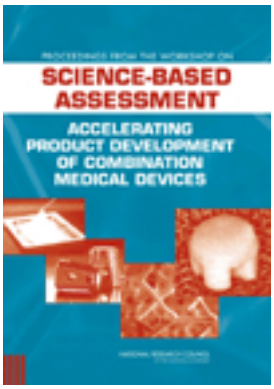

Proceedings from the Workshop on Science-Based Assessment: Accelerating Product Development of Combination Medical Devices

Bonnie A. Scarborough, Editor, Roundtable on Biomedical Engineering Materials and Applications, National Research Council

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PROCEEDINGS FROM THE WORKSHOP ON

SCIENCE-BASED ASSESSMENT

ACCELERATING PRODUCT DEVELOPMENT OF COMBINATION MEDICAL DEVICES

Bonnie A. Scarborough, Editor

Roundtable on Biomedical Engineering
Materials and Applications

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ROUNDTABLE ON BIOMEDICAL ENGINEERING MATERIALS AND APPLICATIONS

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Preface

INTRODUCTION

The Food, Drug, and Cosmetics Act of 1938 and the Safe Medical Devices Act of 1990 have driven the development of much of the current science for assessing materials, devices, drugs, and biologics. The U.S. Food and Drug Administration (FDA) has established testing centers that specialize in the assessment of products belonging to one of three categories:

- *Device:* an apparatus or implant, including any component or accessory, intended for the diagnosis, mitigation, treatment, or prevention of disease or intended to affect the structure or function of the body, that does not achieve its primary intended purposes through chemical action within or on the body and that is not dependent on being metabolized;
- *Biologic:* a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product, or arsphenamine or derivative of arsphenamine applicable to the prevention, treatment, or cure of a disease; and
- *Drug:* (a) an article recognized in the official United States Pharmacopoeia, official Homeopathic Pharmacopoeia of the United States, or official National Formulary, (b) an article intended for the prevention, diagnosis, treatment, or cure of a disease, or (c) an article other than food intended to affect the structure or any function of the body.

New patient therapies are becoming more complex, however. The FDA is just now beginning to deal with the issue of how to evaluate "combination products," that is, products that are made up of components from more than one of these categories. Timely assessment of these devices is important from both a public health and an economic standpoint. The safe and effective development of such combination products requires an understanding of their failure mechanisms as well as an assessment of the risk associated with failure. Currently, devices, biologics, and drugs are all evaluated using different review standards. But for certain combination products, especially breakthrough products, it may not be clear which review standard(s) should apply. In addition, in some cases, scientific methodologies to appropriately assess some combination products may not yet exist or be fully developed, although the therapeutic endpoints for many of these products exist and are well understood (e.g., drug-eluting stents). Combination products thus pose new challenges with respect to the assessment of efficacy and safety. It is important to determine the extent, if any, to which differences in the testing

of combination products may create barriers to innovation or delays in bringing products to those in need.

ROUNDTABLE ON BIOMEDICAL ENGINEERING MATERIALS AND APPLICATIONS

The Roundtable on Biomedical Engineering Materials and Applications (BEMA) is an activity of the National Research Council (NRC) convened with the objective of bringing together government officials, industry representatives, academics, and others to discuss research, development, applications, and regulation of biomedical materials and devices. BEMA provides a forum for participants to identify opportunities for applying engineering principles to create and improve the clinical performance of medically useful materials and devices. In addition, the roundtable discusses strategies for overcoming the technical, legal, and cultural obstacles that impede the transition of new materials and devices into clinical application. BEMA achieves these objectives by:

- Providing a neutral setting for the exchange of information about issues related to biomaterials science, research, and practice;
- Identifying and discussing priority issues in the general area of biomaterials and their application in the development, manufacture, and use of medical devices; and
- Conducting problem-solving and issue-identification activities such as workshops that address these issues in greater depth.

WORKSHOP ON SCIENCE-BASED ASSESSMENT

A workshop entitled "Science-Based Assessment: Accelerating Product Development of Combination Medical Devices" was held on April 22-23, 2003, at the National Academies in Washington, D.C. (the theme was identified in BEMA meetings held the previous year). The purpose of the workshop was to discuss science-based assessment that can be used to effectively evaluate biomedical materials and combination devices. To facilitate discussion, the workshop was organized into sessions on three specific types of combination products: orthopedic repair using bone morphogenetic protein; drug-eluting stents; and cell-matrix cartilage implants. Abstracts of the presentations in each of these sessions are included in this report, as are abstracts of overarching, context-setting discussions of science-based assessment and experimental design. The agenda for the workshop is included in Appendix A and biographical sketches of the speakers are given in Appendix B. The viewgraphs presented by the speakers are reproduced, as originally supplied, on the attached CD-ROM.

NRC roundtables are established solely to provide open forums for discussion of emerging issues. They are prohibited by NRC policy from producing conclusions and recommendations or from offering advice to government agencies. As such, the primary purpose of this workshop was to educate the individuals who attended so that they might take this information back to their organizations and use it in their daily planning and decision making. This proceedings therefore serves primarily as a guide to those participants in remembering the content of the discussions. The abstracts of the workshop presentations and the unedited viewgraphs represent solely the viewpoints of the presenters.

ACKNOWLEDGMENTS

On behalf of BEMA, I would like to thank the speakers, session chairs, panelists, and attendees who participated in the workshop. The strong presence from government, industry, and academia was responsible for the success of the event and the lively discussions that took place. I would also like to thank those BEMA members who worked hard to organize this workshop and who, by their tireless efforts, brought the right people to the right place at the right time. Finally, I would like to thank the NRC staff members who were instrumental in organizing the workshop and preparing this report: Bonnie Scarborough, Toni Maréchaux, Teri Thorowgood, Emily Ann Meyer, Marta Vornbrock, Laura Toth, and Pablo Whaley.

Thanks are also extended to the following individuals, who reviewed the contents of this proceedings volume: Tara Federici, AdvaMed; Jean Jacob, Louisiana State University; John Ranieri, DuPont; and Frederick Schoen, Harvard Medical School. The individual presenters are responsible for its substance.

Robert M. Nerem, *Chair*
Roundtable on Biomedical Engineering
Materials and Applications

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ABSTRACTS

Setting the Context

USE OF SCIENCE-BASED ASSESSMENT IN THE DEVELOPMENT OF STANDARDS

John T. Watson
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Science-based testing uses science, engineering, and technology to assess a product's capability of reliably performing its intended clinical function for a given lifetime and predicted quality of life. This type of testing also assesses the rate of occurrence of adverse events under the specified operating conditions and in the context of the patient's condition. Because scientific knowledge is incomplete and imperfect, the results of science-based testing are imperfect. Assessment based on such testing is nonetheless an essential component of research, regulatory processes, payment decisions, and commercialization decisions. Despite its imperfections, science-based testing provides valuable information when market approval judgments are being made by expert panels.

Science-based assessment should be used as a component of guidelines, not to create standards. Guiding principles should be based on patient safety and benefit, research on science-based assessment methods, clinically relevant testing, and objective measures such as quality of life, adverse events, and patient function. Assessment methods should stimulate, rather than inhibit, innovation. The peer review process can be used effectively here.

An implementation strategy for science-based assessment should open federal lines of communication, minimize duplication of requirements, and use peer review for guidance and approvals. Such a strategy would emphasize safety in premarket conditional approvals, monitor clinical outcomes for decisions on retention of postmarket approval, and include federal agency support for research on science-based testing methods. Federal agencies could jointly support 100 exploratory research grants of $150,000 each over 3 years using the new NIH study sections. In addition, a pilot study could be undertaken where one or two similar products were selected to undergo a parallel review process. A steering committee could monitor how these products went through existing approval processes and determine how these processes could be improved. Finally, a 2-year reliability study could be implemented to determine the postmarket performance of these products.

SETTING THE CONTEXT: CLINICIAN

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Armed Forces Institute of Pathology

An implanted medical device must treat the targeted disease, and, above all else, must do no harm. Clinicians must be trained to look at the disease first, and then the device. Before any device is tested, it is essential to understand the biology of the disease process as well as how a normal organ would react to insertion of the device.

For example, research has been undertaken to determine the consequences of inserting metal stents into atherosclerotic coronary arteries. Work done on animal models (pigs and rabbits) has focused on: (1) determining the type of injury to the vessel wall that is caused by inserting a metal stent following balloon expansion; (2) determining the type of vascular reaction that a foreign body might induce; and (3) determining how a normal vessel wall would react to the placement of a balloon-expandable metal stent. The results of these tests indicate that thrombosis, inflammation, and injury are important determinants of neointimal growth and restenosis.

In addition, retrieved devices have yielded data on human healing following insertion of a balloon-expandable stainless steel stent. These data indicate that: (1) stent strut inflammation is influenced by medial disruption and is associated with restenosis; (2) healing is much slower in human atherosclerotic arteries than in normal animal coronary arteries; (3) the extent of injury is a strong determinant of restenosis; (4) inflammation and fibrin deposition are strong predictors of restenosis, with inflammation related to the extent of injury and type of atherosclerotic plaque; and (5) stent strut penetration of the necrotic core correlates with greater neointimal formation.

Drug-eluting stents may contain cytostatic or cytotoxic agents; there have been both successful and unsuccessful applications of such devices. Studies indicate that the use of stents coated with chondroitin sulfate and gelatin (CSG) containing varying concentrations of paclitaxel (between 1.5 and 42.0 μg) results in smaller neointimal thickness at 28 days postdeployment, although medial necrosis and persistent fibrin deposition occur at higher doses. But the benefit of smaller neointima at 28 days is lost at 90 days.

A registry of 15 patients was created to determine the effects of the QUADS-QP2 (7-hexanoyltaxol) stent implanted in humans. Angiographic restenosis was present in 13.3 percent of these cases after 6 months and in 61.5 percent after 12 months. The mechanisms of this restenosis were toxicity from the high drug dose and reaction to the plastic sleeve, along

with persistent fibrin and smooth muscle cell infiltration in atherectomy specimens retrieved from a few patients.

For these reasons, greater understanding of drug-eluting stents is needed and can come only from examination of retrieved devices at autopsy or surgery (although animal models are an important means of understanding the consequences of device insertion for a normal vessel). Device retrieval enables researchers to see what harm has been done by insertion of the device into humans and thereby enables design improvements. Stents must be designed to do less damage and, when damage is unavoidable, to do damage over a longer, rather than a shorter, period of time. Impurities in the stent, as well as in the polymer carriers used in drug-eluting stents, can have a tremendous impact on the patient's reaction to the therapy.

SCIENCE-BASED TESTING: BALANCING RISK AND REWARD

Paul Citron
Medtronic, Inc.

In the context of a new medical technology, there is a perception that science-based testing is an implicitly good thing. The existence of a panoply of scientifically grounded tests undertaken to prove the safety and effectiveness of a medical technology comports with societal expectations and is perceived to be a means of protecting patients' interests. The existence of such tests provides a sense of comfort due to the perception that risk has been minimized.

A closer examination, however, suggests that science-based testing can have a negative impact on the innovation process in the field of medical technology. This is especially true when such tests are required without adequate consideration of relevance and when it comes to breakthroughs in medical technology. In some cases, therefore, requirements for science-based testing can be contrary to the interests of seriously ill patients who are inadequately treated by available methods and who might benefit from promising new technologies.

Requirements for science-based testing can be overly burdensome and can lead to rules-driven, rather than outcome-driven, processes. Once in place, these requirements may be difficult to eliminate, even if they are not relevant or are no longer relevant. Because of the considerable financial investment required to validate any new technology, requirements for science-based testing may restrict the early obsolescence of existing technologies that have been bypassed by new knowledge and cause significant

delays in the time it takes for new technologies to become available for seriously ill patients. In some instances, requirements for science-based testing can stop the pursuit of life-saving innovations. In a worst-case scenario, science-based testing requirements could become prescriptive and inflexible and could strongly inhibit, if not eliminate, the use of sound clinical judgment.

It is illuminating to examine how several major medical breakthroughs—kidney dialysis, prosthetic heart valves, the transistorized external cardiac pacemaker, and the tined pacing lead—reached clinical practice. In each case, although researchers appreciated the need for science-based testing prior to patient use, clinical judgment overrode the science in decision making. These reasoned judgments served the interests of patients and society by enabling the timely introduction of innovative treatments for diseases that were previously either untreatable or ineffectively treated. In addition, these breakthroughs provided the technological foundation for clinically significant spin-off innovations that are now part of the therapeutic armamentarium.

In summary, although researchers generally appreciate the importance of science-based testing, calculated risk taking based on clinical judgment is often an integral part of innovation. A certain degree of empiricism plays an important role in breakthroughs. In the context of life-threatening, poorly treated diseases, an approach that responsibly minimizes the time from concept to clinic ultimately favors patients and society. For breakthrough innovations addressing unmet clinical needs, a considered balance between a rigorous and relatively inflexible science-based testing approach and judgment-based empiricism may facilitate the more rapid introduction of safe and effective technologies. As technologies become more mature, the importance of science-based testing increases to help ensure favorable performance comparisons, quality, and consistency.

BIOFILMS AND MEDICAL DEVICES

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Montana State University

Biofilms are formed when bacteria attach to surfaces and aggregate in a hydrated polymeric matrix of their own synthesis. Many persistent and chronic bacterial infections—including periodontitis, otitis media, and cystic fibrosis pneumonia—are caused by the formation of these sessile communities and their inherent resistance to antimicrobial agents. New diseases can

become manifest when these bacterial biofilms form on the inert surfaces of biomedical devices; for example, nosocomial infections can occur around sutures and exit sites, catheters, vascular grafts, orthopedic devices, and other implanted materials and devices. Because biofilms are particularly resistant to treatment, removal of the infected device is often necessary.

New analytical tools and cross-disciplinary studies have recently advanced understanding of the basic biology of biofilms. It is now understood that most bacteria cause pathogenesis only when combined with an inert surface, such as a medical device, or in an individual with compromised health. On medical devices, bacteria can attach specifically to different surfaces or coaggregate with multiple other bacteria to form a dense bacterial plaque. Bacterial biofilms consist of microcolonies on a surface, where the bacteria have developed into organized communities with functional heterogeneity.

Biofilms are characterized by a protected mode of growth that allows survival in a hostile environment. The structures that form in biofilms contain channels in which nutrients can circulate. Cells in different regions of a biofilm exhibit different patterns of gene expression. Biofilms grow slowly, in one or more locations, and biofilm infections are often slow to produce overt symptoms. While sessile bacterial cells release antigens and stimulate the production of antibodies, the antibodies are not effective in killing bacteria in biofilms and may cause damage to surrounding tissues. Even in individuals with excellent cellular and humoral immune reactions, biofilm infections are rarely resolved by the host defense mechanisms. Antibiotic therapy typically reverses the symptoms caused by planktonic cells released from the biofilm but fails to kill the biofilm itself.

One mechanism of biofilm resistance to antimicrobial agents is the failure of the agent to penetrate the full depth of the biofilm. The polymeric substances that constitute the biofilm matrix retard diffusion and establish a formidable penetration barrier. Antimicrobial oxidants, such as the products of oxidative burst from phagocytic cells, penetrate poorly into the biofilm matrix before being deactivated. Cells within the biofilm may also become less susceptible to toxic substances through reduced metabolic rates. Finally, cells within the biofilm may develop a specific phenotype that protects them from metabolic attack.

Recent advances in genomics and in the sequencing of microbial genomes have provided clues to the genetic mechanisms associated with biofilm development. Bacteria can undergo programmed events that ensure biofilm formation and colony survival, much like the programmed events that white blood cells undergo when summoned to a site of injury. Detailed studies of *Pseudomonas aeruginosa*, for example, reveal that different genes are involved in the processes of adhesion to a solid surface, formation of microcolonies on the surface, and finally differentiation of microcolonies into

polysaccharide-encased mature biofilms. Cells within the biofilm communicate with each other through the release of soluble factors in a process of quorum sensing that is akin to the process of signal transduction in eukaryotic cells.

A number of important questions remain, however, regarding biofilm development, particularly on biomedical devices. Are the mechanisms of attachment and colony formation the same regardless of the characteristics of the surface? What pathways are used in quorum sensing and is biofilm formation prohibited if any of them are blocked? Do all bacteria communicate in quorum sensing or is this specific to *Pseudomonas aeruginosa*?

An understanding of the underlying biology of biofilm formation can provide the information needed to begin development of more effective modalities and treatments for medical devices. Such treatments could include specific signal inhibitors or drug delivery mechanisms, as well as combined therapies to target both sessile bacteria through specific signaling and planktonic bacteria through antibiotic/metabolic attack. In order to avoid failure and removal of implants, we must leverage our arsenal of microscopic, physical, chemical, and molecular techniques to answer these and other questions and to develop effective therapies for biofilm formation on medical devices.

TESTING FOR SAFETY AND EFFICACY: AN ETHICIST'S PERSPECTIVE

Leonard J. Weber
University of Detroit Mercy

The perspectives in this presentation are offered in an effort to promote ethical best practices, rather than being focused on what must be done to comply with regulations or to avoid wrongdoing. Health care ethics is about clinical care and scientific/professional behavior, but it is also about business practices and decision making in health-related industries. The two issues discussed are how to determine acceptable risk in developing new technologies for clinical application, and how conflicts of interest are handled in clinical trials.

Regarding risk, one of the major implications of ethical analysis today is that the acceptable level of risk should be determined largely by assessing the impact of the new technology on health care quality and cost. A greater risk is more acceptable in a lower-cost treatment than in a higher-cost treatment and in a more beneficial treatment (both in terms of the effect on

the quality of life and compared with other options) than in a less beneficial treatment.

Regarding conflicts of interest in clinical research, there has recently been a growing recognition that the scientific integrity of clinical testing is sometimes threatened by interests that are antagonistic to professional or ethical responsibility and that are substantial enough that they might reasonably affect judgments or actions. These conflicts are frequently not recognized—in fact, are often denied—and inadequate attention is given to the need to prevent or manage them. Best practices that reduce the risk of conflicts of interest include systematic attention to the design of the clinical testing processes and to the financial arrangements involved, with the goal of protecting objectivity. In addition, independent oversight is required.

Science-Based Assessment and Experimental Design

SCIENCE-BASED TESTING FOR COMBINATION DEVICES

Aric Kaiser
Center for Devices and Radiological Health
U.S. Food and Drug Administration

Before a new medical device can be marketed, the Center for Devices and Radiological Health at the U.S. Food and Drug Administration (FDA) must review its risks and effectiveness. A device is defined as an apparatus or implant intended for the diagnosis, mitigation, treatment, or prevention of disease that does not achieve its primary intended purposes through chemical action and that is not dependent on being metabolized. The review process for traditional devices, familiar to most device manufacturers, requires that a manufacturer demonstrate one of two sets of device classification criteria:

- There must be reasonable assurance of the safety and effectiveness of the device based on preclinical and clinical evaluations; or
- The device must have the same intended use as a predicate device, along with either the same technological characteristics or different technological characteristics that do not raise different questions of safety and effectiveness.

Combination devices combine with drugs and/or biologic components to effect a treatment. The review process for these products may be different from that for traditional devices, but generally, although some additional regulatory requirements must be fulfilled, the questions that a manufacturer must address as part of a preclinical or clinical evaluation of a combination product are essentially the same. For example, in the evaluation of any device that is implanted or that has contact with tissues, the materials used in the device must be assessed to determine whether they can safely be used or implanted in the human body (biocompatibility). When a biologic component is combined with a device, an additional determination must be made regarding whether the materials used are free from potentially infectious agents.

SCIENCE-BASED TESTING FOR BIOLOGICS

Darin J. Weber
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U.S. Food and Drug Administration

In general, biological products are complex mixtures of multiple components. Because they are prepared from living sources, special consideration must be given to preventing the transmission or introduction of infectious agents while preserving product identity, purity, and potency. In order to ensure that no infectious agents are present, U.S. Food and Drug Administration (FDA) regulations for biological products include specific science-based testing of the final product.

FDA's General Biological Product Standards (21 CFR 610) include standards for manufacturing safety (sterility, mycoplasma, purity, adventitious viral agents) and for the assessment of product characteristics such as identity, viability, and potency. In addition to testing the final product, safety testing and other assessments are performed throughout manufacturing in order to evaluate the manufacturing process itself and to ensure that the quality and consistency of the product lots are maintained.

Standard test methods are of limited use, however, when testing biological products consisting of living cells. Many of the prescribed tests, such as sterility tests, take days or weeks to complete, and may thus limit the development of products that cannot be stored for such long periods of time. FDA has therefore adopted a flexible approach that allows some products to be used clinically even if the final test results are not available. FDA's Center for Biologics Evaluation and Research also supports and encourages the development of alternative test methods (as described in FDA standard 21 CFR 610.9) to meet the need for fast, sensitive, and reliable test methods for these products.

USING DESIGN OF EXPERIMENT METHODS IN THE INNOVATION PROCESS

James Rutledge
DataVision Statistical Consulting and Training, LLC

It is often said that "knowledge is power," and gaining knowledge is what design of experiments (DOE) methods are all about. Effectively researching, developing, and maintaining a product requires all the knowledge that can

reasonably be obtained about the process used to make that product. A process is defined here as a series of inputs and outputs. Inputs include the various aspects of the process that might influence the resulting product, such as reaction time and temperature, material thickness, vendor source, and lot variations. Knowing the impact on the end product of variance in the inputs is important. Outputs are measurable quantities that describe product characteristics or performance, such as the size of an extruded part or the yield of a chemical process. A mathematical understanding of how process inputs relate to outputs results in profound process knowledge and the power to control and improve processes.

It is very important to have quantifiable measures for inputs and outputs, and the systems used for making those measurements must be repeatable and reproducible. For example, in a measurement system, an engineer would perform a gauge repeatability and reproducibility study. In a chemical system, a scientist would validate the analytical method used for detection to ensure that it is sensitive, repeatable, and reproducible. There are industry standards for many of these tests, although new quantitative or semi-quantitative methods might have to be developed for histological evaluations of inflammation, for example.

The typical alternatives to DOE methods are "best-guess" and "one-factor-at-a-time" (OFAT) methods, both of which are based on the researcher's strong understanding of the system to be evaluated. However, these intuitive approaches may not result in the correct answer or may not be understood and believed by others. They may miss important events, such as the interaction of one input variable with another and how that affects the product output. DOE methods, by contrast, allow the importance of the various inputs to be summarized quantitatively and allow the development of a mathematical model to run simulation experiments of the expected product when the process is run under various conditions.

Modeling is important because it allows us to understand the factors that influence the robustness of the process. This understanding is critical to initial process validation as well as ongoing manufacturing. It is also important in the up-front development process, where it can be used to refine decisions about how to operate the process before experiments are undertaken. This mathematical process, or *in silico* experimentation, is helpful in identifying process specifications that can eventually be verified in confirmation studies.

The modeling process will be most valuable if it is undertaken both to make the product to the desired specifications (targeting the process center) and to manage product variability within acceptable limits (reducing process variation). Controlling product variability is crucial for keeping the process under control and ensuring that every unit produced will fall within acceptable limits of the desired target.

One attribute of DOE experiments that is often overlooked is their efficiency in determining the importance of the inputs and developing the process models with a minimum number of experiments. In fact, DOE techniques require fewer resources than traditional methods because of the efficiency of the design. This is counterintuitive because designing and executing DOE studies seems to take longer. While the up-front planning stages of DOE are often more involved than those of traditional techniques, the efficient design used to analyze information results in the need for fewer experiments, thus saving time and resources. In addition, because more time is invested in planning the experiments, they are more likely to be definitive in their results. DOE experiments can also be used to identify those factors that have no impact on product target or variability. Decisions can then be made about eliminating such factors, or reducing control of those variables in order to save process costs.

In summary, DOE methods improve understanding of what influences the product process, both in hitting the target and in controlling variability; help inform decisions about how to run the process, through the modeling approach; and provide in-depth knowledge about interactions and the quantitative influence of inputs on product performance and characteristics. While computer software can simplify the analysis component of DOE studies, the experimental discipline and creative thinking of the engineer or scientist are what make DOE methods successful.

MAKING IT FLY: CURRENT BOEING CERTIFICATION PROCESSES

Stephen G. LaRiviere
Boeing Commercial Airplanes

When Boeing Commercial Airplanes develops a large transport aircraft, numerous certification processes must be successfully completed. The Federal Aviation Administration (FAA) of the Department of Transportation is the agency with oversight responsibility for these certification processes; Boeing Commercial Airplanes interacts primarily with the FAA Aircraft Certification Service, Transport Airplane Directorate, Manufacturing Inspection Office, Seattle Aircraft Certification Office, and Seattle Manufacturing Inspection District Office. A designated engineering representative (DER) is a Boeing employee who represents the FAA with the agency's concurrence and who facilitates the certification process. The DER is generally a senior engineer who has both technical and communication skills and who is well respected by both the FAA and Boeing colleagues.

Federal aviation requirements are incorporated into all Boeing policies and procedures. Boeing must obtain type certificates (design approval for each airplane to be manufactured), production certificates (approval to build airplanes and airplane parts in accordance with the type design), and airworthiness certificates (approval to deliver and operate an airplane that has been built and tested in compliance with the type and production certification). Airplane type certification covers four areas: structures, materials, systems, and propulsion. For Boeing structural certification, a building block approach is used, with testing on the coupon, element, detail, subcomponent, and component levels. For materials certification, efforts are currently being made to achieve faster qualification through the use of critical-chain project management and, to a limited extent, design of experiments.

Bone Morphogenetic Proteins and Orthopedic Repair

THE BASIC SCIENCE OF BONE MORPHOGENETIC PROTEINS AND THE IMPORTANCE OF TEST METHODS

Barbara D. Boyan
Georgia Institute of Technology

Marshall Urist was a pioneer in the 1970s in understanding the principle of osteoinduction and in determining whether it could be used clinically. His work focused on determining whether the phenomenon involved a protein and, if it did, whether one or more proteins were involved. Dr. Urist coined the term "bone morphogenetic protein" because he recognized that the agent or agents that he was investigating were responsible for initiating the cascade of developmental events leading to bone morphogenesis. In contrast, growth factors were believed at that time to regulate cell proliferation.

Today, we know that bone morphogenetic proteins (BMPs) are members of the transforming growth factor beta (TGFß) superfamily and that at least 15 BMPs exist. We also know that BMPs function in bone formation by recruiting mesenchymal progenitor cells and initiating endochondral ossification in heterotopic sites, that they stimulate osteogenesis in orthotopic sites by acting on multiple cell types, and that they not only affect processes related to bone formation but also are actively involved in the formation of other musculoskeletal tissues as well as nonskeletal tissues such as the kidney and the cardiovascular system. Research today on BMPs focuses on mesenchymal stem cells (MSCs), progenitor cells, and committed cells; ALK receptors and SMAD signaling; how BMPs are synthesized by multiple cell types; autocrine and paracrine actions; and the inhibitors that are cosecreted. During the past 2 years, the first commercial products using BMPs have entered the marketplace.

Challenges that remain in the basic science of BMPs include determining whether response varies among cell types and at different rates of maturation within the same lineage; how target cell specificity can be controlled clinically; what the specific role of each BMP is; and how BMP activity is regulated in vivo.

BONE MORPHOGENETIC PROTEIN COMBINATION PRODUCTS AND ORTHOPEDIC REPAIR

Amy J. LaForte
Stryker Biotech

Bone morphogenetic proteins (BMPs) are a class of proteins that induce bone formation. New technology in orthopedic repair combines BMPs with a carrier matrix to create a combination product that, when implanted in a bony defect, initiates bone formation (osteoinduction) and provides local containment and cell adhesion (osteoconduction). However, orthopedic surgeons currently lack standardized information about the potency to initiate bone formation of either new manufactured products or allograft/autograft bone tissues. To put this in perspective, please note that labeling standards exist that require sunscreens to have an SPF rating, generators to specify a power output, and food to be labeled with a caloric assessment. Development of new products intended to generate bone would be facilitated if a standardized measurement of osteoinductivity were developed. In addition, investment is needed in the development and validation of new methods of imaging and quantifying new bone formation in humans in order to better assess the clinical utility of products and tissues. New methods of evaluating clinical endpoints combined with advances in imaging could shorten clinical development cycles and increase the accuracy of safety and efficacy evaluations.

PRODUCT DEVELOPMENT PROCESS FOR A BONE MORPHOGENETIC PROTEIN COMBINATION PRODUCT

William McKay
Medtronic Sofamor Danek

On July 2, 2002, the U.S. Food and Drug Administration (FDA) approved INFUSE™ bone graft, which contains a recombinant human bone morphogenetic protein (rhBMP-2), for use as a combination biologic medical device in conjunction with a titanium interbody fusion device (LT CAGE™). INFUSE™ bone graft is the first bone morphogenetic protein (BMP) that FDA determined to be safe and effective as a replacement for autogenous bone graft. FDA approval came 16 years after the discovery of rhBMP-2 and after hundreds of millions of dollars had been spent in research and development. The phase that took the most time in the product development process was

regulatory clearance, including the investigational device exemption (IDE) and the premarket approval (PMA) application, which took 6 years from the time that the final concentration and carrier had been identified. Research and development leading up to this final product identification required standard preclinical safety and effectiveness studies that could not have been avoided or accelerated. During this process, however, it was discovered that nonhuman primate bone biology is the most similar to that of human bone biology and the most predictive of effectiveness in humans. Studies using nonhuman primate bone biology were therefore recommended as the standard for testing.

INFUSE™ bone graft consists of rhBMP-2 at a concentration of 1.5 mg/ml delivered on a collagen sponge. Theoretically, rhBMP-2 could be used in any bone grafting procedure, but because FDA currently requires approval for each specific spinal infusion technique or bone grafting procedure, limitations on company resources prohibit the development of products for all procedures. Companies must selectively choose the more commonly used bone grafting procedures for clinical study and FDA approval.

Initial FDA approval of a bone graft replacement requires a well-designed, prospective randomized study demonstrating the safety and effectiveness of the product. Since the contribution of the bone graft replacement in a combination biologic medical device is the initiation of bone formation, the clinical protocol should involve the utilization of thin-slice computed tomography (CT) scans to assess the degree of bone formation and fusion. CT scans have become the gold standard in assessing bone formation and quality.

Less stringent FDA clearances for use of the identical bone graft replacement product in expanded clinical bone grafting indications would significantly accelerate the process development. Adoption of a more methodical, streamlined approach would benefit the patient, companies, and the FDA. The extent of safety and effectiveness data required for expanded indications should be based on how different they are from the original cleared indication. For example, clearance of INFUSE™ bone graft with the same concentration and carrier in any interbody fusion cage should require only abbreviated PMA supplement justification, since animal studies have shown that BMP is effective in all types of interbody fusion devices. Further clearance of INFUSE™ bone graft with the same concentration and carrier used in the posterolateral fusion technique should require a PMA supplement with only limited supporting clinical data indicating safety and effectiveness. If the BMP concentration and carrier are changed, however, a prospective randomized clinical trial should probably be required to support a new PMA application.

In summary, all new bone graft replacement products should undergo rigorous prospective randomized clinical investigations involving CT assess-

ment of bone formation. Subsequent approvals of the same growth factor (BMP) concentration and carrier for expanded indications should be approved via PMA supplements with only animal data or limited clinical data (see Table 1).

TABLE 1 Recommended FDA Approval Processes for Use of Same Product in Expanded Clinical Indications

Technique	BMP Concentration	Carrier	Approval process
Interbody fusion (LT CAGE™)	1.5 mg/ml	Collagen sponge	New PMA application
Interbody fusion (other cages)	1.5 mg/ml	Collagen sponge	PMA supplement (animal data)
Posterolateral fusion	1.5 mg/ml	Collagen sponge	PMA supplement (limited clinicals)
Posterolateral fusion	2.0 mg/ml	Collagen/ceramic composite sponge	New PMA application

Drug-Eluting Stents

DRUG-ELUTING STENTS: CURRENT CLINICAL STATUS

Robert S. Schwartz
Minneapolis Heart Institute

Stents stimulate restenosis, which consists of myofibroblasts and an extracellular matrix. The major determinants of restenosis are thrombus (platelets/fibrin), inflammation, proliferation, and migration/seeding. Polymer carriers are one of the leading anti-restenosis technologies. Their advantages include mechanical integrity/handling; precision dose control with uniform drug distribution, uniform release, the ability to modify release, and the ability to prevent overdosing; and versatility of use with other drugs and platforms. Future developments in drug-eluting stent technology will include new coatings and novel polymer processing; a number of companies are developing these technologies.

Several major drug trials have been undertaken on rapamycin and paclitaxel. Rapamycin is a natural antibiotic found on Easter Island that was developed and marketed for the prevention of renal transplant rejection. This drug acts as a selective proliferation inhibitor with the mechanism of action being a novel cell-cycle inhibitor. Paclitaxel is extracted from the Pacific yew tree, which is found in the northwestern United States and Canada. Drug trials on rapamycin and paclitaxel provide evidence that drug-eluting stents will allow treatment of more serious lesions and of patients with greater disease complexity. Complex lesions may require different treatment strategies and/or adjunctive devices.

Hospital economics, however, may influence the adoption and utilization rate of this technology. Patient allergic reactions to the drugs are also a problem that will have to be dealt with. In addition, the handling of stents must be improved; studies indicate that inflammation is significantly reduced if stents are rinsed after manufacture as well as after handling by surgeons.

DRUG-ELUTING STENTS: PRECLINICAL TESTING CHALLENGES

H. Semih Oktay
CardioMed Device Consultants, LLC

Combination products, such as drug-eluting stents, consist of two or more regulated products, e.g., drugs or biologics and devices. The new Office of Combination Products at the U.S. Food and Drug Administration (FDA) is responsible for determining which FDA center should review each specific combination product based on the product's primary mechanism of action. In general, the Center for Drug Evaluation and Research is the lead unit for approval of a device that primarily delivers a drug and is distributed containing the drug, while the Center for Devices and Radiological Health (CDRH) is the lead unit for approval of a device that primarily delivers a drug and is distributed without the drug, as well as for a device that incorporates a drug but that primarily serves a device function.

In the case of the drug-eluting stent, there are many complex relationships. The stent interacts with the carrier and tissue; the drug interacts with the carrier and tissue; and the tissue interacts with the stent, drug, and carrier. All of the device components and relationships must be evaluated, including the bare stent, the bare stent plus carrier, the drug, and the bare stent plus carrier plus drug. Preclinical testing requirements are risk-based. Requirements may depend on the intended use, e.g., there may be different requirements for the treatment of long lesions (overlapped stents) than for the treatment of in-stent restenosis (stent within a stent).

In addition to the CDRH guidance for bare-stent testing, standardized testing methods are being developed by the American Society for Testing and Materials subcommittee F04.30.06, the interventional cardiology task group. Physical testing includes testing for specification conformance and for clinically desirable stent characteristics, such as radial strength, uniformity, dimensional verification, and kink and crush resistance.

Preclinical safety information required for drug-eluting stents includes toxicological studies. The vascular wall, regional (myocardium) conditions, systemic conditions, and the correlation between in vivo and in vitro pharmacokinetic studies must all be evaluated. Additional preclinical tests are required on coating durability, sterilization of the finished device, and uniformity of drug distribution. Chemical tests performed on the drug and carrier determine chemical composition, check for impurities and stability, and assess manufacturing processes.

There are many variables and interdisciplinary issues to be considered in the assessment of combination products such as drug-eluting stents.

Challenges include the difficulty of obtaining adequate information on in vivo loading conditions; the development of testing equipment; the development of theoretical models; and interpretation of analyses. The development of performance standards may lead to faster regulatory approvals, faster new design development, marketing advantages, and liability protection.

TAXUS: A POLYMER-BASED PACLITAXEL-ELUTING STENT

Ronald A. Sahatjian
Boston Scientific Corporation

Boston Scientific Corporation (BSC) developed the TAXUS drug-eluting stent system during the decade from 1992 to 2002. A focused effort on local drug-delivery technologies was initiated in 1992 and various technologies were investigated, including catheter delivery systems, heparin-coated stents, balloon catheters, and polymer carriers. In developing a polymer-based approach, it was necessary to identify the drug; identify the appropriate polymer carrier; evaluate a maximum dose (loading capacity); identify the maximum tolerable doses; and determine a safe and potentially therapeutic range for the artery. The polymer carrier used by BSC has the necessary mechanical properties (integrity and elasticity) and excellent vascular compatibility.

The TAXUS system is a polymer-based system utilizing paclitaxel release to provide a wide therapeutic and safety window. Clinical trials for the TAXUS system were begun in 2000. Paclitaxel acts on several mechanisms implicated in restenosis, with the mechanism of inhibition being dose and cell dependent. Combined with the appropriate release, paclitaxel continues to demonstrate safety and efficacy in both preclinical and clinical trials. Increases of four times in the total loaded dose of the moderate release formulation demonstrate similar biological responses across doses. In an overlap system, the response to the moderate release formulation remains well within biologically compatible dosing.

Cell-Matrix Cartilage Implants

CELL-MATRIX CARTILAGE IMPLANTS: A CLINICIAN'S PERSPECTIVE

Richard D. Coutts
University of California at San Diego

Cartilage is an important living tissue that is distinctive in many ways: it contains only one cell type; has no blood flow, innervation, or lymphatic system; and has a low metabolic activity. The tissue is extremely slippery and has a unique structural and biochemical composition. For all of these reasons, this tissue is considered immune privileged, making it an ideal candidate for a living tissue replacement therapy.

As in all tissues, structure defines function, and the arcade-like structure of the collagen in the cartilage, along with its high molecular weight aggrecan proteoglycan, are ideal for binding and structuring water in the tissue. Although the cartilage bears a direct load during use, it maintains a high water content, which protects the chondral area beneath. The cellular component of the tissue originates from mesenchymal stem cells and regulates assembly and turnover of the matrix. The cells are nourished strictly by diffusion of nutrients and signals through the tissue and maintain a state of anaerobic metabolism. As the cartilage ages, the ability of the cells to produce matrix is decreased.

Clinically, problems stem from both focal and generalized damage. Focal defects are frequently due to traumatic injury; if left untreated, over 80 percent of patients with focal traumatic defects will develop arthritis an average of 20 years after the injury. Generalized damage due to osteoarthritis is the biggest clinical manifestation of articular cartilage damage, with virtually 100 percent of patients over the age of 50 showing some degree of erosion.

Although a variety of treatments are currently used, none are considered ideal or 100 percent successful. One repair technique involves the creation of small defects in the underlying bone through abrasion or microfracture methods. These defects result in bleeding, which recruits cells to the area and thus creates a fibrous cartilage. Other transplant methods include: mosaicplasty, where plugs are taken from a non-load-bearing edge to fill in the defect; allograft transplant tissues, which take advantage of the relative immune-privileged status of the cartilage; and chondrocyte transplantation, recently introduced by Genzyme.

Efforts to create a true tissue-engineered cartilage face a host of complex questions. What precise requirements must be met, both by the completed living construct and the individual cells, scaffold materials, and growth factor signals? What animal model is appropriate or predictive of human cartilage use conditions and disease states? What is the appropriate clinical trial design and how long should patients be followed? Finally, the complex environment in which the construct must survive must be examined and considered. In addition, issues regarding concurrent pathologies, extent, severity and duration of lesions, patient age, prior treatments, and range of motion must all be taken into consideration when designing a tissue-engineered cartilage.

Clinically, noninvasive measures of construct function are ideal and a number of such methods are currently available. Pain and function assessment tools have been well established and help generate important data to assess quality of life. Magnetic resonance imaging with metabolic labels has improved the imaging of the joint interface. Finally, while a second-look arthroscopy procedure is considered the definitive way to examine the repaired site, such a second surgical procedure incurs both costs and additional discomfort to the patient. The information gained from this procedure, however—including direct visualization of the tissue and a needle biopsy for histological examination of cell density and distribution, collagen patterns, and proteoglycans—is definitive confirmation of a successful reconstruction. Perhaps a balance can be achieved between the ethical considerations and the scientific merit of such follow-up procedures by utilizing a subset population in a study design.

Today, there are no easy or certain answers that a doctor can give a patient when presented with chondral defects of various etiologies and duration. Each situation requires a unique solution that depends on many factors, including the patient's willingness to tolerate new or repeated procedures; expected outcomes; reimbursement; and short- versus long-term success rates. Only through careful study designs (both preclinical and clinical), treatment selection, and detailed patient follow-up will it be possible to clearly differentiate treatment modalities, learn from successes and failures, and continue to advance the treatment of cartilage disease and repair.

CELL THERAPY FOR CARTILAGE REPAIR: PRESENT AND FUTURE

James W. Burns
Genzyme

As a pioneer in the treatment of cartilage defect disease using autologous cell-based therapies, Genzyme worked closely with its clinical and regulatory partners to bring a novel treatment modality to market. The Carticel® product comprises an autologous, cultured, chondrocyte suspension that is harvested from a peripheral donor site and expanded in Genzyme's current good manufacturing practices (cGMP) cell processing center. Once the expanded culture is returned to the clinician for implantation, the cells are localized within the defect with a periosteal cover from the patient's femur. This technique, pioneered by Dr. Lars Peterson in Sweden in a rabbit model of acute chondral defect, was first used clinically in 1987. In 1994, Dr. Peterson published a paper on the excellent early results of his first series in 23 patients. When Genzyme became involved in the process, however, it quickly became obvious that there were clinical, regulatory, and operational hurdles that had to be overcome by a corporate entity involved in such therapies.

The rather surprising, excellent early results obtained by Dr. Peterson enabled rapid approval by the U.S. Food and Drug Administration's Center for Biologics Evaluation and Research (CBER). Carticel® therefore received biologics license approval in August 1997. Behind this seemingly rapid process was a large dedicated effort in the design, development, and validation of all aspects of the autologous cell harvesting and processing facility required to demonstrate compliance with cGMP guidelines. Genzyme worked closely with CBER personnel and others in the field to support the development of new regulatory guidelines for the manipulation of living autologous cells ex vivo for intended structural repair or reconstruction. This effort contributed to the MAS cell guidelines published in May 1996. Considerable effort was also expended in the design and execution of clinical studies, the maintenance of a Carticel® Cartilage Repair Registry, and ongoing postapproval clinical studies.

Some of the greatest challenges encountered were in the preclinical and clinical areas where Genzyme sought improved healing and reduced rehabilitation time for patients, simplification of the surgical procedure with reduced morbidity using minimally invasive techniques, and development of test systems that provide meaningful data to make rapid decisions regarding next-generation product development. For a business, increased product utility, reduced time to market, and increased product adoption are impor-

tant measures of success. Challenges that had to be overcome included ambiguities in preclinical models, the ethics and logistics of conducting controlled surgical trials, the lack of global harmonization, and difficulties in obtaining reimbursement after regulatory approval. Accelerating the development of important, novel therapies such as Carticel® and its next-generation products will require that these and other issues be addressed.

CELL-MATRIX CARTILAGE IMPLANTS FOR ARTICULAR REPAIR AND REPLACEMENT

Anthony Ratcliffe
Synthasome, Inc.

The growth of cartilage equivalents in vitro by tissue engineering has now been achieved and can be reproduced using a cell-scaffold approach, with growth being done either statically or in bioreactors that can impose perfusion and/or mechanical strain. These constructs have been successfully used in vivo for the repair of articular defects in small animals. In large animals, however, simple cartilage constructs have not been shown to be effective, with the problem of fixation into a defect site being a particular issue. The use of more complex scaffolds that provide a bone-attaching and integration site appears to have overcome this problem, and constructs have now been successfully used in the repair of relatively large defects in the knees of large animals. However, some technical challenges remain: the provision of a cell source that provides enough cells with appropriate phenotype has yet to be identified; the mechanical properties of constructs are inferior to those of native cartilage; and lateral integration with surrounding host articular cartilage has yet to be achieved. The importance of these factors is unknown.

Several significant issues remain that hinder a company's ability to efficiently move this type of product through technical and regulatory hurdles. The community must still agree on assessments of the constructs, animal models of repair, and appropriate preclinical and clinical outcome measures. This process would benefit immensely from the establishment of standards and guidance documents such as those generated by the American Society for Testing and Materials with input from academia, industry, and the U.S. Food and Drug Administration. Standards and guidance documents should be designed to be an efficient use of resources and should avoid unnecessary time-points or assessments. The uncertain regulatory pathway, the studies required to meet these regulatory needs, and the lack of international agreement on how to regulate these products are difficulties that can be substantial.

Finally, a successful business must be created in an uncertain environment where the realistic size of the market, reimbursement of the product, and time to market acceptance and profitability are significant issues. In the area of cartilage repair, the size of the market for focal defects will most likely be modest. It would therefore be wise to design the product with potential for expanded use in other applications, such as the treatment of arthritis.

APPENDIXES

APPENDIX A
WORKSHOP AGENDA

Tuesday, April 22, 2003

7:45 AM	Continental Breakfast
8:30 AM	Welcome and Introduction *Robert Nerem, BEMA Chair*
8:35 AM	Setting the Context: Scientist/Engineer *John Watson, NIH*
8:55 AM	Setting the Context: Clinician *Renu Virmani, Armed Forces Institute of Pathology*
9:15 AM	Setting the Context: Risk/Benefit Ratio *Paul Citron, Medtronic, Inc.*
9:35 AM	Discussion *All*
10:00 AM	Break
10:30 AM	Science-Based Testing for Devices *Aric Kaiser, FDA*
10:45 AM	Science-Based Testing for Biologics *Darin Weber, FDA*
11:00 AM	Experimental Design Technologies *Jim Rutledge, DataVision*
11:30 AM	Discussion *All*
12 NOON	Lunch
1:00 PM	Scientific and Process Design *Steve LaRiviere, Boeing*
1:30 PM	Discussion *All*
1:45 PM	BMP-Orthopedic Repair *Session Chair: Joshua Jacobs, Rush Medical College*
1:45 PM	Overview of Science and Test Methods *Barbara Boyan, Georgia Institute of Technology*

2:05 PM	Industry Presentation *Amy LaForte, Stryker Biotech*
2:25 PM	Industry Presentation *Bill McKay, Medtronic Sofamor Danek*
2:45 PM	Discussion *All*
3:15 PM	Break
3:45 PM	Drug-Eluting Stents *Session Chair: Terry Woods, FDA*
3:45 PM	Clinician Presentation *Robert Schwartz, Minneapolis Heart Institute*
4:05 PM	Industry Presentation *Semih Oktay, CardioMed*
4:25 PM	Industry Presentation *Ronald Sahatjian, Boston Scientific Corporation*
4:45 PM	Discussion *All*
5:15 PM	Break
5:30 PM	Biofilms and Medical Devices *William Costerton, Montana State University*
6:15 PM	Reception Great Hall, NAS Building
7:15 PM	Adjourn

Wednesday, April 23, 2003

7:45 AM	Continental Breakfast *All*
8:30 AM	Ethics Presentation *Leonard Weber, University of Detroit*
9:00 AM	Cell-Matrix Cartilage Implants *Session Chair: Crystal Cunanan, Edwards Lifesciences*

9:00 AM	Clinician Presentation *Richard Coutts, University of California at San Diego*
9:20 AM	Industry Presentation *Jim Burns, Genzyme*
9:40 AM	Industry Presentation *Anthony Ratcliffe, Synthasome, Inc.*
10:00 AM	Discussion *All*
10:30 AM	Break
11:00 AM	General Discussion *All*
12 NOON	Adjourn

APPENDIX B
BIOGRAPHIES OF SPEAKERS AND SESSION CHAIRS

Barbara D. Boyan is professor in the Wallace H. Coulter Department of Biomedical Engineering at Georgia Institute of Technology and Emory University. She also serves as the deputy director for research for the Georgia Tech/Emory Center for the Engineering of Living Tissues and holds the Price Gilbert, Jr. Chair in Tissue Engineering. Previously, Dr. Boyan was professor and director of research in the department of orthopedics at the University of Texas Health Science Center in San Antonio. Dr. Boyan's research expertise is in bone mineralization and her laboratory is among the top bone and cartilage cell biology groups in the orthopedic and oral health fields. Her specific research interests include: mechanism of action of hormones and growth factors in chondrocytes and osteoblasts; normal and pathologic calcification; tissue engineering; and response of cells to biomaterials. Dr. Boyan is a founder of Biomedical Development Corp., OsteoBiologics, Inc., and Othonics, Inc., as well as a charter member of the Texas Technology Transfer Association and the BIO Council of Biotechnology Centers. Dr. Boyan holds eight patents and is the author of approximately 300 peer-reviewed papers, book chapters, and reviews.

James W. Burns is senior vice president of biosurgery research and development at Genzyme Corporation, where he has worked since 1986. He is responsible for product development in the areas of surgical adhesion prevention, ophthalmic biomaterials, tissue engineering, drug delivery, and implant biocompatibility. Previous positions held at Genzyme include scientific director of biopolymers research and development, and vice president of biomaterials and surgical products research. In addition, Dr. Burns was a research fellow in the Materials Science and Engineering Department of the University of Florida, working on drug delivery and surface modification of intraocular lenses. Dr. Burns holds 14 U.S. patents and is the author of 22 journal publications and 5 book chapters on topics including drug delivery, prevention of postoperative adhesions, and molecular weight determination of hyaluronate. He is the recipient of the President's Award from Genzyme Corporation, as well as a Fellow of the American Institute for Medical and Biological Engineering; a visiting advisory board member for the Materials Science and Engineering Department of the University of Florida; an adjunct assistant professor in the Department of Bioengineering at Clemson University; and he has served on the U.S. Food and Drug Administration's advisory panel on general and plastic surgery devices.

Paul Citron recently retired as vice president of technology policy and academic relations at Medtronic, Inc., where he had worked since 1972. His responsibilities included identifying and addressing public policy matters that affect medical technology innovation and working with leading biomedical engineering institutions. Previous positions held at Medtronic include vice president of science and technology, vice president of ventures technology, vice president of applied concepts research, and director of applied concepts research. Prior to his tenure at Medtronic, Mr. Citron was a research fellow in the Department of Neurology at the University of Minnesota. He is the author of numerous publications and holds several patents in medical device pacing. He is the recipient of numerous awards, including the IEEE Young Electrical Engineer of the Year (1979), the Invention of Distinction award from Medtronic (1980) for his role as coinventor of the tined pacing lead, and two Governor's Awards for Excellence from the American College of Cardiology. Mr. Citron is a member of Tau Beta Pi and Eta Kappa Nu, a Fellow of the Medtronic Bakken Society, and a Founding Fellow of the American Institute of Medical and Biological Engineering (AIMBE). Mr. Citron was elected to the National Academy of Engineering in 2003.

J. William Costerton is director of the Center for Biofilm Engineering at Montana State University-Bozeman, a position he has held since 1993. Previous academic experience included 23 years at the University of Calgary, as associate professor of biology, professor of biology, AOSTRA Research Chair in Microbiology, and NSERC Industrial Research Chair in Microbiology. Prior to that, Dr. Costerton was assistant professor of microbiology at MacDonald College of McGill University and a postdoctoral fellow at Cambridge University. In addition, he served as Dean of Science at Baring Union College in Punjab, India, for 9 years. Dr. Costerton's research has dealt with biofilms in a wide variety of environments: mountain streams, industrial systems, and medical devices implanted in humans. He is the author of over 575 publications and in 2002 was added to the Institute for Scientific Information's Highly Cited list. He is the recipient of numerous honors and awards including: Excellence in Surface Science Award from the Surfaces in Biomaterials Foundation (2002); Isaak Walton Killam Memorial Prize for Scientific Achievement (1990); and Sir Frederick Haultain Prize for Outstanding Achievement in the Physical Sciences (1986). He is a Fellow of the American Association for the Advancement of Science.

Richard D. Coutts is the medical director for orthopedics at Sharp HealthCare and a practicing physician in a San Diego orthopedic group. In addition, he is an adjunct professor at the University of California at San Diego and codirector of a joint reconstruction fellowship. Dr. Coutts' medical training includes an M.D. from the University of California at Los Angeles Medical

School; a residency in orthopedic surgery at the San Diego County University Hospital; a fellowship in orthopedic research at the Nuffield Orthopaedic Center in Oxford, England; and a clinical and research fellowship at the Massachusetts General Hospital, Harvard Medical School, where he studied joint reconstruction. He has published 200 articles, abstracts, and book chapters, and has been active in a number of professional societies, including as president of the Orthopaedic Research Society; president of the Hip Society; member of the board of directors of the American Academy of Orthopaedic Surgeons (AAOS); chair of the AAOS Council of Musculoskeletal Specialty Societies; and chair of the board and vice president of grants at the Orthopaedic Research and Education Foundation. He is currently the president of the board of directors for the Malcolm and Dorothy Coutts Institute for Joint Reconstruction and Research.

Crystal Cunanan is director of tissue engineering at Arbor Surgical Technologies, Inc. Previously, she was manager of the Biosciences Group at Edwards Lifesciences Corporation. She has over 18 years of industrial experience in the area of permanently implanted devices. Her research has focused on all modes of interaction between biomedical devices and the body. Specific topics have included: the chemistry, design, testing, and qualification of polymeric and biopolymeric implant materials, such as silicones, silicone copolymers, acrylates, hydrogels, collagen, and hyaluronic acid; the development of new in vivo and in vitro models to study material-biological interactions, such as cell adhesion, migration, toxicity, and wound healing; and the identification of cross-functional requirements and their integration into successful project plans. Ms. Cunanan holds 10 U.S. patents and is the author of over 40 papers, presentations, and published abstracts. She is active in several professional societies, including the Board of the Surfaces in Biomaterials Foundation, the American Society for Artificial Internal Organs, and the American Chemical Society. She has served on the Industrial Advisory Board of the Massachusetts Institute of Technology and the Georgia Institute of Technology Tissue Engineering Research Center, and has served as chair of the Industrial Advisory Board Committee of the University of Washington Engineered Biomaterials (UWEB) Engineering Research Center.

Joshua J. Jacobs is Crown Family Professor and associate chair for academic programs in the Department of Orthopaedic Surgery at Rush Medical College, as well as the director of the Section of Biomaterials. In addition, he is an adjunct professor in the Department of Civil and Environmental Engineering at the McCormick Technological Institute of Northwestern University. His medical training includes an M.D. from the University of Illinois Medical School; 2 years of General Surgical Training at the University of Illinois/Cook

County Hospital Program; orthopedic training at the Combined Harvard Orthopaedic Residency Program, where he also served as a research fellow in the H. H. Uhlig Corrosion Laboratory at the Massachusetts Institute of Technology; and a fellowship in Adult Reconstructive Orthopaedic Surgery at Rush-Presbyterian-St. Luke's Medical Center. Dr. Jacob's major research focus is on the biocompatibility of permanent orthopedic implants, particularly joint replacement devices. He is a member of the American Institute for Medical and Biological Engineering (AIMBE) and chair of the American Society for Testing and Materials Committee F04 on Medical and Surgical Materials and Devices.

Aric Kaiser is expert biomedical engineer and regulatory review scientist in the Restorative Devices Branch, Office of Device Evaluation, Center for Devices and Radiological Health at the U.S. Food and Drug Administration (FDA). He has 9 years of experience in the regulation of medical devices with particular expertise in the review of orthopedic devices involving cross-cutting issues in spinal implants, tissue-engineered orthopedic products, and regulatory/legal matters. Prior to joining FDA, he was an assistant professor and research engineer in the Department of Orthopaedic Surgery at the University of Cincinnati, where he undertook basic and applied orthopedic research in implant evaluation, tissue engineering, and orthopedic surgery resident education. Before that, Mr. Kaiser designed and tested hip and knee replacements as a research engineer with Biomechanical Research, Inc.

Amy J. LaForte is director of regulatory affairs at Stryker Biotech, where she has worked for over 5 years. With more than 10 years of experience in the research and development and regulation of novel devices and biologics, Dr. LaForte has been responsible for regulatory clearance of new products in the fields of imaging, cardiology, neurology, oncology, and, most recently, orthopedics. She was instrumental in the first market approvals for a bone morphogenetic protein product worldwide.

Stephen G. LaRiviere is senior manager of the composite and nondestructive evaluation (NDE) groups in the manufacturing research and development department at The Boeing Company. His responsibilities include the development of a fundamental understanding of composites and NDE technologies; the development of low-cost, reliable materials and processes; and the implementation of technologies into the Boeing production and support system. He has worked in the research department of Boeing for 23 years in support of product development, production systems, and in-service product support. He is a Fellow of the American Society of Non-Destructive Testing.

William McKay is vice president of research at Sofamor Danek, a subsidiary of Medtronic, Inc. He has over 20 years of research and development experience in the field of orthopedics, working for the past 16 years on the development of bone graft substitutes. He was involved with the first osteoconductive bone graft substitute that received premarket approval from the U.S. Food and Drug Administration (FDA) for use in long bone fresh fractures. Approval was based on a prospective randomized clinical trial (Collagraft). Recently, he has worked to obtain FDA premarket approval for the first osteoinductive bone-morphogenetic-protein bone graft replacement (BMP-2) for use in spinal fusions (the INFUSE™ bone graft developed by Medtronic Sofamor Danek). Mr. McKay is continuing research and development to seek expanded indications for BMP-2 using new carriers and doses.

H. Semih Oktay is president and founder of CardioMed Device Consultants, a regulatory and engineering consulting firm. In addition, he is an adjunct assistant professor at the University of Maryland, Baltimore County. He has extensive expertise in coronary stents, in balloon angioplasty and its effects on coronary arteries, and in medical device regulatory requirements, device evaluation, and materials science. Prior to founding CardioMed, Dr. Oktay was vice president of regulatory affairs and engineering at MicroMed Laboratories, Inc. His responsibilities there included providing engineering and regulatory consulting services to the medical device and related industries and managing the East Coast office. Prior to that, Dr. Oktay worked for 6 years as an expert mechanical engineer and scientific reviewer for the U.S. Food and Drug Administration in the Office of Device Evaluation, Center for Devices and Radiological Health, Division of Cardiovascular and Respiratory Devices, and Interventional Cardiac Devices Branch.

Anthony Ratcliffe is president and chief executive officer of Synthasome, Inc., a new company focused on the research and development of tissue-engineered products. Prior to forming Synthasome, he worked for six years at Advanced Tissue Sciences, where he served as vice president for research. Previous positions include associate professor of orthopedic biochemistry at Columbia University, where he taught for 9 years, and senior research scientist at the Kennedy Institute for Rheumatology in London. His research has been focused on connective tissue biochemistry, musculoskeletal research, tissue engineering, and reparative medicine. Dr. Ratcliffe is the author of more than 100 published papers. He is active in a number of professional societies and has served as: member of the board of directors of the Orthopaedic Research Society; member of various study sections for the National Institutes of Health; chair of the Grant Review Committee for the Orthopaedic Research and Education Foundation; and chair of the Tissue Engineering Committee for the American Society for Testing and Materials.

James Rutledge is president of DataVision, a company that performs statistical consulting and training. He has over ten years of experience with teaching and consulting, and specializes in teaching powerful statistical tools to nonstatisticians. Most recently, he has been performing Six Sigma training and consulting at companies such as AlliedSignal, General Electric, Raytheon, and SONY. Previously, he served as a missile launch officer in the U.S. Air Force, where he was the senior instructor responsible for training 200 launch officers, and as an assistant professor in the U.S. Air Force Academy, where he taught courses on probability and statistics. Dr. Rutledge also has extensive research experience, with his collaborative research on breast cancer acknowledged as being one of the motivating factors for changing national screening policy. Dr. Rutledge is a member of the Omega Rho and Pi Mu Epsilon honor societies; a member of the American Statistical Association, where he has served as president of the Colorado-Wyoming chapter; and he is an American Society for Quality Certified Quality Engineer.

Ronald A. Sahatjian is the senior member of scientific staff at Boston Scientific Corporation, a position he has held for 15 years. During that time, his achievements have included pioneering a program in drug delivery devices; pioneering work in the development of materials for balloon angioplasty catheters, bioactive coatings, materials compatible with magnetic resonance imaging, and endovascular procedures under magnetic resonance imaging guidance. In addition, Dr. Sahatjian has organized a research and development effort at Boston Scientific focused on less invasive neurosurgery that has led to primary IP positions and new products in aneurysmal therapies, and therapies for occlusive and hemorrhagic stroke. Dr. Sahatjian's work has led to over 30 patents and numerous awards.

Robert S. Schwartz is medical director of the Minnesota Cardiovascular Research Institute at the Minneapolis Heart Institute. Previous positions held include professor of medicine at the Mayo Medical School; director of the Center for Applied Vascular Biology and Interventions at the Mayo Clinic; consultant for the Division of Cardiovascular Diseases and Internal Medicine at the Mayo Clinic; chief cardiologist and cardiopulmonary research chief at the U.S. Air Force School of Aerospace Medicine; and U.S. Air Force Major (Medical Corps) and Flight Surgeon. His medical training includes a postgraduate degree in cardiology and internal medicine from the Mayo Graduate School of Medicine. Dr. Schwartz has published numerous papers and has served on the editorial board of the Proceedings of the National Academy of Sciences. He is active in the American Heart Association, the Council on Clinical Cardiology, and the Society for Cardiac Angiography and Interventions. He is a Fellow of the American College of Cardiology and a recipient

of the Andreas Gruentzig Award for Basic Research in Coronary Restenosis, Thoraxcenter.

Renu Virmani is chair of the Department of Cardiovascular Pathology at the Armed Forces Institute of Pathology. In addition, she is clinical visiting professor of pathology at Georgetown University, George Washington University, and Maryland University, as well as clinical research professor of pathology at Vanderbilt University. Previous positions have included: associate professor of pathology and chief of autopsy pathology at Vanderbilt University; chair of cardiovascular pathology and staff pathologist at the Armed Forces Institute of Pathology; and Fellow at the National Heart, Lung, and Blood Institute. Dr. Virmani's expertise lies in the evaluation of interventional devices, sudden death with special interest in atherosclerotic disease, right ventricular dysplasia, valvular heart disease, vasculitis, and primary cardiac tumors. Her achievements include the establishment of an independent stent laboratory that processes at least 100 stents per month and evaluates many different cardiac devices, and the development of a state-of-the-art immunohistochemical laboratory. Her medical training includes an M.D. from Lady Hardinge Medical School, Delhi University, India; training in pathology at Meerut and Lady Hardinge Hospital, New Delhi, India; a visiting fellowship at the National Heart, Lung, and Blood Institute; and a residency at George Washington University. Dr. Virmani has published over 300 peer-reviewed manuscripts and over 100 book chapters and reviews. In addition, she has coedited five cardiovascular pathology books, one cardiovascular pathology atlas, and a fascicle on primary cardiac tumors.

John T. Watson is director of the Clinical and Molecular Medicine Program in the Division of Heart and Vascular Diseases at the National Heart, Lung, and Blood Institute (NHLBI), part of the National Institutes of Health. Since 1976, he has had pivotal responsibilities and oversight at the NHLBI regarding implantable devices, such as ventricular assist devices and the total artificial heart. Prior to joining NHLBI, Dr. Watson served as chair of the Graduate Studies Program in Biomedical Engineering at the University of Texas Health Sciences Center, assistant professor in the Departments of Surgery and Physiology, and systems engineer at Ling-Temco-Vought. Dr. Watson is the recipient of numerous awards and honors. He was elected to the National Academy of Engineering in 1998 for his work enabling human mechanical artificial heart research.

Darin J. Weber is acting chief of the Cellular Therapy Branch, Center for Biologics Evaluation and Research, U.S. Food and Drug Administration (FDA) where he has worked since 1996. This Branch is responsible for the regulatory oversight of somatic cell therapy products, such as tumor vac-

cines, islet cell transplantation, xenotransplantation, and cell/tissue-based combination products. Dr. Weber is a member of the Multi-Agency Tissue Engineering Science Working Group and serves on a number of FDA task groups involved in developing regulatory policy for human tissues and cellular therapies. Previously at FDA, Dr. Weber served as regulatory scientist officer in the Division of Cellular and Gene Therapies, Office of Therapeutics Research and Review. In this capacity, he reviewed and developed policy on product manufacturing and product safety for somatic cell therapies. Prior to joining FDA, he worked at Rocky Mountain Laboratories, National Institute of Allergy and Infectious Diseases, National Institutes of Health. Dr. Weber holds the rank of Lieutenant Commander in the U.S. Public Health Service Commissioned Corps and has received numerous honors and awards for his service, including the Young Scientist of the Year Award (2001).

Leonard J. Weber is the John L. Aram Professor of Business Ethics at Gonzaga University. In addition, he is on the faculty of the University of Detroit Mercy, where he has taught since 1972 and where he served for many years as the director of the Ethics Institute. He also serves as an ethics consultant to health care organizations. Dr. Weber is the principal author of a column on case studies in ethics published in the journal *Clinical Leadership and Management Review*, and the associate editor for articles related to justice and business ethics in health care for the 3rd edition of the Encyclopedia of Bioethics. He is the author of over 70 articles and has recently published a book on business ethics in health care. He is a past president of the Medical Ethics Resource Network of Michigan.

Terry O. Woods is a mechanical engineer in the Office of Science and Technology, Center for Devices and Radiological Health, U.S. Food and Drug Administration (FDA). Her research expertise lies in the areas of: accelerated aging of absorbable suture; the development of standards for determining the safety of medical devices in magnetic resonance imaging scanners; studies examining device issues related to the cleaning, reprocessing, and reuse of single-use devices; and reviews of bench testing of a range of medical devices, in particular a number of endovascular grafts. She completed postdoctoral work in the Division of Mechanics and Materials Science in the Center for Devices and Radiological Health, with her research focusing on creep and fatigue behavior of intracranial aneurysm clips.