to make fracture plates, screws, hip nails, and other implanted devices, and that they are less susceptible to pitting in high-stress, low-oxygen environments.

Also significant, the NIST-developed processing method—dubbed powder metallurgy-rapid solidification processing—lends itself to near net-shape fabrication, which translates into reductions in machining time and scrap. Because of their highly uniform microstructure, the new alloys are less prone to embrittlement than other nitrogenated stainless steels. With metal powder suppliers, the NIST inventors are exploring options for optimizing their new processing method so that it can be converted to commercial-scale production. (For more information contact Dr. Steve Ridder; stephen.ridder@nist.gov, (301) 975-6175.)

Bone Graft Candidate. About 500,000 bone grafts are performed each year in the United States, and the number is likely to grow as the population ages. Today, most procedures entail harvesting

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bone in the patient's body and shaping this "autologous" bone to fit and function in a new site. This approach has limitations: It requires two surgeries, the amount of harvestable bone is limited, and the autograft is difficult to mold into the desired shape. A collaboration between NIST polymer scientists and researchers from the American Dental Association Health Foundation could add an attractive option to the limited range of synthetic alternatives available for bone grafts. The team modified a self-setting calcium phosphate cement first developed at the foundation's Paffenbarger Research Center, which is located at NIST. A version of the compound, marketed as *BoneSource*® by Stryker Howmedica Leibinger Inc., already is used for cosmetic reconstruction of bones that do not bear significant loads.

Adding a new twist, the team is incorporating a bone growth factor and tiny spheres composed of a biogdegradeable polymer into the mix. Initially, the polymer microspheres stabilize the graft, but then breakdown gradually, leaving a network of pores behind. In laboratory tests of the new material, cells akin to osteoblasts—the precursors of bone cells—colonize on the new composite bone graft, where they develop normally and multiply. Controlled release of the growth factor stimulates bone growth. The results suggest that, in the body, the matrix of modified calcium phosphate cement would be reabsorbed and replaced by new bone that could withstand significant loads.

Should it live up to its early promise, the new material would be an added bonus of work focused specifically on developing measurement methods for assessing the biocompatibility and performance of new, tissue-engineered materials. Using derivatives of calcium phosphate cement as test subjects, the team has been devising techniques for assessing cell morphology, viability, adhesion, and proliferation on substrates of candidate materials for implants and other biomedical applications inside the body. (For more information, contact Dr. John A. Tesk; john.tesk@nist.gov, (301) 975-6799.)

High-Precision Machining of Small Parts at Reduced Cost. Manufacturing without measuring wastes time, materials, and effort. It also causes dissatisfied customers. NIST devotes considerable resources to helping manufacturers make parts and final products within specified tolerances, which decrease by about tenfold every decade. At every scale of manufacturing—from the fabrication of integrated circuits with almost nanometer-sized dimensions, to the production of massive turbines and jumbo aircraft—the room for error is diminishing to challenging levels. Manufacturers use NIST-supplied dimensional measurement tools and references to ensure that their outputs are within tolerances. In their pursuit of higher levels of accuracy in dimensional measurements, NIST researchers have consistently provided technology for improving machine tool performance. Software that compensates for errors caused by changes in temperature or by a machine's structural characteristics, for example, is rooted in early work done by the institute's scientists and manufacturing engineers.

Recently, a NIST team launched a project to explore how advanced measurement technology might be used to raise the cutting performance of low-cost machine tools so that they can produce small, high-precision parts accurately, reliably, and economically. Fabrication of small parts for the medical device industry—parts with dimensions ranging from about 2 centimeters to a few micrometers and even smaller—is one of the exploratory project's chief targets.

Using measurement technology to upgrade machine tool performance could greatly reduce manufacturers' capital costs. Why pay $200,000 or more for a large-frame machine with 0.005 millimeter accuracy to achieve a tolerance of 0.010 millimeter, when a small-frame machine that costs far less could be upgraded to achieve the same level of cutting performance? In addition, the embedding of accuracy-enhancing technology directly into machine tools introduces measurement capabilities for continuous on-line quality control. (For more information, contact Dr. Alkan Donmez; alkan.donmez@nist.gov, (301) 975-6618.)

Working on the Supply Chain. Many different software and hardware systems are used throughout manufacturing supply chains and even within individual companies. These systems perform many vital functions, but their usefulness is often limited by the proverbial "failure to communicate" or, stated in digital age terminology, a "lack of interoperability." Incompatibilities subvert exchanges of information. The output of one application may be indecipherable to another—a serious deterrent to supply chain collaboration through electronic channels.

Cost and uncertainty are two major obstacles to achieving fully integrated supply chains and unimpeded business-to-business (B2B) interoperability. Underlying these understandable concerns is the confusing plethora of technologies and alternative "standards" for linking organizations, processes, applications, and more. At the same time, there is growing recognition of the need to enable more robust and even more functional e-business relationships among companies, their suppliers, and their customers.

NIST is working with its counterparts in industry and at universities to develop the basis for standards and other elements of an infrastructure that can support true interoperability and efficient distributed manufacturing operations. As recommended by a variety of organizations, including the Open Applications Group, RosettaNet, the Automotive Industry Action Group, and several major manufacturers, NIST has created a B2B Interoperability Testbed. This new virtual facility, now under development, will provide a shared infrastructure to support tests and experiments by manufacturers, software vendors, and standards organizations. On an as-needed basis, manufacturers and software developers will use the testbed to demonstrate, measure, and analyze approaches and emerging technologies for on-demand integration of software applications in supply-chain interactions. In support, NIST is developing conformance tests, providing test data, and coordinating demonstrations of manufacturer-suggested integration scenarios, as well as analyzing and reporting the results of these trial runs.

The testbed is but one example of many NIST projects tackling obstacles to true interoperability and efficient distributed manufacturing operations. While several projects focus on

impediments to supply chain integration in specific industries, such as automotive, many of the accomplishments and lessons learned in these collaborations will apply to manufacturing of healthcare products as well as other sectors. (For more information, contact Simon Frechette; simon.frechette@nist.gov, (301) 975-3335.)

Lowering Barriers to Trade. Markets for biomedical products are heavily regulated, requiring demonstrated adherence, for example, to an array of standards. Some of these standards may be international in scope and acceptance and others may be unique to countries. Proving compliance to gain market entry can be burdensome and costly.

NIST contributes to efforts to lower these technical barriers to trade. For example, staff members helped to work out the operational details of the Mutual Recognition Agreement between the United States and the European Union. Covering medical devices and five other product areas that, altogether, account for $50 billion in trans-Atlantic trade, the MRA calls for either party to accept as equivalent the results of tests, inspections and other evaluations performed by accredited laboratories or organizations on either continent. Now, U.S. manufacturers in the sectors covered by the agreement can complete all of the requisite product testing and other conformity assessment activities before they ship their products to Europe.

The 21st century marketplace appears to be moving toward more formalized and more systematic approaches for ensuring measurement accuracy. Major impetus for this transition has come from quality management system standards issued by the International Organization for Standardization, or ISO. Adopted by more than 350,000 organizations in 150 nations, the so-called ISO 9000 family of standards specifies that, when possible, measuring equipment should be calibrated against standards traceable to international or national measurement standards.

Since many large manufacturers require their regular suppliers to be ISO 9000 registered, a growing legion of businesses is becoming familiar with measurement traceability.

In addition, the European Union will require makers of in vitro diagnostic test systems (IVD products) to demonstrate traceability by 2003. Vendors will have the option of establishing the accuracy of their measurement results by other means, but observers suggest that alternative routes to securing the CE mark for IVD products will likely be harder and more circuitous.

NIST is building the machinery to establish the equivalence of measurement results on regional and, ultimately, global scales. NIST has set up the International Comparisons Database, a vehicle for comparing its measurement and calibration capabilities with those of national metrology institutes in 33 other nations in the Western Hemisphere. By means of the database, a Brazilian purchaser of, say, U.S.-made medical devices and diagnostic equipment, could be certain that measurements shown to be traceable to NIST are equivalent to those traceable to INMETRO, Brazil's measurement authority.

In turn, the database supporting the Inter-American Metrology System is associated with a comparison and calibration database maintained by the International Bureau of Weights and Measures, a treaty organization that has the task of ensuring worldwide unification of physical measurements. With links to all of the world's regional metrology organizations, the bureau's database will eventually provide direct and indirect means to judge the equivalence of measurement capabilities in different countries, which could ease the burden and cost of retesting.

"The databases should open the door to achieving traceability by alternative routes," says Robert Watters says, one of the chief architects of the database. "Our aim is to move the database from the exclusive realm of the measurement scientist and make it an easy-to-use tool for companies and regulators, providing them with a clear line of sight for assessing the equivalence of measurement results. Ultimately, our hope is that this tool will help to eliminate technical barriers to market entry."

To learn more about NIST and its programs, check out NIST's web page for the health care industry at: http://www.nist.gov/public_affairs/healthcare.htm. In addition, the institute's Industrial Liaison Office has specialists assigned to the industry. Their job includes linking companies interested in using NIST services or learning more about ongoing or planned research with the appropriate experts or resources. The office's technical advisors for the health care industry are John Tesk (301-975-6799; john.tesk@nist.gov) and Lisa Karam (301-975-5561; lisa.karam@nist.gov). General information on the NIST Industrial Liaison Office is available at: http://www.nist.gov/director/ilo/

Dr. John A. Tesk *has served as Leader of the Dental and Medical Materials Group (1983-1994), as coordinator of the Biomaterials Program in the Polymers Division of NIST, as manager of the NIST Orthopaedic CRADA Research Consortium from 1996 to 2000. He has served on the review/advisory boards of four universities (biomaterials, dentistry, orthopedics); as the the only foreign member of the first review board for a Japanese dental school; on editorial boards for three journals on dentistry and biomaterials; as a contributing editor to the Biomaterials Forum; and on the NIST editorial review board.*

A previous Director of R&D in the Dental Division of Howmedica, Dr. Tesk has served as officer and committee member of numerous scientific organizations and materials/technical societies. He has received recognition for his leadership with standards activities as leader of the United States delegation to ISO TC 106 (dentistry), Chair of ANSI MD 156 Committee on dental standards, and the MOSES award from ASTM Committee F04 on Medical Device Standards. He has approximately 90 archival publications, including a best paper award from the Japanese Society for Dental Materials. Dr. Tesk received his B. S. degree in Engineering Science (1957), M.S. in Metallurgy (1960), and Ph.D. in Materials Science (1963), all from Northwestern University.

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