SPECIAL REPORT

NIST Workshop on Reference Data for the Properties of Biomaterials

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Abstract: A workshop on Reference Data for Biomaterials was held at the National Institute of Standards and Technology (NIST) on July 27, 2000. The primary purpose of the workshop was to determine whether needs existed for the establishment of reference data (RD) databases on the properties of biomaterials. Special attention was given to critiqued RD such as those traditionally found in databases that are established within the NIST Standard Reference Data Program. Critiqued data are data that have been critically evaluated for issues dealing with components of uncertainty, experimental design (details, descriptions, and appropriateness), measurement methods (appropriateness), conclusions drawn from the data, and so forth. Among the workshop's 65 registrants were representatives from industry, the National Institutes of Health (NIH), the Food and Drug Administration (FDA), and academia. These joined with NIST staff to address reference biomaterial property database needs within five categories: orthopedic, cardiovascular, ophthalmologic, tissue-engineered, and dental biomaterials. A general session on other issues focused specifically on database accesses (portals), contents, and maintenance. While the workshop's intended focus was on *critiqued* RD, it was suggested that closely related issues be considered as well. In this way, a more comprehensive assessment of opportunities for the cooperation of NIST with the biomaterials community might be developed. As a result, the needs for *noncritiqued* data and for *reference materials* (RMs), useful for developing data, also became a part of the focus of the workshop. Hence, this article presents the results from the breakout sessions of the workshop according to two categories: reference data and databases, and reference materials. In the following summary, the workshop is presented in the following order: An introduction to databases, resource presentations, action items identified in breakout sessions, assessment of resources (personnel and monetary) needed to work on action items, and portals for databases. Except for the individual concurrent breakout sessions themselves, all other sessions of the workshop were participated in fully by those in attendance. © 2001 John Wiley & Sons, Inc. J Biomed Mater Res (Appl Biomater) 58: 463–466, 2001

BACKGROUND OVERVIEWS

The Workshop began with an introductory presentation on *reference databases*. Dr. Joan Fuller (NIST Standard Reference Data Program) provided the following guidance to workshop participants: "…it is first important to define what a database *is* and *is not* and, secondly, to distinguish between compiled and evaluated databases. *In the most simplistic terms, a database is a collection of…information that (in the workshop's context) is stored on a computer in such a way that it may be used for different applications without the user having knowledge of the storage details*. This definition provides no restrictions on the type or quality of data that is included in the database. In general, scientific databases fall into two categories — data impartially compiled from the known literature and data that are critically assessed by independent experts. There are merits to both database systems; however, critically evaluated data have an inherent value to the nonexpert, because the data have been reviewed and confirmed by experts in the field of research."

Following the introduction to databases, there were three background presentations related to properties and databases. The first, by Harvey Borovetz (University of Pittsburgh), addressed the use of biomaterials in medical devices and the availability (or lack thereof) of reference databases. He noted that one of the key questions of a recent (January 22, 2000) National Institutes of Health (NIH) Workshop on implant retrieval was "What information is necessary to evaluate and improve implant and material performance and device design?" The NIST workshop overlapped this NIH issue, but with a focus on information in the form of databases on the

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properties of biomaterials and with emphasis on critically assessed data. Dr. Borevitz noted that biomaterial property databases could be useful in helping to provide the kind of information asked for in the NIH question.

Next, addressing the need to have data for assessing the suitability of biomaterials for new implants in particular, Robert Baier (State University of New York, Buffalo) provided an overview of the important interactions among the properties of biomaterials and tissues. He emphasized surface chemistry (interfacial composition, organization, and the outermost atomic array) as the most critical determinant with regard to understanding, predicting, and properly controlling the interactions of biomaterials with living systems. "The acute contact periods are when these properties are clearly more important than later, when secondary bulk (property) interactions may ultimately determine an implant's longer-term success."

Elaine Duncan, Palladin Medical, provided an outline guide to the development of biomaterial databases as she foresaw them being useful and enumerated numerous benefits, such as aiding in the identification and selection of biomaterials for new devices and to help reduce redundant testing for properties. Among the required database features that she presented were: relevance to ISO 10993, flexibility with regard to current literature and test data, timeliness (with frequent updating), absence of marketing hyperbole, control of data quality, and content of engineering information on usage (such as applicable shelf life). Among negative features (those she viewed as to be avoided) were: commercial charges for use of the database, administration by a regulatory agency, and data oriented to a *particular* device as opposed to a *type* of device. To conclude her presentation she proposed that a critical need is an online, two-tiered database that would enable users to select and qualify materials rapidly.

The workshop moved on to presentations intended to provide insight into the most important properties, assessments of the status and availability (with strengths and weaknesses) of reference databases on those properties, and delineation of what is needed in them. Focus areas (and resource presenters) were on orthopedic (Jack Parr, Wright Medical Technology Inc.), ophthalmic (John Sheets, Alcon Research Limited), dental (Frederick Eichmiller, American Dental Association Health Foundation at NIST), tissue engineered products (Elsie Effah Kauffman and Joachim Kohn, Rutgers University), and cardiovascular (Jagdish Butany, University of Toronto) properties. Special needs for standards and regulatory purposes were also addressed (Donald Marlowe, Food and Drug Administration).

BREAKOUT SESSION REPORTS

Moderator: James Burns, Genzyme.

Reference Data and Databases

Session leaders are given in parentheses.

Orthopedic Materials Database. (Barbara Boyan, U. Texas, San Antonio and Steve Hsu, NIST.) Data properties deemed to be of most utility were: (1) a composite database comprised of (a) material performance related to wear, biocompatabity, clinical and academic-type laboratory responses of biomaterials and (b) properties of materials according to classical descriptors; (2) biological response to materials: (a) at the cellular level and (b) whole animal responses; (3) bulk and surface properties of materials: (a) pre-implantation and (b) post-implantation. A matrix of structure and composition versus functional performance was considered to have utilitarian value. This group decided that there is a need for a reference database that includes standardized test methods, properties on reference materials, and properties as derived from materials that have been processed according to those required for applications to a device. The need for properties of reference materials led to a listing of reference materials that were deemed important; these are described in the Reference Materials section. Questions also arose as to whether databases should be open and/or without charge; this is covered in the Assessment of Resources Needed and Timeliness section.

Ophthalmic Materials Database. (Lore Ann McNicol, National Eye Institute, NIH, and Jean Jacob, Eye Center, Louisiana State University.) The consensus of this breakout session was that a database was needed, that it should include data on properties that would be useful for providing (test) calibration standards, and that it could be used as a stable benchmark against which other data could be evaluated. This session also stated the need for historical references to the most complete holdings of clinical data. Currently, most intraocular lens implants (IOLs) are fabricated from either poly(dimethylsiloxane), poly(methyl methacrylate), or poly(hydroxyethyl methacrylate), and reference data on the properties of these implant materials are needed for benchmark and calibration purposes. The data most needed are: mechanical properties (obtained from tensile and flexural tests), optical properties (refractive index, transparency), chemical properties (surface hydophobicity, water content), and biological behavior (interactions and safety).

Cardiovascular Materials Database. (Michael Sacks, University of Pittsburgh.) This group resolved that a database on cardiovascular biomaterials should contain the properties of materials that are relevant to specific device applications and not have data presented according to material type and properties. Participants concluded that data for device applications should be limited to realistic applications with immediate needs. The identified device-specific biomaterials and their properties are: (1) chemically treated, bioprosthetic soft tissue valves; virgin mechanical properties according to classical test methods, mechanical properties according to deformation modes, and durability for specific deformation modes; methods of chemical treatment and verification of cross-linking chemistry (for standardizing of methods); (2) cardiovascular device polymeric materials; biocompatibility, plate-

TABLE I. Portal Levels

Portal Level	Access & User	Content	Critical Review Needed?
I	PUBLIC	All materials	No
II	PUBLIC	All materials	Yes, NIST-Led
III	PUBLIC Limited Access	Reference materials	Yes, NIST
IV	FDA-Supplier-User	Specific materials	N/A to NIST

let adhesion, virgin mechanical properties, high cycle fatigue in tension and flexure, and absorption; also needed are analyses of data to assess the appropriateness of time-temperature superposition methods for accelerated durability testing; (3) endovascular stent alloys; corrosion behavior, and shape-memory effects of virgin and low amplitude fatigue tested alloys; (4) and arteriovenous shunts of poly (tetrafluroethylene) (PTFE); burst test results, puncture resistance, recovery and sealability of punctures, biocompatability, platelet adhesion, virgin mechanical properties, high-cycle fatigue in tension and flexure, and absorption.

Dental Materials Database. (Raquel LeGeros, College of Dentistry, New York University, and Frederick Eichmiller, American Dental Association Health Foundation, NIST.) This breakout session identified needs as (1) a database on the composition, properties, and clinical performances of dental materials; (2) reference methods on the characterization and processing of dental biomaterials; and (3) reference materials (identified in the Reference Materials section). Priorities are: (A) metal-implant coatings, (B) bone graft materials (autologous and augmentation substitutes), (C) oolymeric bone-fixation devices, (D) ,barrier membranes, and (E) sterilization methods.

Tissue Engineered Materials Properties Database. (Grace L. Picciolo and Kiki Hellman, Center for Devices and Radiological Health, FDA, and Rosemarie Hunziker, Advanced Technology Program, NIST.) (Author's note: this is a rapidly developing, emerging field with rapidly growing needs.) The session identified two action items: (1) for a database; and (2) for a reference material (identified in the Reference Materials section). Action item (1): acquire non-proprietary data, via completion of a survey that should be made of key tissue engineering research organizations, such as companies, universities, government laboratories, and other research institutes according to: (1-A) *Types of Polymer Biomaterials*, (a) natural: alginate, collagen, chitosan, hyaluronic acid, (b) synthetic resorbable: poly(ethylene glycol), poly(alpha-hydroxyl-esters) such as poly(glycolic acid) and poly (lactic acid), polyphosphazanes, poly(proplylene fumarate), polytryosine, (c) synthetic nonresorbable: biological mimicking pendant group substitutions; (1-B) *Chemical and Physical Characterizations*, (a) bulk chemical composition, (b) porosity, (c) products of degradation, (d) degradation rate, (e) viscosity (apparent, intrinsic), (f) monomer and co-monomer characteristics (block length, random, alternating, etc., (g) molecular mass (mass average, number average, polydispersity), (h) hydrogel properties (osmotic and pH stability, swelling, permeability, diffusion, absorption, partition), (i) surface roughness, (j) protein adsorption; (1-C) *Mechanical Characterizations*, (a) elastic and flexural moduli, (b) compressive, yield, and tensile strengths, (c) effects of porosity and molecular mass on mechanical properties, and (d) interfacial characterizations (surface: morphology, free energy, chemical composition).

Biomaterials in General. (A. Dolye Gant Jr., Center for Devices and Radiological Health, FDA.) This session focused on database portals and identified four portal levels (see Table I).

Reference Materials

Orthopedic Reference Materials. Reference materials were identified as needed for providing baselines against which properties of new materials or those from different processing methods of the "same kind of" material could be evaluated. The use of reference materials for biological responses was considered of great importance. The reference materials identified as needed, in order of priority, are: (1) ultra high molecular weight polyethylene (UHMWPE), in solid and particulate forms; (2) titanium and titanium alloys; (3) cobalt-chromium alloys; (4) aluminum oxide and zirconium oxide; (5) hydroxyapatite (HA) and related calcium phosphate compounds of biological significance and use; (6) stainless steels; (7) poly(methyl methacrylate); (8) poly(lactic) acid and poly(glycolic) acid, and polyfumarates; (9) cements and glues; (10) bioglass; (11) coating and surface modified materials (coatings of silver, diamond, biologics, etc.); and (12) carbon-based composites. (Author's note: UHMWPE Reference Material, RM 8456, was made available from NIST in October, 2000, and SRM 2910 for HA is also available.)

Ophthalmic Reference Materials. This breakout session linked reference materials very closely with reference data. The first data to be used in a reference database were viewed as that being developed from the characterization measurements of the properties of the reference material. The most important reference materials (RMs) needed are: poly(dimethylsiloxane), poly(methyl methacrylate), and poly(hydroxyethyl methacrylate). The properties that should be used to characterize the reference materials include: the elastic moduli, tensile and flexure strengths, refractive indices, phys-

ical chemistry (surface hydophobicity, water content). Biological interactions and safety data should also be included with the certificates that would accompany these materials. Once these RMs have been developed, the next order of need is for monomers from which these materials are fabricated; purity is the most important consideration in this case.

Cardiovascular Reference Materials. The consensus of this group was that there is a major problem with property test results, because the test methods used are inconsistent, even within the same laboratory. To overcome this problem, consistent, reliable reference biomaterials (not just a database) are needed for use as internal checks on test methods employed in laboratories. This is a result of the tendency to test, simultaneously, both materials and testing techniques. Because of the focus of this group on properties for reference data, specific reference materials were not identified other than polyurethanes. This may be an area for a follow-up meeting in the future. (Author's note: work *is* currently in progress with the Polymer Technology Group for the production of a series of polyurethane reference materials under an SBIR grant from the NIH and in cooperation with NIST.)

Dental Reference Materials. RMs related to implants received the highest priorities; these are calcium phosphate/sulphate materials, bioglass, barrier membranes, and metals. (NIST SRM 2910 for HA already exists.)

Tissue Engineering Reference Materials. The reference materials most needed are three-dimensional reference tissue scaffolds of known porosity, interconnectivity, surface and bulk chemistry, physical and mechanical properties, and cellular reactivity. Methods for assessing these properties need to be well described and the properties well defined. The reference scaffolds are viewed as useful for comparative measurements during the development of new material scaffolds having properties and chemistry, etc., that differ from those of the reference scaffold(s). They are viewed as serving as reference baselines for comparative evaluations of new tissue engineering developments.

ASSESSMENT OF RESOURCES NEEDED AND TIMELINESS

(Regina Malczewski, Dow Corning, Auburn, MI.)

All participants assembled to address issues of tasks and resources required for meeting the high priority needs identified in breakout sessions. There was general agreement on the following issues: (1) alliances are needed among industry, government, and academia to accomplish the objectives; (2) RMs and databases are both needed now; (3) action is needed now for establishing databases from whatever methods that can be employed (for both critiqued and noncritiqued data) without waiting for the development of RMs unless data obtained from RMs constitutes the initial input for data; just-in-time availability of data is more important than delays that would result from refinement of data beyond the levels needed; (4) data from model materials is a primary need; (5) there is a need to include both biological and material data in one data source; and 6) portals should be as open as possible without charge; tissue engineering probably needs special (undefined at this time) considerations (attention to needs).

In the forming of alliances, the following roles were perceived for industry, government and academia. *Industry:* For fast responses, industry must assume leadership roles and take the lead in securing funding for RMs (through NIH SBIR Program), provide funding to others (could include subcontracting of an SBIR grant), provide raw materials/final products, share existing data, conduct testing, and develop test methods. *Academia:* Should develop test methods, conduct testing, and evaluate data. *Government:* Catalyze database developments by leading in the formation of alliances, coordinate critiqued database and RM developments, provide funding (NIH for reference materials; NIST for data), evaluate data (NIST lead with FDA counsel), design databases, and assist others in database design (NIST and FDA) and design of test methods.

Examples of Tasks Needed

Databases. Reviews of literature, assessments (critiques) of literature data, design of databases, accrue data, assemblage of databases, maintenance of databases.

Reference Materials. Fabrication or procurement of materials, test design and testing of RMs for properties, statistical analyses of data.

CONCLUSION

The workshop ended with the conclusion that additional meetings were needed for the formation of alliances to develop the data and reference material needs identified during the workshop. As of the time of this the submission of this report for publication, an alliance for ophthalmic reference data and reference materials had been formed, the beginning of an alliance for development of a reference tissue scaffold has been initiated, activities had been pursued for the development of an industry-supplied properties database, links between databases are under consideration, and an alliance for some cardiovascular synthetic reference materials continues. Further alliances are needed for the remaining materials property databases and RMs. Those interested in forming alliances should contact John A. Tesk, john.tesk@nist.gov; for information on the NIH SBIR Program for RMs, contact Christine Kelley, ck53r@nih.gov.