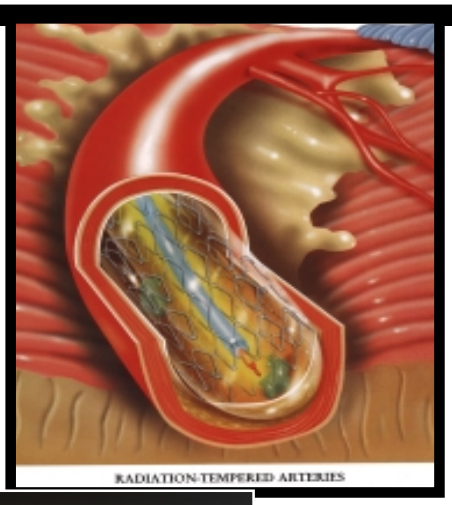
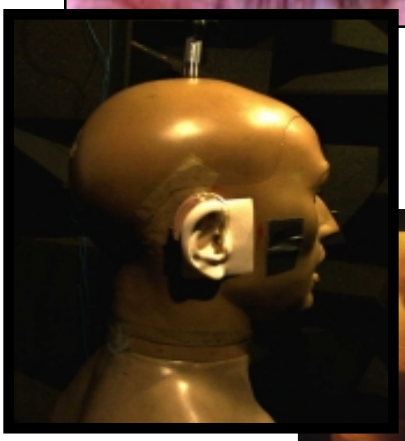
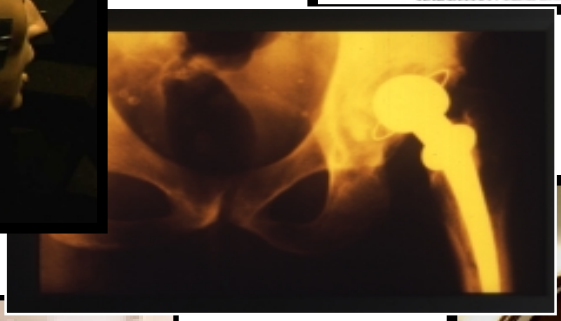
NISTIR 6791

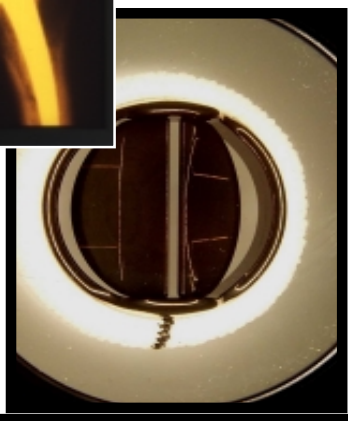
Workshop on Standards for Biomedical Materials and Devices

June 13 - 14, 2001









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Workshop on Standards for Biomedical Materials and Devices

U. S. DEPARTMENT OF COMMERCE
Technology Administration
National Institute of Standards
and Technology
Gaithersburg, MD 20899-8230

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U.S. DEPARTMENT OF COMMERCE
Donald L. Evans, Secretary

NATIONAL INSTITUTE OF STANDARDS
AND TECHNOLOGY
Dr. Karen H. Brown, Acting Director

Introduction

The Workshop on Biomedical Materials and Devices, held June 13-14, 2001, is the latest in a series of workshops and topical meetings organized by NIST in the area of biomedical technology. The workshop complements other recent NIST efforts to make its leadership in standards and measurements more available to the health care industry, which accounts for about 13% of the U.S. Gross National Product and continues to grow rapidly.

The primary goal of the workshop was to identify and prioritize standards needs in selected biomedical materials and devices technologies as the basis for a NIST standards strategy in those areas. The technical focus areas in this workshop,

- Biomaterials
- Tissue engineered medical devices
- Therapeutic and drug delivery systems
- Auditory diagnostic and prosthetic devices
- Manufacturing and processing of prostheses

were chosen because they are areas in which NIST currently has active projects and is prepared to respond to the findings and recommendations of the workshop. The workshop also addressed three crosscutting topics that are common to all of the focus areas and many other biomedical areas as well:

- Data exchange and integrity
- Sterilization
- Harmonization

A second goal of the workshop was to obtain recommendations for collaborations between NIST and other key stakeholders in the biomedical materials and devices industry to address national and international standards issues. NIST has a long history of effective partnerships with others in many technical and industrial fields and has found that such arrangements can facilitate the acceptance and use of new standards, measurement methods, and technology.

The participants for the workshop were chosen from among a core group of idea generators and decision makers from industrial companies; organizations that shape the standards, regulatory, and research and development environment in which those companies work; and the standards community. The findings and recommendations in this report represent the consensus that they reached on critical standards needs and the actions needed to address them. The workshop participants accomplished a great deal in a limited time. The ideas and plans that were developed already represent a significant result. However, the true success of the workshop will be measured by the actions that NIST and others subsequently take in response to the recommendations in this report.

The Workshop Planning Committee wishes to thank all those who organized, facilitated, and participated in the workshop.

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Executive Summary

Dale Hall
Material Science and Engineering Laboratory

The biomedical materials and devices industry works in a climate of ever-higher expectations as the demographic makeup and attitudes of the customer base evolve and technology advances in the field and related areas. Historically, the medical device industry has been both highly innovative and strictly regulated. The emerging relationships between standards applied for use for regulatory and trade purposes has placed increasing importance on the development of standards for biomedical materials and devices. The importance of standards for these purposes is evident in the three primary reasons that were identified at the workshop as to why standards are needed today:

- ***Reduced time and cost of new product introductions***. Good standards can help industry to focus on and set targets for critical product performance characteristics and to speed the approval process. Expediting the front end of the process is crucial. Whenever possible, standards and measurement work should be anticipatory rather than reactionary; work on the basis for a standard can be begun before the technology is fully developed.
- ***Harmonization and competitiveness***. Harmonization is the process of making national standards compatible, which can cut the cost of doing business and remove impediments to international commerce. Standards, in turn, are the common denominators that make harmonization possible. Despite the business advantages of harmonization, consensus is not always easy, but must not be achieved by watering down standards to the lowest common denominator. Strong international standards can encourage convergence in national regulatory practices.
- ***Regulation***. The work of regulators is facilitated by standards that are clear, unambiguous, and technically rigorous. On the other hand, overly restrictive standards can stifle innovation and leave some technological approaches either disadvantaged or infeasible. The goal is to balance the needs for innovation and new product introduction with the need for acceptable safety levels and public confidence. Good standards can ease the regulatory burden on industry, by reducing the cost of compliance, and on regulators, by reducing the cost of device evaluations and approvals.

The workshop produced clear, and in most cases, quite specific technical priorities in all of the technical focus areas. These will not be repeated here, as they are summarized succinctly in the body of the report. What follows here is a summary in a broader, more strategic sense, of the findings and recommendations that emerged from the workshop.

Although the workshop focus was on paper standards, external participants encouraged NIST to expand its efforts in standards and standards-related work in a number of ways. Rather than defining a particular, narrow, across-the-board standards function for NIST, workshop participants made it clear that the work needed from NIST depended on the specific technical area and included the following:

- ***Standards writing and standards development***; in particular, work toward consistent terminology across standards-writing groups
- ***Committee leadership and participation***, in both national and international standards; join existing organizations that are meeting the needs, and form new subcommittees when necessary
- ***Measurement and calibration methods*** with high accuracy and reliability: summarize current baseline practices and recommend and pursue further advances
- ***Test method validation***; especially in the area of performance tests
- ***Databases***
- ***Standard Reference Materials*** (SRMs) ***and other Reference Materials***

The common denominator was the call for NIST to play to and build on its existing strengths.

Several workshop participants cited NIST's value as a neutral, objective party in technical matters. NIST can bring unbiased public sector data into standards development and the regulatory process. When disagreements must be resolved, NIST's long-established role of rendering sound, unbiased technical judgments helps to give all parties the assurance of an impartial recommendation. NIST's potential value in coordinating and convening key stakeholders in open forums, e.g., for strategy and planning, was also cited.

NIST's value as a source of information was stressed by many of the workshop presenters. One difficulty facing those outside NIST was the distributed nature of NIST's work on biomedical materials and devices. Projects span several laboratories, and finding all of the relevant programmatic information can be difficult. NIST was encouraged to develop and disseminate an inventory of all NIST activities in the field. Such an effort should begin with, but not necessarily be limited to, NIST's website. NIST was also encouraged to collect and make available a summary of all existing standards in the field, worldwide, i.e., a database of what is available and where it can be found.

Within the biomedical materials and devices community, there are a number of boards and committees where critical issues are discussed. NIST was strongly encouraged to maintain a continuing and regular presence on these key councils. By doing so, NIST will hear about important issues at an early stage. One important council is the Medical Devices Standards Board (MDSB). NIST has often attended MDSB meetings, but has not been a full member. At the workshop, NIST committed to becoming a full member and has subsequently done so. NIST's ability to maintain such connections has been strengthened recently by the creation of an internal Industrial Liaison Office, and two of the principal organizers of this workshop have joined that office, specifically to work with the health care industry.

While the workshop came to many specific recommendations, it was clear that some of the priority areas require further definition. As a result, some of the technical focus groups recommended further meetings and workshops to pursue those subjects. To ensure that these meetings will be action-oriented and customer-focused, they will be co-sponsored and co-organized by NIST and external partners whenever possible. We expect that the technical focus groups at this workshop will take proprietorship of these meetings and will form their nuclei.

Perspectives on the Needs for Biomedical Materials and Device Standards

Lisa Karam
Industrial Liaison Office
John A. Tesk
Materials Science and Engineering Laboratory
and
Industrial Liaison Office
Dale Hall
Materials Science and Engineering Laboratory

Introductory Remarks:
The meeting was opened with a welcoming address by Karen Brown, Deputy Director and Acting Director of NIST. Brown described the role of NIST toward improving the economy and the quality of life in the U.S. Brown emphasized the importance of health care to the economy, saying that the U.S. spends $1.1 trillion annually on health care, which is estimated to be 17 % of the GDP for 2002.

Leslie Smith, Director of the Materials Science and Engineering Laboratory at NIST, provided an introduction to health related activities at NIST. He noted that of the 3000 NIST SRMs (Standard Reference Materials) sold in 2000, approximately 10 % were health related. As an example he described NIST's role in the development of SRMs used for cholesterol measurements. NIST efforts for measurement methods and standards for electromagnetic fields, laser calibrations, medical materials collaborations (with FDA), new materials for tissue engineering, and the mammography field (26 million procedures/year for $3 B) were cited; NIST provides the standard used for 17 types of mammography machines. The important workshop held at NIST on Nov 2-3, 2000 , dealing with the European Union In Vitro Device Directive was noted (Beckman Coulter, Dade Behring, Abbott Laboratories, and Ortho Clinical companies participated).

Dale Hall (NIST) explained that the workshop was being held to identify and prioritize key standards needs in selected areas of the biomedical industry, in which NIST already has active programs on which to build. He stated the workshop could address standards in a broad sense, including consensus paper standards, reference materials, reference data, standardized test methods, standard practice procedures, standardized measurements, or anything else similar. He emphasized our interest in hearing from and responding to the industry needs on its needs, consistent with our mission, resources, and programs. It is NIST's intent to use the workshop results as a guide in the development of future plans for addressing the standards needs of the biomedical community.

Following the introductory remarks were a series of resource presentations.

Jack Lemons (Professor and Director of Laboratory Surgical Research, School of Medicine, Division of Orthopaedic Surgery, University of Alabama) provided an overview of biomedical material and device standards issues. He spoke of standards issues and a need for SRMs to serve as stable references against which the properties of new biomaterials could be assessed. He also spoke of a need for new materials for biomedical devices. It was his opinion that NIST could provide research infrastructure to address this field which is evolving to devices that use ever-smaller components for their applications (measurement resolutions are needed at the nanometer level and detection of compositions at the 10^{-9} % fraction levels). For the field of orthopaedics he described a specific need for the development of a synthetic fluid that would mimic synovial fluid, but which would not degrade under the conditions of in vitro wear testing of materials and devices. For cardiovascular, orthopaedic, and ophthalmic devices there have been problems with absorption, wear, and damage; standards were mentioned as needed to help assure safety, efficacy,

and durability. Without alluding to specific problems, he drew attention to the fact the number of tooth implant procedures is becoming a larger fraction of all implant procedures.

John Watson (Director, Molecular Biology Program and Clinical and Molecular Medicine Program, National Heart, Lung, and Blood Institute, NIH) addressed emerging biomedical issues. He discussed the need for standards that have clinical relevance. New standards and guidelines are needed for data and the use of the Internet. A big need is for implants to last a lifetime, so there is a vital need for basic research into design, in vivo assessment of implants, retrieval, and retrieval analysis. He briefly discussed the new NIH institute (National Institute of Biomedical Imaging and Bioengineering) and that it is the first of the NIH institutes with an explicit mission to encourage and support the development of relevant standards and guidelines in the field.

Don Marlowe (Director, Office of Science and Technology, FDA) covered standards and the FDA needs for device submissions. He described how the existence of standards can help to ease some of the burden of new device approvals through the citing of conformance, in a device approval application, to applicable standards. There is much to be done in standards development in anticipation of future trends in medical device technology. One of his concerns is that up-front cost containment issues can be a huge impediment to standards development.

Bernie Liebler (Director of Technology and Regulatory Affairs, AdvaMed) gave an industrial perspective. He noted that the medical device industry is not driven by standards; it has been, traditionally, very highly innovative while strictly regulated. NIST has provided traceable calibrations (he mentioned thermometers), traceable standard reference materials (for measurements, comparisons and calibrations) and test methods and equipment. Major drivers for standards development include standards-based EU-device approvals, globalization of markets, and strong efforts to harmonize requirements. The needs he focused on were for patient safety, harmonization, traceability, standard materials, test methods, and NIST participation as technical experts on standards committees. He made reference to the EU-IVD directive (calibration materials to provide reproducibility and traceability) and round robin testing of results. These were discussed at the Nov 2-3, 2000, workshop at NIST (Angelo, J.B. and Margolis, S.A., "1998 Round Robin Collaborative Study: Precision, Bias and Method Detection Limit," ASTM Research Report for Method D 1533, no. D27-1012, 1999). He presented some industry needs for NIST action, such as calibration standards, databases, test method validations, test/calibration methods and tools, and standards development participation. He wanted NIST to 'come to the table' and specifically asked for NIST to become a full member of the Medical Devices Standards Board (Editorial note, NIST responded in July, following the workshop, by resuming full, voting participation, in the MDSB).

Henry Heffernan (A staff member from the Clinical Center, NIH) addressed the crosscutting issue of data. He noted information technology as being at a critical stage with needs in the explosion of patient information portability, security, privacy, encoding of data, and transmission. Heffernan saw NIST expertise as essential in helping to meet these burgeoning needs. He mentioned the assemblage of a data group for the workshop and its task to identify issues and needs for data across focus group breakout sessions of the workshop.

Michael Scholla (Global Business Director, Tyvek Medical Packaging) addressed the crosscutting issue of sterilization, which he believes is already a relatively mature process (internationally, in Europe and in the US). He was speaking specifically of standards for medical device sterilization (dealt with in ISO/TC198, CEN/TC204 and in AAMI groups among others, for over 100 standards already published – many of which are recognized by the FDA). He sees needs for the development of sterilization methods for materials of biological origins and for inactivation of prions (methods, equipment, process validation, indicators and standards related to these are in need of development). There is a lack of an ASTM-type

organization in Europe for development of validated test methods, and there is no one single organization, such as NIST, to call on for assistance.

Richard Kayser (NIST) addressed the crosscutting issue of harmonization that is, making national standards compatible. The goal is to simplify life by facilitating mutual recognition and uniformity, and ultimately reducing costs associated with meeting standards. He mentioned that, historically, NIST has played a role as consultant to committees. There is a need for long-term commitment by all stakeholders to the standards development process and a need to bring them to the table with enough data to distinguish among methods and reach consensus based on mutual understanding.

Alan Andersen (President, National Committee for Clinical Laboratory Standards, NCCLS) talked about biomedical materials and clinical testing. He too described the importance of determining the health status of the patient after an implant has been placed. Standards (materials and methods) will be needed for clinical tests that can determine, from patient monitoring, effects such as those that may arise during the lifetime of the device, for example, from impurities leaching from an implant, leakage from silicone, toluene diamine from polyurethane degradation, and so forth.

Technical focus areas: For each area, a breakout session report follows. The report represents the consensus, not necessarily unanimous, of the participants in that session. Each focus area report responds to what was asked for by NIST, e.g., what are the needs of the biomedical industry, in the development of standards, to which the industry would like NIST to respond? NIST's intent is to respond to those needs, consistent with its resources, mission, and the priorities of the needs identified, and to use this information as an aid in the planning of future applications of its resources to assist the biomedical devices industry.

Breakout Session Reports

Breakout Session Leaders

Biomaterials:
James Burns, Genzyme, Inc. & Rebecca Bergman, Medtronic, Inc.
NIST Facilitators: Francis Wang, Bruno Fanconi - Scribe, Chad Snyder

Therapeutic and Drug Delivery Systems:
Arthur Courey, Genzyme, Inc. & Gary Strathearn, Radiance Medical Systems, Inc.
NIST Facilitators: Christopher Soares, Bert Coursey - Scribe, Brian Zimmerman

Auditory Diagnostic and Prosthetic Devices:
William Cole, Etymonic Design, Inc. & Ronald Scicluna, Argosy Electronics, Inc.
NIST Facilitators: Victor Nedzelnitsky, Jonathan Fiscus - Scribe, Victor Nedzelnitsky

Manufacturing and Processing of Prostheses:
Craig Blaschke, Biomet, Inc. & Jean (Jan) Champion, Medtronic Heart Valve, Inc.
NIST Facilitators: Howard Harary, Matthew Davies - Scribe, Ron Dixson

Tissue Engineered Medical Devices:
Peter Johnson, Tissue Informatics, Inc. & Nancy Parenteau, Organogenesis, Inc.
NIST Facilitators: Eric Amis, Lori Goldner - Scribe, Newell Washburn

Standards for Biomaterials

Stephen Freiman
John Tesk
Materials Science and Engineering Laboratory
NIST

Overview

"Biomaterials " are materials that are applied for use in medical devices that require intimate contact with tissues and body fluids. Biomedical devices are a growing business that in 1995 was estimated at $32 B, with a positive balance of payments in trade of $2.7 B. In 2000, the market was $42 B. Biomaterials are finding increased use in products that replace or augment the function of body parts, for which normal function has been lost. Devices such as orthopaedic joints, intraocular lenses, heart valves, membranes, and pacemakers are increasing the life span and productivity of the population while improving the quality of life for patients and their families through new designs and new or improved biomaterials. Standards (consensus standards, standardized test methods, standard methods of analysis, reference materials, reference data) related to the performance of biomaterials can lead to more rapid submissions and approvals of new devices that provide benefits to patients, reduce costs to health care providers through benchmarks for reliability of performance, and eliminate wasteful, redundant duplications of testing of materials and devices by manufacturers. Further, standards hold the potential of helping the United States maintain its world leading position in medical devices. Both industry and the Food and Drug Administration (FDA) would like to see standards that would help increase the availability of new materials for devices.

The breakout session on Biomaterials included sixteen (16) non-NIST participants representing a wide spectrum of companies that included orthopaedic, heart valve, ophthalmic, and soft tissue implant companies; the FDA; industry associations; and two highly respected biomaterials researchers who provide leadership in the development of consensus standards. The participants identified numerous issues related to test methods and the development of standards that they considered important for consideration of needs on a group basis. Needs were prioritized by considering 1) clinical importance, 2) questionable results (reliability) of current test methods, 3) potential for easing of regulatory burden, 4) global impact of adoption, 5) the potential for resolving unexplained phenomena, 6) the expected importance relevant to new technologies, and 7) the inability of individual companies to provide the resources needed to work on the methods.

In summary, NIST was seen as an important contributor in biomedical standards activities by serving in the following roles:

- Provide technical support for the development of new biomaterial test methods.
- Provide technical consultation to industry and standards developing organizations
- Be a technical representative on efforts to internationalize national standards
- Conduct root cause analysis of ineffective or questionable standards. This includes evaluations of standards and test methods that may not be optimal.

Action Items Needed. For each of the following items, industry expressed interest in having AdvaMed organize a 1-2 day workshop to develop a plan with action(s) required to satisfy the need identified. NIST will initiate this activity by working with AdvaMed to form and convene a steering committee under AdvaMed's leadership. In each case the same organizations were recognized as needed participants in the planning of the workshops. These are: the Advanced Medical Devices Association (AdvaMed), the FDA, NIST, ASTM, the American Dental Association, and the American Association for Medical

Instrumentation (AAMI). Industry participation in the planning and in the workshops was noted as being especially important.

- **New biocompatibility test methods are needed**. Existing biocompatibility tests are inadequate because they fail to predict long-term adverse events. Unless materials cause gross cytotoxic responses, they pass the screening tests currently defined in consensus standards. Among the key needs are predictive biocompatibility tests to assess the effects of: long term leaching of material components, materials on immune response, and carcinogenicity of materials.

- **Accelerated life tests that can predict clinical performance of biomaterials**. Numerous simulator test methods exist that provide indications of long-term performance of a medical device, but these are not predictors of long-term performance of the materials that are used in the device. Because of the numerous devices and simulators used for device testing, it is virtually impossible to compare in a meaningful way the results from one simulator test to another in order to predict the behavior of the material in its intended application. In addition, duplications of efforts using simulator testing for regulatory approval are required for testing according to international standards that specify test methods/equipment that are different form those commonly found nationally. What is needed are accelerated material tests and unifying methods of analysis that can superimpose the effects from different test and simulator-device tests and that can be applied universally (internationally). Hence, NIST should work toward the development of well-established test methods and then follow through, with its technical staff and credentials, toward their inclusion in international standards.

- **Methods for characterization of biomaterials and biomolecules**. New applications of macro- and bio-molecules are being found in biomedical materials and devices. The ISO 10993 series describes testing that is required, but there is serious concern over adopting tests that are not well targeted for the need, which is risk assessment of an implantable device. New test methods for assessing host response, targeted to the use and pathway for eliciting response, must be developed. For example, in consideration of the effects of a leachable component (such as uncured monomer) from a device over long periods of time, the guidelines for tests are coming from outside of the biomedical community. Inhalation dosage tests that were developed by the Environmental Protection Agency for airborne toxins, or dosage tests developed by the FDA for ingestion of foods, are being used. It is clear that inhalation and ingestion provide quite different pathways for dosing by a foreign substance. Tests are needed that relate to long-term implantable materials, which dose through direct contact or through the bloodstream, etc. NIST, because of its measurement and test method development expertise, is seen as a valuable partner for cooperation in the design and validation of new test methods.

- **Develop standardized test methods for evaluation of biostability of materials**. Tests for relevant assessment of the long-term stability of materials proposed (or used) as biomaterials do not exist. The 10999 series of tests address only short term stability and need to be reviewed as to how well they satisfy the need. NIST should be a partner in guiding root cause analysis of why existing tests may not be appropriate. This issue was also raised in the manufacturing and processing of prostheses breakout group report on surface finish and characterization.

- **Effects of sterilization on materials**. Many methods for sterilization exist. Others are needed for tissue engineered medical products (TEMPs). How sterilization by different methods may impact on long term biostability, risk assessment, lifetime performance, and biocompatibility needs to be considered. New sterilization methods are needed for TEMPs. Standardized tests for assessing the effects of sterilization need to be developed.

Therapeutic and Drug Delivery Devices[1]

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Industrial Liaison Office
Bert Coursey
Physics Laboratory
NIST

Overview

Therapeutic devices are instruments or structures that deliver pharmaceuticals, radiation, or biologics to the body for purposes of ameliorating a disease or potential disease condition. The use of biomaterials as delivery devices to treat disease represents a major growth market in advancing U.S. health care. Such advances include the development of systems based on novel delivery technologies currently being implemented by the pharmaceutical industry. Other systems, based on emerging delivery technologies, are just beginning to be understood, and these started entering the marketplace in the late 20th century. The field continues to grow significantly and has begun to compete with conventional means of drug delivery for such conditions as heart disease, cancer, stroke, and diabetes, which are among the largest crippling and fatal diseases affecting the U.S. public today. With the current acceleration in the development of biomaterials, a plethora of potential delivery systems are either in the market, under development, or anticipated. New measurement methods are needed to characterize the properties of these new devices. *In vitro* methods must be developed for prototype designs. *In vivo* monitoring, through minimally invasive methods, will be needed to evaluate the efficacy of the delivery systems. Increasing numbers of researchers are involved in the development of new entities for the delivery of precise, controlled dosages to specific sites of the body. Hence, for consistency in tracking the effects of the treatments and for the health and safety of patients, there is a critical need for standards for measuring the dose, pharmacokinetics, efficacy, and untoward effects of treatments.

This breakout session included nine non-NIST participants representing companies with interest in delivering radiation, pharmaceuticals, or chemicals using implanted or inserted devices. These representatives, along with others from standards organizations, determined several niches for NIST activity in the development of standards for this segment of the biomedical industry. These niches include: 1) exploring the trend coming out of the European Union (EU) in regulation requiring standards, 2) developing systems for determining release rates of drugs from different matrices and elimination from the body (pharmacokinetics), 3) developing reference hydrogel or pore size standards and a standard medium to mimic drug release in different body fluids (this would require FDA consultations), 4) developing new standards and methods for sterilization of new and emerging materials that are biologically based and may suffer from degradation by usual sterilization methods (maybe a series of degradable polymers to test sterilization methods), and 5) developing standards for destructive activity assay and dosimetry methods (or recommended practices) and transfer standards (to hospitals) for dose measurements (material/artifactual standards)

In summary, NIST was seen as an important contributor in biomedical standards activities by serving in the following roles:

Providing technical support for the successful development of drug/radiation delivery methods and devices.

- Providing unbiased technical consultation to industry and standards-developing organizations, with adherence to rigorous use of terminology.

[1] The participants narrowed their discussion to "Therapeutic Drug and Radiation Delivery Systems

- Acting as technical representatives on efforts to internationalize national standards (particularly in view of new standards coming out of the European Union).
- Evaluating standards and test methods on an "as needed" basis.

Action Items Needed. For each of the following items, industry expressed an interest in having either follow-up workshops or continuing interactions with NIST in order to more clearly define the expressed need or determine plans to satisfy the need. Standard technical methods (both physical and consensus) were recognized as being extremely useful for assessing whether a product is safe, effective, and reproducible in addition to providing a consistent measurement basis (prediction or comparison of clinical outcomes) and a means for gaining acceptance of products by regulatory agencies and in foreign markets. The needs that NIST could address or meet were rank order prioritized according to urgent, highest, high, or moderate for the industry:

Urgent and On-Going Priority
- Material standards (national) for radio-activity
- Transfer standards for dosimetry
- Harmonization of international standards

Highest Priority
- Consistent terminology
- Formal (written) international standards for delivery device characterization

High Priority
- Health and Safety Issues

Moderate Priority
- Activity measurements
- Dosimetry measurements
- Guidance (technical papers) for new sources, fields, applications
- Labeled materials, standards for radiopharmaceutical uptake (long-term)

- **Methods and Standards for Determining Release Rates of Drugs from Different Matrices**. The scientific expertise at NIST is seen as a resource in the development of artificial reference materials that could be used to mimic *in vivo* behaviors of drug release. Such materials act as *in vitro* models for tracing the pharmacokinetics (elimination from the body) of pharmaceuticals that are delivered by implanted devices (and are consequently extremely difficult to monitor). In addition, it was felt that NIST might be in a position to develop methods that can be used to measure pharmaceuticals in different tissues of the body (fluids, muscle, skin, etc.). Of particular use would be the development of systems for determining release rates of drugs from different matrices for *in vitro* methods, such as reference hydrogel or pore size standards; and methods of finding drugs in tissue and tracking elimination from the body, including a standard medium to mimic drug release in different body fluids [requires FDA consultations], other matrix and excipient materials. Container closure issues associated with implantable infusion systems, including biocompatibility and stability also need to be addressed. NIST can use its expertise to develop methods for determining drug/matrix compatibility; release, absorption and elimination monitoring; and to develop test media that mimic body fluids. Although NIST is not prepared for animal studies, *in vitro* and cell studies are possible (collaborative work off-site is possible and is already being done in many cases). NIST should work toward the development of degradable matrix and excipient test reference materials standards that can be used *in vitro* in the development of products and test methods that are intended for use *in vivo*, as well as methods to measure pharmaceuticals in bodily tissues.

- **Methods and Standards for Determining Dose and Activity of Radiation Delivery Devices**. The FDA requires reference standards for clinical applications of inserted radiation delivery devices (such as coronary stents and balloons, radioactive seeds for *in situ* therapy, etc.). The dosimetry for measuring the activity of such devices is well defined by NIST ("traceability"). Aside from disparate

publications, there are no measurement standards for destructive activity assays (necessary for activity determination), dosimetry methods, or recommended practices available for developers of radiation delivery devices. Formal (written) standards for source and safety characterization as well as secondary ("transfer") standards (material/artifactual standards to the clinical setting) for dose measurements are needed. Historically, NIST has taken a lead role in the development of international standards in this field, and was encouraged to continue to do so. NIST should continue in its publication of methods used for activity and dose determinations, encourage the compilation of these methods into documents of "recommended practices" (under the auspices or organizations such as the American Association of Physicists in Medicine, Society of Nuclear Medicine, or the Council on Ionizing Radiation Measurements and Standards) and continue work in the development of activity and dosimetry transfer standards for the clinical setting.

- **Methods and standards for device sterilization**. With new and emerging materials being developed for implantable devices that deliver drugs and radiation, a new set of difficulties arises with regards to sterilization. New standards and methods that can sterilize without deactivating or degrading the device material must be developed. Current methods are not applicable, and the development of new sterilization methods is prohibitively expensive since, in essence, a new device must be thoroughly developed before the sterilization method can be evaluated. To ameliorate this, NIST should work on the development of a series of standardized, degradable polymers that will be representative of the material components used in delivery devices. These could be used for testing of new sterilization methods, prior to full device development. The expenses and lost time associated with the full development of a device for sterilization without material degradation would be avoided.

- **NIST participation in standards writing committees**. The scientific and technical expertise at NIST is recognized as being critical to the continuing development of implanted or inserted drug/radiation delivery devices. The fact that NIST presents an unbiased view is a large positive for this traditionally competitive field. In addition to some of the specific needs related to physical standards, such as better *in vitro* models for the body, and the determination of the physics/mechanics of the actual delivery devices, needs within written standards were also considered. Increased participation in the development of consensus standards by NIST scientists, who have historically brought a rigor of terminology to the development of standards, is a way by which standards efforts could be enhanced. Because of the increasing need for harmonization with European standards efforts (for international marketing of devices and for international partnering in their development), the emphasis should be on international (rather than simply national) standards. Although industry has traditionally not been anxious to incorporate standards, trends in the development of standards in a global regulatory environment (such as from the EU, FDA, etc.) must be explored. NIST is encouraged to determine a need (or needs) that it could meet and then join standards organizations that address that need (or needs). If no such activity exists, NIST could lead toward getting the appropriate standards activity organized. NIST should cultivate relationships and interactions with the major players in the field of standards for drug delivery and radiation delivery, which are the standards organizations (ISO, ANSI, AAMI, NCCLS, etc.), regulatory agencies (FDA, NRC), user communities (IEEE, AAPM, SNM, ADA, etc.), international organizations (ICRU, WHO, DIN, IAEA) and other Federal agencies (NIH). Technical staff at NIST should work towards increasing their participation with standards writing committees in both the national and international arenas.

Auditory Diagnostic and Prosthetic Devices

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Overview

Hearing loss afflicts approximately 30 million Americans including two recent presidents (Clinton and Reagan), and is certainly among the most frequently occurring health impairments in the U.S. Americans of all age groups are affected, including more than 30 % of people over age 65, 14 % of people between 45 and 64, nearly 8 million people from 18 to 44, and over a million school-age children. Of the "treatable population," about 5 % to 10 % can be helped medically or surgically (including implants), and the remaining 90 % to 95 % can significantly (but not totally) correct their hearing loss with hearing aids. About 2 million hearing aids were sold in the U.S. in the year 2000. However, more than 16 million Americans with substantially correctable hearing loss are not using hearing aids and would benefit from modern aids: the Better Hearing Institute estimated (1999) that the annual cost of lost productivity, special education, and medical care because of untreated hearing loss is $56 B. Proper diagnosis and treatment of hearing loss is critically important for successful patient outcomes in all age groups, but is especially so for children who have not yet acquired language.

Auditory diagnostic and prosthetic devices include a wide variety of analog (not containing components such as digitizers and microprocessors) instruments and, more recently, single-band and multi-frequency-band programmable digital devices containing such components and capable of digital signal processing. The greatly enhanced features and capabilities of recent and evolving devices call for suitable standards enabling performance specification, replicable measurements, production testing, and quality assurance, so that manufacturers and practitioners can provide safe and effective patient outcomes.

Eight non-NIST participants attended this session. Among the participants in this session, the numerous manufacturers of auditory prosthetic and diagnostic devices were represented by the Chair of the Hearing Industries Association (HIA) Technical Committee and the chairs (or other impartial representatives) of ANSI-accredited standards committees and working groups with strong industry participation. There was also participation from hearing instrument manufacturers and a major supplier of transducers and other critical components to most manufacturers in the hearing industries. Other participants with major research, clinical, and health care responsibilities, very broad experience, and knowledge in this field came from the National Institute on Deafness and Other Communication Disorders (NIDCD) of NIH, the Dept. of Veterans Affairs (VA), and the research arm of a private clinic that sees over 35,000 patients per year and is one of the leading centers for auditory implants in the U.S. and the world. The Acoustical Society of America (ASA) Standards Committee S3 Bioacoustics, referenced below, is ANSI-accredited.

Participants considered many auditory diagnostic (where diagnostic is meant broadly to include devices used for functional assessment or screening, as well as more elaborate devices capable of diagnosing specific causes of hearing impairment) and prosthetic devices that are, or may become, subjects of standards activities, including:

- Various types of hearing aids (e.g., behind-the-ear, in-the-ear, in-the-canal, completely in-the-canal, eyeglass, body, linear, compression [nonlinear], directional, programmable, and digital hearing aids),
- Middle-ear implants, cochlear implants, and auditory brainstem implants,
- Assistive listening devices and systems (talker's microphone signal broadcast or propagated as FM radio, infrared, or via "looping" [Faraday induction] to listener's personal receiver),
- Ear, head, and torso simulators used in research, device design, and quality control testing,

- Audiometric couplers used to calibrate and characterize earphones,
- Audiometers (pure-tone, speech, transient signals),
- Real-ear probe-tube sound measurement systems for *in situ* hearing aid measurements,
- Electroacoustical signals and transducers for auditory brainstem response (ABR) audiometry used to predict hearing sensitivity and to assess the integrity of Cranial Nerve VIII and auditory brainstem structures,
- Signals and transducers for eliciting other auditory evoked potentials (AEP) usually distinguished by their latencies of measured time-domain response,
- Instruments for measuring otoacoustic emissions (OAE),
- Programmers/interfaces for programmable hearing aids and audiometers,
- Devices used to determine acoustic impedance or admittance at the eardrum.

The participants identified items needed for standardization and arranged them in three priority groups. The harmonization of ANSI and international standards is a large and essential task that has already begun, and must be completed. Although it was considered separately during the session, and therefore not ranked with the other items, it is of such essential importance that it has been included here in the group with the highest priority. The listed groups and items are shown in Table 1. A list of specific actions was developed for the items in Table 1, and is given below that table.

TABLE 1: Prioritized list of industry needs with comparable priority within a group.

Group 1 (Highest Priority):

Harmonization of ANSI and International Standards

Clinically Useful Performance Tests for Hearing Aids

Standards on Biomaterials and Functional Performance for Active Implantable Auditory Devices

Standards for ABR Systems, Evoked Response Systems, and Otoacoustic Emission Analyzers, Especially Regarding Infant Screening

Standardized Hearing Aid Terminology

Establishment of U.S. Positions on Standards Involving Electromagnetic Compatibility (EMC) of Auditory Diagnostic Equipment and Hearing Aids

Group 2 (Very High Priority):

Auditory Device Data Issues

Standardized Environments for Functional Performance Testing of Hearing

Group 3 (High Priority):

Issue of Electromagnetic Interference with Audiometric Equipment in Sound Rooms

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Action Items Needed:

- **Proactive Participation in Harmonization of ANSI and International (Primarily IEC) Standards**. Existing standards for many auditory devices are becoming harmonized because of ongoing activities toward, and effects of, global consolidation. The auditory device industry is now dominated by 5 groups of which 4 are European with large presence in North America, so that industry members now have very strong voices in the relevant ANSI and IEC working groups. Consequently, these ANSI and IEC groups now are more effectively cooperating on harmonization issues. For audiometers, acoustic impedance (or admittance) measurement devices, real-ear probe measurement systems, and hearing aids, principal harmonization activities can be achieved in ANSI (especially in Accredited Standards Committee S3 Bioacoustics and its working groups) and IEC (especially Technical Committee 29 Electroacoustics and its working groups) standards activities, with proactive participation by industry, NIST, and directly interested parties. Usually, the lead on audiometric diagnostic procedures, fitting, and other clinical issues will come from audiologists, other

biomedical professionals, and researchers employed or supported by the industries, academic institutions, and other government agencies with current and future representatives on these committees and working groups. NIST should continue and extend its service in these committees (particularly ANSI-accredited S3 Bioacoustics and IEC TC 29 Electroacoustics) and their working groups, in close cooperation with physical scientists/engineers from industry, to resolve harmonization issues involving physical data and measurements.

- **Participate in Study Sub-Groups of S3 Bioacoustics WG 48 Hearing Aids to Develop Clinically Useful Performance Tests for Hearing Aids.**
  There is a need for clinically useful performance tests for hearing aids. Data from existing standards are useful for quality control purposes but frequently are not very useful clinically. Utility to the hearing aid wearer necessarily involves performance with speech signals in the presence of varying degrees of noise (including competing speech signals) and reverberation. Examples of specific issues that need to be addressed are: stimulus, analysis, and data presentation issues involving speech, speech in noise, speech in noise and reverberation, feedback suppression, etc. Directional hearing performance and the relative positions of the hearing aid user, signal source, and noise source(s) are also important. NIST should participate in study sub-groups of Accredited (by ANSI) Standards Committee S3 Bioacoustics, Working Group 48 Hearing Aids. Usually, NIST and physical scientists/engineers from industry will be most closely involved with physical measurement issues, data, and signal processing/data analysis, while the lead on audiometric diagnostic procedures, fitting, benefit to the patient, and other clinical issues will come from audiologists, other biomedical professionals, and researchers employed or supported by the industries, academic institutions, and other government agencies with current and future representatives on this working group and its sub-groups.

- **Organize Study Group or Workshop on Crosscutting Issues for Standards on Biomaterials and Functional Performance for Active Implantable Auditory Devices.**
  Active implantable auditory devices include middle-ear, cochlear, and brainstem implants. There is an urgent need for these standards, which will have regulatory application. Some functional performance issues for hearing aids are also relevant here: for example, utility to an implant user also involves performance with speech signals in the presence of varying degrees of noise (including competing speech signals) and reverberation. There are additional crosscutting issues critically important for implants, for example, concerns within user communities, biocompatibility over long as well as short time periods, device lifetimes, need for unbiased implant retrieval studies, clinically useful performance tests, etc. NIST should organize a study group or workshop to further investigate crosscutting issues on such devices.

- **Advise (When Requested) on Electroacoustical Measurement Issues for Standards for ABR Systems, Evoked Response Systems, and Otoacoustic Emission Analyzers, Especially Regarding Infant Screening.**
  There is an urgent need for standardization in this area, especially regarding the growing requirements for infant screening for hearing loss. Such screening is already mandated by a large and increasing number of states, and is nationally recommended by NIDCD. There is existing ANSI standards work in this area, although there is a lack of normative data, and a lack of advice and information on physical measurements. There is not yet sufficient agreement among practitioners to establish a consensus for standardization of procedures. The recommended role for NIST is to provide informal technical advice regarding electroacoustical measurement issues. ANSI Working Group Chairs in this area are to inform NIST of requests as they evolve. This can be achieved by notifying the NIST institutional membership representatives on Accredited (by ANSI) Standards Committees S1 Acoustics and S3 Bioacoustics, and the addition of NIST experts to working groups of these committees as needed.

- **Develop Standardized Hearing Aid Terminology.**
  Good communication among basic researchers, clinical researchers, practicing clinicians, design and quality control engineers and technicians, component suppliers, programmers, dispensers of hearing aids, purchasing agents, patients and patient advocates, and regulatory authorities is crucially important to the improvement of hearing aids, hearing aid fitting and other clinical procedures, and patient outcomes. Successful communication is often difficult or impossible when there is no commonly understood or accepted terminology. Some terms are available in existing standards and glossaries but newer terms (and sometimes inconsistencies of existing definitions) cause major difficulties. In some cases, marketing departments are defining terminology, with obvious problems for the field regarding clarity, correctness and consistency. To initiate this activity NIST should contact a trade association such as the HIA, for example, (working with a trade association avoids copyright issues and permits postings of work on unrestricted Web sites) or a standards developing organization.

- **Name Experts on Generic Electromagnetic Compatibility (EMC) Standards to Help Establish U.S. Positions on IEC Standards Involving EMC of Auditory Diagnostic Equipment and Hearing Aids.**
  EMC is meant here in its most general sense to include both the issue of susceptibility (immunity) of a device to interference from radiated or conducted (e.g., via connection to the power line) electromagnetic disturbances from other devices or sources, and the issue of radiated or conducted disturbance produced by a device that causes interference to other devices. For establishing U.S. positions on draft international standards involving electromagnetic compatibility (EMC) of auditory diagnostic equipment and hearing aids, there is a need for closer involvement of NIST experts familiar with generic international EMC standards used as normative references in these drafts. The Technical Advisor (Victor Nedzelnitsky) to USNC (U.S. National Committee)/IEC for TC 29 Electroacoustics will ask EEEL to name experts who can comment on auditory device standards involving EMC and references to generic EMC standards. These experts will then receive copies of the relevant IEC TC 29 draft international standards as they appear, and can furnish comments for inclusion in the Technical Advisor's recommendation to the Secretary, USNC/IEC for transmission as the USNC/IEC position.

- **Provide Specific Expertise (e.g., on XML) to S3-WG 86 for Auditory Device Data Issues**.
  Electronic storage, transmission, and exchange of data are important to users. For example, Dept. of Veterans Affairs (VA) is very interested in data flow from devices to patient databases, and to electronic commerce orders for hearing aids. In an existing standards effort, there is a need for additional expertise for certain software and input-output issues. In particular, NIST should participate in Accredited (by ANSI) Standards Committee S3 Bioacoustics Working Group (WG) 86 Audiometric Data Structures to provide expertise in XML and related input-output issues. Len Gallagher of ITL, NIST was asked to contact NIST management and report to the Chair (William Cole) of S3-WG86 whether NIST could send an expert to the meeting of S3-WG86 on June 29, 2001 in Alexandria, VA. Len Gallagher did attend this meeting and offered some suggestions that seemed to be well received by the WG. He has agreed to review any drafts produced by this WG.

- **Organize a Study Group or Workshop on Standardized Environments for Functional Performance Testing of Hearing.** The absence of such standardized environments, including the absence of reference materials (such as appropriately controlled, presented and recorded auditory stimuli) from appropriately and adequately specified environments (degrees of noise and reverberation, locations of signal source and noise source[s], etc.), is a significant barrier to improved functional performance testing of hearing. This improved testing is needed for improved audiological testing of patients and fitting of hearing aids. Improved fitting is necessary for improvements to

success in patient outcomes. NIST should organize a study group or workshop on this subject; participants to consider include HIA, VA, NIH, FDA and ANSI-accredited Standards Committees; S1, Acoustics; S3, Bioacoustics; S12, Noise; and their working groups.

- **Address the Issue of Electromagnetic Interference with Audiometric Equipment in Sound Rooms**. In busy, well-equipped clinical facilities, audiometric equipment is typically installed so that the hearing of a patient can be examined with the patient in a very quiet sound room that isolates the patient from excessive ambient noise sounds. Data on susceptibility (immunity) of individual items of equipment to electromagnetic interference are limited or, most frequently, unavailable or inapplicable due to differences (for example, in cable lengths and orientations) between test conditions and installed conditions. Data on interfering ambient electromagnetic fields in hospitals and clinics are also often limited or unavailable. Some diagnostic instruments (e.g., ABR systems) are particularly susceptible because they must use electrodes to measure very small electrical potentials that are produced by mechanoelectrical transduction and subsequent neuronal activity. The session participants recognized that there is a need to address the issue of electromagnetic interference with audiometric equipment in sound rooms, but could not identify who would be likely to have the funding support and technical capability to address this issue on the national and international levels. Currently, it is an issue for individual hospital systems and clinics to consider for themselves. One reason that it has not been prioritized more highly is that its generic solution would probably require a much greater level and variety of resources than would be needed to provide significant progress toward the other standards needs cited.

Manufacturing of Prostheses

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Overview

The implantable prosthetics industry has three primary components: (1) artificial limbs and mechanical aids; (2) orthopedic implants, including hip, knee, and other joint replacements; and (3) non-skeletal implants including breast implants, heart valves, intra-ocular lenses, and implanted pacemakers. The widespread clinical acceptance of prostheses can be illustrated by a few revealing statistics. Approximately 245,000 knee replacements are done annually in the United States, and this number is expected to grow rapidly as the population ages. About 50,000 substitute heart valves are implanted annually in the United States, and this number is also growing. At present, the leading mechanical valve design has been implanted in more than one million patients worldwide. In total, the prosthetics industry exceeds $10B annually and is expected to grow rapidly in the next few decades; the orthopedics industry alone has been growing steadily at 10% annually. The establishment of more comprehensive, suitable, industry-wide, standards for manufacturing methods, inspection, and quality assurance may help to avoid the risk of potentially disastrous failures such as have previously occurred occasionally with mechanical heart valves, pacemakers, and orthopedic hip implants.

This breakout session included approximately nine non-NIST participants; primarily from the orthopedic and heart valve industries. We were also fortunate to have had an orthopedic surgeon who brought a much different and very useful perspective to the discussion. After a brainstorming session in which the participants identified issues that NIST might address in the area of manufacturing and testing of prosthetic devices, a rationale and some detailed action items bullets were recorded for each issue . The participants then ranked the issues in terms of importance. A final ordered list was compiled, as shown in Table 1. A list of specific actions was developed for the first five issues in the list, which is summarized below.

TABLE 1: Prioritized list of industry needs. Scoring done by allowing each participant one vote on each item: MOST IMPORTANT = 3 points, MODERATELY IMPORTANT = 2 points, and IMPORTANT = 1 point.

Item	Point Total
Reference Materials and Surfaces	18
Cleaning and Cleanliness	13
Surface Characterization	5
Medical Imaging Models	5
Dimensional Measurement	5
Non-Destructive In-Vitro/In-Vivo Testing	3
Characterize Effect of Manufacturing Process on Device Performance	2
Encouraging/Facilitating Clinician Participation in Standards Development	1

Action Items Needed:

- **Develop Reference Materials and Reference Surfaces.** In order to better understand the behavior of implants and their interaction with the human body, it is necessary to develop standard materials and surfaces that better allow medical researchers to design consistent experiments and interpret their results. The most critical of these materials, identified by the focus group, were: (1) standard surfaces and/or better surface measurement techniques for characterizing the surface finish of orthopedic implants; (2) standard particulate debris that can be used as references against which the biological responses of debris from retrieval experiments and in-vitro wear simulation (and other) tests can be prepared; (3) a stable, synovial fluid analog that can be used in place of bovine serum; (4) a blood analog(s) for accelerated, durability and performance testing of new heart valves; and (5) a bone analog for performance evaluation of orthopaedic prostheses. NIST should work with other organizations such as ASTM to develop these reference materials and materials analogues, beginning by organizing a consensus committee from industry and appropriate other bodies, such as the American Association of Orthopaedic Surgeons. To work to develop these reference materials and material analogs. NIST would take the lead for the development of standard surfaces and in finish characterization of implants. NIST would also lead the development of standards for wear debris. NIST could serve a useful function by taking the lead toward the formation of alliances needed for the development of synovial fluid, blood, and bone analogs, and could provide some of the scientific, measurement, and engineering expertise that will be needed for development of these complex materials.

- **Establish Standardized Cleaning Practices for Ensuring Cleanliness**. Recent incidence of contamination of implants from unknown sources, despite adherence to good manufacturing practices, has indicated the need for additional test/test validations/process controls and definitions of best cleaning practices to provide 100% assurance of freedom from contamination during the manufacturing process. To accomplish this, NIST must first organize and convene a formal or informal committee of representatives in the field of implant manufacturing to develop a database of current cleaning methods and then from that to codify best practices. Such an activity could help greatly by identifying gaps in current practice and making the best methods more widely used. From this database and prioritized list of needs, NIST would then take charge of developing the measurement/measurement science and methods for detecting contamination of different types. NIST would probably not lead this effort, but would seek consensus by working with bodies such as ASTM.

- **Develop Standardized Surface Characterization Methods and Tests**. Surface finish and characterization are critical for the proper functioning of implants. In orthopedic implants finish can affect wear rates at moving interfaces and bone integration; and in heart valves, finish affects the interaction of the blood with the implant and, potentially, mechanical failure mechanisms, although these are at present rare. Therefore, in order to ensure accurate comparisons of experimental data, a common description of surface finish and character across the implant industries is needed. Because NIST has substantial expertise in the methods and technology associated with surface measurement, it would serve a vital role to the industry by helping to define the best practices and techniques that are applicable to the industry. Also, NIST could assist the industry by developing a translation/organization matrix of existing surface finish standards to map existing standards to applications in prosthetic manufacturing. Furthermore, NIST would work to develop methods that can be used to cost-effectively monitor finish on the shop floor. To accomplish this, NIST should sponsor a workshop on Surface Finish Measurements in the Biomedical Device Industry to better define the issues, and then report the results of the workshop to the industrial users of surface finish measurement equipment. NIST is uniquely positioned to take a lead role in this activity.

- **Develop Common Methods for Improved Evaluation and Analyses of Medical Images**. Medical imaging techniques are central to the diagnosis and treatment of patients and provide invaluable tools for the evaluation and quantification of experimental and clinical results. However, medical imaging devices often use different methods for interpreting and presenting information, making cross comparison more difficult. NIST could serve a vital role in this area by reviewing current practice from a metrological and scientific viewpoint and by providing an independent technical evaluation of current practice. NIST could also participate in a consensus committee for: (1) developing algorithms to improve medical imaging; and (2) specifying medical artifacts for calibrating and testing medical imaging systems (for example, the determination of the bone-flesh interface in the CT scan). The leadership for these activities was not decided by the breakout working group. However, it would seem that an appropriate response by NIST would be to take the lead in bringing together a critical mass of experts to work on these issues and providing a forum through which leadership could be assigned.

- **Identify Best Practices and Reference Artifacts for Dimensional Measurements and Control**. Dimensional measurements and the maintenance of adequate part tolerances are critical to the function of most mechanical and optical implants. This affects the wear rate of joints in orthopedic implants and the performance of heart valves and optical devices. Furthermore in a different sense, dimensional measurements are also important for the in-vitro measurement of medical implants for wear or migration during their lifetime. A valuable role for NIST in this area is similar to the role envisioned for surface finish, i.e.; to convene a workshop and develop a report summarizing best practices and to inform the biomedical device industry about methods that could be used to monitor part tolerance (for example, ball sphericity or dimensional deviations of a complex contoured surface) on the shop floor. Standard surface-finish artifacts may also be extremely useful to manufacturers and experimental clinicians by ensuring that surface definitions are widely accepted and used. NIST is uniquely positioned to take a lead role in this activity.

Tissue Engineered Medical Devices

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Overview

The intent of this session was to learn how NIST might assist industry in the development of standards for Tissue Engineered Medical Products (TEMPs). TEMPs often use scaffolds, alone or in combination with biologicals that contain animal or human cells, such as biosynthetic skins, heart valves made of scaffolds seeded with patient's own cells etc. Development of Tissue Engineered Medical Products (TEMPs) has been challenging due to complex and diverse interactions among a device's components. In 1997, a voluntary standards effort was initiated under the auspices of the American Society for Testing and Materials (ASTM) to develop standards for TEMPs. It is apparent from the enormous number of issues that have evolved from the ASTM effort that there are likely to be many occasions for which NIST involvement could be of benefit to the standards processes. This session focused on many of those issues. It included a good representation from the industry as well as from NIST, other federal agencies, including the Food and Drug Administration (FDA) and the National Institutes of Health (NIH), and standards-developing organizations, such as ASTM, and the American Dental Association. Overall, there was a significant emphasis on the need for new test method development and material characterization. Moreover, the group felt that there was a need for a meaningful strategic role for NIST. The group overwhelmingly urged NIST to take a leadership position, working with collaborators in industry, NIH, FDA, clinicians, and standards organizations.

A number of high priority issues related to the FDA's approval process. These processes are listed separately below (bullet action items 1.x) to identify and highlight the regulatory concerns in this area and to distinguish them from the more purely commercial/industrial interests (bullet action items 2.x).

Action Items Needed: High priority action items for NIST regarding industry needs relative to the FDA approval process include**:**

- **1.1 Develop rapid, highly-accurate, phenotypic determination methods (see 2.1 & 2.2)**. Although it is very important for industry to have reliable and accurate phenotyping of their products, it is not always essential for the industrial methods to be rapid. However, timely regulatory approval of TEMPs and the establishment of good manufacturing practices will hinge upon the ability to determine the phenotypic classification of cell types as quickly as possible. NIST should organize a task force/group with representatives of the TEMP community to establish consensus on phenotype determination methods. This group should then establish a plan that leads to the development of rapid and highly accurate methods making the needed phenotypic determinations. Participants should include NIH, FDA, industry, and academic members of the TEMP community.

- **1.2 Develop methodology to characterize human-animal co-cultured TEMPs, (particularly with respect to determining the percentage (number-fraction) of each cell type).** New products are becoming available with mixtures of cell types, and it is necessary to validate the percentage of each type, since this may have impacts on other tests and patient responses. It may also be necessary to address the relative distribution of mixed cell types in mixed species tissue devices. Standards and standard methodologies that minimize damage to TEMPs are needed for assessing the percentages of mixed species cell types and their relative distributions within engineered tissues. NIST should organize and/or participate in a standards task force/group within the ASTM F04, Division IV

standards development activities. Participants should include NIH, FDA, industry, and academic members of the TEMP community.

- **1.3 Develop criteria for assessing the persistence of degradable material**. Scaffold or other materials used in TEMPs are often intended to dissolve over time while cells proliferate to repair or replace tissues. The presence of the material may then become an impediment to an optimal therapeutic outcome. Standardized methods are needed to measure and validate that the materials are degrading as designed. This information will be critical for the clinical tracking of TEMPs and determination of whether or not the patient is having or is likely to have a problem as a result of the implanted material. NIST should organize a task force/group that will act toward establishment of the criteria for evaluating and tracking degradable implanted materials and devices. Participants should include NIH, FDA, industry, and academic members of the TEMP community.

- **1.4 Development of non-invasive imaging methods.** Because the TEMP field is emerging, there is a corresponding need for new, in-situ measurement methods for tracking the performance of implanted TEMPs and to assure that they are functioning as they were intended. . This is a broad topic, relevant to many areas. It would be useful to coordinate information about applicable techniques and methodologies, in addition to attempting to develop new measurement methods. NIST should lead in the organization of an interest group to track, develop and report on new measurement methods as well as those that have been accepted by the regulatory agencies. Key participants will include FDA and NIH as well as industrial and academic members of the TEMP community.

- **1.5 Pooling of information useful for facilitating developement of TEMPs (see DATA Crosscutting Issues section elsewhere in this workshop report).**

The high priority industry action items for NIST include:

- **2.1 Develop test methods for phenotype analysis and characterization**. There is a need to develop clinically relevant methods for confirmation of a phenotype of the cells that are engineered to go through a specific differentiation pathway and for detecting changes in cells over time, in culture to ensure consistency of cells used in TEMPs. Meeting this goal will require identification of a set of markers per specific cell type (e.g., fibroblasts, osteoblasts) and development of inexpensive tests, such as microarray methodology, for this task. NIST should lead in the organization of a task force/group from the TEMP community to establish the criteria for phenotyping of cells and for determination of the appropriate methods for these criteria. Participants should include NIH, FDA, standards organizations, industrial trade associations, and leading researchers from industry and academia.

- **2.2 Stem-Cell Analysis/Characterization (This is a separate, special consideration of action item 2.1**). Stem cells have the potential to differentiate into cells that can develop into any of the body's specific tissues/cell types. However, once a stem cell has differentiated along one pathway, it maylose the capability for differentiation into other cell types (i.e., skin cells may not be able to differentiate into pancreatic islet cells). Therefore, it is essential to have the most accurate characterization possible as to whether a particular cell is still a stem cell or if it has begun differentiation. This is a critical area of research and needs attention separately from general cellular phenotypic characterization, because of the high potential transience of this cell type. NIST should organize a special task force/group from the TEMP community to establish the criteria for phenotyping of stem cells and for determination of the appropriate methods for measuring these criteria. Participants should include NIH, FDA, industry, standards organizations, industrial trade associations, and leading researchers from industry and academia.

- **2.3 Develop consensus test-standards for temporary components of TEMPs; Cells, Bioactive Agents and Solid Phase Materials.** This need overlaps that of the regulatory need described in section 1.2 for determining the percentage of cell types (human or animal) that make up a particular TEMP. It is recognized that many of the test methods employed will need to be rapid, due to high reactivity and, in the case of cells, developmental transience. The test methods are needed to assure quality and optimize the TEMP development process. These standard methods could be agreed on as a result of round-robin testing of methods that may have been developed from a variety of sources including industrial, academic and government laboratories. Those agreed upon as a result of the round-robin-testing will provide the advantage of being the best available. As the quickly developing TEMPs industry changes, new tests can be quickly implemented and improved as the industry needs them. NIST can help by leading in the organization of or participation in a round-robin-testing group from the TEMP community to identify test methods for standardization, and for organization of round-robin, test-validation committees. The objective will be to obtain the most accurate testing standards available (NIST should provide the necessary technical oversight for assurance of validation procedures.) Additionally, the test group should lead in the establishment of a clearinghouse for accumulating tests to be considered for evaluation by the round-robin process. The participants should include FDA, NIH, standards organizations, and industry and industrial trade organizations, and leading academic and industrial researchers.

- **2.4 Identify or develop standards for preservation of cells**. While guidelines for the preservation of cells, tissues and organs may exist, there are no existing consensus standards. Therefore, there is a need for identifying and developing materials, standards, and standard protocols for the storage and preservation of cells and tissues. NIST can organize a workshop to determine the current needs in this area. The steering committee should include ASTM, FDA, American Tissue Cell Culture, and key researchers from the TEMPs community and from the Society for Biomaterials.

- **2.5 Develop biomarkers for the identification of potentially infectious agents or xenogenic cells from co-cultures that are employed in the manufacturing of TEMPs.** There is a need to develop accurate, high-throughput assays for detection of potentially infectious agents in TEMPs (e.g., prions) and a need for developing a rapid and highly sensitive sterility assay. Meeting this goal will require collaboration with other federal agencies such as NIH, and with academia and the industry. NIST should organize a task force/group from the TEMP research community to coordinate the many activities in this area. Participants should include FDA, NIH, standards organizations, and leaders from industry and academia.

- **2.6 Develop *in vitro* safety and efficacy assays for individual components of a final TEMP**. The ISO 10993 biocompatibility tests pertain to biomaterials and are not optimal for assessing the safety of combination products. To evaluate the *in vitro* final efficacy of an engineered device (alginate–cell mix, bioartificial skin, or bioartificial bone combined with a growth factor) is challenging. There is a need for novel test methods for evaluating safety and efficacy of individual components (e.g. cells, biomaterials, biomolecules) of TEMPs and the final device. Substrate characterization is of great importance in this regard. Development of the needed tests will be challenging and will involve collaborations with industry, other federal agencies, and groups such as NCCLS. NIST can help by leading in the organization of a task force/group that should coordinate the needed developmental activities (which may be combined with Action Item 2.7, below). Participants should include FDA, NIH, standards organizations, and leaders from industry and academia.

- **2.7 Develop standard, non-cell based safety and efficacy assays (e.g. *in vitro* calcification model) and reference materials for detecting residuals on TEMPS.** The non-cell based assays are needed

to predict *in vivo* behavior of TEMPs. Reference materials are needed for residuals such as DMSO. Both the validation of assay test methods and the development of models for predicting efficacy are needed (these can work synergistically by complementary refinement to enhance the precision of each). A collaborative effort will be needed with other federal agencies, academia and industry. NIST can help by leading in the organization of a task force/group to coordinate these activities (which may be combined with Action Item 2.6, above

- **2.8 Develop Genomic/Proteomic Assessments.** It would be of great use if a mechanism for rapidly annotating cells and tissues with genomic and proteomic data were available. This would allow new cellular markers to be quickly assigned to TEMPs, for both quality control and precision identification (i.e., production lot identification). This would require software for facilitating the harvesting of genomic and proteomic data as well as the tools to help users map markers to cells and tissues from any source (e.g., human, porcine, etc.). NIST should organize a workshop to establish who, within and outside the TEMPs community, should be contributing to this effort as well as for establishing the pertinent issues resulting from the follow-up workshop.

Crosscutting technical areas: These dealt with the crosscutting issues of: Harmonization of Standards and Data in separate breakout sessions. The discussion leaders in each session wrote the reports. The Harmonization group met after each of its members attended the first half of other technical focus-area breakout sessions and reached consensus on the action items reported on. The data group also dispersed itself among the technical area breakout sessions for their entire 3 hours of meeting and then met to discuss issues that its members became aware during that time. Consensus on action items was not reached; hence, the report contains the perceptions of various individuals of the data group regarding data management and security needs and what they, as individuals, would like to see NIST address.

Crosscutting Issues Reports

Crosscutting Issues Session Leaders

Data - Henry Heffernan, National Institutes of Health
NIST Facilitator: Michael Hogan - Scribe, Arnold Johnson

Harmonization - Sharon Stanford, American Dental Association
NIST Facilitator: Mary Saunders - Scribe, Belinda Collins

Harmonization of Standards

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Overview

Harmonization of standards means development and use of a single standard that is universally acceptable to all affected parties. Ideally, this will include compatibility with worldwide requirements of both government and industry. Drivers for harmonization include the emergence of a global market affecting both trade and travel, extensive regulation for the biomedical industry (sometimes with conflicting regulations and supporting standards), and a growing body of diverse information that standards can help to make uniform. To be effective, harmonized standards must be globally accepted, technically correct, practical, responsive to regulatory needs, and readily accessible.

Why should standards be harmonized? Because **not** harmonizing is too expensive. Harmonization avoids the duplication of effort required to develop multiple standards. Multiple standards on the same topic waste resources, are confusing to the users, can be expensive to conform to, and are generally burdensome. Hence, as such standards arise from different sources, harmonization is needed as a continuing process toward reducing them to one standard for all applications. The resulting harmonized standard must have global acceptance. If the harmonized standard is developed by an international organization, such as ISO and IEC, it will typically have quick global acceptance. When the standard is used in a regulatory application, regulators, not just in the United States, but also around the world, must also be encouraged to cite it. Finally, it must be used by the market, that is, by manufacturers, suppliers, and customers around the world.

In the development of harmonized standards, the ideal standards process should adhere to the principles of due process. It should be open, balanced, and involve all parties who have an interest in a particular area. During the process, participants should consider the market relevance and any particularly appropriate clinical relevance of the intended standard. The resulting standard should also be timely, flexible and efficient, both in terms of initial development and on-going maintenance.

Despite all the benefits of standardization, the standards process is often criticized as too political, too slow and tedious, or too easily dominated by a single interest so that all voices aren't heard. Other concerns relate to lack of adequate funding, particularly for ensuring participation of academic, consumer, or other diverse interests in a consensus process. Finally, there is concern that the resulting standard, being based in consensus, may be below the lowest acceptable common denominator, because too many compromises have been made. Despite these criticisms, the harmonized standard still remains the best way to meet market needs in both health and safety, as well as in trade and manufacturing.

To achieve a harmonized standard, interested parties must determine if a standard(s) already exists and they may have to conduct pre-standardization research to resolve technical problems before attempting to standardize procedures or test methods. They must find and work through an appropriate sponsoring standards development organization (SDO) toward a consensus standard. Often validation of the standard will require round robin testing to ensure that it will, in fact, produce the desired results.

In all of these steps, NIST can play an important role to facilitate the development and the use of harmonized standards.

Proposed Roles for NIST in Harmonizing of Standards.

- Challenge the underlying technical assumptions, such as "sterilization is under control" (when, in fact, discussion at this workshop indicated that sterilization of TEMPs remains a complex problem that needs to be solved).
- Conduct pre-normative research on technical issues so that the path to harmonized global standards is smoothed.
- Develop sound test methods for particular topics in conjunction with industry and government agencies, to meet the needs of both.
- Assist in the verification of proposed test methods so that the standards developed using those test methods are valid and reliable.
- Facilitate not only the development, but also the use, of harmonized standards.
- Consider developing a database of all existing biomedical standards worldwide and their reference in regulations to enable interested parties to determine the need for new standards quickly.
- Provide (or continue to provide) an open forum for discussion of industry and government needs in standards.
- Educate important stakeholders on the value of standards and the need for participation in developing sound, harmonized standards.
- Ensure that NIST staff participates at the technical level in processes that will result in internationally accepted standards.
- Look for gaps and disharmony in the standards development process and alert stakeholders. To achieve the roles laid out for NIST above, NIST will need more funding for scientific participation in the standards process, including biomedical standards.

In conclusion, NIST must develop a formal, ongoing and continuing working mode with industry sectors that involves SDOs and regulatory authorities when appropriate.

Data Management and Information Technology Requirements

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Overview

Computer-based data management and communications have become pervasive in the many specialized segments of the nation's biomedical industry. In recognition of this fact, the NIST Workshop on Standards for Biomedical Materials and Devices included in its design a small data group, composed of industry and government experts experienced in data management and information technology. This group participated in the discussions of the five breakout groups to identify the data management and information technology requirements that were discussed in those sessions. Based on those requirements, the data group formulated action plans for NIST to cooperate with industry in developing the needed measurements and standards. These action plans are also intended to promote the long-term development of standards-based information technology capabilities that will be needed for the successful industry-wide adoption of science and technology for advanced biomedical materials and devices.

"Just-in-time" manufacturing and inventory management requires advanced data management capabilities. The continuous need for progressive improvements in the quality and performance of biomedical materials and devices requires new information technology (IT) approaches. The lead position of U.S. companies in the global biomedical materials and devices markets can be helped by a judicious selection of strategic technical support projects for advancing their data management capabilities through standards. The following fifteen action plans will enable NIST to cooperate with industry in designing and developing standards-based IT capabilities.

The following fifteen action items are not prioritized. We recommend that priorities be assigned as NIST cooperates with government and industry stakeholders on pursuing these action items. This workshop begins a process for NIST to comprehensively cooperate with various segments of the biomedical materials and devices industry and other federal agencies in working through strategic data standardization issues. There are interdependencies among many of the action items, some of which are described in the Appendix. In particular, action items 1, 2, 3, 4, 5, 12, 14, and 15 could be dealt with together; items 8, 9, and 10 could be dealt with together. They have been described separately because their domains do not completely overlap and describing them together would be cumbersome. In the sense of dealing collectively with the action items there would be only six of them. Successful implementation of one action item may require the concurrent work on one or more of the other action items. This provides both a challenge and an opportunity for the stakeholders to work together on related action items.

Action Items Needed:

- **(1) Develop a Standard Interface to Properties of Materials Databases**
  Manufacturers of biomedical devices need access to publicly available information about the physical, chemical, and performance characteristics or properties of materials used in the manufacture of such devices. They need a standard way to represent different kinds of properties in a properties database so that a single software application can access multiple materials databases. Collaboration is needed by the stakeholders on a standard way to communicate with these materials

knowledgebases. The Oasis/ebXML/Registry (see glossary, appendix) project is developing standard ways to query and make submissions of new data so that materials databases can interoperate. The Oasis/ebXML/Registry specification needs specialization to fine-tune it to operate as a registry for Properties of Materials. NIST can provide leadership for an initial meeting to coordinate standards development, conformance test development, and implementation cooperation.

- **(2) Develop Standardized Identifiers (tags) for Measurements**.
  Users of materials intended for biomedical applications would benefit from having materials properties readily available with properties that have been measured by known and well understood techniques . Manufacturers of materials intended for biomedical application would benefit from having their products exposed to users and labeled with properties determined by independent researchers using standardized property description formats. The biomedical materials and devices industry needs collaboration by stakeholders on standardized tags to identify physical and chemical measurements (e.g. the NIST/MatML project), and standard ways to represent different kinds of properties in a properties database so that a single software application can access multiple materials databases. Participants at the June 26-27 NIST MatML workshop can be the kernel of industry and user participation. NIST can provide leadership for an initial meeting to coordinate standards development, conformance test development, and implementation cooperation.

- **(3) Conduct a Workshop on Standardizing Biomedical Materials Data Registry Methodology**
  The description of the data elements that correspond to the characterization of biomedical materials by one organization is usually not consistent with the characterization data developed by other organizations, which is a barrier to effective communications within the industry. An initial workshop would enable biomedical materials and device industry representatives, materials research and clinical quality control specialists, and interested government representatives to familiarize themselves with the ISO/IEC 11179 Data Standardization methodology, and develop a coordinated strategy for applying this data registry standard in a uniform way throughout the biomedical materials and devices industry. The NIST ITL has the experience in standardizing data registries, and the contacts with the leaders in data registry development; thus, ITL should lead in the organization of a workshop for the biomedical materials and devices industry segments.

- **(4) Provide Technical Assistance for the Development of Audiometric Data Structures**.
  A standardization effort already established as WG86 within ANSI-accredited Acoustical Society of America Standards Committee S3, Bioacoustics, is combing through existing ANSI and IEC standards, and current industrial practice, to identify appropriate data elements for construction of higher-level data structures appropriate for the interchange of data related to Hearing Devices, Programmers, and Test Instruments, and their use in the evaluation of human hearing. The working group is composed of audiologists and representatives from groups that produce auditory devices, but it has very little experience in data modeling or in the representation of data structures as XML documents. A data representative with experience in XML and data modeling is needed to work with domain experts of ANSI S3/WG86 to develop Audiometric Data Structures. This action item has been partially addressed --- see Appendix regarding NIST representative meeting report from June 29, 2001, S3/WG86 meeting. Participation in this effort should include a NIST representative with expertise in XML and data modeling, along with the current membership of ANSI S3/WG86.

- **(5) Initiate a Technical Working Group on Ontology for Clinical Responses**.
  Biomedical materials manufacturers, user organizations, and clinicians have a need for uniformly classifying responses to biomaterial as well as conventional devices. The development of consensus agreements on how these in vivo responses to biomaterials and devices are to be classified and related to one another in a domain ontology requires an on-going Task Force or Working Group. The

working group, in addition to recognized representatives of the biomedical materials and devices industry, should include scientists experienced in knowledge representation methodologies and software systems that draw inferences from the data, and clinicians to evaluate and adopt appropriate terminology. The objective of the working group would be to develop a plan for describing the clinical responses of patients to biomedical materials and devices, and defining the ontological relationships between these clinical responses in machine-interpretable formats. To facilitate the acceptance and adoption of these ontological definitions and formats, a representative group of clinicians and data specialists is needed to define the scope of this effort and to identify the domains where progress could be expected to be made first. NIST can provide leadership for an initial meeting with NIST ontology specialists to assist in defining the scope and program of work for the working group, along with FDA and NIH participation.

- **(6) Develop Data Interchange Standards among Biomedical Instruments and Implant Devices** Many devices implanted within the human body, acting as sensors to collect data, need to communicate with instruments, databases, and expert systems located outside of the body. In addition exterior software systems need to communicate with one another, sharing data received from sensor devices within the body. Common high-level standard formats and data structures for interchanging biomedical data are needed for this communication that are equally applicable for wireless data interchange and for connected data interchange. XML is universally accepted as an appropriate markup language for messages to be sent among cooperating software systems. The Biotechnology Industry Organization (BIO) is cooperating with several major software vendors (e.g. Sun, IBM) to define standard biological data structures that can be transmitted, queried, and modified by different software systems with no loss of semantics (http://www.washtech.com/news/biotech/9972-1.html). The BIO effort to identify data structures and a parallel effort to represent those structures as XML documents for interchange, needs participation from interested parties. All segments of the bio-technology industry that need to exchange structured data, and all government agencies that need to exchange biomedical data with themselves or with industry, should be invited to participate in this project. Whether this specific focused effort is included in the Biotechnology Industry Organization (BIO) program as a priority that will be addressed early, needs to be determined. If it is not a priority for the BIO project, then NIST should take the initiative toward identifying a device industry standards development organization that will lead in this effort.

- **(7) Develop Round-Robin Testing Protocols for Assuring Accuracy and Precision of Measurements**. In round robin testing (see glossary, appendix) for validating and refining standards for materials and manufacturing processes, the specifications for the statistical measures used by different testers can be different from each other. These differences in measurement among testers reduce significantly the confidence that can be placed in the final results of the round robin testing. Round robin tests are often performed under the auspices of a standard protocol of a standards organization. These form necessary rudiments for the comparisons; however, subtleties in the use (or non use) of traceable calibration standards or in the failure to extend statistical analyses to more robust methods may substantially reduce the value of the information that could be derived from data. Generic protocols and tailored protocols for round-robin testing need to be developed to assure that the appropriate numerical methods and statistical controls can be maintained throughout the round-robin testing process. Standards development organizations, biomedical materials and devices manufacturing firms, NIST materials scientists, manufacturing, and computational statistics personnel should be involved. NIST statistical engineers and computational statisticians, working with the industrial statisticians and materials standards development committees, could provide initial models of statistical approaches that would provide examples for industry groups to follow.

- **(8) Establish a Working Group to Develop Patient Anonymization Standards.**
  Just as traceability of test measurements to standard reference materials and test methods standards is essential, so also there is a need for clinical researchers, and evaluators of materials and devices research, to be able to trace results back to the individual patients from which the measurements and responses were derived. Materials and devices manufacturers have a need for a uniform method for tracking patients with devices over time that complies with applicable privacy and confidentiality requirements. For the effective monitoring of the clinical use of biomedical materials and devices, and for device/patient tracking over time periods, there is a need for patient anonymization standards. An on-going Task Force or Working Group is needed to identify, evaluate and adopt the appropriate standards. Included in the positive outcomes is expected to be the streamlining of approval processes through acceptance of these standards by regulatory agencies, state legislatures, funding agencies, and Institutional Review Boards (IRBs), thereby facilitating clinical trials. The working group should include Clinicians from academia, government and the biotechnology industry, as well as data and IT security specialists who are working in the health area. For the initial start up and definition of the scope of this activity, NIST security standards specialists could chair the group, with support from FDA and NIH clinical research specialists

- **(9) Establish a Working Group to Develop Device/Patient Tracking Standards**.
  There are a number of longitudinal data tracking and coordination issues that need to be addressed for the effective evaluation and clinical use of biomedical materials and devices. A particular need is for device/patient tracking standards. Clinicians and device manufacturers have a need for uniformly tracking these devices and patient responses over time, requiring a consensus on the types and methods of data tracking. The representatives need to be recognized representatives of the data and clinical communities to effectively facilitate the acceptance and adoption of these ontological definitions and standards. The dimensions of the solution to this need can be determined by assembling a representative group of device manufacturers, clinicians and data and IT security specialists to form a Working Group on device/patient tracking standards. The working group should include clinicians from academia, government and the biotechnology industry, along with data specialists who are working in the health area. NIST data engineers should convene the working group in order to define the scope and program of work of the working group, with cooperation from FDA and NIH clinical research specialists.

- **(10) Develop Standards for the Security of Data on the Measurements of Biomedical Materials and Devices.** The increasing use of information technology (IT) systems and IT-enabled devices for electronically gathering, storing and transmitting medical data of individual's has resulted in national rules and policies regarding the privacy and security of healthcare information such as the Department of Health and Human Services (HHS) Health Insurance Portability and Accountability Act of 1996 (HIPAA), and Healthcare Financing Agency (HCFA) Proposed Internet Security Policy (HISP). Clinical researchers, evaluators and users of biomedical materials and devices capture and use patient healthcare information, which must be protected in accordance with national laws and regulations. Materials and devices manufacturers and users have need for standards and measurements for protecting the integrity and confidentiality of patient data/information. A forum is needed to address such questions as: what are the medical data privacy and security issues associated with biomedical materials and devices; what standards are needed in this area; what Government policies on privacy and security of medical data, (e.g., Health and Human Services (HHS) HIPAA) must biomedical materials and devices comply with; what IT security features do biomedical devices have, what standards must they follow, and how is compliance assessed? Participants in the forum should include biomedical materials and device providers, clinicians, academia, government, as well as data and information security specialists who are working in the health area. NIST can provide

leadership by holding an initial meeting to coordinate standards development, conformance test development, and implementation cooperation.

- **(11) Identify Internal NIST Knowledgebase and Information Expertise.**
  The various NIST laboratories and technical services have extensive data management and advanced information processing expertise, but there has been little cross-unit awareness and knowledge of this expertise, and the capabilities that this expertise can offer to the U.S. Biomedical Materials and Devices Industry, no matter in what division or laboratory that expertise may be found. Coordination of the NIST internal information and data expertise is needed, so that the appropriate expertise can be identified and approached for possible collaboration and CRADA projects by organizations in the biomedical materials and devices industries.. A series of workshops of NIST personnel that support information handling in all NIST laboratories and programs should be held. The goal of these workshops would be to (1) identify and categorize the expertise in information and data management in these NIST personnel, and to catalogue the aspects of this expertise in a way that can be understood across the NIST organizational units; (2) provide NIST personnel with an understanding of the categories and range of complementary expertise in other NIST personnel for developing a coordinated strategy for representing this expertise to the various industries that NIST supports with its programs, with particular emphasis on the biomedical materials and devices industries; (3) to communicate these information management capabilities to relevant industries where CRADA and other cooperative programs and voluntary standards activities are conducted.

- **(12) Conduct a Workshop on Ontology Technology for Nomenclatures, Biomedical Materials Characterizations and Device Performance Characterization.** A fundamental difficulty in the characterization of biomedical materials and the performance of devices is the need to describe many interconnected parameters and attributes in terms of how they affect the performance of the materials and devices in different operating contexts and under different operating conditions. The semantic interconnectedness of these data items in operational contexts can be represented in computer-interpretable forms through domain ontologies. These domain ontologies can support the compatibility and consistency of the knowledge bases of each organization that supplies products in the value chain of the manufacturing processes of the specialized industry segments for different biomedical materials and devices. These domain ontologies, appropriately developed and validated through round robin testing and refinement by firms in the industry segments is needed for the kinds of "databases" support needed to respond to the variety of uses that the industry participants had mentioned in the focus sections. A NIST-sponsored workshop that will be informative for participants from the biomedical materials and devices industry segments is needed. No individual company can develop the ontology content for its knowledge base in a sufficiently complete and consistent manner that can assure its consistency and compatibility with the knowledge bases of other companies in its industry category, and with the knowledge bases of the companies in its supply chain, as well as those in its client or customer organizations. A group effort is needed. In addition, coordinating these knowledge base developments with clinical research organizations and the approval processes of FDA and its EU and Asian counterparts is not going to happen without a technical support organization that is thoroughly familiar with consensus processes and is recognized internationally, such as NIST. The workshop will provide the opportunity for identifying industry participants in the planning and organization of the projects that will develop the domain ontologies.

- **(13) Develop Conformance Tests for the Advanced Features of SQL '99.**
  The biomedical industry requires that its various databases be interoperable and provide compatibility in their management of the complex data structures used for representing properties and performance characteristics of materials and devices. The standardization of data management features in an earlier SQL '92 version of SQL and the development of test suites to enforce those standards proved very useful to industry in achieving compatibility. The advanced features of the ISO/IEC database standard

SQL '99 contain additional capabilities helpful for managing these complex data structures; however, conformance tests for the new features in SQL '99 do not yet exist. Many of the complex characterizations of materials and of the performance of devices in their operational environments need to be represented in databases in ways that can be automatically (without human examination and interpretation) interpreted by rules in other databases. Without conformance tests, implementation agreements, and protocols for interoperability testing, major errors can occur in processing data structures across different databases that can result from mistaken interpretation of database schemata across different database management systems. Database standard developers, database systems vendors, and government agency data experts could participate in the development of conformance tests for the advanced features of SQL '99. NIST ITL personnel were active in development of the existing SQL '92 test suite and have experience in the complete life cycle of conformance test suite development, and in the participatory consensus processes that are necessary for confirming the validity of conformance test products. NIST could use this experience to act in a limited advisory or consulting role for new initiatives from the industry.

- **(14) Provide a Forum and Technical Support for the Automation of the Regulatory Submission/Reporting Processes** Manufacturers need to make submissions to various government agencies regarding the biomedical products and devices that they manufacture. Currently it is common practice to fill out the forms used by these agencies manually. It would save the industry both time and effort if there were a catalog of standard government reporting forms, using a commonly defined XML document type definition (DTD) and a standard set of basic elements for the interchange of common information so that a manufacturer's data management software could prepare and submit the required reports in a form that a government agency could receive and process them, without human intervention to type and re-type or re-format the data. A forum is needed where biomedical device manufacturers that prepare reports and the government agencies that receive them can meet to agree on the structure and content of reporting forms. Also necessary as a catalyst for success is participation of personnel skilled in data and process modeling and representation of data structures in some interchange format like XML. NIST could help with creation of the appropriate forum for such groups to present their requirements and discuss potential standardization, and NIST personnel with experience in data modeling and data interchange, and knowledge of existing standards, could assist in molding those requirements into candidate specifications for joint approval by the affected groups. Participants in this project should include all agencies with submission or reporting requirements related to biomedical devices (e.g., FDA, NIH, VA), all manufacturers subject to submission or reporting requirements, representatives of the Clinical Data Interchange Standards Consortium, representatives of the HCFA initiative for the U.S. Healthcare Information Knowledgebase, NIST personnel familiar with setting up effective standardization structures, and NIST personnel familiar with data modeling and data interchange. NIST can provide leadership for an initial planning meeting to coordinate participation of representatives from the government agencies, including NIST, and the manufacturer industry segments that will benefit from submission and reporting standards.

- **(15) Identify Coordination Issues between Clinical Data Standardization and Materials and Devices Biomedical Data Requirements.** Currently there is significant work being done in a number of standards development organizations to standardize clinical data elements. As the data requirements of the biomedical materials and devices industry become better understood, it will be important to assure that no conflicts or incompatibilities are developed between clinical data standards and biomedical materials and devices data agreements. The ANSI Healthcare Informatics Standards Board (HISB) is coordinating standards development for electronic messages that include clinical data, and is addressing the implementation agreements required for the Administrative Simplification requirements of the Health Insurance Portability and Accountability Act (HIPAA).

The ANSI Medical Devices Standards Board (MDSB) coordinates standards for medical devices. The involvement of NIST data scientists in supporting various facets of the U.S. biomedical materials and devices industry would provide a unique vantage point for identifying compatibility issues and bringing these issues to the appropriate standards bodies for clarification and resolution. To accomplish this action, NIST data scientists need to establish working relationships with various standards development committees.

Appendices

Appendix: Auditory Diagnostic and Prosthetic Devices

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Overview

This Appendix furnishes some background and explanatory material regarding auditory diagnostic and prosthetic devices. This subject is complicated because the human auditory system is complicated in its anatomy, physiology, and function. Signal transmission and coding in the auditory system involves complex sounds (speech, music, noise) and acoustical environments, acoustical transmission to and reception by the external ear, sound-induced vibration of the tympanic membrane (eardrum), conduction of mechanical vibration via the ossicles in the middle ear to the cochlea (fluid-filled inner ear), hydromechanical frequency analysis within the cochlea, transduction to electrical potentials including auditory nerve fiber action potentials, subsequent further nonlinear signal transmission, coding, and processing via ascending (afferent) and also descending (efferent) neuronal pathways to and from the brain, and binaural interactions between the left and right ears and portions of the brain. The variety of hereditary and environmental factors, diseases and injuries that can produce ranges of damage in various parts of the auditory system, and consequently in types and extents of hearing losses, in different individuals at various ages, has led to the wide variety of diagnostic and prosthetic devices in this field.

Further, the size of the auditory device industry is expected to increase significantly as a result of (1) demographic and medical trends due to dramatic increases in the average age of populations in industrialized nations, (2) the rapid development of new technologies resulting from the continued integration of electrical and mechanical systems (mechatronics), advances in signal processing, improved transducers and arrays, and miniaturization, and (3) benefits of continued basic and applied research involving (but not limited to) signal transmission and coding in the auditory system, auditory perception and speech reception, functional performance testing of hearing, screening and diagnosis, and prescription (fitting) of auditory prosthetics. To illustrate, in the U.S. the elderly population (ages 65 and over) is expected to double in the years 2000 to 2030.[1] Also, regarding recent trends in the last few decades up to the current (2001) population, "some evidence points to an increase in the prevalence of hearing impairment among persons 45-69 years of age, especially among men."[1] Not unrelated, these same years are expected to see a dramatic change in the number and types of technologies and devices that are developed - custom auditory prosthetics including improved programmable and digital signal processing hearing aids, better cochlear, middle ear, brainstem, and other auditory implants, and better metrology-intensive diagnostic devices and procedures needed for proper selection and fitting of prosthetics to better understood, diagnosed, characterized, and measured hearing losses of patients. At present, only a small minority (about 16%) of physicians routinely screen for hearing loss.

Among biomedical devices, auditory devices are unusual in that they are quickly growing in importance not only to the rapidly increasing number of the elderly, but also to all age groups including infants. Sergei Kochkin, Ph.D., in "FAQ About People with Hearing Loss" prepared for the Better Hearing Institute, noted that there are "close to 8 million people between the ages of 18 and 44 with a hearing loss and more than a million school aged children." Proper diagnosis and treatment of hearing loss is critically important for successful patient outcomes in all age groups, but is especially so for children who have not yet acquired language. Without proper diagnosis and treatment many of these children might never exceed the 3rd-grade educational level!

Consequently, the screening of newborn infants for hearing loss is recommended nationally by the National Institute on Deafness and Other Communication Disorders (NIDCD, an Institute of NIH), and is legally mandated by a large and increasing number of states . According to the American Speech-Language-Hearing Association (ASHA), the number of states that have passed early hearing detection and intervention (EHDI) laws has grown from 12 in 1998 to 32 in July 2000. This early screening for hearing loss necessarily involves methods that do not require linguistic communication with the infant. Such methods include measuring sounds produced by the auditory system called otoacoustic emissions (OAE, which may be evoked or spontaneous), and auditory brainstem response (ABR) methods used to predict hearing sensitivity and to assess the integrity of Cranial Nerve VIII and auditory brainstem structures by measuring evoked potentials (electrical signals produced in the auditory system in response to sound stimuli). These methods are also used on other patients (e.g., older children or adults), particularly when necessary for diagnosis, or when patients are unconscious or otherwise unresponsive to examiner-patient communication.

Regarding the breakout session item "Address the Issue of Electromagnetic Interference with Audiometric Equipment in Sound Rooms," some additional aspects are relevant. For busy hospitals or clinics to which patients frequently must travel considerable distances (or undergo some other hardships) for tightly scheduled appointments, the use of electromagnetically shielded sound rooms is sometimes considered a necessary procedure that prevents continuous or intermittent ambient electromagnetic interference from causing invalid or misleading diagnostic instrument readings. Such interference is often critically dependent on relatively minor details of how interconnections are made between instruments (including cable lengths and spatial orientation), and how signal cables, power lines, or other penetrations are carried through shielded enclosures. Consequently, the efficacy of electromagnetically shielded sound rooms should be tested *in situ* after the rooms and all instrumentation have been installed and positioned exactly as they are used. There is an existing VA procurement specification for audiometric sound rooms that includes electromagnetic shielding specifications that are believed to be the most advanced of their type for these rooms, but there is no comparable national or international standard.

This session has identified numerous action items that would enable NIST to build upon its current capabilities and greatly to extend its contributions to the rapidly expanding field of standards for auditory diagnostic and prosthetic devices. At present, NIST's Manufacturing Engineering Laboratory (MEL) works with industry and government agencies, especially the Department of Veterans Affairs (VA), to develop methods to measure the electroacoustical performance characteristics of various new types of hearing aids. NIST also provides reference laboratory services (calibration and characterization of critical audiometric measuring instruments) when requested by the U.S. Public Health Service. Other relevant work at NIST (ITL) involves speech recognition programs and systems, natural language characteristics of speech, and higher-level information extraction. NIST (EEEL) has extensive capabilities regarding electromagnetic field measurements, EMC issues, and related standards development. These capabilities and the biological and medical resources of NIH are being applied in a collaboration to study biological effects of electromagnetic fields from cordless telephones.

Reference:

1. M. Desai *et al.*, "Trends in Vision and Hearing Among Older Americans," Aging Trends No. 2, Centers for Disease Control and Prevention, National Center for Health Statistics, March 2001.

APPENDIX CROSSCUTTING DATA ACTION ITEMS

A - SCOPE OF THE CROSSCUTTING DATA ACTION ITEMS

As stated in the overview of the data report, the action items listed assume that NIST will cooperate with industry in providing technical support for reference materials, materials databases, test and measurement development, and participation in appropriate standards development. The report also assumes that NIST will continue to cooperate with the biomedical materials and devices industry segments and other federal agencies in working through strategic technology issues as they emerge. The data group did not include within its scope consideration of possible NIST relationships with: the Biomedical Information Science and Technology Initiative (BISTI) that is underway at the National Institutes of Health, the new National Institute for Biomedical Imaging and Bioengineering (NIBIB), the United States Healthcare Information Knowledgebase (USHIK) initiative of the Health Care Financing Administration (HCFA) in cooperation with the medical care organizations of the Department of Defense, the Department of Veterans Affairs, or the Indian Health Service. However, a number of the recommended action items above have direct relevance for supporting these other initiatives.

Through participating in the discussions of the five breakout sections of the NIST Workshop on Standards for Biomedical Materials and Devices, the data group identified relevant data standards issues and recommended the action plans described in the body of this report. The data group recognized that there is a need to facilitate the application of refined database technology and semantic structures to reference databases to meet the strategic needs of the U.S. biomedical materials and devices industry segments. The data group also recognized that appropriate NIST staff could undertake a number of technical support roles in the U.S. and international standards development organizations that are actively developing information-related standards that will affect U.S. firms in the biomedical materials and devices industry segments, and that there is an early opportunity to accelerate the introduction of electronic interchange of data within and between the databases of organizations in the biomedical materials and devices industry segments and government agencies.

There are many data issues relevant to the Biomedical Devices and Materials community for anyone who is now trying to conduct business electronically. Data issues often become an impediment to successful electronic business deployments. Crosscutting issues with data include data acquisition, data interchange, and data security/privacy. Solving these issues requires technically sound standards, testing, and guidelines. There are many generic standards in place or under development for data elements, databases, data dictionaries, knowledge representation, and data security/privacy.

NIST technical expertise in data standards and testing should be applicable to many data issues that may be of relevance to the Biomedical Devices and Materials community.

B - INTERDEPENDENCIES AMONG ACTION ITEMS

B 1 - CHARACTERIZATION INFORMATION AND NOMENCLATURE

NIST is active in the ongoing ANSI and ISO standards work for metadata registries, using standards, such as, ISO 11179 (Specification and Standardization of Data Elements) and ANSI X3.285 (Metamodel for the Management of Shareable Data). A metadata registry, in which all information is defined and mapped to physical representations in databases and e-commerce data exchange formats, assists users in the sharing and exchange of mutually agreed information. This registry technology has unique usefulness for clarifying the attributes and semantics of data exchanged between databases. At present there is a major

joint activity underway to develop a Healthcare Information Knowledgebase for the United States by building a data registry to assist in cataloging and harmonizing data elements across organizations.

For biomedical materials and devices, to move forward in many of the activities related to data standards and interchange it will be necessary to first address the related problem with nomenclature. For example, the term polyethylene, can refer to a wide variety of materials with different characteristics and performance parameters. It may not be necessary to actually come up with a standard nomenclature, but the rules to be followed in "naming" an object, and the schema of the attributes or properties that are required for a particular entity should be agreed upon. The main difference between what has been called a "nomenclature", "controlled vocabulary", or "terminology" and an "ontology" is the degree of definition or meaning of each of the terms included, and the capability of computer software to accurately identify the logical implications of the use of a term in a context. Ontologies are semantically interpretable by software. *Larry Reeker, NIST ITL, has the experience in this field and the contacts with the leaders in ontology development that will guarantee the success of an informative workshop for the biomedical materials and devices industry segments*

For the large, complex structures of characteristics, measurements, and relationships that are needed in reference databases for materials and devices, ontologies can relate nomenclatures/vocabularies and their meanings with explicit, expressive, and well-defined semantic encodings that can be interpreted accurately and precisely by computer-based inferencing software. Ontologies limit the possible other meanings of terms to the set of meanings that are intended. Nomenclatures, controlled vocabularies, and terminologies typically assume that humans will look at the words, names of objects, or terms and supply the semantics through the memory recall of the human interpreter. Ontology technology is designed to shift much of that "semantic interpretative burden" to computers and have them understand what the terms mean. This technology enables the computer software to identify and suggest remedies for errors of human interpretation of data.

B 2 - DATA INTERCHANGE BETWEEN SYSTEMS AND DEVICES

For data interchange between information systems, NIST has recently developed an extended Extensible Markup Language (XML) Test Suite in partnership with the Organization for the Advancement of Structured Information Standards (OASIS). The XML standard provides methods for defining, interacting with, and exchanging data for a variety of domain specific applications. NIST also has a standard reference data program that generates sets of critically evaluated data and widely disseminates them both as computer databases and publications.

Clinical data interchange requirements are increasing. Data interchange remains difficult and resource intensive. Further, proprietary information must be protected, and legislative mandates (e.g., the healthcare data interchange standards requirements of the Healthcare Insurance Portability and Accountability Act (HIPAA)) for ensuring privacy are going into effect. Applying existing IT standards and possibly developing new standards will be needed to achieve these goals. *James Nell, in metrology and manufacturing standards work at NIST, has worked on enterprise integration projects and standards for many years, and is internationally recognized as a leader in coordinating the wide range of information processing specialties and international standards for data interchange in manufacturing enterprise activities.* Based upon specific standards needs, there should be, at the very least, exploratory meetings held to further discuss and define these needs. Participants should include organizations involved in clinical studies and NIST.

The following is a summary from the NIST representative to the June 29, 2001, S3/WG86 Meeting.

As the result of lively discussions, the Workshop on Standards for Biomedical Materials and Devices breakout session on Auditory Diagnostic and Prosthetic Devices group asked the chair and the NIST representative to pursue with NIST management the possibility of NIST attendance at a June 29 ANSI S3/WG86 meeting to take a more serious look at defining an Audiology Information Model that could be the basis of structured messages among audiologists and manufacturers of auditory devices. Such messages usually contain data structures that describe the settings of test instruments and the curves resulting from tests on human subjects. The June 29 S3/WG86 meeting was a success. The Audiometric Data Structures project is now revitalized with manufacturers and audiologists in apparent agreement on a strategy for defining a higher-level Audiology Information Model to support XML representations of device and test instrument profiles, client evaluations, and test curve results. NIST involvement in the future of S3/WG86 is open. *The effort could be initiated under the leadership of Bill Cole, Co-chair of S3/WG86.*

B 3 - SECURITY AND PRIVACY

Legislative mandates (e.g., the healthcare data interchange standards requirements of the Healthcare Insurance Portability and Accountability Act (HIPAA)) for ensuring privacy are going into effect.

NIST was instrumental in developing the Common Criteria standard, ISO/IEC 15408: 1999 (Common Criteria for Information Technology Security Evaluation), a standard for defining and measuring security requirements in information technology (IT) security enabled products (software, firmware, hardware, devices, etc.) and systems that are expressed in user-defined Protection Profiles or vendor-defined Security Targets, and FIPS 140 Cryptographic Modules. NIST has been instrumental in the development of conformance testing programs for IT security standards such as ISO/IEC 15408 Common Criteria for IT Security Evaluation, FIPS 140 Cryptographic Modules, PKI, etc. which could be useful in supporting the biomedical devices and materials community in complying with government regulations and protecting medical information.

NIST also helped organize The Forum on Privacy and Security in Healthcare in November 1998. One purpose of this Forum is to serve as venue for healthcare stakeholders to define common, user-defined IT security requirements in the form of Common Criteria-based Protection Profiles. NIST presently has a Draft Federal Information Processing Standard (FIPS) for the Advanced Encryption Standard (AES) available for public review and comment. The AES specifies a cryptographic algorithm for use by U.S. Government organizations to protect sensitive (unclassified) information. NIST also anticipates that the AES will be widely used on a voluntary basis by organizations, institutions, and individuals outside of the U.S. Government.

B 4 - COORDINATION WITH STANDARDS ORGANIZATIONS

In addition to the standards committees and accrediting organizations for standards development that are active in the biomedical materials and devices sciences and technologies, a number of other standards development organizations are actively working on data-related standards for healthcare information services, *such as HL7, X12, ASTM E31, the ANSI HISB, the SNOMED RT project, the LOINC project, the Clinical Data Interchange Standards Consortium (CDISC), the USHIK, the NLM UMLS, and the NCVHS.* These other standards development organizations have active working relationships with standards development organizations in other nations and at the international level. As healthcare extends beyond national boundaries, the impact of standards becomes more critical for an organization. While national health information standards have led the way to systems interoperability within the US, the North American-based industry must remain cognizant of the importance of growth and harmonization with international standards. The international standards process will have an impact, not only on the

healthcare standardization process within the US but also on business directly. Some relevant U.S. standards committees are the following:

ANSI S3: Bioacoustics, which addresses hearing aids, ear and brainstem implants, and other auditory devices. S3 has a working group WG86 on Audiometric Data Structures that wants to define and exchange its data structures in XML.

ANSI HISB: The American National Standards Institute's Healthcare Informatics Standards Board (ANSI HISB) provides an open, public forum for the voluntary coordination of healthcare informatics standards among all United States' standard developing organizations. Every major developer of healthcare informatics standards in the United States participates in ANSI HISB. The ANSI HISB has 25 voting members and more than 100 participants, including ANSI-accredited and other standards developing organizations, professional societies, trade associations, private companies, federal agencies, and others. The ANSI HISB meet four times a year. Please see Meeting Info for meeting information. Please also visit the Healthcare Informatics Meeting Calendar -- listing of up-coming Healthcare Informatics Meetings through 2001.

ASTM Committee E31 on Healthcare Informatics: [Staff Manager: Daniel Smith (610) 832-9727] ASTM Committee E31 on Healthcare Informatics develops standards related to the architecture, content, storage, security, confidentiality, functionality, and communication of information used within healthcare and healthcare decision making, including patient-specific information and knowledge. Established in 1970, E31 meets semi-annually as a committee in May and November. Members and visitors attend three days of meetings that include technical subcommittee sessions and a plenary meeting. Some subcommittees occasionally meet on an accelerated basis. The committee, with current membership of approximately 270 members, currently holds jurisdiction of over 30 approved standards and additional draft standards. Approved standards are published annually in June in the Annual Book of ASTM Standards, Volume 14.01.

US TAG to ISO 215: ISO TC 215 has been established to develop international health informatics standards. Consensus on these standards will influence health informatics standards adopted in the US and the interoperability of national and international health information exchange. Efficient exchange of healthcare information and the interoperability of health information systems are important for industry's viability in this expanding market. A representative should join the U.S. TAG to TC 215.
The US TAG develops the national position, which is submitted to the TC. Membership in the TAG provides U.S. citizens with the following benefits:
* input into the development of the U.S. position on issues under consideration by the TC,
* opportunity to influence the work program and strategic initiatives within the TC,
* ability to affect the international standards that influence your business,
* notification of and attendance at U.S. TAG meetings,
* access to all TAG and TC documents, including minutes, meeting notices, ballots,
* opportunity to serve as a national delegate to and U.S. expert at the TC meetings.

Glossary of Terms:

•**data:** Any representation subject to interpretation (such as through analysis or pattern matching) or to which meaning may be assigned, such as by applying social conventions or special agreed upon codes. Data can be processed by humans or by automatic means.
•**data dictionary:** A database or file that provides definitions for data entities. Synonymous with data element dictionary.

•**data registry**: A database containing the metadata that is necessary to clearly describe, inventory, analyze, and classify data, providing an understanding of the meaning, representation, and identification of each unit of data (data element), along with the registration status of the data element.
•**data security**: Computer security applied to data.
•**data transmission:** The sending of data from one place to another by means of signals over a channel.
•**information:** The meaning that is currently assigned to data by means of the conventions applied to these data.
•**information interchange:** The process of sending and receiving data in such a manner that the information content or meaning assigned to the data is not altered during the transmission.
•**knowledgebase**: a database of information wherein the semantics of all data elements are described within the database.
•**metadata:** Data about data, including their data descriptions, ownership, access paths, access rights, and data volatility.
•**Oasis/ebXML/Registry:** OASIS is the Organization for the Advancement of Structured Information Standards (http://www.oasis-open.org). It is the international, not-for-profit consortium that advances electronic business by promoting open, collaborative development of interoperability specifications. With the United Nations, OASIS sponsors ebXML, a global framework for electronic business data exchange. OASIS operates XML.ORG, the non-commercial portal that delivers information on the use of XML in industry. The XML.ORG Registry provides as an open community clearinghouse for distributing and locating XML application schemas, vocabularies and related documents. OASIS serves as the home for industry groups interested in developing XML specifications. OASIS technical work embraces conformance, security, business transactions, repositories and other interoperability issues.
•**round robin test:** An interlaboratory study (ILS) or "round robin" that is utilized to generate the final data used to support the statistical validity of the test method. Typically, a series of laboratories conduct the same tests (a minimum of six is recommended in ASTM standard E 691).
•**ontology**: A database of concepts and terms, their meanings and semantic relationships to contexts, along with the structured encodings that make it possible for a computer to interpret and draw inferences from the definitions of the concepts and their semantic relationships.

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Standards for Biomedical Materials and Devices Workshop
June 13 – 14, 2001
University System of Maryland - Shady Grove Center

AGENDA

Wednesday Afternoon, June 13

12:00 PM- 1:00 PM	Registration and Lunch	
	Biomedical Standards Resource Presentations	
1:00	***Welcome***	
	Karen Brown	Acting Director, NIST
1:15	***NIST's Role in Biomedical Science and Technology - An Overview***	
	Leslie Smith	Director, Materials Science and Engineering Laboratory, NIST
1:30	***Objectives of the Workshop***	
	Dale Hall	Deputy Director, Materials Science and Engineering Laboratory, NIST
1:40	***Overview of Biomedical Material & Device Standards Issues***	
	Jack Lemons	Professor and Director of Laboratory Surgical Research, School of Medicine Division of Orthopedic Surgery, University of Alabama Birmingham
2:15	***Emerging Biomedical Issues***	
	John Watson	Director, Molecular Biology Program and Clinical and Molecular Medicine Program, National Heart, Lung, and Blood Institute, NIH
2:35	***Standards and the FDA Needs for Device Submissions***	
	Don Marlowee	Director, Office of Science and Technology, FDA
2:55	***An Industrial Perspective***	
	Bernie Liebler	Director of Technology and Regulatory Affairs, AdvaMed (Speaker)
	Jim Benson	Executive Vice President of Technology and Regulatory Affairs, AdvaMed
3:15	Break	
	Crosscutting Issues (Data/Sterilization/Harmonization)	
3:35	***Data***	
	Henry Heffernan	Staff, Clinical Center , NIH
3:45	***Sterilization***	
	Michael Scholla	Global Business Director, Tyvek Medical Packaging
3:55	***Harmonization***	
	Richard Kayser	Director, Technology Services, NIST
4:05	***Biomedical Materials and Clinical Testing***	
	Alan Andersen	President, National Committee for Clinical Laboratory Standards
4:25	***Instructions for Thursday's Sessions***	
	John Tesk	Coordinator, Biomaterial Standards and Reference Materials, Polymers Division, Materials Science and Engineering Laboratory, NIST
4:40	Adjourn	
6:00	Cash Bar, Reception, and Dinner at Quality Suites Hotel	

Thursday, June 14

8:00 AM Coffee & Pastries

8:30 Instructions for Breakout Sessions

8:40 Disperse to Breakout Session Rooms

Breakout Sessions

8:50 AM– 12:00 PM **Focus Area Breakout Sessions: Chairs & Co-Chairs,**

- **Biomaterials:** James Burns, Genzyme, Inc. & Rebecca Bergman, Medtronic, Inc.

  NIST Facilitators: Francis Wang, Bruno Fanconi - Scribe, Chad Snyder
- **Therapeutic and Drug Delivery Systems:** Arthur Courey, Genzyme, Inc. & Gary Strathearn, Radiance Medical Systems, Inc.

  NIST Facilitators: Christopher Soares, Bert Coursey - Scribe, Brian Zimmerman
- **Auditory Diagnostic and Prosthetic Devices:** William Cole, Etymonic Design, Inc. & Ronald Scicluna Argosy Electronics, Inc.

  NIST Facilitators: Victor Nedzelnitsky, Jonathan Fiscus - Scribe, Victor Nedzelnitsky
- **Manufacturing and Processing of Prostheses:** Dane Miller, Biomet, Inc. & Jan Ann Champion, Medtronic Heart Valve, Inc.

  NIST Facilitators: Howard Harary, Matthew Davies - Scribe, Ron Dixson
- **Tissue Engineered Medical Devices:** Peter Johnson, Tissue Informatics, Inc. & Nancy Parenteau, Organogenesis, Inc.

  NIST Facilitators: Eric Amis, Lori Goldner - Scribe, Newell Washburn

10:20 AM–12:00 PM **Breakaway Sessions**

- **Data** - Henry Heffernan, National Institutes of Health

  NIST Facilitator: Michael Hogan - Scribe, Arnold Johnson
- **Harmonization** - Sharon Stanford, American Dental Association

  NIST Facilitator: Mary Saunders - Scribe, Belinda Collins

Breaks Taken as Needed (Coffee etc., available from 10:00 AM to 11:00 AM)

12:00 PM Lunch

1:00 **Full Assembly**

Breakout Session Reports with 5 minute Discussions

Peter Johnson, Tissue Informatics, Inc., Chair

Joshua Jacobs, Rush Presbyterian St. Luke's Hospital, Co-Chair

Dale Hall, NIST, Convenor

1:00 • **Biomaterials**

1:20 • **Tissue Engineered Medical Devices**

1:40 • **Therapeutic and Drug Delivery Devices**

2:00 • **Manufacturing and Processing of Devices**

2:20 • **Auditory Diagnostic and Prosthetic Devices**

Cross Cutting Breakaway Session Reports

2:40 • **Data**

2:55 • **Harmonization**

Discussions & Refinements of Issues and Priorities

3:10 NIST Facilitators: Stephen Freiman & Bruno Fanconi

3:40 • **Action Items:** Dale Hall, NIST

4:00 • **Summary:** Leslie Smith, NIST

4:10 • Adjourn

Speaker Biographical Sketches

Workshop on Standards for Biomedical Materials and Devices
Rockville, MD
June 13-14, 2001

Karen H. Brown is the acting director and deputy director of NIST. Brown came to NIST as deputy director in January 1999. Previously she was a Distinguished Engineer at IBM Microelectronics in Hopewell Junction, N.Y. Her 22-year career at IBM concentrated on solving problems in semiconductor lithography and microelectronics. Brown also served (on assignment from IBM) as director of lithography for SEMATECH from 1994-1998. She has a proven track record in management, having successfully met the challenges of moving ideas from the laboratory into manufacturing. A native of Schenectady, N.Y., Brown holds a B.A. in chemistry and in history, and a Ph.D. in chemistry from the University of Rochester.

Leslie E. Smith is director of the Materials Science and Engineering Laboratory at NIST. Dr. Smith joined NIST in 1969 and worked extensively on interfacial phenomena of polymers. In particular, he has investigated the measurement of the conformation of adsorbed polymers and the relationship of adsorbed polymers to biocompatibility of synthetic implants. Dr. Smith is currently responsible for a comprehensive program of fundamental research of measurement methods, standards, and scientific concepts to support the U.S. industrial production and use of materials. Dr. Smith received his B.S. in chemistry at the Case Institute of Technology, and his Ph.D. in chemistry at the Catholic University of America.

Dale E. Hall is the deputy director of the Materials Science and Engineering Laboratory at NIST. During his years at NIST he has had several responsibilities, including chief of the Office of Intelligent Processing of Materials. Before joining NIST, he worked in industry for 14 years in electrochemistry and advanced materials development, including seven years at the International Nickel Company as principal scientist. He received his BS, cum laude, in chemistry, and his Ph.D. in physical chemistry from Rensselaer Polytechnic Institute. He is a former president of The Electrochemical Society.

Jack Lemons holds degrees of Associate in Engineering, Bachelors and Masters in Metallurgical Engineering, and a Doctorate in Materials Science from the University of Florida. After employment as a Director of Physical Metallurgy at Southern Research Institute he was an Assistant Professor of Interdisciplinary Studies at Clemson University. This was followed by a NIH sponsored fellowship in Medicine and Dentistry in 1970-73 at the University of Alabama at Birmingham with academic promotion to full professor in 1976. Dr. Lemons served as Chair of the Department of Biomaterials from 1978-1990 with transition to Professor and Director of Laboratory Surgical Research for the Departments of Prosthodontics and Biomaterials in Dentistry and the Division of Orthopaedic Surgery in Medicine since 1990. Publications and presentations exceed 600 including four books, and he has served as chair for more than 140 students' graduate committees. Research focus has been on biomaterial and biomechanical properties as they relate to the biocompatibility of implant devices. He has provided leadership in numerous standards related capacities with organizations that include the ASTM, the American Dental Association, the American Association of Orthopaedic Surgeons, and the Society for Biomaterials

John T. Watson is the Director Clinical and Molecular Medicine, Division of Heart and Vascular Diseases, National Heart, Lung, and Blood Institute, National Institutes of Health. Dr. Watson came to NIH in 1976 from the University of Texas Health Science Center where he was Chairman of the Graduate Study Program in Biomedical Engineering and Assistant Professor of Surgery and Physiology. He has bachelor's (Univ. Of Cincinnati) and master's (Southern Methodist Univ.) degrees in mechanical engineering and earned a doctorate in physiology from the University of Texas at the Southwestern Medical School. Dr. Watson experience includes 10 years in industry, 10 years in academia, and 24 years in the public sector. His research interests include medical implant design and science, biomaterials, imaging and heart failure. He is a Founding Fellow of the American Institute of Medical and Biological Engineering and a member of the National Academy of Engineering.

Donald E. Marlowe is the Director, Office of Science and Technology, Center for Devices and Radiological Health (CDRH), Food and Drug Administration (FDA). He directs the CDRH laboratory programs in areas of electronics, computer science, materials science, mechanical engineering, toxicology, bioeffects, and physics. He is currently Chairman of the Board for the American Society for Testing and Materials (ASTM). Mr. Marlowee received an

A.B. in Physics (1964), a B.M.E. (1964) and a M.S.E. in Solid Mechanics from Catholic University (1966). He holds several technical committee assignments and professional society memberships, including the American Society of Mechanical Engineers, the Association for the Advancement of Medical Instrumentation, and the American Society for Testing and Materials.

Bernie Liebler is Director, Technology & Regulatory Affairs at AdvaMed. As a member of the Technology and Regulatory Affairs Department, he is responsible for the technical aspects of standards, testing, and certification issues relating to medical devices. He is the Technical Advisor for the U.S. Advisory Groups for IEC TC 62 and SC 62A, international standards committees preparing horizontal standards for the safety of electrical medical devices. He also addresses quality assurance, biomaterials, software, and other regulatory issues. He received a B.S. in Physics from the City College of New York and an M.A. in Nuclear Physics from the State University of New York at Stony Brook.

James S. Benson is the Executive Vice President, Technology and Regulatory Affairs at the Advanced Medical Technology Association (AdvaMed). He is the lead strategist for the Association's regulatory agenda, which included the passage of the Biomaterials Access Assurance Act of 1998 and the FDA Modernization Act of 1997. Prior to joining AdvaMed, Mr. Benson held various positions at the Food and Drug Administration, including Acting FDA Commissioner (1990), FDA Deputy Commissioner (1988-1991) and Director for the Center for Devices and Radiological Health (1991-1992). Mr. Benson serves on the National Academy of Sciences Roundtable on Bioengineering and on the National Cancer Institute's Technology Evaluation Committee. He is a fellow of the American Institute of Medical and Biological Engineering (AIMBE). He is on the board of advisors to the Food and Drug Law Institute (FDLI). Past appointments include Board of Trustees of the American Society for Artificial and Internal Organs and the Institute of Medicine's Roundtable on Research and Development of Drugs, Biologics, and Medical Devices. Mr. Benson received a B.S. degree in Civil Engineering from the University of Maryland and an M.S. degree in Nuclear Engineering from the Georgia Institute of Technology.

Henry G. Heffernan, currently on the staff of the NIH Clinical Center, has nearly 30 years of experience in the development of information technology standards, and in the development of medical information systems. With an academic background in economics, he participated in early efforts to refine CLIA requirements before the legislation, and in defining requirements for the reliability and safety of the software systems. Improving biomedical computing infrastructure capabilities is a current
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Michael H. Scholla is Global Business Manager within DuPont Nonwovens with responsibility for the TYVEK(R) Medical. His diverse research background includes activation of cryptic genes, biological nitrogen fixation, antimicrobial polymer additives, and laser induced antimicrobial activity in polymers. His research has focused on issues affecting sterile package integrity and the microbial barrier properties of porous medical packaging materials. He holds key positions on several industry committees including Co-chair of the US technical advisory group for ISO TC198/WG7 on medical packaging; Chair of the Sterilization Task Force and Chair of the Standards Task Force for the Advanced Medical Technology Association; the Association for the Advancement of Medical Instrumentation International Standards Committee and Co-chair of the Packaging Committee. Dr. Scholla was awarded BS and MS degrees in Microbiology from the University of Central Florida and his Ph.D. from North Carolina State University.

Richard F. Kayser is the Director of Technology Services at the National Institute of Standards and Technology. Dr. Kayser joined the National Bureau of Standards in May 1976 as a National Science Foundation Postdoctoral Fellow and joined the Thermophysics Division as a permanent staff member one year later. He became chief of the Thermophysics Division in May 1989 and chief of the Physical and Chemical Properties Division in 1996. Dr. Kayser received a Sc.B. in chemistry from Brown University in 1973 and a Ph.D. in chemistry from Rice University in 1976.

F. Alan Andersen is Director and Scientific Coordinator, Cosmetic Ingredient Review (CIR), an independent group tasked with assessing the safety of individual chemicals used in cosmetics. Prior to joining CIR in 1993, Dr. Andersen was Acting Director, Office of Device Evaluation, and Director, Office of Science and Technology, Center for Devices and Radiological Health. Currently, he is President of the NCCLS, a organization of volunteers from industry, the professions, and government that develops standards for clinical testing. Dr. Andersen received his B.S. from Muhlenberg College and his M.S. and Ph.D. from Penn State.

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