PREFACE

The mission of the Food and Drug Administration's (FDA) Center for Devices and Radiological Health (CDRH) is to promote and protect the health of the public by ensuring the safety and effectiveness of medical devices and the safety of radiological products.

The Office of Science and Engineering Laboratories (OSEL), is an essential component of CDRH, providing immediate access to laboratory capabilities to assist in regulatory decision making. OSEL serves as the laboratory science nucleus for the Center. Specifically, OSEL supports the ***scientific basis*** for the Agency's regulatory decision-making by developing independent ***laboratory information*** for regulatory and other public health activities of CDRH. In addition to providing consultation to the Center's regulatory experts, OSEL researchers are involved in mission-oriented science activities including test methods development, risk assessments, forensic investigations, product evaluations, and technology forecasting.

From a science standpoint, OSEL conducts laboratory and field research in the areas of physical, life, and engineering sciences as related to the human health effects of medical devices. CDRH relies upon this work to support its efforts ensuring public safety in areas as varied as accredited mammography facilities, breast implants, or drug eluting stents.

Since mid-2003, the Office has undergone at least three major transformations which have helped shape a strong organization. The first was the move of the Division of Biology to the newly constructed FDA Life Science Laboratories in White Oak, Maryland. This move was the beginning of a planned consolidation of FDA facilities. The remaining OSEL divisions joined the Division of Biology in early 2007. The second change involves what has been termed the *science prioritization process*. In the beginning of 2004, the Office instituted an ongoing process of conducting reviews of all OSEL research programs. This process is continuing to evolve and has made significant changes in the way research is proposed and how its value to the Center is evaluated. The third major change is the reorganization itself. OSEL was formally reorganized in early 2004 to improve the overall operating efficiency of the Office and to better integrate it into the mission and functions of CDRH. The reorganization created a new structure in which six new divisions replaced four former divisions and removed branch structure. OSEL is continuing to make significant strides in meeting these long-term goals.

Over the past few years, with MDUFMA (Medical Device User Fee and Modernization Act of 2002) legislation and accompanying resources, the Office has been broadening and improving its scientific program. This provided OSEL management an excellent opportunity to increase collaboration with other components of CDRH. One such example is the Office of Surveillance and Biometrics and OSEL forged a collaborative research

effort that provides opportunities for OSB statisticians to work alongside OSEL scientists on both defined research projects and general collaborations. Further examples include

- OSEL has appointed senior staff members as liaisons to pre- and post-market functions of the Center. These liaisons serve as one of their primary functions in coordinating OSEL interactions in all aspects. This activity has significantly improved OSEL presence in regulatory functions of the Center.

- OSEL invites specialists from industry and academia to present seminars at the Center to learn of the latest findings in device science and technology. There is a standing seminar series at the White Oak campus organized by the Division of Biology in OSEL in which highly renowned scientists are invited to speak on variety of topics of interest to the Agency.

- OSEL funds research fellowships for undergraduate or doctoral students from targeted universities, such as the University of Maryland, Johns Hopkins University (JHU), and The George Washington University School of Engineering and Applied Science, who have a direct interest in medical devices. Students fill part-time or summer positions at OSEL to perform their research in OSEL laboratories. These fellowships are similar to those offered in the Center's Medical Device Fellowship Program. The goal of these interactions has been to develop a coherent framework of interactions encompassing such activities as:

    - Collaboration in scientific investigations
    - Shared scientific expertise and facilities
    - Provision of a range of temporary and part-time CDRH positions for students and faculty
    - Joint participation in integrating FDA regulatory issues into engineering curricula
    - Joint workshops and conferences on topics of common interest, e.g., leading edge developments in medical device technologies
    - Creation of a regular venue for technical presentations by scientists from each institution

Additionally, OSEL has developed active collaborations, CRADAs, and IAGs with the National Institute on Disability and Rehabilitation Research (NIDRR), The Telemedicine and Advanced Technologies Research Center (TATRC), The National Science Foundation, National Institute of Health (NIH), National Institute of Standards and Technology (NIST).

The OSEL Annual Report provides current information about the Office's organization and intramural science activities; provides a summary of the Office's direct laboratory support for pre-market review and post-market evaluation; and provides a bibliography of scientific publications, presentations, and research seminars for the fiscal year. The report

is presented along the line of OSEL organization structure where the divisions are described first, followed by descriptions of the research laboratories. The laboratory descriptions contain research goals, description, and their accomplishments. This report also cites a few examples of the regulatory support work that OSEL provides to the Center's post-and pre-market offices.

OSEL management welcomes comments on the programs described in this report. We hope you find this document useful and informative, and your comments are welcome.

For additional information, please visit the OSEL web site at http://www.fda.gov/cdrh/osel or contact us at 301.796-2530.

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REGULATORY SUPPORT ACTIVITIES

The two primary functions of the Office are:

1. Strategically managed research with the aim of providing a scientifically sound basis for responding to current needs and anticipating future regulatory challenges, and
2. Provide technical consults in support of the Center's pre-market, post-market, and compliance activities.

Both activities are coordinated within OSEL in an effective manner so as to best meet the Center's regulatory science needs. The strategically managed research of the Office is described in subsequent sections in great detail. This research activity is the cornerstone upon which the Office provides the regulatory support function. The laboratory research is largely based on investigations related to the mechanistic understanding of device performance or test procedures to enable the Center and device manufacturers to gain an improved understanding of issues related to safety and efficacy. In general, although the research is directed toward issues identified at the *pre-market* approval level, the reality is that the research has the major impact on the post-market end of the Center's business because most often the research is anticipatory in terms of potential issues of medical devices identified at the pre-market level.

The regulatory support function of the Office is provided through consults in support of both pre-market decisions and post-market actions using expertise developed in the laboratory. A consult is a request for expert advice or information of a specific nature, where it is perceived that expertise is more discipline related than medical device related. Consult provides information which contributes to sound regulatory decisions. Consults may be based on acknowledged scientific/engineering principles or on independent data generated in OSEL laboratories.

The following provides a consolidated picture of the breadth of OSEL consults in 2006:

Number of consults to pre-market issues:	1159
Number of consults to post-market issues:	213
Number of activities related to standards	353

The information provided by a consult is used in some of the following ways:

- evaluating a pre-market submission (IDE, HDE, PMA, 510(k));
- supporting a compliance action (regulatory case support/development, Health Hazard Evaluation, Health Risk Assessments, etc.);
- assisting in a scientific collaboration;
- answering a consumer inquiry;
- providing opinions on guidance documents;

- providing edits to one pagers for the new device approval page; and
- assisting in health hazard evaluation/health risk assessments or in device determinations/classifications.

In many post-market as well as pre-market regulatory issues, OSEL reviews and investigations provide an independent assessment of claims made by a manufacturer or other party concerning safety or effectiveness. In other cases, OSEL reviews may assess the adequacy of a design, a failure investigation, a production process, or a quality process employed by the manufacturer. These reviews and analyses rely on in-house expertise and are often augmented by expertise solicited from colleagues in academia, other government laboratories, or even other industry sectors. OSEL laboratory investigations may be undertaken in instances where the veracity of a performance claim needs to be independently verified by testing, or when the claimant lacks the resources to conduct the investigation. Specifically, OSEL provides analytical support to post-market regulatory activities in a variety of ways:

- Provide scientific and engineering reviews and analyses;
- Conduct laboratory investigations of product performance;
- Participate in inspections of medical device establishments;
- Conduct forensic reviews and investigations;
- Identify device safety and performance issues;
- Provide training to FDA and industry; and
- Contribute to Center-wide teams on issues identification as well as science-based analysis of post-market device performance.

Standards and measurements are important products of this office. OSEL provides innovative solutions to public health problems through the development of generic techniques that lead to national and international standards to enhance product safety and effectiveness. A major activity related to standards is staff participation in standards development at the national as well as international level by conducting research to develop standard procedures and by managing, developing, and supporting standards used for regulatory assessments.

The following examples illustrate the depth and breath of OSEL consults:

Division of Biology

Bioeffects and Toxicology of Nanomaterials: Nanotechnology has great potential for medical applications and presents FDA with an emerging area of clinical products for regulatory review. In spite of remarkable advances in the use of nanomaterials, there is a paucity of knowledge in understanding the toxicology of nanomaterials. Properties of nanoparticles, such as small size, large surface area, and high reactivity that make them unique and impart tremendous potential for technological advances, are also the very properties that may be responsible for adverse effects.

Several recent government and independent reports, and a Citizen Petition, have raised concerns as to whether the FDA has the appropriate regulatory framework, including standardized methods, to properly assess the safety of nanomaterials-based medical products. If nanotechnology is to fulfill its enormous potential for development of FDA-regulated products, it is critical to understand if patients are at an increased risk from exposure to nanomaterial-based medical products. FDA and CDRH do not have a regulatory framework to explicitly address pre-market or post-market issues with nanotechnology-based medical devices. CDRH scientists are conducting targeted research to develop a framework to evaluate the safety of nanotechnology-based medical devices, both those already approved (post-market) and those under development and early in the product life cycle (pre-market). A better understanding of relationships between physicochemical properties of nanomaterials and adverse effects will enable CDRH to determine if new safety test methods and protocols are needed to move nanomaterial-based medical products forward from preclinical and clinical development to the bedside. CDRH laboratory scientists have established research collaborations with outside research institutions to establish and/or refine methods for assessing the potential adverse effects of nanoparticles used in medical products, and to develop consensus standards to facilitate the regulatory review process.

Division of Chemistry and Materials Science

Scientists in the DCMS Laboratory for Active Materials have been focusing on the effect of processing variables on the rate of release of therapeutics and on the morphology and surface characteristics of model stent coatings. These results have led to a better understanding of the relationship between changes in processing temperature and the resultant changes in drug release rates. The knowledge gained from this work has enhanced our ability to ask crucial questions regarding manufacturing issues. Specifically, these results have recently been used in support of review of PMA supplements for manufacturing changes (ODE/DCD) where the sponsor requested a change of processing temperature of their coating procedure. Finally, recent issues regarding late stage thrombosis has led the lab to focus some of its attention on the changes in surface roughness and topology as drug elutes which may be a contributing factor to these issues.

Division of Electrical and Software Engineering

NIH FOX Study: OSEL medical device engineering expertise was used to support the NIH Fetal Oximetry Trial that provided the major component of a post-market approval study plan for the Nellcor intrapartum fetal pulse oximeter when it was approved in May 2000 (P990053). An OSEL systems engineer collected clinical requirements from 14 clinical sites ranging from large university hospitals to smaller rural clinical centers. Based on these requirements, OSEL engineers developed a personal-computer-based data acquisition system using a custom-modified fetal oximeter provided by Nellcor and maternal-fetal monitor provided by Corometrics. Following design validation, the system was deployed to all 14 sites and ultimately used to acquire data from 5,341 women. The data was analyzed by the NIH team with the definitive conclusion that the device had minimal

effectiveness. The product was subsequently withdrawn from the market by the manufacturer. The study results were published in the New England Journal of Medicine in November 2006.

Software Forensics Lab**:** The analysis of medical device software to detect design defects has traditionally involved laborious manual review of the source code. The enormous size of modern software applications make such manual review practically impossible. In recent years, advances in processing power and mathematical modeling have enabled the development of static and dynamic analysis tools that allow an analyst to quickly isolate a wide variety of software design defects, from poor workmanship to inadvisable design practices and even to the types of errors which could not normally be found even by rigorous testing. However, a high degree of skill and experience is required to use these tools successfully.

The Software Forensic Laboratory located has been consulting with other federal agencies involved with software integrity issues, including the DOD, FBI, NIST and NASA, and has leveraged the latest academic research to implement a state-of-the-art software forensic capability during 2006. This capability may be used in any phase of the product life cycle, but is particularly valuable in understanding the root causes of adverse events due to software failures. We believe that this science-based capability is found nowhere else in the federal regulatory environment.

In 2006, this new capability was used to the great benefit of the Center in several high-profile compliance cases. Ultimately, such tools will increasingly be used by medical device manufacturers in their own product development phase, thereby reducing the frequency of software defects and the incidence of adverse events and product recalls. In 2007, the Software Forensics team plans to acquire more tools for reverse abstract modeling of embedded system software thought to be responsible for a medical device adverse event, and an ongoing goal of the team will be to improve its response time and throughput.

Division of Imaging and Applied Mathematics

Performance Assessment Accounting for Reader Variability in Medical Imaging Diagnostics: The OSEL Division of Imaging and Applied Mathematics (DIAM) has a strong history in researching clinical study design and performance assessment methodologies. This research is critical to characterizing diagnostic devices of all types, and specifically, to evaluating the use of imaging devices by physicians in the field. Interpretation of images by physicians is perhaps the weakest link in the diagnostic process, involving a lot of reader variability. Therefore, scientific evaluation of diagnostic imaging devices requires tools needed to estimate and understand reader variability and the interaction of the reader and the device. The field where these tools are being developed is often referred to as Multi-Reader, Multi-Case (MRMC) variance analysis, and several key contributions to this field have been made by several of DIAM scientists.

Dr. Brandon Gallas provided a consult in 2005 on a diagnostic imaging device for the ODE Division of Reproductive, Abdominal and Radiologic Devices (DRARD), Obstetrics and of Gynecology Devices Branch (OGDB): the LUMA™ Cervical Imaging System by Medispectra Inc. During his review, Dr. Gallas pointed out that the variance assessment did not account for reader variability, a subject that he encountered during his Ph.D. work and one that he was vigorously studying with his colleagues in DIAM. However, in the complicated world of device review, reader variability was not a high priority: the issue had never been mentioned to the sponsor during early meetings on the pivotal study protocol, and no one had a ready-to-go method to account for reader variability according to the sponsor's study design.

Since (and during) that review, Dr. Gallas developed a new MRMC variance estimation tool for AUC according to a fully-crossed study design: AUC denotes the area under the Receiver Operating Characteristic Curve (ROC) and is a diagnostic performance metric; a fully-crossed study design is one in which every doctor diagnoses every patient. While AUC is an extremely useful measure of diagnostic performance and the fully-crossed study design is a statistically efficient use of cases, the strategy may not be practical for all sponsors. Another, perhaps more common assessment strategy taken by sponsors, is to estimate sensitivity and specificity according to a doctor-patient study design (doctors diagnose only their own patients). Thus, Dr. Gallas has generalized his MRMC variance estimation tool to this strategy and other common reading protocols. This newly developed analysis methodology has already been employed in the review of Fuji Computed Radiography Mammography Suite. OSEL anticipates this becoming part of the analysis for devices that depend on a physician interpretation of the device outputs.

Division of Physics

Analysis of Electrosurgical Unit Ground Pad Heating: The OSEL Division of Physics (DP) has an extended history of investigating thermal injury and heating issues associated with low frequency electromagnetic devices. This research is a critical cross-cutting area for premarket and postmarket review of all types of radiofrequency ablation, hyperthermia, and other thermal therapy devices. Research work and computational analysis have played an integral part in the development of standardized test methodologies and relevant regulatory standards and were recently applied to the analysis of electrosurgical unit ground pads. Ground pads (dispersive electrodes) are commonly used for all classes of radiofrequency ablation products in addition to its uses for electrosurgery. In July 2005, a post-market issues (PMI) group was convened to address adverse events resulting from severe burns (2^{nd} and 3^{rd} degree) located at the ground pad sites. Each year, CDRH receives over 650 adverse reports related to ground pad burns

Dr. Isaac Chang was the OSEL representative to the PMI action team. He provided an extensive analysis that demonstrated that the standardized test methodology used to approve ground pads was flawed. According to AAMI HF-18 and IEC601-2-2, the

temperature beneath ground pads under testing conditions should not exceed 6°C and should have an impedance that does not exceed 75 ohms. The standard test methodology, assesses these two attributes separately. Dr. Chang developed computational tools to assess the thermal and electrical problems *simultaneously* and found that electrodes with identical electrical characteristics could differ in the maximum temperature rise by as much as 10 degrees C; which may explain why identical ground pad specifications resulted in skin burns in some cases, and not in others. In 2006, Dr. Chang expanded his computational studies to test over 815 different ground pad configurations under the AAMI HF-18 test conditions on an anatomically correct rendering of a human male model (based on MRI images) at 5 cubic millimeter resolution. The developed model is the first whole-body computational model that simultaneously solves the electric field, temperature distribution, and predicts thermal injury with over 32 million degrees of freedom. Graphics tools were developed to allow plane-by-plane analysis, which allowed Dr. Chang to visualize not only topical skin burns, but thermal injury to subdermal tissues as well. He experimentally verified his findings under *in vitro* and *in vivo* conditions and validated the results of his computational analysis. Dr. Chang documented the results in a 65-page white paper, which was distributed to each office in CDRH.

As nearly all devices using a return ground pad employ an impedance cutoff as an emergency shutoff feature, Dr. Chang's results indicated that hundreds of medical devices may be affected by these findings. Worse still, the AAMI HF-18 and IEC601-2-2 standards are an integral part of pre-market review since they are the primary electrical safety standards used by CDRH for all high frequency medical devices. Dr. Chang worked with the standard's coordinator for both standards in October 2006 and submitted recommendations to modify the test methodologies. He is currently in the process of publishing his findings to raise the level of awareness of this problem in both the clinical and manufacturing communities.

Division of Solids and Fluid Mechanics

Test methods for high intensity focused ultrasound: CDRH is receiving increasing numbers of regulatory submissions for high intensity focused ultrasound (HIFU) surgery. HIFU holds the potential for radically advanced surgical techniques, including ablation of both malignant and benign lesions and cessation of internal bleeding in injured vessels and organs, all with minimal damage to the surrounding tissue. However, the lack of standardized methods to assess the acoustic and thermal characteristics of the focused beams has challenged the regulatory review of these devices, especially in the pre-clinical phase, and has been burdensome to the industry. In the past, CDRH scientists and engineers have developed measurement instrumentation and computational modeling techniques for characterizing other types of medical ultrasound devices such as diagnostic imaging and therapeutic ultrasound, and this work has resulted in the creation of numerous regulatory guidance and standards documents. This expertise is being used to accelerate the review of submissions for HIFU devices. For example, one challenge to testing HIFU devices is the lack of suitable tissue-mimicking materials that not only have tissue-like

acoustic and thermal properties, but also can withstand the intense acoustic fields without damage. CDRH laboratory staff members have developed and tested a gel-based material with the requisite properties. This work has been leveraged by funding under an interagency agreement (IAG) from DARPA, which has interest in HIFU test bed development because of a project to develop a HIFU system for treating battlefield wounds. This research, as well as other laboratory products, is being used as input to international standards that are under development for HIFU. These standards will help expedite the regulatory review process.

MRI Safety and Compatibility of Implants and Medical Devices: Millions of patients undergo MR imaging each year. Unfortunately thousands of patients who would benefit from the information gained via MRI cannot undergo the procedure because they have electrically active implants like pacemakers that can fail or malfunction in a MRI scanner. This danger became clear to CDRH when in 1992, a woman with an intracranial aneurysm clip was killed as she was brought near an MR scanner in preparation for an MR examination. The aneurysm clip was moved by the magnetic field, tearing the clipped artery and killing the patient. CDRH has been actively involved in assuring the safety of medical devices within MRI scanners since that first fatal accident. For example, under OSEL leadership, ASTM has now published four standard test methods for determining MR safety and one method for marking devices for safety in the MR environment. These are the only existing standardized test methods for determining MR safety of medical devices. This past year OSEL has made a number of contributions to expand the standards to apply to electrically active implants and equipment. In particular, OSEL is working the international MRI community to more appropriately address RF heating of active devices during MRI. Significant short-comings in the ASTM testing protocols were identified and are being addressed. These short-comings are most significant for electrically active implants with their inherent conducting leads and wires. OSEL is continuing its activities in this area and is now actively working with both ISO and IEC to address problem of MR compatibility with implants.

Comment [K1]: L. Kessler quoted comment: "Good history – but I bet we can document. These issues are still current." KDV 4/11/07

Corrosion testing: In 2006 OSEL scientists helped conduct the first round robin validation tests for corrosion resistance of small devices such as stents. This test method, known as ASTM F2129, has become one of the most referenced standards for cardiovascular stents, particularly those made of Nitinol. Nitinol is a metal increasingly used for metal components of implants because it is typically strong, light, and very inert, with a very high corrosion resistance. However, this corrosion resistance depends upon the final condition of the Nitinol surface and can be inadvertently destroyed. CDRH became aware of this unexpected property of Nitinol in the late 1990's while reviewing the corrosion testing data on several Nitinol stents that showed a high corrosion and pitting rate. This result was surprising, since from past experience with the alloy, a very low corrosion rate would be expected. CDRH scientists then conducted laboratory tests and observed similar high pitting corrosion rates. CDRH scientists then drafted F2129 and worked with ASTM to get this standard approved and recognized. It was accepted almost immediately as the

best available protection for implanted devices against undesired failure from corrosion. CDRH and industry worked together via the ASTM standards process to revise and refine the method and this year a formal evaluation round-robin test was conducted, with OSEL as one of the 12 participating laboratories. To everyone's relief, the data were in reasonable agreement. OSEL continues to be active in the further evaluation of this most important standard.

DIVISION DESCRIPTIONS

DIVISION OF BIOLOGY (DB)

DB participates in the Center's mission by conducting research, participating in device review activities, developing consensus standards both domestic and international, developing regulatory guidance, testing forensic and regulatory samples, and providing educational programs in the area of biological sciences. Specifically, DB conducts research to support the Center's mission to assure the safety and effectiveness and promote the improvement of medical devices in the areas of biological risk assessment, biosensors/nanotechnology, genomic and genetic technologies, infection control and sterility, tissue-device interactions, toxicity/biocompatibility, and radiation bioeffects. Through laboratory studies, researchers evaluate the potential adverse effects of medical devices on host biological systems and, in collaboration with engineering divisions, identify the source and impact of product degradation on organ systems both under acute and chronic conditions. The Division staff develops measurements methods and analytical procedures to characterize and evaluate devices and products, studies molecular and cellular mechanisms and bioeffects of biomaterials, and supports the Center's enforcement and product testing activities.

The DB staff members are primarily biologists, chemists, and biomaterials scientists.

Laboratories

- Biological Risk Assessment
- Biotechnology
- Biomolecular Mechanisms
- Cardiovascular and Interventional Therapies
- Radiation Biology
- Toxicology

DIVISION OF CHEMISTRY AND MATERIALS SCIENCES (DCMS)

DCMS participates in the Center's mission by conducting research, participating in device review activities, developing consensus standards both domestic and international, developing regulatory guidance, testing forensic and regulatory samples, and providing educational programs in the area of chemistry and materials sciences. Specifically, the DCMS focus is on the developing experimental data, test methods and protocols for regulatory and scientific activities involving multicomponent mass transfer, reaction kinetics, absorption and swelling of network polymers, polymer processing, modeling of

physiological processes, and materials degradation. Research conducted in the division includes polymer synthesis; synthesis of polymeric nanocomposite materials; sensors; thermodynamics; thermal transitions and phase stability; hydrogel and biopolymer synthesis and characterization; polymer formulation; separations; spectroscopy; small-angle x-ray and neutron scattering; and shelf-life and service life prediction. DCMS tests the performance of chemical processes of importance to medical devices, such as mass transfer through membranes used in dialysis and blood oxygenation, and manufacturing processes used to fabricate materials.

The technical disciplines of the DCMS staff include physical chemistry, chemical physics, polymer science, pharmacology, materials science, and biomedical and chemical engineering.

Laboratories

- Active Materials
- Experimental Pathology
- Materials Performance

DIVISION OF ELECTRICAL AND SOFTWARE ENGINEERING (DESE)

DESE participates in the Center's mission by conducting research, participating in device review activities, developing consensus standards both domestic and international, developing regulatory guidance, testing forensic and regulatory samples, and providing educational programs in the area of electrical engineering and software. Specifically, the DESE works in the application of electronics, software engineering, and systems engineering body of knowledge to the regulation of medical devices and electronic products that emit radiation. The division addresses the cutting edge of medical devices through all phases of the product life cycle and all aspects of the product manufacturer’s business, from research and development through procurement, production, and ongoing customer support. DCMS hosts the following resources and capabilities: analog and digital circuit design, data acquisition and display, embedded microprocessor and PC-based systems, software-based virtual instruments, quality management and risk management as applicable to electronics and software, testing for hazards arising from the use of electrical and electronic technology in medical products, and electronic design including components, circuits, and analytical techniques for controlling high voltages and/or currents.

DESE staff members are primarily electronics engineers, physicists, biomedical engineers, and general engineers.

Laboratories

- Electrical Engineering

- Software
- Systems Engineering

DIVISION OF IMAGING AND APPLIED MATHEMATICS (DIAM)

DIAM participates in the Center's mission by conducting research, participating in device review activities, developing consensus standards both domestic and international, developing regulatory guidance, testing forensic and regulatory samples, and providing educational programs in the area of medical imaging and applied mathematics. Specifically, DIAM provides scientific expertise and carries out a program of applied research in support of CDRH regulation of radiation-emitting products, medical imaging systems, and other devices utilizing computer-assisted diagnostic technologies. Medical imaging research encompasses ionizing and non-ionizing radiation from data capture through image display and observer performance. The computer-assisted diagnostics work of DIAM is focused on the appropriate mathematical evaluation methodologies for sophisticated computational algorithms used to aid medical practitioners interpret diagnostic device results. The Division is charged with developing and disseminating performance assessment methodology appropriate to these modalities. DIAM operates a calibration laboratory for ionizing radiation detection instruments and participates in a full range of programs in support of the Public Law 90-602 mission of the Center.

DIAM staff members are primarily physicists, mathematicians, and physical science technicians.

Laboratories

- Image Analysis
- Imaging Physics
- Ionizing Radiation Metrology

DIVISION OF PHYSICS (DP)

DP participates in the Center's mission by conducting research, participating in device review activities, developing consensus standards both domestic and international, developing regulatory guidance, testing forensic and regulatory samples, and providing educational programs in the area of physics. Specifically, DP conducts research and engineering studies to support the Center’s mission to assure the safety and effectiveness of medical devices and electronic products, and to promote their improvement. Scientific and technical specialties in the division include optical physics and metrology, sensors, fiber optics, electromagnetics, electromagnetic compatibility and electromagnetic interference, electrophysics and electrical stimulation technologies, electrophysiology, radiofrequency/microwave metrology, and minimally invasive optical and electromagnetic

technologies. The Division develops measurement methods, instrument calibration capabilities and analytical procedures to characterize and evaluate devices and products, and supports the Center's enforcement and product testing activities. DP evaluates interactions of electromagnetic and optical energy with matter, analyzes implications for the safety and effectiveness of devices and products, and develops and evaluates procedures for minimizing or optimizing human exposure from such devices.

The technical disciplines of DP staff include physics, mathematics, biophysics, biomedical engineering, electronics, and general engineering.

Laboratories

- Electrophysiology and Electrical Stimulation
- Electromagnetic and Wireless Technology
- Optical Diagnosis
- Optical Therapeutics and Medical Nanophotonics

DIVISION OF SOLID AND FLUID MECHANICS (DSFM)

DSFM participates in the Center's mission by conducting research, participating in device review activities, developing consensus standards both domestic and international, developing regulatory guidance, testing forensic and regulatory samples, and providing educational programs in the area of solid and fluid mechanics. Specifically, the core responsibilities of this division involve issues for which mechanical interactions or transport are of primary concern, such as those involving motion; structural support, stabilization, or vibrations; device and material mechanical integrity; materials durability; and biologically relevant parameters of device and materials. The division has expertise in the areas of fluid dynamics, solid mechanics and materials, acoustics and ultrasonics. DSFM develops measurement methods, instrument calibration capabilities, and analytical procedures to characterize and evaluate devices, device materials, and products, and supports the Center's enforcement and product testing activities. The division staff also evaluate interactions of ultrasound energy with matter and the implications of these interactions on the safety and effectiveness of devices and products.

Technical disciplines of the DSFM staff include mechanical engineering, materials science, biomedical engineering, general engineering, and physics.

Laboratories

- Fluid Dynamics
- Mechanics
- Ultrasonics

STANDARDS MANAGEMENT STAFF (SMS)

The SMS is responsible for managing the Center's standards program. The staff in this program is responsible for developing, managing, and supporting standards used for regulatory assessments. SMS supports participation in medical device standards committees. The staff accomplishes these tasks with the help of Standards Task Groups (STGs). This involves working closely with the Standards Developing Organizations (SDOs), advertising standards liaison representative positions, facilitating a Center recommendation to serve on a particular standards activity, maintaining a standards database that provides access to established standards to all CDRH staff and field inspectors.

SMS increases the recognition of voluntary consensus standards for medical devices and radiation-emitting electronic products. The Standards Program was created as a result of the Food and Drug Administration Modernization Act (FDAMA) of 1997. Although CDRH had been involved in the development of medical device standards for decades, FDAMA formalized the process. As part of this responsibility, the staff publishes lists of recognized standards annually and consistently increases the list of available standards.

MANAGEMENT SUPPORT STAFF (MSS)

MSS provides leadership and support to the Office of the Director, Division Directors, and laboratory professionals on all administrative, general management, and knowledge management issues. MSS is responsible for planning, developing, and implementing Center and OSEL programmatic matters concerning financial management, personnel, procurement, contracts, inter-agency agreements, employee training, and facilities. MSS is tasked with the managing and administering OSEL resources designed to support ongoing programs. The staff ensures the proper distribution of operating and payroll dollars, facility plans, procurement and property, travel requests and ADP needs. MSS advises the Office of the Director on potential issues that may affect resources, staffing, and management issues to comply with policies and avoid potential conflicts. In addition, MSS directs and conducts special assignments or projects for the Center as well as the Office Director.

MSS is also tasked with Knowledge Management Support (KMS) responsibility for the office. The KMS team provides technical support for the acquisition, retrieval, and analyses of data supporting the office's mission including developing specialized databases and related applications where needed. Additionally, the staff performs specialized activities associated with the development, design, installation, and administration of data processing systems, particularly those that are integral to laboratory functioning.

The KMS team collaborates with the Office of Systems and Management (OSM) and the Office of IT Shared Services (OITSS) in developing major initiatives involving OSEL, CDRH, and FDA data and systems. The KMS staff also coordinates OSEL activities with these offices to assure compliance with Center and FDA policies regarding data structure and format and with FDA initiatives to assure data consistency and compatibility.

DESCRIPTION OF OSEL LABORATORIES

Biological Risk Assessment Laboratory (Division of Biology)

Scope

Risk assessment is the process of determining the extent of human health hazard relative to exposure conditions. Staff in the OSEL Laboratory of Biological Risk Assessment: 1) conduct research to address CDRH's regulatory need for improved methods of detecting and quantifying risks associated with chemical compounds, microbial agents, and radiation released from medical device materials; and 2) conduct risk assessments to inform risk management decisions in the Center. Research is focused in three areas:

- **Safety of reprocessed medical devices**: Research in this area includes the assessment of the toxicity of residual disinfectants/sterilants and the efficacy of methods to remove residual bioburden on reprocessed devices.

- **Development of clinically relevant biomarkers and preclinical animal models:** Research in this area was identified as being central to the FDA Critical Path Initiative.

- **Bioeffects of ultrasound and ultrasound contrast agents**: Involves an assessment of the extent of the vascular endothelial and smooth muscle damage by microbubble-based ultrasound contrast agents and its role in the pathogenesis atherosclerotic changes.

Background

OSEL staff has long been responsible for conducting risk assessments of compounds or microbial agents released from medical device materials. These risk assessments have been directly used to support regulatory decision making in the Center (e.g., microbial risk assessment to support Sterility Assurance Levels, DEHP Safety Assessment to support the issuance of a Public Health Notification and draft labeling guidance, ethylene oxide risk assessment to support the revision of the ISO 10993-7 standard). Research done in this laboratory program is used to support risk management decision in the Center, notably, those involving infection control, the preclinical biocompatibility testing of devices, and the biological effects of ultrasound and ultrasound contrast agents.

Research Program Description

FDA's Center for Devices and Radiological Health (CDRH) is responsible for ensuring the safety and effectiveness of medical devices and eliminating unnecessary human exposure to man-made radiation from medical, occupational and consumer products. This broad mandate requires chemical, microbial, and radiation risk assessments to be performed to support regulatory decision making in these areas. Chemical risk assessment activities in CDRH focus on three areas: 1) the development and validation of new risk assessment methodologies, 2) bench-top research to provide information for the hazard identification and dose-response assessment stages of the risk assessment process, and 3) the application of risk assessment approaches to assist with regulatory decision making. The research component of the laboratory's effort is key in addressing uncertainties regarding the response of sensitive subpopulations to the effects of chemical compounds and ultrasound energy and to determine the effectiveness of reprocessing strategies for medical devices that are cleaned and reused.

Relevance to FDA/CDRH's Mission and Public Health Impact

The OSEL program in risk assessment involves laboratory-based efforts to address risk assessment uncertainties, development and validation of new risk assessment methodologies, and use of risk assessment to support regulatory decision-making.
The goal of research in the Biological Risk Assessment laboratory is consistent with the goal of FDA's Critical Path Initiative to stimulate the development of new evaluative tools for assessing the safety and efficacy of new medical products, specifically, tools such as proven biomarkers and clinically relevant animal models. A key laboratory-based effort is directed towards examining whether critically ill or injured patients represent a sensitive subpopulation and can be more susceptible to adverse effects of chemicals. Research is also being conducted to address the effectiveness of cleaning/reprocessing strategies for reused devices and uncertainties in biocompatibility assessment. Data from these efforts will be directly used in the ISO and ASTM standards development process. Finally, research on the bioeffects of ultrasound and contrast agents may have an impact on the regulation of this imaging technique and standards addressing ultrasound exposure.

Three Year Goals

- Investigate the effectiveness of low energy radiation sources alone or in combination with other devices or drugs.
- Conduct a pre-clinical translational radiation biology study and test the safety and efficacy of a drug/device cancer therapy for melanoma.
- Conduct research on changes in skin following exposures to ultraviolet radiation, and on the doses of UV needed to produce and maintain a tan.
- Conduct research on UV response of differently pigmented groups on the U.S. population to modernize public health policies in the area of national and international standards on UV exposures.

- Complete our efforts in describing the cancer risks and benefits associated with exposure to tanning lamps.

Accomplishments

Safety of reprocessed medical devices

- Participated as one of 10 laboratories in the Interlaboratory Collaborative Study to develop a validation protocol for the quantitative three-step method for determining the sporicidal efficacy of liquids, liquid sprays, and vapor or gases on contaminated carrier surfaces. This project has regulatory significance for FDA since CDRH regulates chemical disinfectants and sterilants for medical devices. Manufacturers must submit data using valid protocols to demonstrate their products are safe and effective.

- Conducted research to develop/establish "acceptable" cleaning criteria for reusable "single use" devices (SUDs).

- Collaborated with two local healthcare facilities to help monitor changes in the design of some SUDs and identify new SUDs being reprocessed.

- Characterized the toxic effects of intravenously administered ethylene glycol in the pig. Ethylene glycol is a breakdown product of the sterilant, ethylene oxide. A poster describing this work was awarded the "Outstanding Presentation" award by the at the 2006 annual meeting of the Society of Toxicology.

- Determined the effect of hyperthermia on detergent- and disinfectant-induced hemolysis and the interactive effect of detergents and disinfectants with regard to their ability to produce toxic effects.

Development of clinically relevant biomarkers and preclinical animal models

- In collaboration with investigators at CDER, Harvard University and Biotrin International, Ltd., we have identified sensitive biomarkers that are able to detect kidney damage in rats at an earlier stage than existing biomarkers. This work is consistent with the goals articulated in the FDA Critical Path Initiative to develop a better product development "toolkit" for assessing target organ damage (http://www.fda.gov/oc/initiatives/criticalpath/whitepaper.html).

- Developed/refined animal models (rat and pig) of endotoxemia. Since critically ill patients are often endotoxemic, these animal models may be more clinically

relevant than the healthy animal models that are currently used for preclinical biocompatibility assessment of medical device materials.

- Identified plasma and target tissue levels of inflammatory biomarkers in pigs following administration of endotoxin.

- Biomarker detection from urine samples of renal insufficient rats: Developing a new method for early stage diagnosis of renal insufficiency. This is a corporate project with Laboratory of Toxicology (Division of Biology).

- Biomarker detection from urine samples of renal insufficient rats: More than 160 rat urine samples have been collected and tested on six targets (biomarkers). The project is in good progress and satisfied results have been obtained.

Bioeffects of ultrasound and ultrasound contrast agents

Examined the cytotoxic effect of an ultrasound contrast agent, Optison, on murine macrophages, fibroblasts, and endothelial cell lines, and rat explanted arteries as part of a research effort funded by the FDA Office of Women's Health.

Radiation Biology Laboratory (Division of Biology)

Scope

This laboratory conducts research to investigate the public health impact of electromagnetic radiation exposure from medical devices and non-medical electronic products.

Background

One important example of possible radiation bioeffects involves the use of cellular phones. Currently over 100 million Americans use wireless phones. Data relating to the safety of radiation from wireless phones are inadequate; however, they suggest that exposures to radio frequency radiation at levels relevant to wireless phone use may cause biological effects. In this area, the OSEL bioeffects project serves as the coordinator of independent research conducted in several laboratories.

Research Program Description

Current efforts are directed toward better understanding of the risks of non-ionizing radiations from wireless telecommunication devices, assessing the skin cancer problem associated with use of tanning lamps, and quantifying the differences in UV response in differently pigmented populations in the U.S. Also, in line with the Center's new initiative

to focus on the most pressing radiological problems and to anticipate the evolution of new medical radiation systems, we are concentrating our research efforts in ionizing radiation to better understand radiation-drug and radiation-heat interactions, and to provide the Center with expertise on a new class of low dose x-ray therapeutic devices entering the market. The laboratory also monitors the scientific literature and maintains expertise in other radiation areas, such as laser, visible, and extremely low-frequency radiation.

Relevance to FDA/CDRH's Mission and Public Health Impact

- Scientific oversight of extramural research by scientists from the Laboratory of Radiation Bioeffects is defining the health risks from radio-frequency radiation. The Center has been charged by Congress to address the safety of electromagnetic emissions from products such as cell phones and our work is periodically monitored by the Government Accounting Organization.

- The research characterizes the effectiveness of low energy x-ray emitting devices for cancer therapy. This is directly related to device reviews requested by the Radiation Devices Branch at ODE.

- Combinations of radiation-emitting medical devices or radiation-emitting medical devices with therapeutic drugs can improve tumor response, but little is known about safety and efficacy of some drug/device combinations. Our research tests the safety and efficacy of device/drug combinations and serves as a repository of knowledge for the bioeffects of combination therapies at FDA.

- Research on the doses of ultraviolet radiation needed to produce and maintain a tan leads to recommendations for dramatic lowering of the UV burden for those individuals who choose to use sunlamps. This should lead to fewer cases of skin cancer, the most common cancer in this country. This research was requested by TEPRSSC as a part of preparations for changes to the Performance Standard for Sunlamp Products.

- Preliminary results suggest that medical claims cannot be made in general about all tanning bulbs or devices because they have different outputs in the UVA (long wave, 320-400 nm) and UVB (shortwave, 280-320 nm) regions of the UV spectrum. This is important because only UVB can make vitamin D, while UVA cannot make any at all, but rather can only break it down. In addition, different emissions from the bulbs can make vastly different amounts of vitamin D3. The different emission spectra of tanning bulbs are similar to the sun in some ways, but different in others; so it is not clear if all bulbs will make the predicted amount of vitamin D and some may not make any at all. In fact, the high-pressure emitting UVA devices may only break down existing vitamin D. We have performed many

risk assessments for skin cancer from these different UVB emitting tanning devices and have balanced those with some benefit assessments, i.e., vitamin D production.

- Laboratory research gives our staff the scientific credibility needed to help with device reviews and development of international standards and guidelines.

- Serve as a radiobiology resource for homeland security issues.

Three-Year Goals

- Conduct a pre-clinical translational radiation biology study and test the safety and efficacy of a drug/device cancer therapy for melanoma.
- Conduct research on changes in skin following exposures to ultraviolet radiation, and on the doses of UV needed to produce and maintain a tan.
- Conduct research on UV response of differently pigmented groups on the U.S. population to modernize public health policies in the area of national and international standards on UV exposures.
- Complete our efforts in describing the cancer risks and benefits associated with exposure to tanning lamps.

Accomplishments

Radiofrequency studies and oversight of CRADA on cell phones

- Gave a presentation (invitation) at the 2006 Joint Workshop on Radio Frequency and Health hosted by the Japanese Ministry of Internal Affairs and Communication in Tokyo, Japan.

- As members of IEEE International Committee on Electromagnetic Safety Sub Committee 4, Division of Biology scientists participated in the revision of the current radio frequency exposure standard, titled "Standard for Safety Levels with Respect to Human Exposure to Radio Frequency Electromagnetic Fields, 3 kHz to 300 GHz (IEEE C95.1)". The revised standard was published in 2006.

- Provided scientific oversight for FDA/CTIA CRADA-funded projects; and for investigators performing RF exposure assessment submitted final reports and manuscripts for publication.

- In collaboration with investigators in the CDRH/OSEL/Division of Physics, the Center for Biologics and Evaluation Research, and the Center for Drug Evaluation, Division of Biology scientists participated in a project investigating the effects of exposure from RF-ID readers on pharmaceuticals and biological products.

- Hosted a meeting between government scientists from FDA, NIOSH, EPA, FCC and OSHA and members of IEEE to discuss the revisions made to IEEE C95.1.

- Participated in a workshop hosted by the "International Commission for Non-Ionizing Radiation Protection (ICNIRP)" to discuss needed changes and updates to the ICNIRP human exposure safety standard.

Laboratory research on models for therapies that use low LET ionizing radiation, drugs and hyperthermia

- With the assistance of two summer students the Radiation Biology laboratory:
    - Established the growth of human melanoma tumor cells under control conditions as well as under "tumor-like" low pH conditions.
    - Produced a family of thermal dose-response curves for control and low pH grown cells from 37 to 44ºC for times up to 240 minutes.
    - Produced a family of radiation dose-response curves for human melanoma cells grown under control and "tumor-like" low pH conditions. Three different kV's (240, 125 and 60) and four different dose rates (240, 110, 30 and 17 cGy/min) were used to dose control and low-pH growing cells.
    - The data from these experiments is currently being analyzed and reduced for graphic display.

Initial hyperthermia dose-response data and initial radiation dose-response data were presented at the OSEL summer student poster session in August 2006.

Laboratory research on Thermoradiotherapy in Human Melanoma Xenografts

- A DB scientist completed a series of experiments designed to examine the safety of this multi-modality therapy on normal murine bone marrow progenitor cells. This work was done at Thomas Jefferson University in the Laboratory of Experimental Radiation Oncology in the Department of Radiation Oncology.
- Presented two posters at the National meetings of the Radiation Research Society and the Society of Thermal Medicine.
- DB scientists presented on the concept of multimodality therapy and its effect on normal murine bone marrow at the Division of Biology's "Pay-Day" seminar series. A manuscript is planned.

Risk/Benefit analyses of UV-emitting tanning devices

- Co-chaired a symposium on "UV Doses" at the American society for Photobiology meeting July 8-12, 2006

- Did laboratory work to determine if report about UVA not making any i D is true or not and found that it does not make any vitamin D at any dose level that is physiologically relevant

Biotechnology Laboratory (Division of Biology)

Scope

The biotechnology laboratory's mission is to study various aspects of microbial pathogen contamination of medical devices and to reduce the risk of microbial infection from contaminated medical devices and to study the biocompatibility of nanoparticles. The laboratory's main research projects are focused on evaluation of nanoparticles properties and on microbial detection and analysis, using an interdisciplinary research approach that integrates engineering and molecular biology.

Background

Microbial infections associated with medical devices are a major health risk factor, especially with the use of intravascular catheters. The common hospital practice of reuse of single use devices, the spread of antibiotic resistance microbial strains and the potential use of microbial pathogens as bioweapons all add to the need for better microbial detection and diagnostics. Nanotechnology is an emerging field; effective CDRH regulation of the technology requires better understanding of the biocompatibility of nanoparticles.

Research Program Description

The laboratory is working on five major research projects related to detection and analysis of microbial pathogens funded in part by the FDA's Office of Science and Health Communication, HHS/ORDC and by the USDA:

- *Mycobacterium tuberculosis* antibiotic resistance: Identifying point mutations in MTB genes associated with drug resistance and developing microarray-based methodology for detecting MTB gene mutations. This project was funded by the FDA's Office of Science and Health Communication.

- DNA microarrays for analysis of microbial pathogens and their virulence factors: The project to develop these arrays was funded by the FDA's Office of Science and Health Communication (two awards) and the USDA.

- High-speed, low-volume portable PCR thermocycler for regulatory and biodefense applications: The project to develop this device was funded by the FDA's Office of Science and Health Communication.

- Microfluidics in devices that detect microbial pathogens and their toxins: This collaborative bioengineering project (with the University of Maryland) is supported by ORDC.

- Evaluation of biocompatibility of nanomaterial used as medical devices:
  A new Dynamic Light Scattering based tools are being developed for vitro evaluation of the behavior, properties and biocompatibility of various nanoparticles under physiological conditions.

- Prioritizing sources of variability in genomic profiling data for standards and guidance development (inter-center collaborative project)

Relevance to FDA/CDRH Mission and the Public Health Impact

CDRH-regulated products such as heart valves and intravascular catheters are a cause of microbial infections, which is a major health risk factor in hospitals. The common hospital practice of reusing single use devices, the spread of antibiotic resistance microbial strains (especially *S. aureus)* and the potential use of microbial pathogens and their toxins as bioweapons all add to the need for better microbial detection and diagnostics for medical devices. Nanotechnology is a new emerging field; effective CDRH regulation of the technology requires better understanding of the biocompatibility nanoparticles.

FDA bears the responsibility for approving microarray-based genetic and genomic diagnostic devices (CDRH) and for evaluating this data submitted as evidence of safety and efficacy of therapeutic products (all product centers). Standards for submission and/or evaluation of genomic microarray data have not yet been generated, require novel

approaches, and are a source of concern for both FDA and industry. Sources of variability are known, but not their relative contribution to the often cited lack of reproducibility in microarray data. This project has implemented a set of inter-lab experiments designed to prioritize different sources of variability allow us to focus on the more important aspects during regulatory review. The project also enhances the resident FDA expertise in this area, by hands-on experience. This and other work provides a framework for integration of new genetic and genomic technologies, as they arise.

Three-Year Goals

- Improve the prototype of the portable PCR thermocycler for regulatory and biodefense applications; plan to optimize the wiring, design a holder for the capillaries, and develop an electro-optical detection module and a PDA-based controller.
- Develop DNA microarrays for detection and analysis of enteric bacteria and improving the *S. aureus* microarray. The new arrays will be tested for the ability to detect pathogens in devices such as heart valves and intravascular catheters.
- Develop whole genome amplification methods for microarray analysis of microbial contaminants.
- Improve the assembly of our microfluidics device for use in detection of microbial pathogens.
- Develop Dynamic Light Scattering based methodology for evaluating the biocompatibility of nanoparticles.
- Provide statistically valid, experimentally based information on prioritization of variables in microarray data;
- Facilitate hands-on experience in FDA labs in this new technology;
- Develop a scientific infrastructure suitable for integration of new genetic and genomic technologies as they evolve.
- Develop a fractional factorial design maximizing the number of variables that could be tested with 60 microarrays per lab
- Create a large scale biological sample for testing in multiple labs.
- Create our own microarrays on four chemically different surfaces.
- Comparatively process four different microarray surfaces in four FDA laboratories.
- Analyze data by different statistical approaches.
- Prioritize variables (e.g., biological variability, sample preparation, inter-lab, inter-experiment processing within a lab, microarray surface, microarray generation) based on statistical analysis.
- Provide hands-on experience in FDA labs in this new technology.
- Build inter-Center teams of both review and bench scientists.
- Provide a basis for integrating new technology as it evolves.

Accomplishments

- Developed a prototype of a rapid and portable PCR thermocycler for regulatory and biodefense applications: The miniature portable prototype powered by a regular 9 volt battery is based on a new thin-foil heater and is controlled by a computer. The prototype was used successfully for rapid (30 cycles within 17.5 minutes) *Bacillus cereus* DNA amplification.

- Analysed *Mycobacterium tuberculosis* (MTB) antibiotic resistance: A method which combines DNA microarray and allele-specific PCR techniques was developed for rapid and accurate identification of mutations in the MTB genes (*rpoB, katG, and rpsL*) that confer resistance to the antibiotics rifampicin, Isoniazid and streptomycin. The method was tested with 20 MTB strains.

- Developed microarray-based detection of Bacillus virulence factor genes including those encoding enterotoxins, phospholipases and exotoxins: The method requires an initial multiplex PCR amplification step, followed by identification of the PCR amplicons by hybridization to an oligonucleotide microarray containing genes for all three types of virulence factors.

- Analysed of Staphylococcal contamination of medical devices (heart valves and intravascular catheters): Microarrays were developed for detection and analysis of *Staphylococcus aureus* and *Staphylococcus epidermidis*.

- Developed a hand-held microfluidics multi-channel lab-on-a-chip for detection of microbial pathogens and their toxins: The lab-on-a-chip based on polymer microtechnology with laser microfabrication consists of a several layer plastic cartridge assembled with a thermal press. Samples and reagents for the assay are delivered to the reaction chamber through microcapillaries using a miniature built-in manual vacuum pump. A prototype device was tested for activity detection of botulinum toxin A (none toxic) light chain.

- Developed a portable detector for lab-on-a-chip: The computer control detector consists of LED light source and cooled CCD camera. A prototype detector was tested for microfluidics detection of botulinum toxin A (none toxic) light chain.

- Developed bioinformatics tools: New software were developed and tested for automated selection of oligonucleotides for microarrays and for analysis of our detector data.

- Developed an *in vitro* evaluation method for the behavior, properties and biocompatibility of various nanoparticles under physiological conditions. In this collaborative research with scientists from Thomas Jefferson University, we are evaluating the biocompatibility of nanoparticles by studying aggregation of various nanoparticles using Dynamic Light Scattering. Our aim is to assess the

nanomaterial response to perturbations in the properties of the solution environment, such as pH and ionic strength.

- Experiments were completed in microarray printing on four surfaces in three laboratories, swapping and processing in four FDA laboratories (CDRH, CBER, NCTR and CVM).

- Data are presently being analyzed by a statistician. Some initial statistical analyses of the experiments were presented at the FDA Science Forum in 2006. One of the surfaces exhibited an unexplained set of variations. We are examining the possibility that there was sequence dependence of binding of some of the probes to this particular microarray surface.

Cardiovascular and Interventional Therapeutics Laboratory (Division of Biology)

Scope

The Laboratory of Cardiovascular and Interventional Therapeutics (LCIT) investigates the safety and effectiveness of a range of interventional therapeutics, including cardiovascular and minimally invasive devices and related adjunctive agents. This includes the application of emerging imaging technologies to guide the delivery of novel therapeutic devices and agents. Local delivery of therapeutic devices alone or in combination with other agents via percutaneous catheters or direct surgical access has shown great clinical promise for the treatment and prevention of vascular disease and cancer. The laboratory's Research Program includes both normal biology and the pathologic basis for disease and device failure at the genetic, molecular and tissue levels and the development of animal models that are predictive of clinical safety and effectiveness.

The focus is on studying existing models and developing more predictive models of device use and related failure modes including identification, evaluation and development of more optimal clinical treatment algorithms for image guided interventions and drug delivery, e.g., tumor ablation. In addition, retrospectively, the models have been used to support applications for vascular devices. The *in vivo* models under study include both normal swine and swine models of human disease, i.e., those with vasculopathy induced by diet (atherogenic high fat/high cholesterol diets), mechanical manipulation (iatrogenic injury from balloon angioplasty or stenting), hormonal manipulation (castration, hormone replacement therapy), hemodynamic alterations (vascular ligation, fistulas) and/or metabolic manipulation (diabetes mellitus). These preclinical animal studies address the problem of identification and assessment of regulatory science issues associated with novel interventional and combination therapeutics and delivery technology including image guidance tools for the treatment of vascular disease and cancer.

Together, these studies will identify the critical scientific and safety issues for current and emerging technologies based on failure modes analysis and clinical outcome. For cardiovascular, neurovascular and peripheral vascular devices, this represents a critical component of review of device applications prior to entry into clinical trials, market access and post-approval study outcomes.

Background/Research Program Description

Coronary, peripheral and neurovascular disease represent the leading cause of death in the United States in both men and women. There are gender differences in both the development of disease and in patient treatment and survival following myocardial infarction. Over one million angioplasty balloons and stents are deployed in the United States each year. Interventional devices, alone or in combination with drugs and biologics, and novel delivery technology to treat vascular disease represents greater than 50% of the IDE and PMA activity in the Center.

Cancer, as a whole, is the second major cause of death. Under the current NCI strategic plan, there is a major push to substantially eliminate suffering and death due to cancer by the year 2015. Currently, CDRH (ODE and OSEL) are working closely with NCI to facilitate investigations of image guided therapies for cancer. These efforts, together with complementary efforts by NIBIB, will accelerate the development of new technologies and progression into clinical trials and marketing.

Relevance to FDA/CDRH Mission and the Public Health Impact

The identification of intervention-specific safety and effectiveness issues as they relate to vascular function, vessel wall injury and tissue remodeling will allow for more consistent and accurate recommendations regarding preclinical study, clinical study and labeling. In addition, the significant increase in the clinical investigation of combined therapies (e.g., estrogen, paclitaxel, rapamycin, etc.) or hybrid interventional devices with novel local delivery technology require a greater understanding by the Agency of these interventions and related regulatory science. The findings of these studies are expected to provide support for the regulatory input to 1) predictive pre-clinical modeling for endovascular grafts, combination drug-device products and novel local delivery technology; 2) identification and evaluation of safety (and effectiveness) of emerging local delivery and combination technology; 3) development of Instructions For Use and labeling for these devices alone or in combination with drug and biologic therapeutics; and, 4) appropriate clinical trial design, study endpoints and expected outcomes, based on the predictive preclinical studies.

Devices that deliver or release therapeutic agents in order to mitigate disease or enhance device performance are being developed and entered into clinical trials. These devices

require greater understanding through preclinical bench and animal models in order to ensure their safety and efficacy and the identification of regulatory science issues prior to entry into clinical trials and broader marketing. In these studies, the safety and effectiveness of delivery technology and the treatments will be evaluated at the tissue-device interface along with the pharmacodynamics and pharmacokinetics. This study will result in formal recommendations for the conduct of predictive preclinical studies and clinical trials as well as regulatory review of these emerging technologies to be used in the management and treatment of vascular disease.

The utilization of thermal ablation techniques is increasing with rapid advances in image guided robotic control and placement of devices. For thermal ablation techniques, adequate treatment may be challenging due to lesion size, configuration, proximity to critical anatomic structures and the limited ability to treat large volumes. Treatment failure occurs at the margins of the ablation or adjacent to vascular structures due to incomplete heating. This body of work will lead to more accurate treatment planning and should improve the safety and effectiveness of thermal ablation.

Three-Year Goals

Animal Models of Vascular Disease, Intervention and Local Drug Delivery

- Define the effects of long term exposure to diet high in fat and cholesterol on endothelial gene expression.
- Define the cause and effect relationship between disturbed flow and gene expression.
- Evaluate the safety, pharmacokinetics (PK, drug distribution) and pharmacodynamics (PD, biological effects) of three drugs (estrogen, paclitaxel, and rapamycin) in a model of coronary angioplasty and stenting, in healthy and atherosclerotic male swine.
- Characterize the carotid and iliac artery as models for neurovascular and peripheral vascular interventions, i.e., long segment stenting in a muscular peripheral artery in both normal and atherosclerotic blood vessels.
- Develop preclinical animal model recommendations for collection of safety and effectiveness data for interventional and combination devices including novel delivery technology, particularly local drug delivery.

Image-guided device therapeutics and targeted drug delivery

- Model the relationship between the thermal ablation lesion and vascular geometry, blood flow, method of energy delivery and ablation parameters using *in vivo*, bench and computational models.
- Determine the electrical and thermal properties as a function of frequency, tissue temperature and tissue (or tumor) type in swine and in humans.

- Develop preclinical animal models for image-guided device therapeutics, including safety and effectiveness of both image-guided device placement and the specific intervention.

Accomplishments

- Established multi-modality image-guided interventions suite: computed tomography, angiography, ultrasound, robotics, magnetic tracking of devices.
- Developed preclinical vascular atlas report for draft level 2 guidance for peripheral vascular interventions.
- Developed web cast course entitled "Interventional Techniques and Preclinical Data Evaluation: Bedside to Bench."
- Developed pharmaco-imaging tool and reported on pharmacokinetics of vascular drug delivery.
- Developed and reported serial tissue sampling techniques in support of preclinical safety and pharmacokinetic evaluations of emerging interventional technology.

Toxicology Laboratory (Division of Biology)

Scope

This is an interconnected program of laboratory research, risk assessment, and standards development activities designed to provide a scientific basis for regulatory decision making in CDRH. Researchers evaluate the potential adverse effects of medical device materials and chemicals, including nano-sized particles, using *in vivo* and *in vitro* experimental models and approaches. Scientists use data to reduce uncertainties in assessing risks to patients exposed to physical and chemical exposures, and ultimately protect their health.

A primary focus of the program in 2006-07 is evaluating bioeffects of nanoparticles. The unique properties of nanoparticles (very small size, large surface area, increased biological activity) drive the current explosion in nanotechnology innovation in health care delivery. FDA-regulated products expected to utilize nanotechnology include: implants and prosthetics, sensors for disease diagnosis, and drug delivery and personal care products. In contrast, these same properties may impart negative or undesirable effects on biological systems. Attempts to understand the potential adverse effects of nanoparticles are limited, and very few resources have been committed to research needed to address and understand risks to patients.

Background

The 1983 merger of the Bureau of Radiological Health and the Bureau of Medical Devices resulted in the Center for Devices and Radiological Health. This merger presented the new Center with a unique challenge for its research programs: to bridge the discontinuity that existed between classical chemical toxicology research and the potential adverse health effects posed by exposure to materials or compounds associated with medical devices. The primary emphasis of this program that has evolved since the merger is the development of research approaches and methodologies for toxicological risk assessment for compounds and materials associated with medical devices, including nanoparticles.

One primary focus of the program in 2005-06 is evaluating bioeffects of nanoparticles. The unique properties of nanoparticles (very small size, large surface area, increased biological activity) drive the current explosion in nanotechnology innovation in health care delivery. In FY 2005, the federal government spent over $1 billion on nanotechnology R&D. FDA-regulated products expected to utilize nanotechnology include: implants and prosthetics, sensors for disease diagnosis, and drug delivery and personal care products. In contrast, these same properties may impart negative or undesirable effects on biological systems. Attempts to understand the potential adverse effects of nanoparticles are limited, and very few resources have been committed to research needed to address and understand risks to patients.

Research Program Description

The Laboratory of Toxicology research program:

- Conducts a wide variety of projects that generally focus on the evaluation of biological effects of chemicals released, intentionally or unintentionally, from medical device materials in order to increase the understanding of potential adverse effects of these substances on biological systems with a goal to improve product safety.
- Develops or refines test methods that improve preclinical testing of device materials, including improved animal models and biomarker discovery.
- Develops or refines analytical methods for measuring the amount of chemicals released intentionally or unintentionally from medical devices and device materials.

Studies in this laboratory currently fall into several major subcategories:

Biological effects of nano-sized materials

- The broad research objectives are to 1) understand the toxicokinetics of nanoparticles, i.e., the uptake and tissue/cellular distribution of nanoparticles, 2) understand the toxicodynamics of nanoparticles, i.e., the toxic, immunotoxic, inflammatory, and proliferative effects resulting from the cellular interactions with nanoparticles, and 3) identify and adapt relevant methodologies in order to develop a panel of standard tests for the FDA's preclinical evaluation of nanotechnology-based products, or formed as wear debris from implanted devices. Nanoparticles are any material that has at least one dimension below 100 nm; collaborations are ongoing with CDER, CVM, National Cancer Institute – Nanotechnology Characterization Laboratory, and NIST).

- Study the transport of nanoparticles across the placenta and resulting effects on the developing fetus (collaboration with George Washington University).

The nanoparticle bioeffects project received a highly favorable peer review in 2005 from FDA's Office of Science and Health Coordination.

Toxicity of compounds released from medical device materials

- Investigate adverse effects of compounds (e.g., metals, DEHP, ethylene oxide, bisphenol A, endocrine disruptors) released from medical device materials using small and large animal models.
- Identify and characterize chemical constituents released from medical device materials.
- Develop more sensitive biomarkers to detect early cell and tissue damage caused by compounds released from devices.

Relevance to FDA Mission and Public Health Impact

The experimental studies in this laboratory generate independent data for use in assessing toxicological risks and for developing standards and guidance documents, thus providing a firm foundation for OSEL and CDRH to remain at the forefront in medical device toxicology.

FDA Critical Path: The goals of this laboratory are responsive to the Critical Path initiative that calls for a "new product development toolkit" containing powerful scientific and technical methods such as more predictive and clinically relevant animal models, and the development of more sensitive and clinically relevant biomarkers of safety and effectiveness.

Regulatory Impact: Pre-market – Laboratory data serves as a scientific basis for development of Standards, such as:

- ASTM standards for testing biological responses to particles both *in vivo* (F1904-98) and *in vitro* (F1903-98)
- ASTM International Committee on Nanotechnology (E56)
- ISO Standard 10993- Part 17 for establishing tolerable intake values of medical device residues and ISO Standard 10993 - Part 7 for the measuring ethylene oxide sterilization residuals.
- Post-market – Serves as basis for risk management decision-making in the Center (e.g., FDA Public Health Notification for DEHP in medical plastics).

Public Health Impact: The recent explosion in nanotechnology research and development for health care delivery will result in an increasing number of patients exposed to nanoparticles. Developing *in vivo* and *in vitro* experimental models, discovering more sensitive biomarkers, and quantitating the release of chemicals from medical products will help reduce uncertainties in the preclinical safety assessments of medical devices and other FDA-regulated products.

Three-Year Goals

- Develop and establish test methods and models for evaluation of potential adverse effects of medical devices and device materials, including nano-sized materials.
- Elucidate new, clinically relevant, and sensitive biomarkers to predict adverse effects for use in preclinical phases of product development.
- Develop and establish analytical test methods to identify and quantitate the chemicals released either intentionally or unintentionally from medical device materials.
- Characterize the potential adverse effects using preclinical laboratory models and utilizing the data to predict the likelihood of adverse effects in humans.

- Initiate and/or maintain collaborations with other FDA Centers, other Federal government agencies (e.g., NIH-NCI, EPA, NIST), and academic centers.

Accomplishments

Analytical Chemistry

Two studies were conducted under the laboratory goal of developing analytical test methods to identify and quantitate chemicals or residues released either intentionally or unintentionally from medical device materials.

- Because ethylene glycol is a toxic by-product of ethylene oxide hydrolysis, levels of ethylene glycol and glycolic acid, another metabolite, were quantified in pig serum following intravenous exposure to ethylene glycol. The results of this effort can be used to directly support the next revision of the ISO 10993-7 standard.
- The effect of different extraction solutions and conditions in the extraction and analysis of ethylene oxide released from medical devices and medical device materials is currently being investigated, in direct support of ISO 10993 part 7.

Nanotoxicology

A study of nanoparticles was conducted under the Laboratory goal to develop test methods to evaluate adverse effects of medical devices and device materials, including nanoparticles.

- A study was undertaken to determine the effects of titanium dioxide nanoparticles. Variables evaluated were route of exposure (subcutaneous and intravenous), dose, and time effects were examined. Tissue distribution of the nanoparticles was evaluated using microscopy, energy dispersement mapping, and electron microscopy. Immunological endpoints and bone marrow proliferation were examined in vivo and in vitro. Results indicated after administration, particles distributed to liver, spleen, lymph node and lung. Evidence so far suggests that once in these tissues, the particles are cleared only slowly, although there is some variation depending on the route of administration. Further, the particles appear to be acting like an immunological adjuvant resulting in increased responses of the immune system. Portions of this research were presented at the 46th Annual Meeting of the Society of Toxicology, March 2007.

Biomolecular Mechanisms Laboratory (Division of Biology)

Scope

New genomic and genetic technologies are expected to impact CDRH in major ways. The Center is beginning to receive submissions of genomic and genetic diagnostic microarray devices and expects more--some in co-development with drug or biological therapeutics. In addition, these technologies will be used to evaluate the safety of products such as implants and materials (toxico-genomics). However, considerable technical uncertainties impede the acceptance of these products and data. The Genomics Laboratory is providing support to the Center via 1) prioritization of the technical issues affecting microarray data that impact product review, and 2) application of the new technologies to both new and long-standing problems, including medical device adverse events, identification of medical device pathogen contaminants, and safety evaluation of products. In addition, the Cell Biology Laboratory is investigating immunotoxicity related to particular patient susceptibility, in regards to biomaterials and devices that contact patient blood

Background

New genetic and genomic technologies provide opportunities and challenges for CDRH. The opportunities include new products to improve human health and new methods for the evaluation of medical devices. Challenges arise when the new technologies must be judged for appropriate practical application in new products. Keeping up with new technologies as they evolve is an ongoing challenge. The OSEL Genomics Laboratory provides a resource to the Center via laboratory projects that utilize and evaluate the new technologies (e.g., microarrays). We maintain expertise as a test laboratory for new instruments and reagents. Scientists from the regulatory review and statistical branches are involved in our projects, and we participate in their discussion groups. These activities aid the conjunction of Genomics Laboratory activities and regulatory need. Additionally, the OSEL Cell Biology Laboratory is providing guidance and standards on immunotoxic reactions to implanted biomaterials and devices that contact human blood. Of particular concern is complement activation and nitric oxide generations. The conditions and amounts whereby biomaterial contaminants such as endotoxin present concentration problems in hyaluronic acid or alignate device configurations are being determined.

Research Program Description

There are different types of microarray devices coming to CDRH for review, including genetic and genomic testing devices. Both endpoints can be detected by microarrays, but the basic molecules, sample preparation and analytical/ bioinformatic issues are quite diverse. Although microarrays can accomplish multiple high throughput reactions, substantial problems related to the reproducibility and value of microarray data have been and are still being reported. Presently the laboratory is covering technical issues related to genetic testing (DNA-based) and gene-expression (RNA based) microarrays. We are the lead laboratory in a multi-center OSHC genomics project which addresses and prioritizes the variables affecting genomic microarray data. Within this project we are addressing the lack of an RNA standard for genomic microarrays as a proposed ERCC consortium

(government/industry) test site for RNA controls. Another gene-expression project employs genomic profiling to understand a medical device adverse event. A third project uses genetic microarray technology to rapidly identify pathogens that contaminate medical devices. A fourth project is proposed to use the new genomic technology in the safety evaluation of medical devices. Another project of the Cell Biology Laboratory is determining inflammation-generating effect levels for impurities contained within tissue filler products, ophthalmic-injection projects, and products used in treating osteoarthritic knees.

Potentials of BEAMing technique for early cancer detection and relapse

Early cancer detection and personalized cancer care using molecular DNA biomarkers are highly demanding. We have been validating/optimizing a DNA mutation and magnetic beads/emulsion PCR based technique (BEAMing) at the Genetics and Genomics Laboratory at FDA.

BEAMing technique has a potential of detecting very rare mutant species of genomic DNA from a complex background of wild type tumor DNA shed into the blood. In collaboration with Johns Hopkins University Kimmel Cancer Center, we are looking at the possibility of using this technique using as general cancer detection as well as specific cancers with no early detection methods available such as pancreatic cancer in a relatively early stages of the development.

Relevance to FDA/CDRH Mission and Public Health Impact

Data obtained in several of the projects should facilitate the development of appropriate standards for microarrays, in particular the OSHC project, with the major focus on the factors leading to the highest levels of variability in microarray data. All of the projects are cross-Center and/or cross-Office projects. They provide a basis for continued inter-Center/external collaboration on technical issues, as the technology evolves. The knowledge and experience gained will enable OSEL scientists to 1) participate effectively in the CDRH regulatory review of pre-market device applications, 2) critically evaluate data obtained with diagnostic devices based on genomic and genetic technology, and 3) contribute to writing standards and guidance documents. The latex allergy genomics project will also demonstrate ways in which new genetic and genomic approaches can enhance public health. The pathogen project is designed to prepare us for possible future projects involving the rapid detection of microorganisms and human host responses associated with biodefense.

The projects in this program support the CDRH Strategic Plan, especially the Total Product Life Cycle and Magnet for Excellence. Additionally, collaborations within FDA, with other government organizations, academia and industry have provided ample opportunity for significant leveraging of resources and expertise. Also, individual susceptibility to inflammatory reactions is an important concern as an adverse reaction to

implanted devices. Defining the conditions and impurity levels responsible for these reactions in individuals is a pressing regulatory concern.

Three-Year Goals

- Develop data for standards development
- Prioritize variables contributing to genomic microarray data (OSHC)
- Develop data on medical device adverse events (Latex allergy)
- Utilize genomic and genetic technologies to address device issues
- Use gene expression profiling as a predictor of latex allergy development
- Develop protein microarray technology (Proteomics): scaffolds and stents
- Develop microarray screening method for pathogens contaminating devices/foods
- Develop a new system for safety evaluation using genomic technologies
- Determine threshold activation levels for bacterial impurities, degradation products, and pre-existing inflammatory disease conditions for adverse immune reactions with implanted biomaterials.

Accomplishments

- Established platelet functional assays; examined the effects of taxol and rapamycin on platelet function.
- Set up several assays to monitor endothelial function; studied the effects of taxol, rapamycin and VEGF upon endothelial function.
- ASTM Standard Test Method accepted: F 2567, "Practice for Testing for Classical Pathway Complement Activation in Serum by Solid Materials."
- Achieved assay capability for measuring extremely low levels of endotoxin.
- Obtained a series of low molecular weights of hyaluronic acid, with the lowest (10,000 Daltons) assayed for modulating effects on inflammatory reactions.
- "No observable effect levels" (NOELs) and "Lowest observable effect levels" were assayed for endotoxin in alginate microspheres.
- Assay conditions were determined for observing effects on islet cell function by chemically-generated or co-culture macrophage-produced nitric oxide.
- Microcapsule generation techniques were established for preparing alginate capsules of desired sizes incorporating porcine or murine islets.
- We have recently established BEAMing technique in the lab and initial results indicate that it is highly reproducible with numerous potential uses for cancer detection.
- Developed a number of functional assays to assess the effect of anti-proliferative drugs upon thrombus formation, endothelial cells and arteries. Research is relevant to device reviews on drug-eluting stents.
- Defined the immunological properties of chondrocytes and cultured them under selected conditions with growth factors to maintain their differentiated state.

- Research on chondrocytes is critical to pressing regulatory/review issues for cartilage replacement.

Electrical Engineering Laboratory (Division of Electronics and Software Engineering)

Scope

The scope of this laboratory's activities is the support of CDRH pre-market and post-market activities through the establishment of relevant in house expertise and the identification, qualification, quantification and communication of conformity assessment techniques and criteria which the Center can use to fulfill its mission.

Background

Electrical engineering is an enabling technology for many, if not most, classes of medical devices. Devices that incorporate this technology are inherently complex and require that engineers must be able to skillfully peel back many layers of abstraction from the underlying mathematical and physical models that govern device operation, to their hardware and software realizations, and down to the physical characteristics of component parts.

A large body of knowledge has developed within the electronics, embedded software, and systems engineering communities to assure successful application of these technologies. The mission of the DESE Electrical Engineering Laboratory is to apply this body of knowledge to the regulation of electronic medical devices and electronic products that emit radiation.

The breadth of the engineering disciplines needed poses a significant challenge. The body of knowledge is segmented into numerous areas of specialization, power engineering, electromagnetic and static immunity, microminiaturization and signal processing. Within industry, large manufacturers typically have sizable organizational components to address those engineering segments (specialties) having most relevance to their needs. Small manufacturers typically have specialists in just a few key areas and rely on consultants or other external resources to augment their in-house capabilities.

We maintain a suite of special-purpose, computer-aided engineering tools and laboratory facilities having broad applicability to medical device electronics and embedded software and we rely on external sources for specialized capabilities that are needed on an occasional basis.

Research Program Description and Relevance to FDA/CDRH Mission and Public Health Impact

The Electrical Engineering Laboratory embraces three key aspects of medical electronics having immediate applicability to the mission of the Center and relevance to the public health.

Electronic Instrumentation. We provide custom instrumentation, i.e., measurement and control systems, for use by internal FDA customers and regulatory partners. Our capabilities include analog and digital circuit design, data acquisition and display, signal processing, embedded microprocessor and PC-based systems, and software-based virtual instruments. This work provides two benefits to the Center. First, we provide an in-house R&D capability which is easy to access and attuned to the unique needs of our stakeholders. Second, the engineers in this laboratory gain insight into the problems (and solutions) confronting medical device manufacturers as well as maintaining institutional knowledge of the latest developments in electronic technologies.

Electrical Safety. This activity focuses on the design of medical devices to assure that the risk of harm due to electrical shock and electrical fire is adequately mitigated in the design. The laboratory also addresses other hazards arising from the use of electrical and electronic technology in medical products, including thermal burns and fires, electromagnetic interference and coordinating with other agencies innovation in wireless communications related to medical devices.

Power Electronics. This activity focuses on an aspect of electronic design that poses continuing challenges to designers of medical devices. It deals with components, circuits, and analytical techniques for controlling high voltages and/or currents as well as challenges derived from the use of cutting edge battery and fuel cell technology. Historically, power electronics has been a factor in many medical device recalls. Our strategy is to stay abreast of the evolving body of knowledge in the power electronics area so that we are prepared to probe for design weaknesses in the pre-market review, thus heading off potential problems. We also maintain a suite of analytical tools and measuring equipment that can be brought to bear on emergent problems.

Three-Year Goals

The laboratory is focused on both maintaining its current knowledge base and in increasing it substantially to incorporate expertise in evaluating nano-technology, micro-electronic systems, oximetry motion artifact removal, operating room of the future and new battery technologies.

Accomplishments

***Post-market regulatory support*.** DESE engineers provided just-in-time analytical support in a substantial number of recalls, adverse event investigations, and enforcement actions, helping to clarify the root cause of reported problems and shaping the regulatory response to each.

- We have experienced major growth in our knowledge base of battery technology and testing methods as we learn to fully exploit the new industrial battery testing equipment obtained from the Arbin Instrument Co. One DESE staff member received factory training in the use of this equipment in April 2006 and since then has been working with it as time permits.
- Staff has performed considerable research on different battery technologies in preparation for presenting a short course on battery technology.

Software Laboratory (Division of Electronics and Software Engineering)

Scope

The scope of this laboratory's activities is to support CDRH pre-market and post-market software evaluation activities by establishing relevant in-house expertise and identifying, qualifying, quantifying, and communicating conformity assessment techniques and criteria which the Center can use to fulfill its mission.

Background

Software is one of the most ubiquitous enabling technologies for many, if not most, classes of medical devices. Devices that incorporate this technology are inherently extremely complex and require that engineers must be able to skillfully peel back many layers of abstraction from the underlying mathematical, behavioral and physical models that govern device operation, to their hardware and software realizations, and down to the physical characteristics of component parts.

A large body of knowledge has developed within the software engineering community, embedded software industry, and systems engineering communities to assure successful application of these technologies. The mission of the DESE Software Laboratory is to apply this body of knowledge to the regulation of electronic medical devices and electronic products that emit radiation.

The breadth of the engineering disciplines needed poses a significant challenge. The body of knowledge is segmented into numerous areas of specialization, embedded systems, formal methods, advanced verification techniques and software quality assurance. Within industry, large manufacturers typically have sizable organizational components to address

those engineering segments (specialties) having most relevance to their needs. Small manufacturers typically have specialists in just a few key areas and rely on consultants or other external resources to augment their in-house capabilities.

As regulators, we have followed a similar approach, building depth in those key areas that repeatedly surface as regulatory concerns and augmenting our in-house capability by leveraging additional "just-in-time" knowledge from our colleagues in academia, other government laboratories (e.g., NSA, NIST, ARO, TATRC, JPL), and the standards community.

Our strategy for maintaining the required depth is to recruit senior engineers from industry, each having broad experience in a number of engineering specialties. While each staff member brings a unique mix of engineering skills and experience, we strive to maintain enough overlap to maintain critical mass in the key areas. We also place strong emphasis on staff development. It is notable that two of our experienced staff members have acquired graduate degrees in recent years, and our research activities are conducted by doctorate-level staff, postgraduate students, and external faculty hosted during sabbaticals, thus, significantly enhancing our capability in the emerging areas of technical risk management and software engineering.

Another essential element of the program is to identify and develop in-house specialized analytical tools and laboratory facilities. We maintain a suite of special-purpose, computer-aided verification tools and laboratory facilities having broad applicability to medical device software and embedded software, and we continue to leverage external sources for specialized capabilities that are needed on an occasional basis.

Research Program Description and Relevance to FDA/CDRH Mission and Public Health Impact

The Software Laboratory embraces several key aspects of medical software having immediate applicability to the mission of the Center and relevance to the public health.

- Formal methods – mathematically based requirements and design
- Safety – safety architectures and coding patterns
- Security – security architectures and coding patterns
- Certification – provable design and performance criteria
- Forensic analysis – reconstruction & analysis of failures
- Enabling technologies for future medical devices
- Implantable devices, networked biosensors, telesurgery, robotic surgery
- Foundations for integration of medical device systems/models
- Component-based foundations for accelerated design and verifiable system integration

- System of systems (including models, medical devices, care-givers, patients)
- Distributed control & sensing of networked medical device systems
- Robust, verifiable, fault-tolerant control of uncertain, multi-modal systems
- Patient modeling & simulation
- Large scale, high-fidelity organ and patient models for design and testing
- Embedded, real-time, networked system infrastructures for medical device software and systems
- Architecture, platform, middleware, resource management, QoS (Quality of Service), PnP (Plug-and-Play) of Medical Device Software and Systems
- High-Confidence Medical Device Software Development & Assurance
- Care-giver requirements solicitation and capture, design and implementation V&V (verification and validation)
- Heterogeneity in environment, architecture, platform in medical devices
- Medical practice-driven models and requirements
- User-centered design, risk understanding, and use/misuse modeling in medical practice
- Certification of medical device software and systems
- Quantifiable incremental certification of Medical Device Software and Systems, role of design tools
- COTS, non-deterministic and self-adaptive medical device systems

Three-Year Goals

The laboratory is focused on both maintaining its current knowledge base and increasing it substantially to incorporate expertise in evaluating a nascent house capability to perform advanced static analysis routinely as part of pre-market and post-market assessment. This will be the basis for a forensic analysis tool set which will grow throughout 2006 and 2007.

Continued efforts will be made to incorporate and encourage the use of formal methods based methodologies in the design and verification of medical device software. Open-source models depicting the use of these methodologies will be made available to vendors and academia.

In keeping with current trends in distributed computing and integrated clinician environments, an object-oriented architecture will be developed to leverage a Plug-and-Play operating environment.

Accomplishments

Historically, FDA's oversight of software development in medical products has concentrated on the software life cycle processes used by manufacturers to develop and maintain the software. There is currently no process that will consistently yield error-free

code. To address this problem, a model-based approach to medical device evaluation was investigated. A case study involving a generic infusion pump usage model was carried out.

- Usage model state data was collected with the help of a sole-source contractor, in consultation with domain experts.
- The usage model state transition probabilities were defined and corroborated.
- The model was implemented with the help of formal methods based tool suites, and exhaustively verified for anomalies and inconsistencies.
- Test scripts were derived for the generic pump model, to be used as a basis for manufacturer software validation.

In order to correctly establish the safety and effectiveness of medical device software, a safety-assurance framework has been defined.

- The Adelard tool for creating formal notations of safety cases was successfully installed, allowing for a systematic consistent format for building of a safety case.
- Example case studies involving the safety assurance framework were carried out.
- A problem space (ontology) for a target guidance document was established.

Systems Engineering Laboratory **(Division of Electronics and Software Engineering)**

Scope

This laboratory applies a systems engineering perspective to medical device regulatory issues.

Background

With the advent of systems of devices, closed-loop devices, and intelligent devices, the fabric of regulation and FDA's historic enforcement discretion policy needs to be continually revisited to determine its ongoing ability to get as many safe systems to market and to allow them to remain safe while there.

Research Program Description

The laboratory is currently focusing on four distinct areas:

Quality Systems and Risk Management. This program aims to improve industry practices in the area of quality management and risk management, principally those practices which are applicable to electronics and software. The conceptual framework that we have been developing to accomplish this is finding its way into relevant consensus standards, industry

guidance, professional engineering publications, and education and training for both FDA and personnel and the regulated industry.

Advanced Medical Systems. This program is directed at developing methods and tools that can be used by device manufacturers, users, and regulators to objectively assess the monitoring and diagnostic performance of intelligent medical devices. Intelligent medical devices operate by acquiring and analyzing physiological waveforms to monitor and diagnose clinical conditions. The program seeks to develop methods to assess specific aspects of the safety and performance of these devices in the health care environment of the future, such as detection ability in the presence of physiological and environmental noise and artifact, and to understand and quantify the effects of these conditions. Our research is intended to stimulate the development of more effective diagnostic and monitoring products, thus improving the public health.

Cybersecurity in medical devices. This program is directed toward assessing the risks and providing leadership in the emerging field of malware threats to medical devices currently fielded in use in health care facilities.

Medical device plug-and-play systems. This program is directed toward facilitating interoperation between medical device systems by providing an object-oriented architecture for plug-and-play systems and software. The plug-and-play system acts as the focal point for multi-device procedures that allow the clinician to focus on the essentials of the procedure, while virtualizing device characteristics. The project scope includes building an executable architecture of the supervisory node, with simulated pluggable devices, for the purpose of demonstrating a workable technology that does not require much increase in the intelligence of existing devices.

Relevance to FDA Mission and the Public Health Impact

The expertise developed through this laboratory is being used to educate reviewers across the Center and provide a basis for the evaluation and drafting of new classification regulations, guidance documents and enforcement policy.

Three-Year Goals

The laboratory will sustain its commitment to Center-wide reviewer education in the use of the key standard ISO 14971 as part of pre-market review, while contributing to the measured development of assessment methods pertaining to ORA's inclusion of the risk management processes in their inspections. The development of advance operating room environments will receive further input in order to calibrate FDA's view of unfinished devices (components) as part of an integrated assembly of systems. The industry adherence to the recently published cybersecurity guidance will be monitored to measure its utility in helping manufacturers of device systems maintain those systems in the marketplace.

Finally, in keeping with current trends in distributed computing and integrated clinician environments, an object-oriented architecture will be developed to leverage a plug-and-play operating environment.

Accomplishments

Cybersecurity. DESE staff took the lead in developing a guidance document addressing cybersecurity of networked medical devices.

- We developed a creative regulatory approach that substantially reduced conflict among stakeholders. We developed a guidance document to clarify the legal obligations of medical device manufacturers. The guidance was published early in 2005, and had an immediate effect in the marketplace, helping to build a consensus among the stakeholders for addressing the problem in a constructive fashion. As a result, many medical device manufacturers and health care organizations are better prepared today to deal with emergent cybersecurity threats, and the stakeholders are actively engaged in a cooperative effort to develop long-term cybersecurity solutions. A recent article in an information technology trade publication cited high praise for OSEL/DESE's role in addressing the cybersecurity problem.

Risk Management. DESE engineers are helping to make new medical devices safer by teaching manufacturers how to manage risk in the design of new medical products.

- DESE engineers played a key role in developing the second draft of ISO 14971, ***Risk management for medical devices***, published in 2005. We have helped inform industry by serving as faculty members in courses on risk management offered by AAMI and ASQ, and by giving invited presentations on the topic at other industry meetings. DESE staff wrote an award-winning paper on software risk management in 2003, which became the impetus for an AAMI Technical Information Report on the same topic published in 2005. This work is changing the way manufacturers address product safety and is also leading to improvements in the way risk information is presented in pre-market submissions.

- DESE engineers also contributed to revision of the IEC 60601 family of standards, the seminal safety standard for electrotechnical medical devices used in clinical settings. The newly published version of the parent standard, IEC 60601-1, incorporates major changes to more closely align the standard to the risk management principles embodied in ISO 14971.

Materials Performance Laboratory (Division of Chemistry and Materials Science)

Scope

Scientists in the Materials Performance Laboratory investigate materials used in devices in which the physico/chemical properties of a material impact its performance and the long-term behavior of these properties affect the device's safety or effectiveness. For example, the long-term performance of implanted electronic devices, such as cochlear implants or pacemakers, depends on the continued hermiticity of the devices' casings. Intraocular lenses used in cataract and other surgeries need to maintain their optical properties over time. Finally, mechanical performance and degradation of hydrogel materials, such as hyaluronic acid, may affect the safety and effectiveness of adhesion barriers and other devices.

Background

The use of new materials and processing technologies is a challenge to the regulation of new medical devices. The knowledge gap between the Center's understandings of existing materials used in devices evolving technologies will tend to increase the time required for the review of these submissions, as our staff "comes up to speed" in these areas. Through directed research activities, it is the goal of this laboratory to develop such expertise and insights into the behavior of new materials used in devices and the effects of manufacturing on their safety and efficacy.

Materials serve two primary purposes. They can serve as the active component of a device, providing its mode of action, or they can act as a physical barrier to the environment of the human body, such that active electronic devices perform with maximum safety and efficacy. There are common features that involve both classes of materials. These include materials formulation and sensitivity to manufacturing parameters. Devices whose materials provide their primary function will also have mechanical, transport, optical and surface properties as critical parameters in their performance. Devices where materials serve a secondary role of protection, such as active implants, have barrier, and electrical properties as additional concerns. All materials have the issue of biostability, their resistance to the effects of the foreign body response and biocompatibility, the impact of the materials on the local environment of the host.

The range of experimental techniques available within this laboratory allows for in depth analysis of device performance and safety. For materials where the role is structural in nature including implants for orthopedic procedures, stents for maintaining patent vasculature, adhesives, bulking agents and occlusive materials (sealants), physical properties such as mechanical strength, elasticity, rheology and interfacial behavior are critical parameters can be characterized. In the realm of ophthalmics, material's optical and oxygen transport properties play the most import roles in their performance and safety.

Surface properties play crucial role in surgical barrier materials, in tissue adhesives and in the joining processes used in the manufacture of most medical devices.

As active implants increase in their complexity and decrease in their size, the challenges for the physical and electrical isolation of their active logical components requires manufacturers to utilize novel encapsulation technologies. Many of these technologies are translated from the non-medical manufacturing arena to device manufacture and as such may not be directly applicable, or have hidden long term consequences. As sponsors seek to incorporate newer polymers or processing techniques, we must be mindful of both the biocompatibility of these materials and the impact of their degradation products on the human physiology as well as the biostability of these materials for their ensured long term performance. Finally, traditional encapsulation technologies rely on physical enclosures to isolate the active electronic components from the biological environment. Here, testing for hermiticity can be readily achieved using well established standards and procedures. With the use of polymer coatings for encapsulation, new techniques must be developed to validate the long term performance of these barriers to establish the device's safety.

The range of technical expertise required to fully grasp these diverse topics requires active scrutiny of the current technical literature, participation in the relevant technical societies and active laboratory research in these areas. To that end, the members of the Materials Performance Laboratory are carrying out a number of research projects.

Research Program Description

The current research projects in the Laboratory for Materials Performance examine how materials properties and processing impact on materials performance in device applications. The laboratory has the capabilities for fabricating surrogate materials and device mimics in order to be able to evaluate the mechanisms of action and behavior of these systems in *in vitro* models and, in collaboration with the Division of Biology, *in vivo* models.

In the area of ophthalmic devices, we are studying the impact of new materials on devices performance. As cataract surgeries use smaller incisions, the industry has moved to flexible intraocular lenses (IOLs). One potential problem with these materials is the observation of "glistenings," which are vacuoles forming in the optical portion of the lens. We are trying to understand the origins of these defects, their potential impact on the patient quality of life and provide guidance to the industry in ways to predict their formation. In extraocular devices, with the advent of new classes of contact lens polymers, there may be a need to re-classify these materials as to their compatibility with existing aftermarket cleaning and lens care solutions. Finally, as advances are made toward retinal stimulators, the use of polymer coatings as hermiticity barriers will be addressed as part of our hermiticity program.

Long-term stability of medical plastics exposed to the environment and in operation is an area of continuing concern. We continue to examine methods for evaluating the shelf life and effectiveness of barrier materials such as condoms and gloves. More recently we have been involved in questions regarding the effects of cleaning and disinfection on the housings of non-critical medical devices (pumps, medical electronics, etc.). The potential for environmental stress cracking and internal contamination in these materials can lead to device failure and a compromise of the patient's safety.

A major new thrust in this laboratory is the issue of hermiticity in active medical devices. These devices range from implantable cardio defibrillators to implantable insulin pumps to retinal implants. In all cases, active electronics must be able to operate in the 100% humidity environment of the body. Traditional enclosures have a history of hermiticity failure and existing testing methods for hermiticity are not necessarily relevant to the operating environment of the body. In addition to the "can" enclosure, where gas leak testing is the standard for ensuring hermiticity, new proposed methods using conformal polymer coatings as a moisture/vapor barrier raise challenges to testing the long term performance/stability of electronics protected in this manner.

Finally, hydrogel materials, polymers which readily imbibe large amounts of water yet retain their form have a wide range of applications in devices. These include sealants, biopsy markers, adhesives, tissue augmentation treatments and adhesion barriers. We have a large effort aimed at understanding the interfacial behavior, mechanical properties and breakdown behavior of hydrogel polymers. We are also studying the impact of cross link chemistry and density on the rate of polymer degradation and how that relates to its clearance from a variety of tissues.

Relevance to FDA's and CDRH's Mission, Program, and the Public Health Impact

The FDA/CDRH mission is to assure the safety and effectiveness of medical devices. This laboratory program helps to identify potential risks associated with the application of new materials and processing technologies used to fabricate medical devices. The test methods and models developed are used to characterize device safety, which in turn leads to recommendations for regulatory guidance to the industry, as well as input for consensus standards the Center can adopt in its regulatory review process. Presentations and publications in the peer-reviewed literature both publicize the research findings and enhance the reputation of the Center's laboratory efforts. Furthermore, project products provide important and practical input for appraising post-market performance and identifying post approval problems.

Three-Year Goals

- To understand the key physical and chemical properties of hyaluronic acid and other hydrogels that may impact the safety and effectiveness of devices using these materials; to develop test methods, as needed, for measuring such properties.
- To develop a general understanding of the physical phenomena underlying the formation of vacuoles in intraocular lenses; to develop a laboratory test method for determining the propensity of IOLs to form vacuoles.
- To understand the effectiveness and stability of polymeric coatings, such as parylene, as moisture barriers either alone or in combination with other chemically vapor deposited materials to assure the long-term reliability of Active Implantable Medical Devices (AIMDs); to develop test methods for assessing moisture "leak rates" through conformal, polymeric materials used on AIMDs.

Accomplishments

- Identified the importance of elasticity as an indicator of underlying crosslinking. Whereas viscometry is often used as a quality control specification, we have found that some gels or viscoelastic solutions are better characterized by a combination of viscosity and elasticity. In particular, elasticity of FeHy gels is more sensitive to underlying crosslinking than viscosity.

- Demonstrated the sensitivity of viscosity (and, therefore, underlying structure) of FeHy to exposure to shearing conditions. Therefore, (a) shear histories must be provided when viscosity is used to characterize materials; (b) manufacturers should assess the shears that materials will be exposed to and account for these shears when providing viscosity measurements of their materials.

- Demonstrated the high sensitivity of FeHy product (as indicated by viscosity and product homogeneity) to small perturbations of reaction condition (pH).

- Developed laboratory capability to observe vacuoles in IOLs on a controlled temperatures stage via the following light microscopy systems: Zeiss Axiovert 200; Olympus IX70.

- Developed framework for a laboratory protocol to be used to compare the propensity for vacuole formation of new IOLs to existing IOLS for which there is clinical experience.

Experimental Pathology Laboratory (Division of Chemistry and Materials Science)

Scope

The challenges that overlie the development, manufacturing and assessment of safety and performance of a replacement heart valve (i.e., mechanical, bioprosthetic, polymeric, biological and tissue engineered) centers about the complexity of native heart valve biology, valvular disease and the remodeling of valvular tissue and biomaterials in response to a dynamic hemodynamic environment. The identification of critical design features, fabrication processes and the *in vivo* evaluation of valve safety, performance, and valve-related pathology are the principle objectives of this laboratory.

Background

This laboratory has been primarily focused on the *in vivo* effects of pre-implantation processing of tissue-derived biomaterials and the identification potential clinical failure

modes associated with replacement heart valves. The majority of these investigations have involved clinical explanted valves and preclinical *in vivo* studies conducted in juvenile sheep. The following preclinical *in vivo* models are routinely used to assess replacement heart valve safety and performance: mitral valve replacement using mechanical and bioprosthetic valves (juvenile sheep), right ventricular outflow tract reconstructions using decellularized aortic valve allografts (juvenile sheep), non-orthotopic implantation of stentless bioprosthetic valves and cyropreserved and/or decellularized allograft aortic valves (juvenile sheep) and recently the development of a pulmonary valve monocusp and mitral valve bi-flap surgical model (juvenile sheep) to assess tissue engineered scaffolds provided as sheet materials.

Research Program Description

A well characterized and consistently manufactured replacement heart valve product is imperative for the interpretation of clinical trial findings. Currently there is very limited scientific information that addresses the issue of cell/scaffold-based tissue engineered heart valve (TE HV) product characterization due to the fact that TE HV development is primarily in the discovery phase of research. In anticipation of the emergence of an investigational TE HV as a potential candidate for Phase 1 clinical trials, the need to encourage basic research intended to identify ways to ensure consistent manufacturing of an investigational TE HV is rapidly approaching. It is also expected that during the translational research phase of TE HV product development it will be possible to identify specific research findings and develop test methods that will contribute to product quality control and facilitate the establishment of product release specifications. Conducting this translational research effort provides an approach for evaluating TE HV preclinical safety and performance that is consistent with regulatory expectations.

Relevance to FDA's and CDRH's Mission, Program, and the Public Health Impact

The Laboratory for Experimental Pathology program is aligned with the overall FDA identification of research areas that are expected to speed the development and approval of medical products as recently published in the FDA Critical Path Opportunities List (March 2006) in the following areas:

1. Cardiovascular biomarkers
2. Animal disease and tissue injury models
3. Moving manufacturing into the 21st century: tissue engineering-manufacturing, scale up and quality management

The investigational contributions made by this laboratory program are expected to identify pre-market and post-market *in vivo* failure modes associated with the application of new heart valve design features, biomaterials and tissue processing technologies used to fabricate the next generation of replacement heart valves. Experimental pathology

protocols and replacement heart valve explant pathology findings are anticipated to 1) provide scientific credibility, as the result of publication of investigational findings in the peer reviewed literature, in support of the identification of regulatory deficiencies in 510(k), IDE/PMA and IND/BLA submissions; and 2) support the periodic revision of existing regulatory replacement heart valve guidance to industry and international consensus standards recognized by the Center as required by new replacement heart valve designs and technologies.

Three-Year Goals

The regulation of cardiovascular tissue products having both biological and device components is an emerging area of product development which is maturing rapidly requiring the ad hoc review of IDE/IND regulatory submissions and the provision of regulatory guidances for bioprosthetic, biological and tissue engineered heart valves. These regulatory responsibilities require the development of evaluative tools (*in vitro* and *in vivo*) capable of assessing the effects of cardiovascular tissue processing and bioreactor preconditioning on biological and tissue engineered heart valve biology and pathology. The objectives of this research project are to identify suitable evaluative tools to 1) characterize the morphologic effects of tissue processing and bioreactor preconditioning on heart valve tissues and cardiovascular tissue-derived biomaterials; 2) assess the effects of cardiovascular tissue processing and bioreactor preconditioning on *in vivo* heart valve remodeling; and, 3) identify potential clinical failure modes, based on preclinical *in vivo* safety and performance studies, attributable to the pre-implantation processing and bioreactor preconditioning of heart valve tissues.

Accomplishments

- Histologic, ultrastructural and immunohistochemical methods were established using native ovine aortic valve conduit tissue.
- Initial studies of native ovine aortic valve conduits were conducted establishing uniaxial biomechanical testing endpoints.
- Explant pathology studies of decellularized (anionic detergent-treated) aortic valve and pulmonary valve conduits were completed following 10 and 20 weeks of implantation in the right ventricular outflow tract of juvenile sheep.
- Allograft valves were decellularized and stored using either an anionic detergent and antibiotic storage or a nonionic detergent and cryopreservation. Decellularized valves were implanted for 10 or 20 weeks. Valve performance was evaluated (echocardiography; direct pressure measurements). Non-implanted and explanted valves were studied using macroscopic, radiographic and histologic methods. Acceptable hemodynamic performance was demonstrated between the two methods.

Active Materials Laboratory (Division of Chemistry and Materials Science)

Scope

Scientists in the Active Materials Laboratory investigate materials used in devices in which the time dependence of materials properties is a key component of how the device's mode of action is provided. This includes combination products in which medical devices incorporate some material-based mechanism for drug delivery, such as drug eluting stents. It also includes nano-materials, in which the properties of the nano-particles are critical to delivery of expected results.

Background

A growing number of devices are combination in nature. That is, in addition to their physical mode of action, a therapeutic is added so as to aid in the efficacy of the device. A prime example is the drug-eluting stent. Here the primary mode of action is the physical stabilization of the vascular lumen. However, an increasing array of therapeutic technologies, including the actual dissolution of the stent, is being presented to FDA. An understanding of the rates of therapeutic elution and scaffold dissolution are critical to their regulation. One route to achieving controlled release is using nanoparticulates as additives in conventional materials. Thus the chemical/physical behavior of nanoparticles is an area of growing impact on medical device regulation.

The inclusion of therapeutics into medical devices puts them in the category of combination products, those regulated by more than a single center. Thus coordination of technical expertise between CDRH, CBER and CDER is a critical component of this laboratory.

For devices where biodegradation is a mode of action, as in resorbable polymers used in stents and orthopedic applications, our understanding of degradation rates must be coupled with the changes in mechanical properties to allow for this information to be most useful in the regulation of these products. This requires a strong interaction between this laboratory and its counterparts in the Division of Solid and Fluid Mechanics.

Determination of the rates of chemical/physical changes in an active system can be addressed both experimentally and computationally. In the former, time-resolved analytical chemistry is utilized to examine the rates of release of small molecules and/or the changes in molecular weight of polymers. In the case of metals, the corrosion rates or rates of ion release serve the same purpose. As release changes the overall composition of a material, its morphology may also undergo changes. These can be followed by diffraction and microscopy techniques. First principle’s modeling, using thermodynamics, and transport properties, can be used to develop time-resolved models for the elution behavior and structural evolution of active materials.

Research Program Description

Research projects in the Laboratory for Active Materials focus on the time-dependent properties of materials whose mode of action is driven by such changes. One major effort of this laboratory is to understand how manufacturing process parameters impact the therapeutic release characteristics of drug eluting stents. To that end, members of the laboratory employ simulated manufacture, computer modeling and elution testing to examine how variance in process parameters modulates the performance of polymer/drug composites. The availability of several variants of commercial drug elution testing apparatus allows this laboratory to assess how well a given mode of elution rate measurement can reliably provide data for use in making sound regulatory decisions.

A number of sponsors and surgeons have begun to include antibiotics in bone cements. While no claims are currently being made as to efficacy of these therapeutics in preventing infection, the growth of this practice requires a careful examination of how manufacturing and/or clinical technique impacts on the cure rate, structural and release characteristics of these drug/polymer combinations.

The growing use of silver as an antimicrobial raises important regulatory questions. As part of our general efforts in understanding the impact of nanotechnology on medical devices, we have focused our research of the behavior of nanoparticulate silver, in terms of the stability of the nanoparticles (their tendency to aggregate) and on the release of silver ions (the ultimate bacterical/viracidal agent).

Relevance to FDA /CDRH Mission and the Public Health Impact

The programs of this laboratory help to identify potential risks associated with devices, where the release of therapeutic agents or the incorporation of nanoparticles is a component of their mechanism of action. The test methods and models developed are used to characterize device safety, which in turn leads to recommendations for regulatory guidance to the industry. Additionally, these data are used as input for consensus standards the Center can adopt in its regulatory review process. Presentations and publications in the peer-reviewed literature both publicize our research findings and enhance the reputation of Center's laboratory efforts. Furthermore, products of this project provide important and practical input for appraising post-market performance and identifying potential post-approval problems.

Critical Path: The central goal of this project is directly aligned to one of the six objectives within critical path. We are focusing on moving manufacturing of new and advance medical devices in to the 21st century by advancing fundamental understanding of rate of drug release to variation in manufacturing.

Three-Year Goals

A wide range of controlled release devices, designed for local (or targeted), low-dose, long-term delivery, are the subject of intense focus in academic and industrial research. These next generation combination products based on new and complex technology are already being submitted to FDA for regulatory approval. There is every expectation that their breadth and complexity will increase over the next several years.

Our vision for the Active Materials Laboratory is to be a center of expertise within FDA, for these new types of controlled-release devices, with a wide range of capabilities in computing and predicting drug release behavior, manufacturing and characterization of surrogates, analytical and elution capabilities, to test and validate low-level drug dose released over a long period of time. The laboratory research will help us acquire the necessary expertise and tools to assess both the safety and efficacy of these complex devices which is one of the primary goals of both CDRH & FDA.

We already have taken several initial research steps which have helped in the regulatory process of some these devices such as drug eluting stents. We will continue to build this capability over the next 3 to 5 years by these "one-line" objectives, details of which are explained elsewhere in the KM database. The exact chronology of these goals may change depending on results.

- Enhance computational capability to include a large variety of complex polymers;
- Enhance manufacturing and characterization capability to include spray technique and variety of quantitative analysis techniques;
- Compare and contrast different analytical elution methods;
- Submit a proposal to acquire commercial DES through willing industry participants and then validate our elution system on basis of commercial product;
- Explore active pharmaceutical ingredient (API) other than drugs, e.g., biologics;
- Explore controlled devices which are exclusively API, i.e., do not contain rate limiting matrix such as polymer matrix; and
- Explore a variety of indications (e.g., contact lenses, bone cement, urological).

Accomplishments

- Identified collaborators at the U.S. Pharmacopeia to develop CRADA to leverage research effort.
- Set up operational dissolution laboratories at FDA and USP for testing controlled release coatings using both USP 4 and USP 7 methodologies and variations of these methods.
- Derived equations for coating fabrication for a drug-polymer-solvent system.
- Developed preliminary models of flow and batch dissolution tests.

- Developed ambient conditions casting procedure as well as a spray coating procedure to fabricate controlled release coatings.
- Designed and fabricated a controlled environment spray coating chamber.
- Set up AFM, SEM, and optical microscopy methods to examine coating morphology.

Image Analysis Laboratory (Division of Imaging and Applied Mathematics)

Scope

A wide variety of new digital imaging and display devices is under development by academia and industry, with a broad range of performance characteristics. The Center requires augmented support for the evaluation of such devices. To this end, OSEL scientists in this laboratory are developing a fundamental understanding of how these new devices operate and are developing a unified methodological approach for validating the applicability of these new diagnostic medical systems. The emphasis of the Image Analysis Laboratory is to understand the building block of computer software tools and developing assessment methodologies that appropriately estimate performance and improve clinical and non-clinical trail designs. Application areas include mammography, optical imaging, computed tomography, nuclear medicine, immunohistochemistry, computer-aided diagnosis, and gene expression. This program is located within the Division of Imaging and Applied Mathematics (DIAM).

Background

The Medical Imaging Program at CDRH was initiated in the early 1970s by its predecessor, the Bureau of Radiological Health (BRH). The goal was to go beyond the traditional BRH laboratory approach of simply measuring the level of radiation emitted by an electronic or diagnostic modality, to measurement of the level of imaging performance as well. Laboratory measurement methods were developed for assessing the performance of contemporary and new technologies.

In the late 1980s it was realized that many of the multivariate statistical methods developed for image evaluation were applicable to the assessment of conventional and neural-network systems for computer-aided diagnosis (CAD) in medicine. These include the fundamental paradigm of the receiver operating characteristic or ROC plot of true-positive fraction (or sensitivity) versus the false-positive fraction (or one minus the specificity). The ROC paradigm provides the unifying framework for the evaluation of all diagnostic devices. Starting in the mid-1990s and up to the present, OSEL's imaging group has made fundamental contributions to the multivariate ROC statistical approach to assessment of medical imaging and CAD systems. A multivariate approach is needed for several reasons,

including the great reader variability associated with medical imaging and CAD as has been demonstrated in recent years.

Current work includes developing software for standalone performance and clinical trial design and analysis. Contemporary in-house programs address reader variability across a wide range of common study design, the development of task-based estimation strategies for evaluating drug-response with imaging data, and computer-aided diagnosis. The developed assessment techniques can be applied to a wide range of medical devices including CAD software tools, DNA micro-arrays, and most medical imaging systems.

Research Program Description

The clinical assessment of medical imaging systems is complicated by the great variability observed in readers in radiology. This variability leads to the necessity of a multivariate approach that includes the range of patient case difficulty, the range of reader skills, and correlations among the patients, readers, and imaging technologies under comparison. Thus a primary goal of this program is to develop statistical methods for analyzing the performance of imaging systems within the context of reader variability. At the same time, new and increasingly sophisticated computer techniques for medical diagnosis are being developed by academia and industry to aid/augment the human reader in the interpretation of high-dimensional image data sets. A second major goal of this program is to develop study designs, objective measurements, and analytical methods for the laboratory and clinical assessment of imaging and other diagnostic systems, systems for computer-aided diagnosis (CAD) used in medical imaging, and stand-alone image-based computerized diagnostic modalities such as high-dimensional DNA micro-arrays (DNA chips).

The methodological tools under development for analyzing the performance of imaging systems within the context of reader variability are referred to broadly as the multiple-reader, multiple-case (MRMC) receiver operating characteristic (ROC) paradigm. The paradigm is a multivariate analysis of the map of reader true-positive rates versus false-positive rates as a function of the variables listed above. A key question we are investigating is that of analyzing not only reader or system average performance but also the multivariate uncertainties that result from the finite sample of patients and readers. The approach to the assessment of systems for computer-aided diagnosis and high-dimensional DNA arrays is an extension and application of the multivariate approach to ROC analysis. In the case of CAD and DNA micro-arrays, the key question is that of analyzing the multivariate uncertainties that result from the finite sample of patients used to train the system, the finite sample of patients used to test the system, and their interaction. The general subject of uncertainty analysis also addresses the classical problem of the “generalizability” of performance of a CAD or micro-array algorithm. We make use of advanced statistical tools for diagnostic decision making under uncertainty, including classical Bayes' discriminants, neural-network architectures, and fuzzy logic, in our studies of CAD algorithms and their performance.

In the last few years CDRH has been receiving an increasing number of pre-market submissions for digital imaging modalities and modalities used for CAD, not only in imaging but also for clinical laboratory diagnostic tests. Statistical and analytical methods developed in the OSEL imaging group have been directly used to assist with both the design and the data analysis for several of these submissions, both in imaging and CAD. OSEL has played a significant role in the statistical evaluation of device submissions such as those for automated Pap smear readers, lung cancer, and breast cancer detection devices. A current emphasis is on the development of a draft guidance document, in collaboration with scientists in OSB and ODE, to provide industry and academia with "best" and "acceptable" practices for the laboratory and clinical assessment of diagnostic devices. We are also pursuing the potential for coordinating MRMC ROC clinical study designs in such a way as to optimize the expenditure of resources over the total product life cycle of an imaging technology—from university research, through pilot clinical trials and pivotal FDA studies, to confirmatory ACRIN (American College of Radiology Imaging Network) trials, through downstream cost/benefit studies of interest to public policy makers and insurers working at that higher level.

The most recent extension of our research efforts are focused on expanding the utility of medical imaging in drug trails. Falling within the scope of the FDA Critical Path Initiative of developing surrogate markers of drug response, this effort strives to understand the fundamental limits of quantitating patient response associated with the imaging technology, imaging technique and software tools. Common response metrics include change in lesion size or volume on CT and lesion uptake in nuclear medicine. We anticipate that this research will provide sponsors not only with the achievable performance but also with a set of practical assessment methodologies for validating new technology in this field. We expect this to improve coordination between CDRH and CDER in the assessment.

Relevance to FDA /CDRH Mission and the Public Health Impact

The expertise developed through this program is being applied to the review of PMAs for new digital radiographic imaging and software analysis devices. Investigations of computer-assisted diagnosis devices provide the Center with the scientific basis to effectively regulate this fast growing field. Finally, our research in quantitating drug-response directly impacts the FDA Critical Path Initiative of developing surrogate imaging markers of drug response. This research effort should also foster a closer relationship with the CDER imaging group improving the assessment of imaging tools and drug trails.

Three-Year Goals

Researchers in the Image Analysis Laboratory have made fundamental contributions to the field of statistical analysis of diagnostic imaging and computer-aided diagnosis systems.

Future efforts in the Image Analysis program will focus on contemporary and emerging issues of regulatory interest. In the process, we are seeking the most efficient or statistically powerful approaches to the evaluation of medical imaging and computer-assist decision modalities. An ultimate goal is the development of a multiple-reader (e.g., multiple radiologists, multiple pathologists) multiple-case (MRMC) version of our current software for ROC analysis in the absence of ground truth (i.e., without a gold standard). We will continue extending the MRMC assessment framework to non-standard clinical trail designs where every reader does not necessarily read every case and to different performance metrics including measurements of only sensitivity and specificity.

Development of such systems would address one of the most difficult yet most common assessment problems in the field of diagnostic medicine. Likewise we would like to gain a fundamental understanding of how the choice of the imaging technology and the specific imaging technique influences our ability to estimate and quantify patient response. Many statistical problems in the new field of bioinformatics remain unsolved. We would like to extend our contemporary successful research into new realms of bioinformatics that are opening up due to the accumulation of data from multiple testing and patient demographics. This will require continual upgrading of our computational facilities.

Accomplishments

- We have reported on the impact of concurrent vs. sequential reading paradigms on the detection performance of human observers using a CAD algorithm in a simplified mammography-like context.

- We have developed and reported on approaches for determining confidence intervals for FROC (free-response receiver operating characteristic curves) using resampling techniques.

- Methods have been reported for the determination of the variance in the percent correct (PC) under a multi-reader, multi-case reader study in which not all readers read all cases, in particular, the doctor-patient study design.

- A major review titled “Assessment of Medical Imaging Systems and Computer Aids” by RF Wagner (OSEL), CE Metz (U. of Chicago), and G Campbell (OSB) was accepted by the journal *Academic Radiology* and is scheduled for publication in the June 2007 issue.

Ionizing Radiation Metrology Laboratory (Division of Imaging and Applied Mathematics)

Scope

The scope of the Ionizing Radiation Measurements Laboratory (IRML) is to provide metrology support to the Center's Radiological Health and Medical Device safety mission. IRML maintains measurement and calibration capabilities for ionizing radiation. The ISO17025-compliant laboratory provides traceability for standards-enforcement measurements, provides metrology expertise for pre- and post-market issues, performs evaluations of x-ray emissions from regulated products, performs evaluations of measurement methods, and represents the Center on appropriate consensus standards efforts.

Background

The x-ray calibration program began in the early seventies with the implementation of mandatory performance standards for electronic product radiation. With nationwide compliance testing of x-ray equipment it was necessary that measurements be consistent. The program provided field inspectors with uniform instrumentation which was accurate but simple to use. A state-of the art calibration laboratory was developed in order to provide the Bureau of Radiological Health (later CDRH) with a large-volume of high-quality, low-cost calibrations at a time when such calibrations where not available elsewhere. Operating its own calibration laboratory gave the Bureau complete and independent control over the traceability of field measurements. This facilitated the validation of compliance measurements when they were challenged, provided uniformity of data for analysis, and eliminated possible conflicts of interest.

In the nineties, with the implementation of MQSA, the laboratory's workload increased as FDA began annual inspections of mammography facilities. The laboratory was instrumental in the development of the national calibration standard for mammography x-ray beams maintained by the National Institute of Standards and Technology (NIST). Laboratory personnel contributed to several national and international standards and accreditation criteria for calibrations of ionizing radiation measuring instruments. In 1992 the laboratory was the first to receive accreditation from the National Voluntary Laboratory Accreditation Program (NVLAP) for this type of calibration. Through the years the laboratory has provided FDA and collaborating state agencies with reliable ionizing radiation calibrations and metrology support.

Research Program Description

Historically, the laboratory has maintained and calibrated a large stock of over 250 FDA-owned MDH model 1015 radiation monitors, over 200 state owned MDH model 1015 radiation monitors, in addition to calibrating or maintaining hundreds of other instruments in support of x-ray field support. The FDA-owned equipment is owned by the Center and placed out on loan to ORA, many state radiation control programs, and defense department personnel. The MDH instruments are based on a 1974 design that is out of date, and no longer being manufactured. The laboratory has begun the process of identifying and evaluating replacement instrumentation that will meet the future needs of the Center. It is anticipated that a smaller inventory of instruments will be maintained in the future, with little or no provision of instruments for the states. Some of the field support funds will be used in FY 2007 to begin purchasing modern x-ray measurement instruments for Center and ORA use. It is also anticipated that an inventory of approximately two dozen instruments of various types will be purchased over the next 5 years and maintained on a rotating basis. The majority of the present inventory of MDH instruments will soon be offered to other federal government agencies, state programs, or will become surplus property.

The laboratory has operated a NVLAP accredited facility for the routine calibration of its large inventory of MDH instruments. This calibration activity has begun to shrink dramatically, with the cessation of MQSA calibrations and planned reduction of state partnerships. For FY 2007 there will be a continued tapering down of the calibration activity, so that in the future, calibrations will be performed for a much smaller but more varied family of instruments.

Relevance to FDA and CDRH Mission and the Public Health Impact

This laboratory allows CDRH to fulfill its responsibilities for monitoring the safety of electronic products that emit potentially hazardous levels of radiation. IRML is continuing to work with OCER in developing a plan to phase out instrument calibration service while maintaining "for cause" measurement capabilities. The laboratory provides expertise for quantifying radiation emissions from emerging technologies and new products. The laboratory also provides expertise for the development of voluntary standards and guidance documents aimed at limiting the public's exposure to non-medical x-radiation.

Three-Year Goals

The reorganization of the Center's radiological health program and the move to the White Oak campus will bring new challenges during the next 3 years. The CDRH plan calls for refocusing the radiological health effort into five main areas: Standards, Monitoring, Education, Research, and Program Management. The IRML is most affected by the planned reduction of routine product testing. This will likely mean a greatly reduced number of measurements and thus a reduced number of instrument calibrations needed, starting with FY 2007. During the next 2 years or so, the IRML will be readjusting its work

output to make the greatest possible contribution to the Center's implementation of the new plan. The laboratory will focus on reducing the volume of calibrations while increasing the scope and range of the measurement capabilities. This calls for fine-tuning the design of new laboratory apparatus and related software to be installed in the new White Oak building. The laboratory will continue to monitor and evaluate measurement instrumentation and methods. As the Center settles into new ways of executing its radiological mission, the IRML will seek to optimize its resources for the greatest contribution. This means that not all changes for the next 3 years are predictable at this time.

The White Oak move will present the task of characterizing a new x-ray generator with expanded capabilities in addition to reestablishing, validating, and updating the existing calibration ranges. Internal and external resources that should support this type of endeavor are currently not available due to attrition or lack of documentation in support of existing computer program applications. A critical part of adapting to current needs will require IRML to review and determine what components of the existing infrastructure that is relevant to FDA's current public health needs. The FY 2007 FTE proposed allotment will include the outside contractual resources to support this process.

Accomplishments

- Operated the CDRH X-ray Calibration Laboratory accredited by the National Voluntary Accreditation Program (NVLAP). The laboratory provided 840 radiation calibrations of general diagnostic instruments, 202 radiation calibrations of mammographic instruments, 484 electrical calibrations of radiation monitors, 147 calibrations of non-invasive kVp meters, and 36 calibrations of light meters.
- Provided instrumentation and logistics support to FDA and Agreement-State inspectors for compliance testing of general radiography installations, mammography machines, and voluntary surveys under the Nationwide Evaluation of X-ray Trends (NEXT) program.

Imaging Physics Laboratory (Division of Imaging and Applied Mathematics)

Scope

A wide variety of new advanced imaging systems with solid state detectors and digital display devices are under development by academia and industry, with a broad range of performance characteristics. To support the Center's need for assistance evaluating such devices, OSEL scientists are developing evaluation methodologies for diagnostic medical imaging systems such as mammography and fluoroscopy, computed tomography, nuclear medicine, diagnostic ultrasound, and magnetic resonance imaging, as well as for novel

soft-copy display devices for viewing medical images. This program is located within the Division of Imaging and Applied Mathematics (DIAM).

Background

The Medical Imaging Program at CDRH was initiated in the early 1970s by its predecessor, the Bureau of Radiological Health (BRH). The goal was to go beyond the traditional BRH laboratory approach of simply measuring the level of radiation emitted by an electronic or diagnostic modality, to measuring the level of imaging performance as well. Laboratory measurement methods were developed for assessing the performance of contemporary and new technologies in the fields of radiography, mammography, computed tomography, diagnostic ultrasound, radioisotope imaging, magnetic resonance imaging, with current emphasis on digital detectors and displays. The program led to contributions to consensus measurement methodology and international standards that are used by the Center today in the approval process for new technologies, in particular, digital radiography and mammography, and diagnostic ultrasound. In-house research and collaboration with academic investigators have also led to laboratory and clinical systems that optimize the ratio of imaging performance to radiation exposure in mammography.

Research Program Description

DIAM scientists are engaged in developing appropriate methods for evaluating medical imaging system performance and dose. Investigations take the form of theoretical analysis, numerical simulation of the entire imaging chain, and experimental validation. In some instances, improved/optimized system designs are validated through actual system construction and clinical evaluation. Measurement and analysis procedures are also being developed to evaluate the performance of new soft-copy display devices that can have dramatically different light-emitting structures and associated performance characteristics whose impact on the image interpretation process is currently unknown. OSEL scientists provide reliable, quantitative laboratory measurements of imaging system characteristics to the imaging research community. OSEL scientists are also elucidating the fundamental mechanisms underlying the interaction between the image-forming radiation and the anatomy being imaged.

Improved knowledge of the fundamental imaging mechanisms leads to a better understanding of the sources of variability in imaging data. Having that, inter-machine and inter-facility measurements can be corrected, leading to absolute, quantitative measures which can then be codified through a measurement standardization process. The x-ray spectral measurements program provides a source of otherwise unavailable data to the entire mammography research community for use in accurate *in silico* models of imaging systems and for the developing of new equipment performance standards, special procedures and test equipment for MQSA, and will be used to inform decisions on marketing clearance for new products and in compliance actions.

Relevance to FDA /CDRH Mission and the Public Health Impact

The expertise developed through this program is being applied to the review of PMAs for ultrasound bone sonometers and new digital x-ray imaging systems, the development of amendments to the diagnostic x-ray performance standard, and the development of an advisory pertaining to pediatric CT exposures. These investigations inform the Center's regulatory decision-making on new digital imaging devices. The expertise developed through this program is being applied to the review of PMAs for ultrasound bone sonometers and new digital radiographic imaging systems. This program contributes to the development of pre-market guidance documents including "Information for Manufacturers Seeking Marketing Clearance of Digital Mammography System" and "Bone Sonometers PMA Applications: Final Guidance for Industry and FDA." This program has also provided independent data to support the ongoing down-classification of bone sonometers and full-field digital mammography systems. OSEL scientists have recently applied their expertise to the development of a CDRH web site on CT, the development of amendments to the performance standard for diagnostic x-ray equipment, and the development of an advisory pertaining to pediatric CT exposures.

Three-Year Goals

Future efforts in the Imaging Physics program will focus on contemporary and emerging issues of regulatory interest. In the field of digital imaging, these issues include characterizing imaging performance without the underlying assumptions present for analog imaging systems, validating and refining consensus measures that apply to novel imaging detectors and displays, optimizing overall system performance through advanced simulation and experimental verification, and assessing tissue parameters from the digital data. Special emphasis with respect to imaging performance and patient exposure will be put on emerging techniques for volumetric imaging of the human anatomy including cone-beam computed tomography and tomosynthesis using flat panel detector arrays. In the field of ultrasound, topics of interest include tissue characterization, bone densitometry, contrast agents, ultrasonic imaging system performance characterization, temperature mapping, elastography, high-frequency imaging, harmonic imaging, and the use of ultrasonic measurements in pattern recognition systems. While DIAM continues to work in the area of ultrasound, the largest OSEL ultrasound activity for this year involves high-intensity focused ultrasound, and is described in the program description for Fluid Dynamics and Ultrasonics.

Accomplishments

- ► Imaging scientists in OSEL played a major role in the preparation of materials for a public panel meeting on the reclassification of digital

mammography x-ray systems. These systems allow mammograms to be taken using digital rather than the analog film/screen detectors traditionally used, permitting immediate benefit from the wider latitude and computer signal processing capacity of the digital systems. The laboratory carried out detailed physical measurements of the basic capabilities of the new systems to show that their performance should be equivalent or better than the older technology. Laboratory research was used in developing a related review guidance document that will serve as the basis of the reclassification of these systems into Class II, further easing their access to widespread clinical practice.

- The Office of Women's Health funded a proposal written by a DIAM scientist titled "Implications of Gender-based Differences in Cardiovascular Disease on Imaging for Treatment and Diagnosis." Under this effort, a team of CDRH and NIH researchers was awarded the Cum Laude award for the best poster at the SPIE 2006 Medical Imaging Symposium for its presentation of "Gender-specific statistical models of pathological coronary arteries for generating simulated angiograms." The goals of this project are to develop methods and procedures for the evaluation and optimization of imaging systems based on the specific tasks performed during the diagnosis and treatment of coronary artery disease. This project will result in new or improved guidelines and recommendations for imaging system and imaging protocol designs based on gender differences and imaging tasks. It will also address the efficient use of patient dose for the high image quality and the reduction of total volume of contrast agents used on women during angiographic procedures.

- Our Monte Carlo computer simulation activity has been greatly extended via the development of a realistic, high-resolution computer phantom based on the use of a morphology-based three-dimensional segmentation of a coronary artery tree from CT scans, which is incorporated into a novel object-oriented geometry package that allows simulations with homogeneous objects of arbitrary shapes. Using these new resources, coronary angiograms were simulated using a tessellated version of the NURBS-based Cardiac-Torso (NCAT) phantom. The phantom models 330 objects, comprised in total of 5 million triangles. The dose received by each organ and the contribution of the different scattering processes to the final image were studied in detail.

- We have made the Monte Carlo simulation code MANTIS, jointly developed by our group and Dr. Josep Sempau of the Institut de Tecniques Energetiques, Universitat Politecnica de Catalunya in Barcelona, Spain, publicly available. A short course on the use of this code was presented at

the 2006 Medical Imaging Symposium. The code is downloaded several times weekly. We have utilized the code to investigate the angular-dependent imaging properties of digital radiographic detectors, and validated our simulations with experiments in the lab. These studies have particular relevance to limited-angle tomographic geometries under investigation by academic groups and industry for breast tomosynthesis.

- In the area of display evaluation, DIAM scientists have developed new approaches for determining the temporal response for monitors used in evaluating display devices that will be used for dynamic viewing of 3D imaging. Additionally, we are developing display evaluation methods that make use of model observers, incorporating the contrast sensitivity of the visual system, to allow prediction of the impact of the response time of a display on target detection probability.

- Scientific research on diagnostic medical ultrasound being conducted in DIAM has led to a number of significant publications and presentations in 2006 and has contributed to improved standardization of bone sonometry measurements.

Electrophysiology and Electrical Stimulation Laboratory (Division of Physics)

Scope

Medical devices that rely on electrophysiology and electrical stimulation for safety and efficacy cut across all medical specialties. The most important examples are devices that work in the heart and nervous system including: cardiac pacemakers, defibrillators, retinal stimulators for blindness, brain stimulators (for Parkinson's disease, pain, motor function, hearing), electroconvulsive therapy, magnetic brain stimulation, cochlear implants, middle ear hearing devices, spinal cord stimulators, vagus nerve stimulators, and peripheral nerve stimulators (including those for locomotion, breathing, bladder and bowel control). The less obvious examples are devices for the electrical detection of cancer (from breast, colon and cervix), the transdermal electrical extraction of glucose for monitoring, and a number of "complementary and alternative medicine" devices. The scientific discipline of electrophysiology forms a unified basis for the scientific evaluation of all of these devices. The scientific issues involve the basic electrophysiology of a number of body systems, and the biomedical engineering of the devices.

The scope of our work ranges from work directly applied to a single device type (the retinal stimulator), to broader work that is relevant to a class of devices (cardiac

stimulators for treating arrhythmias and heart failure), to far-reaching work on the development of optical stimulation of excitable tissue (supported extramurally).

Background

There is large and increasing interest in the scientific and medical communities in the use of electrophysiology and electrical stimulation in diagnosis and treatment of diseases and disorders. Between 1998 and 2002 electrophysiological devices comprised 22% of all PMAs and 31% of all IDEs for CDRH. The need for specialized skills from OSEL-related research in electrical stimulation has increased. As a result, seven personnel appointments have been made in the electrophysiology laboratory since September of 2003. Three cardiac physiologists/biomedical engineers are now on staff along with a visual physiologist, a neuroscientist and two general biomedical engineers. Five staff members are shared with other offices within CDRH, and we play major regulatory roles as leads in the review of PMAs, 510(k)s, IDEs and in developing guidance documents. The need in the Center divisions for scientific expertise in these areas is substantial, and we emphasize both our laboratory research and direct regulatory involvement in sister divisions.

Our largest commitment is to research related to cardiac devices. This is because of the new regulatory challenges caused by innovations and because heart disease is the number one killer in the U.S. One prime example of a device used to prevent sudden cardiac death (affecting 330,000 Americans annually) is the implantable cardioverter defibrillator (ICD). In 2002, 100,000 ICDs were implanted in the U.S. This number has increased greatly because the American College of Cardiology recently advised its expansion of indications for heart failure patients, and the Center for Medicare and Medicaid Services greatly enlarged the reimbursable uses for these devices. There is also a host of new cardiac electrical stimulation device applications being submitted or recently approved; these include over-the-counter automatic external cardiac defibrillators, new methods of defibrillation, cardiac resynchronization therapy for congestive heart failure for the treatment of heart failure, and other stimulation devices for heart failure. We also anticipate cardiac stimulation devices that will take advantage of chaotic properties of pathological states for therapy that use considerably less energy than cardioversion or defibrillation. In total, there is a need for CDRH research as part of a team that will help formulate and clarify issues related to the approval of new devices and the surveillance of the expansive market of approved devices.

Our work in cardiac electrophysiology cuts across both pre-market and post-market regulatory concerns and their underlying biological substrates. The pre-market concerns are addressed by research that seeks better ways of testing and evaluating new cardiac devices. We are focusing on electrical stimulation devices for the treatment of heart failure. This work includes the development of computational models for human arrhythmias in the failing heart that encompass electrical therapy. As the sophistication and reliability of these models increases, we will be able to employ them to focus clinical trials to the

critical issues of safety and effectiveness. We are performing laboratory studies and developing animal models that demonstrate how new therapies will alter cardiac properties that determine safety and effectiveness.

Similarly, there is a strong relationship of our laboratory work in shaping post-market studies. At present, cardiac devices typically come to our attention when the device malfunctions, e.g., when there is a short circuit in the header of an ICD or when there is an unintended hardware reset. We typically do not see reports when death or hospitalization occurs from drug interactions or cardiac remodeling that change pacing needs or the response to defibrillation shocks. It becomes even more complex when there are gender differences in the underlying pathologies (primarily heart failure) and drug responses. A potential example of harm caused by a device working "as designed" is when inappropriate shocks occur; OSB reports that approximately 2,200 out of the 22,000 adverse event reports for ICDs in the MAUDE database cite "inappropriate shock" as a device problem. These reports describe exposure to risk from the interventions performed to relieve patients from such shocks, and some reports describe events in which such shocks have accelerated a rhythm to a fatal VF. The consequences to public health, even when a device functions "as designed" can be greater than for frank device malfunction. Of course, pre-market studies are usually limited in size and duration, so unusual interactions would not be detected. Our laboratory studies will provide the basic knowledge regarding the lesser-known effects of shocks with drug interactions, heart failure and gender differences. We will be integrating our work with present pos-tmarket research at CDRH.

In ophthalmics, retinal stimulators have become devices of major public interest because of their potential to treat the blindness afflicting millions of Americans. Surprisingly, clinical trials are being conducted without the knowledge of safe limits of electrical stimulation to the retina. Here we are determining the safe limits of electrical stimulation of the retina with morphological and electrophysiological techniques.

A new area of interest in the neural devices community is the use of optical stimulation. This is because electrical stimulation has come to its limits, especially for neuroprosthetic devices. With 100% extramural funding during 2006, we are seeking to determine the key limits of safety and effectiveness of optical stimulation, and this work is being performed in collaboration with the optical therapeutics group.

The diversity of the devices and the large number of regulatory applications has mostly focused our laboratory work broadly on the basic mechanisms by which these devices exert their effects. Understanding of basic mechanism, especially regarding safety, is a unique primary concern of CDRH. These studies permit expert consultations for preclinical device reviews in every area of CDRH activity; they serve as part of the approach that assists firms with the least burdensome route to approval and help reviewers meet MDUFMA goals by defining the form of "valid scientific evidence" of safety and effectiveness, as required by 21 CFR 860.7.

Research Program Description
OSEL's investigations of electrophysiology and electrical stimulation center on clarifying the mechanisms of interaction of the technology with the body. The work is specifically aimed at forming the scientific basis for regulatory decisions that speed device approvals and industry safety standards for electrical stimulation. Our specific areas of investigation relate to two of the prevalent causes of cardiac death, i.e., heart disease, a highly visible device, i.e., retinal stimulators for blindness, and for a future technology, i.e., optical stimulation. These areas map onto the anticipated regulatory needs of the Center in this broad area of medical devices. Our current projects, each led by one or several principal investigators, fall into broad and overlapping areas of investigation.

Primary Projects:

Optimizing Electrical Stimulation by Retinal Prostheses – One million people are blind due to retinal photoreceptor degenerative diseases. However in these blind patients, their retinal ganglion cells often remain functional and can send information to the brain. A variety of retinal prostheses for the blind are currently being proposed for clinical trials that use electrical stimulation to activate the remaining retinal pathways to retinal ganglion cells. The objective of this project is to determine safe levels and more optimal methods of retinal ganglion cell stimulation by using experimental and computational methods. The results of this project will help generate new guidelines for safe stimulation levels and develop more effective methods of electrical stimulation of the retina by visual prostheses.

Safety and Efficacy of Selective Optical Stimulation for the Damaged Nervous System – Traumatic injury to the *nervous system* leads to loss of limb function, and frequently, persistent pain. Clinical management of nerve injury includes immobilization of the affected area and surgical grafts, yet these are often not sufficient to promote recovery of function. *Traditionally, neural stimulation is accomplished with implanted metal electrodes*. However, electrical stimulation is limited by the non-selectivity of neuronal activation and the risk of adverse tissue reactions. Optical stimulation (OS) of neurons and neural tissue may provide a superior alternative. Micro- and nano-scale fiber-optic probes can deliver OS with greater precision and, potentially, less cellular damage. Stimulation may be achieved by the direct interaction of light on neurons. The proposed research will determine safe and effective OS rates and light radiation dose levels using two models of sensory neurons. Electrophysiological and histochemical techniques will be used to determine the range of OS intensity, duration and frequency that can *safely evoke action potentials* while simultaneously avoiding neurotoxic side-effects. We will employ an injured-nerve model using axotomized sensory nerve afferents to evaluate and compare differences in the sensitivity of injured and uninjured mechanoreceptors and nociceptors to OS. This study will aid in the development of OS technology as a potentially valuable clinical therapy for nerve-damaged patients.

Functional Remodeling in Heart Failure: Device Implications **-** Heart failure (HF) afflicts 4.7 million Americans (1.5% of the population). With the increased survival from myocardial infarction and improved arrhythmia management, the incidence of HF is rising rapidly. Mortality from HF has increased by 20.5% between 1993 and 2003, while the overall death rate declined by 2.0% (Heart Disease and Stroke Statistics – 2006 Update, American Heart Association). Investigations of effects of medical devices upon HF fall under both pre-market and post-market areas of regulatory concerns. On the pre-market side, we are faced with new devices for treating HF as well as cardiac devices that could have unintended effects in HF patients. On the post-market side, there has been an expanded use of approved and marketed electrophysiological devices for HF patients. For example, in 2005 the Center for Medicare and Medicaid Services (Decision Memo for Implantable Defibrillators, CAG-00157R3) decided to expand the reimbursable indication for ICDs to include the HF population without any arrhythmia present. This is in addition to the increased implantation of pacemakers and ICDs for concomitant arrhythmia in the expanding HF population. The large number of HF patients and expansion of the marketed devices into this new patient population necessitates the ability to understand device interactions in failing hearts as part of the scientific component of postmarket studies. This work simultaneously addresses most of the FDA Critical Path Initiative. Understanding the basic remodeling changes that occur with HF and device interventions will provide the information necessary for better preclinical evaluation tools that will enable more streamlined clinical studies and reviews. It helps address the public health need for better treatments of a rapidly increasing disease, and it will consequentially lower HF disabilities in the at-risk elderly population.

Arrhythmogenesis in Normal and Diseased Cardiac Tissue: Device Optimization for Prevention and Treatment – Devices to treat cardiac arrhythmias, including pacemakers, implantable cardioverter defibrillators, and ablation therapy devices, are the subject of considerable pre- and post-market review at the Center. The objective of this research is to investigate the mechanisms underlying the onset and treatment of cardiac arrhythmias by such devices in the context of electrodynamics, a field of mathematics that has yielded much insight into those factors that may cause, sustain and terminate arrhythmias. The results of this study will contribute to the evaluation of device efficacy, thus allowing for optimization of device performance, promotion of science-based pre-market review, and anticipation of failure modes that may present in post-market device review.

Relevance to FDA's and CDRH's Mission, Program, and the Public Health Impact FDA

FDA laboratories are defining the safety and efficacy concerns regarding electrical stimulation in the nervous system and heart. Within the aging population, the prevalence of heart disease, especially for heart failure, has increased along with blindness due to age-

related macular degeneration. The application of our laboratory work will aid in moving safe and effective devices to market faster and to help focus post-market analyses.

Each of these efforts is designed to identify the critical scientific questions early in the Total Product Life Cycle for new technologies, and to provide reliable testing and evaluation methods to answer those questions. This work is being implemented with the Critical Path Initiative in mind.

This program serves all of the Critical Path categories:

- *Better Evaluation Tools* – a human model of cardiac electrophysiology will increase our ability to evaluate new or modified electrical therapies.
- *Streamlining Clinical Trials* – developing models of heart failure and defining safe limits of retinal stimulation decrease size and duration of clinical trials.
- *Harnessing Bioinformatics* – advanced bidomain models of the heart takes advantage of the wealth of electrophysiological studies and advanced computational techniques.
- *Moving Manufacturing in the 21st Century* – development and safety testing of optical stimulation is cutting-edge research that we expect to soon be implemented in neurological devices.
- *Developing Products to Address Urgent Public Health Needs* – heart disease is the primary killer of Americans, and our projects address the both arrhythmia prevention/treatment and pump (heart) failure treatment; similarly we are addressing regulatory and safety concerns for devices intended to treat blindness.
- *Specific At-Risk Populations* – the program is focused on prevalent diseases of the heart, and on blindness. While these diseases are most prevalent in the elderly, their impact is notably devastating in the pediatric population.

Additional value is added to FDA and public health by the expertise developed in this research. It provides CDRH with the scientific expertise to rapidly form multidisciplinary teams for any of the numerous and unpredictable regulatory problems involved in electrical stimulation. It permits the development of science-based guidance and methods for efficient and economical device evaluation and approvals. One such collaborative effort has been the development of a draft guidance document for electroconvulsive therapy. Such initiatives are substantial contributions to CDRH's commitment to MDUFMA goals and "least burdensome" approaches for sponsors and manufacturers. CDRH's scientific credibility is a crucial element in these programs, and it is enhanced by this cost-effective public health tool to the Center.

Three-Year Goals

The use of electrical stimulation and electrophysiology in medical devices will continue to grow for the foreseeable future. We focus on developing research that will have

applicability to both pre-market and post-market regulatory processes that include providing the scientific expertise for reviews, guidance document development and contributions to industry standards. This program will continue to examine new devices and technologies for safety and effectiveness. This information will be obtained from our independent laboratory studies, and from in-house research that is conducted to anticipate new directions of this technology. The results of the work will also be disseminated in the form of peer-reviewed publications, consultative reviews, and guidance documents. The program also offers laboratory capabilities (expertise and equipment) to other offices to collaborate and answer immediate scientific questions. It will assist in speeding the rapid movement to market of safe and effective medical devices and serve as a science base for post-market evaluation.

The specific plan includes the development of the science necessary for interpreting pre-market and post-market clinical data for devices that stimulate the heart and nervous system with electrical current. Our objectives:

- **Develop computational human model to test cardiac electrophysiology devices**: We will progress towards the development of a realistic 3-dimensional computer model of electrical activity and device stimulation and device stimulation. The model will be refined with optical recording from 256 locations in live animal hearts. It will also account for pathological states of the heart. Our advanced computer models of heart will be part of a consortium for establishing realistic human models for device testing that will supplement present animal and *in vitro* models. This will permit the studies related to regulatory approvals. Current issues amenable to such studies are those longer duration/lower current defibrillation shocks, and the presentation of sequential defibrillation shocks.
- **Investigate the basis of arrhythmia generation in heart:** As part of our effort to study device treatment and prevention of arrhythmias, we will determine how different forms of "therapeutic" pacing may contribute to the generation of secondary arrhythmias, and understand the underlying basis of cardiac memory and restitution in arrhythmia generation. We also anticipate the development of a new generation of cardiac devices that will strategically stimulate with low-energy shocks to correct arrhythmias that now require high-energy cardioversion or defibrillation.
- **Study how devices interact in remodeling of cardiac tissue with heart failure:** One of the main effects of heart failure is a remodeling of the heart. This work will examine the plastic changes in heart tissue that result from heart failure and with various forms of therapy, including ablation and new pacing modalities. This work is directly related to the safety and effectiveness of such devices. An *in-vitro* model will be used to cardiac pacing that is in, or out-of-phase with mechanical activation. This will mimic the effects of cardiac resynchronization therapy, a rapidly growing device therapy for heart failure. A primary endpoint of the study will be the

determination of *junctional conductances* between cells – a primary determinant of arrhythmia generation.

- **Defibrillation and pacing differences in remodeled heart cells:** This work will determine changes caused by heart failure and various medications upon calcium handling in response to pacing and defibrillation in single cardiac cells. (Calcium is the main regulator of function and rhythm in the heart cell.) We will specifically be looking for gender differences in calcium handling from cells taken from the porcine model for heart failure (in collaboration with Dr. Mark Haigney, Director of the Division of Cardiology, Department of Medicine at the Uniformed Services University of the Health Sciences in Bethesda, Maryland).
- **Safety and efficacy limits of retinal prosthetics:** The research that determines physiological limits of stimulation of the retina. The results will be written into a guidance document to assist device sponsors and used for the development of industry standards.
- **Optical stimulation of neurons:** This extramurally sponsored study will test the safe limits of optical stimulation of neurons in single central neurons and in cultured spinal cord neurons. It will also determine effectiveness for microstimulation of neurons – a major hurdle in the development of neuroprosthetics.

Accomplishments

- Examined the effects of rapid-rate stimulation in computer-modeled and real nerve cells. Stimulation at these rates will induce nerve depolarization and the irregular firing of nerve impulses; this was shown by the model and by actual experiments. The work positioned the Center to anticipate safety issues early, and it was applied to a broad number of regulatory reviews, several international standards and several FDA guidance documents.
- Initiated an investigation of shock effects upon human blood. In these experiments, human blood is exposed to defibrillator shocks in a controlled manner *in vitro*. Electrode current density is calibrated to that that used in clinical defibrillators. Platelet activation is assessed by the expression of platelet P-selectin. Antibody binding assays and flow cytometry to measure alterations in selectin levels under the experimental conditions tested. Damage to blood cells is assessed by measuring the concentration of hemoglobin in cell-free plasma and by photomicrography of blood smears. The results showed that electric shocks (at clinical levels) will cause mild hemolysis. Platelet activation, due directly to the electric shock or due to hemolytic products from damaged blood cells, is being investigated.

Electromagnetics and Wireless Technology Laboratory (Division of Physics)

Scope

The research here focuses on the several needs associated with medical devices that utilize or are affected by electromagnetic (EM) fields. The primary need is to address the rapid deployment of wireless technology around and into medical devices and the safety and effectiveness concerns associated with electromagnetic interference (EMI) disruption of medical devices and the deposition of the electromagnetic energy in the human body. Another need is to develop methods to evaluate medical devices used for ablation of body tissues and the measurement and evaluation of EM heating and the evaluation of devices used intentionally to hear body tissues. A principle goal of this effort is to develop standard techniques for the measurement and evaluation of RF heating for both high and low frequency electromagnetic devices. A third area involves the safety of patients undergoing magnetic resonance imaging procedures. Patients with implanted devices, and electrodes or other devices attached to the body, are being imaged by MRI, and some are being injured or even killed due to heating from the intense EM fields produced by the radiofrequency (RF) coils during clinical imaging procedures. Medical device manufactures are submitting requests to approve of their devices as MRI compatible, e.g., allowed to be in or attached to the patient during MR imaging procedures

The laboratory covers a wide range of medical device areas that includes essentially all electrically powered devices, as well as the human exposures and energy deposition from a wide range of commonly used radio frequency emitters (e.g., cell phones, wireless computer links, security systems). The objective of the program is to develop independent data, measurement and computational techniques, and test methods that will serve as solid scientific foundations for regulatory guidance, proposals for national and international standards, and peer-reviewed technical publications. All of the work is driven to promote the public health by developing and coordinating vital information that is unavailable elsewhere.

The wireless technology revolution together with a flood of new medical devices incorporating sensitive microelectronics is leading to a highly unstable situation. Dangerous malfunctions and numerous patient injuries have been induced in medical devices via electromagnetic interference (EMI) from electromagnetic fields emitted by wireless equipment. This equipment includes cellular phones, magnetic-field emitting security devices (such as airport metal detectors), radiofrequency identification (RFID) systems and other medical devices such as shortwave diathermy and magnetic resonance imaging (MRI). DP leads the FDA effort to make all electrically-powered medical devices electromagnetically compatible (EMC) with the electromagnetic environment where they are used. In addition to EMC, concerns are continually raised by the public and the news media about the possible harmful effects of exposure to radio frequency (RF) electromagnetic fields (also known as non-ionizing RF radiation) from handheld wireless (cellular) telephones and other wireless personal communications devices.

Radiofrequency ablation devices are used to deliver therapeutic energy with the intent of thermally necrosing tissue: in the heart, ablation is used to treat abnormal heart rhythms (arrhythmias): in the brain, it is used to treat Parkinson's disease; in soft tissues, such as the liver, breast, and kidney, ablation is used to eradicate tissue lesions and tumor tissue; in the uterus, it is used in the treatment of menorrhagia and fibroids. In the recent past, members of the EMW lab have developed hardware test setup and computer models capabilities (using multiphysics (EM – thermal) finite difference software) to evaluate the heating of perfused tissues by realistic models of RF ablation catheters.

In addition to medical device safety, CDRH has the responsibility in the federal government to study and assess the complex and challenging risks of exposure to humans from electromagnetic non-ionizing radiation from radiofrequency and microwave emitting electronic products. Scientists in the Electromagnetics and Wireless Laboratory work continually with other government agencies (e.g., Federal Communications Commission) and professional societies such as the IEEE International Committee on Electromagnetic Safety (ICES) to perform measurements and computational analyses to asses the safety of non-medical sources that expose persons to EM fields. Additionally, the researchers attempt to stay abreast of the many hundreds of papers produced annually on this subject.

Background

Wireless Technology and Electromagnetic Compatibility (EMC) For Medical Devices: For the past 10 years OSEL responded to numerous adverse event and other reports and evaluated many types of medical devices for their susceptibility to interference from electromagnetic-field-emitting sources such as wireless (cellular) telephones and magnetic-field emitting security devices. OSEL found the causes of several specific EMI problems and published results in the peer reviewed literature. In addition, OSEL was assigned by the CDRH Director’s office to lead the Electromagnetic Compatibility (EMC) working group that develops Center-wide solutions for medical device EMI problems (e.g., interference from metal detectors has caused many injuries to patients with implanted spinal stimulators). In a separate but related area, CDRH has been involved in responding to a number of concerns expressed by numerous groups about the safety of human exposure to electromagnetic radiation emitted by handheld wireless (cellular) telephones and other wireless devices. OSEL began addressing this issue by chairing or actively contributing to several international standards-setting groups. The groups developed wireless phone measurement standards that have been adopted by the FCC and others to test and approve cellular phones. A well-defined measurement standard is necessary if both the manufacturers of wireless devices and the regulatory agencies are to agree on compliance testing standards.

Computer Modeling and Laboratory Measurements to Determine Implanted Medical Device Heating Compatibility with MRI: Hundreds of thousands of MRI exams are administered per year, with a small but growing number of exams administered to patients

with medical implants. Additionally, surgical and diagnostic instruments are used during MRI exams. Manufacturers of these devices claim to FDA/CDRH (in their pre-market applications) that patients using these devices are safe since the devices are “compatible with the MRI environment.” In order to make a claim of MR compatibility for a device, manufacturers are asked to determine heating of the device produced by the pulsed RF fields used during imaging. They also are asked to determine magnetically induced forces and torques on the device, and image artifacts produced as a result of the presence of the device. In addition to implants, other medical devices are developed for use very close to MRI systems, such as leads attached to patients or instruments used during intraoperative MRI-guided surgery. The safety of patients with implants is generally good, but a number of serious injuries or deaths have occurred when implant-bearing patients have been exposed to MRI fields during routine exams. Additionally, burns under transcutaneous electrodes and other skin-mounted patches are well documented. This is due to the rapid heating to very high temperatures of metallic materials. The heating is caused by currents induced in the metallic object by strong RF magnetic fields emitted by MRI systems. In the past, OSEL engineers have performed relatively simple computer analyses and calculated the RF-induced energy delivered (and the heating rate) to a computer model of the human body (patient) during exposures to magnetic fields emitted by MRI systems, with a simple model of a single wire implanted in the body. The results were published in a peer-reviewed MRI journal (H. Ho 2001) describing that actual temperature increase of various body tissues was not calculated with blood flow and the resulting cooling.

Computational Modeling of Thermal Effects from RF and Microwave Medical Devices: Radiofrequency ablation devices refer to a diverse class of medical devices operating between 460-550 kHz that are used to deliver therapeutic energy with the intent of thermally necrosing tissue. In the heart, ablation is used to treat abnormal heart rhythms (arrhythmias). In the brain, it is used to treat Parkinson's disease. In soft tissues, such as the liver, breast, and kidney, ablation is used to eradicate tissue lesions and tumor tissue. In the uterus, it is used in the treatment of menorrhagia and fibroids. As a technique, radiofrequency ablation is widely used because it is inexpensive and relatively non-invasive.

In the past decade, ablation has supplanted surgery as the standard of care for many of its clinical usages. However, given the diversity in device design (i.e., probe geometry, power, number of electrodes, energy source, antennas), deployment methods (i.e., intravascular catheter design, laparoscopic "biopsy", percutaneous insertion), feedback mechanisms (i.e., constant power, constant temperature, PI/PID type controllers, gating, multistep control loops), and boundary constraints (i.e., vascular cooling in the liver, intracavity cooling in the heart and the uterus), it is not possible to generalize the performance of the devices from one model to the next through clinical study alone. An alternative means of evaluating the performance of ablation devices is through computational modeling. However, at present the techniques used in computational modeling efforts result in substantial inaccuracies of 40-50% or more. The inherent inaccuracies in present modeling

efforts limit the usefulness of computational modeling as an effective evaluation tool for ablation devices. This results in delays in the review process due to deficits in our ability to assess the most efficient means of establishing efficacy and safety. Current effort is directed at improving the accuracy of these models through refined computational and experimental techniques.

This is likely to impact the quality of reviews and can result in (1) the development of guidance documents; (2) improved computational analysis tools that identify key safety issues; and (3) new bench test methods that allow characterization of critical ablation parameters.

Research Program Description

Wireless Technology and Electromagnetic Compatibility (EMC) For Medical Devices: This project will utilize and build upon the expertise and facilities amassed in OSEL for medical device EMC and wireless technology research and production of much needed regulatory guidance and independent technical information. Key information must be gathered through laboratory measurements of the emissions of various products (e.g., wirelessly connected computer components, security type metal detectors, RFID) to assess the exposures and adequacy of existing medical device EMC design and testing criteria from appropriate standards. Additionally, many medical device standards do not address EMC or the use of wireless technology in or around the devices.

OSEL/DP also performs computations and measurements of the EM fields received by victim medical devices. OSEL must therefore develop the testing methods for device that minimize perturbation of the exposure field and testing artifacts, perform device testing, and develop standardized test methods that are cost-effective, consistent and reproducible by device and product manufacturers and EMC test laboratories. In addition, under this project computer modeling will be performed to simulate the wireless EMI situations that can arise when several emitters are located in proximity to one another. The project also includes studies and computer modeling of human expose and assessment for public health concerns. From the experience and success of previous work by OSEL in developing independent data and test methods for standards and guidance documents, we expect this project to succeed in producing vital data and valuable information for Center priorities.

Computer Modeling and Laboratory Measurements to Determine Implanted Medical Device Heating Compatibility with MRI: DP will measure temperature rises near many metallic implants in the ASTM and other tissue equivalent phantoms in clinical MRI systems and in their own whole-body RF coil from an MRI system. Additionally, DP will compute the temperature rise near metallic implants in models of a patient's body and in the ASTM phantom, exposed to RF fields from MRI devices. Computations will use realistic computer models of the human body, RF coils of MRI systems, and models of the various devices that are implanted or in contact with the body. A computer model that has

been validated by comparison to experimental data will be an extremely useful tool for ODE reviewers and for medical implant manufacturers. This can decrease the time and cost of demonstrating if a new MRI system will not cause RF heating. It can decrease the time spent by ODE on review, allowing products to be brought to market more quickly. DP will lead experts from around the world in an evaluation of the ASTM 2182-02a standard. DP will begin the of measurements and data analysis for an international intercomparison of heating from medical implants based on ASTM standard. In addition, whole-body SAR machine readings from MRI systems will be compared with measured SAR in phantoms, using calorimetry. This involves DP taking measurements in clinical MRI systems and collecting and analyzing the data from over ten other participants. The wok on SAR intercomparison will be vital in developing the next revision of the ASTM F2182 safety standard for MRI heating of medical implants.

Computer modeling: DP will analyze induced electromagnetic energy and the resulting heating in realistic computer models of a human body and MRI RF coils. Finite difference time domain software (FDTD) will be used. The FDTD software has high resolution (1 mm or smaller). DP will use a realistic computer model of the MRI coils, the human body, and the medical implants. Three representative MRI systems (1.5, 3 and 8T) will be modeled. The human model will have a realistic human shape and the electrical properties of at least 25 different tissue types. A second, simplified model using a gel and several rectangular areas (specified in ASTM F2182-02a Standard Test Method) will be used. The FDTD modeling will include thermal solver to account for cooling by blood flow.

Experimental methods: DP will calculate the rate of energy deposition (termed the local spatial specific absorption rate or SAR) and the rate of heating throughout the ASTM and other phantoms. DP will use its full-size 1.5 T MRI body coil to accurately produce RF exposures. In addition, DP will use a 3T MRI and other clinical systems at NIH clinical center. The temperature rise will be measured at points throughout a full-size model of a human with different medical implants. These data can be compared with computed heating information. DP will continue, in collaboration with others, to assess the observed measurement problems with fiber optic probes. We have performed feasibility studies to assess the utility of proton resonance frequency shift (PRFS) thermometry with several NIH clinical MRI systems. PRFS thermometry allows temperature to be measured throughout an entire body by the MRI system itself, without any external thermal probes.

Computational Modeling of Thermal Effects from RF and Microwave Medical Devices: Work will focus on computational model development, computational efficiency, and experimental measurement of the temperature-dependent properties of tissues. The goal of this effort is to develop compact and accurate modeling platforms that can aid CDRH in the pre-market review of new radiofrequency and microwave devices. The availability of validated computational tools may aid manufacturers in submitting more relevant data and

analysis that can significantly speed up device review. A significant portion of this work focuses on developing models that simulate the response of tissues to thermal injury.

Relevance to FDA /CDRH Mission and the Public Health Impact

Medical Device EMC -Hundreds of thousands of active (electrically powered) medical implants are prescribed per year. All of the patients with such implants are exposed to EM fields from security devices, cell phones, and other strong EM field sources. OSEL has demonstrated using *in-vitro* tests that interference in some of these devices can occur, and clinical problem reports validate these findings. Test methods developed under this project result in new test standards (e.g., pacemaker-defibrillator - AAMI PC69) that are implemented by active implant manufacturers, and thus protect patients. Additionally, this project addresses concerns about the possible harmful effects of persons exposed to radio frequency from wireless devices such as (cellular) telephones and other wireless devices. This project has produced measurements standards that have been adopted by regulatory agencies such as the FCC. This led to the limiting by cellular telephone manufacturers of emissions form their devices so that human exposures were reduced to the levels prescribed by international safety standards.

Computer Modeling and Laboratory Measurements to Determine Implanted Medical Device Heating Compatibility with MRI - Hundreds of thousands of MRI exams are administered per year, with a small but growing number of exams administered to patients with medical implants. Most patients with implants are denied MRI imaging. This can cause lethal tumors and other serious conditions to go undetected, even if they are imaged by other, less sensitive modalities. Without MRI, In addition, surgical and diagnostic instruments are used during MRI exams. This project can increase the safety or effectiveness of MRI compatible implants or bring them to market sooner and supports ODE in their reviews of medical device heating compatibility with systems. ODE review quality and timeliness will improve with the development of guidance documents; improved computational analysis tools that identify key safety issues; and the development of new bench test methods that allow characterization of critical parameters. This information will be used to assist with reviews and will result in definitive answers to important safety issues.

Computational Modeling of Thermal Effects from RF and Microwave Medical Devices: Over 200,000 Americans die annually from sudden cardiac death. Over 1,000,000 Americans are cancer patients. Over 40% of reproductive age women suffer from uterine fibroids and/or mennorhagia. All of these conditions are treatable with radiofrequency ablation. A number of ODE divisions have requested extensive information on thermal ablation in order to complete reviews (DRARD, DGRND, DAIGD and DCD). The lack of information has resulted, in some cases, in long review times and contentious advisory panel meetings. FDA is faced with a large number of therapeutic device applications that intentionally cause heating inside the body. We need to know the effects of ablative

heating on internal living tissues. Our scientific measurements of induced heating and tissue damage will be applied systematically to device approvals to prevent injuries and deaths caused by device interactions or inappropriate use of ablation devices. This project supports ODE directly in their reviews of ablation devices. ODE review quality and timeliness will improve with the development of guidance documents; improved computational analysis tools that identify key safety issues; and the development of new bench test methods that allow characterization of critical parameters. This information will be used to assist with reviews and will result in definitive answers to important safety issues.

Three-Year Goals

Wireless Technology and Electromagnetic Compatibility (EMC) For Medical Devices – OSEL/DP will perform measurements and computations for medical device EMC and will provide key information and independent data about medical device EMC and the use of wireless technology. It will develop specific test methodology and proposals for medical device and wireless emitter standards.

DP will also perform computations and measurements of the EM fields received by victim medical devices from widely used emitters of EM fields. These emitters will include high frequency emitters such as wireless local are network transmitters (Bluetooth, 802.11) and UHF Radiofrequency Identification (RFID) systems, and low frequency emitters such as metal detectors. DP will also perform measurements and computer models to address the safety of human exposure to electromagnetic radiation emitted by new wireless devices and other of personnel exposure such as metal detectors.

Computational Modeling of Thermal Effects from RF and Microwave Medical Devices - DP proposes a series of studies that are aimed at decreasing the error associated with computational modeling and improving the performance of bench testing. DP researchers also propose to conduct basic science studies to develop a sophisticated modeling platform that accounts for patient geometry and secondary phenomena, such as tissue perfusion, vasculature, temperature-dependent tissue properties, and tissue damage. Finally, DP proposes to develop and evaluate bench test methods with the development of computational models.

Computer Modeling and Laboratory Measurements to Determine Implanted Medical Device Heating Compatibility with MRI - DP will perform realistic computer modeling and confirmatory experiments in their labs to determine MRI-induced heating at the tips of implants such as neurostimulators and cardiac pacemaker electrodes. DP will develop efficient methods to verify medical device manufacturers' claims of limited MRI heating of existing or new implants. The methods will utilize advanced computational modeling and experimental methods. Measurements will be performed in clinical MRI systems to validate the computational methods. DP will work with ODE to draft an FDA guidance

document that will contain methods that manufacturers can use to demonstrate MRI heating compatibility. DP will investigate the weaknesses in the ASTM standard on MRI heating of implants and will work with the leading MRI safety researchers to improve the standard.

Accomplishments

Electromagnetic Compatibility (EMC)

Electromagnetic and Wireless Technology (EM) engineers developed a novel test method for generating high level magnetic fields from 0 to 1 MHz, and performed magnetic field susceptibility of medical implants. This system included a modified Helmholtz coils interfaced to a high current amplifier and was used to test implantable cardiac pacemakers and defibrillators in a tissue simulating saline tank. Results of the testing were presented to the AAMI PC69 Pacemaker EMC Committee, and at the 2006 FDA Science Forum. The test method and sample results were submitted and accepted for publication in a peer-reviewed journal. Of the Institute of Electrical and Electronics Engineers (IEEE).

EMW engineers developed a test method in collaboration with the Association for the Advancement of Medical Instrumentation (AAMI) Cardiac Rhythm Management Device Committee to assess the electromagnetic compatibility (EMC) of active cardiac implantable devices (pacemakers and implanted defibrillators) with the emissions from RFID (radio frequency identification) systems. Laboratory testing was performed with 22 different implantable pacemakers and 19 defibrillators. Seven different RFID readers (operating at 124 kHz, 13.56 MHz and 915 MHz) were used. Reactions were noted in several cardiac devices. Preliminary findings were shared with the AAMI committee, who is using the information to update the AAMI PC69 consensus standard. We presented the findings to the AAMI committee and are preparing a technical conference presentation and journal publication.

EMW in collaboration with the FDA's Center for Drug Evaluation and Research and the Center for Biologics Evaluation and Research performed a study of the effects of EM fields from RFID systems on solid and liquid pharmaceuticals and biologics. The RF fields generated by our systems are similar to those emitted by radiofrequency identification (RFID) readers operating in the U.S. licensed HF and UHF bands (13.56 and 915 MHz respectively). Our systems can exposed drug samples (pharmaceuticals and biologics) to uniform electric (E) and/or magnetic (H) fields at levels that are much higher than those experienced by drugs near "worst-case" readers at a distance of 20 cm. Exposures were performed for each drug in both its retail primary package and in 54 mm diameter culture dishes. We exposed a wide variety of formulations of drugs and biologics (tablets, liquids,

powers, capsules, creams). A detailed engineering paper was written for presentation at a 2007 RFID conference, and publication in the proceedings.

EMW staff led the development of a Level 1 guidance document titled "Draft Guidance for Industry and FDA Staff: Radio-Frequency Wireless Technology in Medical Devices." There is an expected public announcement of this document in early 2007. This deals with RF wireless emissions from one product or device that can affect the function of another. Current RF wireless technologies include Wireless Medical Telemetry Service (WMTS), cellular (mobile) telephones, wireless computers and computer networking components, personal digital assistants (PDAs), and RF identification (RFID).

Magnetic Resonance Imaging (MRI) Safety

There are significant problems in the current methodology used for the measurement of implant heating in MR systems per the ASTM F2182-02 standard. This is because testing of implanted medical devices (such as cardiac pacemaker leads) heating relates the temperature increase to the whole body specific absorption rate (SAR). To address this problem, EMW engineers developed an international SAR Intercomparison Protocol. The SAR Intercomparison Protocol is intended to determine the error in implant heating measurements when phantoms are used. Over 10 participants from several countries participated in this intercomparison which began in 2006. Preliminary results show a very wide variation (more than several hundred percent) in the results of the different participants.

Computer Modeling of Medical Implants In Patients Imaged By MRI

Finite Difference Time Domain electromagnetic computer simulations for active implantable medical devices (AIMDs) are currently performed in collaboration with our Virtual Family CRADA partner. Local SAR and heating of pacemaker and defibrillator leads are evaluated using different anatomical models. Based on the results we will be able to define realistic worst case test configuration for the ASTM phantom for heating measurements.

EMW engineers initiated a cooperative research and development agreement (CRADA) with The Foundation for Research on Information Technologies in Society (IT'IS).

Under the CRADA, EMW is collaborating in the development of four high-resolution anatomical whole-body computer aided design (CAD) models of an adult female, an adult male and two children (3-6 and 7-14 years of age). These very detailed models can be used with any electromagnetics program that accepts CAD models. Then, the program can be used to analyze heating around small (submillimeter) implanted leads in humans or other electromagnetic safety problems. All four models will be provided to the scientific community at no cost. Four volunteer persons have been scanned by MRI: a male, 34 years, 1.74m, 70kg, a female, 26 years, 1.60m, 58kg, a girl, 11 years, 1.48m, 34kg, and a

boy, 6 years, 1.07m, 17kg. The processing of the images (segmentation) is currently being performed to produce a CAD model of each.

Optical Therapeutics and Medical Nanophotonics Laboratory (Division of Physics)

Scope

The Optical Therapeutics and Medical Nanophotonics Laboratory (OTMNLab) was established as part of CDRH/OSEL's Division of Physics in September 2006. OTMNLab is responsible for the following:

► Maintaining state-of-the-art knowledge of the biomedical optics and laser field to assist the Center and Agency in the following:

- Evaluating new medical therapeutics devices that employ the latest minimally invasive medical laser technology.
- Evaluating critical fundamental parameters of key laser and fiber-optic components employed in recently developed optical therapeutics devices, including:
    - new therapeutic lasers such as ultra-short pico-/femto-second pulse lasers; low-power therapeutic lasers; ultraviolet, visible and near-/mid-infrared lasers;
    - new fiber-optic-based laser delivery systems such as solid-/hollow-core optical waveguides; ultraviolet, visible and infrared delivery fibers; and
    - new therapeutic monitoring and biosensing systems including ultrahigh-resolution nanoscopy and nanobiosensing.
- Developing standard test methods for evaluating the safety and effectiveness of new optical therapeutics devices and laser/fiber-optic components.
- Regulating hazardous emissions harmful to the unaware population.

► Studying fundamental mechanisms of light-tissue interactions at cellular/intracellular levels using state-of-the-art fiber-optic-based nanobiosensing, imaging and monitoring techniques such as smart fiber nanosensing probes, effective low-level laser therapeutics systems, ultrahigh-resolution confocal microscopy and optical coherence tomography.

► Studying working light-tissue interaction mechanisms for optimizing effectiveness and safety of

- laser therapeutic devices
- photodynamic cancer treatment
- low-level laser therapeutic devices

- precise laser-tissue manipulation/ablation in ophthalmology, dentistry, dermatology, cardiology and neurosurgery
- cellular/tissue repair
- light-assisted neuron stimulation/growth

Background

Biophotonics is an emerging biomedical technology that is increasingly being applied in the extensive areas of life sciences and medicine. Minimally invasive biophotonics techniques have been recently developed as potential alternatives to conventional medical methods for diagnostics, monitoring and treatment of a variety of diseases, drug discovery, proteomics, and environmental detection of biological agents. These techniques offer a non-contact, effective, fast and painless way for sensing and monitoring of various biomedical quantities. Medical devices utilizing minimally invasive biophotonics technology are rapidly finding their way into the mainstream for early disease diagnosis and improved patient acceptance and comfort.

Currently we are faced with the need to prepare for evaluation of devices being developed to optically diagnose and threat various diseases including pre-cancer and cancer conditions. Optical therapeutics approaches are being proposed that use high-intensity ultra-short laser radiation, precise delivery fiber optics and near/mid-infrared biosensing and monitoring. However, although there have been extensive research efforts recently, there is a fundamental lack of understanding the working mechanisms of light-tissue interactions involved with various optical therapeutics techniques and devices. These mechanisms need to be understood at the cellular and intracellular level in order to optimize effectiveness and ensure safety of laser therapy, photodynamic cancer treatment, precise laser tissue manipulation, ophthalmic therapeutics, pain relief, light-assisted cellular and tissue repair.

Furthermore, recent research efforts and developments in the area of biophotonics technology have confirmed its compatibility with the modern nanotechnology trends, which has opened new horizons for development of alternative technologies that provide unprecedented, ultra-high nanoscale resolution for single cell and intracellular monitoring and manipulations as well as nanobiosensing of specific target molecules and intracellular analytes. Thus, exploiting the nanophotonics approach in the optical therapeutics field will provide new quantitative knowledge of the molecular and cellular mechanisms of light-tissue interactions for optimizing effectiveness and critical parameters of recently developed optical therapeutic techniques and devices.

Research Program Description

OTMNLab research program is determined by an integrated biophotonics laboratory structure that includes the following four basic components of an optical/laser therapeutics technique and device:

- ► therapeutics coherent (lasers) or non-coherent light source
- ► fiber-optic laser delivery system
- ► therapeutics monitoring and biosensing system including ultrahigh-resolution nanoscopy and nanobiosensors
- ► novel optical therapeutics systems including alternative light-tissue interaction mechanisms

Based on this integrated research structure, the OTMNLab research program consists of the following current research and regulatory related projects:

Optical Nanobiosensors for Minimally Invasive Intracellular Monitoring

Minimally invasive photonic biosensor techniques are potential alternatives to conventional medical methods for diagnosis of diseases. These techniques offer an effective, fast and painless way for sensing and monitoring of various biomedical quantities. Over the past several years, progress in nanotechnology has led to the development of novel optical nanobiosensors, which are sensors with dimensions on the nanometer scale. This has opened up new horizons for single cell and intracellular sensing and measurements. Cellular and intracellular light-tissue interaction mechanisms and photochemical processes need to be understood in order to optimize effectiveness and ensure the safety of laser therapy, photodynamic treatment, cell-microbe interactions, and microbial ecology.

The project objective is focused on the study of fundamental light-tissue interaction mechanisms at the cellular and intracellular level using fiber-optic nanobiosensor probes equipped with tapered nanometer scale sensing tips. The nanobiosensors will be utilized for direct probing and chemical analysis within individual cells and within the subcellular organelles. In this way we will be able to detect small concentrations of target molecules or intracellular analytes such as reactive oxygen species, calcium, and glucose. To realize the project goals, we will apply various experimental approaches and methods including direct optical spectroscopy, time-correlated single photon counting method, smart fiber-optic sensor probes, and high-resolution imaging techniques. The results of the study are important to understanding basic medical processes including the process of photodynamic cancer cell killing, the introduction of cancer causing environmental agents through the epidermal barrier, the generation of beneficial chemicals and cellular repair, and the effects of light activated oxygen. The mechanisms of light-tissue interactions identified by the experiments could play a pivotal role in determining safety and effectiveness both in laser and photodynamic therapy.

Minimally Invasive Optical Imaging of Biological Tissue

Despite the broad range of currently available microscopic methods, conventional optical microscopy remains the most widespread imaging technique because it is noninvasive, nonionizing, reliable, inexpensive, and easy to use. Two of the most extensively used and promising modern optical imaging techniques are confocal microscopy and optical coherence tomography (OCT). Because of their ability for high–resolution, minimally invasive optical sectioning, confocal and OCT techniques not only enable three-dimensional high-resolution microstructure imaging of bulk tissue specimens, but are also used to study cellular and intracellular structures and processes. These technologies have been applied to human brain function imaging, living cell tracing, gene mapping, breast cancer detection and high-speed intravascular monitoring. The aims of this research include studying the fundamental principles, critical parameters, advantages, and limitations of the confocal microscopy and OCT as high-sensitive three-dimensional bioimaging and sensing modalities, evaluating critical parameters of novel fiber-optic-based systems and investigating novel techniques for characterization and diagnostics of tissue optical properties.

Toward Accurate Photodosimetry in Minimally Invasive Laser Therapeutic Devices Based on Laser Beam Propagation Through Turbid Tissue

To optimize the effectiveness and safety of both continuous-wave (CW) and ultra-short (pico- and femtosecond) pulsed laser systems used as diagnostic and therapeutic medical devices, knowledge on both dynamic behavior of basic laser parameters such as wavelength, intensity, specific temporal and spatial beam characteristics, and the optical tissue properties including its absorption and scattering characteristics is of fundamental importance. The primary objective of this project is to study the fundamental principles and effects at both CW and ultra-short pulsed laser beam propagation through biological tissue with various optical properties including highly scattering and thick tissue samples in order to improve the accuracy and specificity of photodosimetry in minimally invasive laser therapeutic procedures and devices.

The study includes various independent theoretical and experimental approaches such as: 1) direct three-dimensional imaging (both optical and thermal imaging) of CW and ultra-short Gaussian laser beam profiles though tissue using a single-mode-fiber based technique; and 2) a simulation method for a comparative analytical study of CW vs. ultra-short laser beam parameters at laser beam propagation in highly scattering tissue samples with various optical properties (scattering and absorption coefficient, anisotropy factor, thickness). We have experimentally and theoretically studied fundamental CW and ultra-short laser beam propagation parameters including intensity beam distribution, divergence, beam focal sizes, temporal pulse shape dispersion, possible thermal lensing and defocusing effects, at Gaussian laser beam propagation in single and multi-layered tissue samples. The findings of this work are useful for understanding basic laser-tissue interaction mechanisms at CW and ultra-short pulsed laser beam propagation in highly scattered tissue media. Relevant results will be incorporated into test methods for evaluation of critical

laser photodosimetry parameters and safety criteria for diagnostic and therapeutic laser devices.

Laboratory Evaluation of Intraocular Lens Implants

This research and regulatory related project is focused on the development of a standard test method for evaluating glare from intraocular lenses (IOLs), to obtaining data on high negative and positive diotric power lenses, special high accuracy dioptric power lenses, and toric lenses, and on the development of a standard test method for evaluating the optical quality of glistenings in IOLs. The major technical accomplishments included the development of a simple, accurate, completely objective, quick and inexpensive method for measuring the focal length of various focusing elements including positive and negative IOLs, objectives, lenses, contact lenses, eyeglasses, and mirrors. Based on this novel test method, a PCT International Pending Patent was filed and FDA is proposing that this method be incorporated into national and international IOL standards. We have developed also a standard test method for evaluating glare from IOLs, which methods can be used to characterize and pinpoint the source of extraneous glare images from intraocular lens implants from point light sources. The haptic insertion in the optic of three-piece IOL's has been identified as a source of line glare images.

Therapeutics Lasers: Ophthalmic, Cardiovascular, Dermatological

CDRH's interest in the use of ablative lasers for ophthalmic corneal surgery and cardiovascular indications (myocardial revascularization, and laser angioplasty) continues. Ablative lasers of immediate interest include an Er:YAG solid state laser for photo-refractive corneal surgery and, both a CO_2 gas laser and the Ho:YAG solid state laser for transmyocardial revascularization. These laser devices are in various stages of approval while their trial or clinical use remains very controversial. Currently, there are no guidelines or standards for determining the ablative performance of a therapeutic laser device, with the exception of the excimer laser used for corneal surgery. This project will contribute to our understanding of the laser-tissue ablation process and to the development of guidelines for these ablative lasers. The above work applies to all ablative lasers, i.e., ophthalmic, cardiovascular, and cosmetic. This work will also add to the knowledge base for ablative laser technology so that when changes are sought for approved devices, the criteria for the required qualifying bench testing will be established, and additional clinical trials may not be necessary.

Relevance to FDA /CDRH Mission and the Public Health Impact

Optical Radiation-Emitting Devices

This project provides direct support for regulatory activities related to optical radiation emitting products and medical devices. In addition, through the measurements efforts of this laboratory, OSEL scientists gain the needed expertise to develop and improve national

and international standards for the safety and efficacy of optical radiation-emitting devices and often serve as consulting reviewers for IDEs, PMAs and 510(K)s. The use of standards to which manufacturers can claim conformance of their products shortens review time for new medical devices.

Optical Radiation-Transmitting Devices

Stakeholders have been engaged in all aspects of the work undertaken on this project. All of the work performed on this project in recent years was requested by stakeholders (colleagues in DOED/ODE). The use of standards which are developed as part of this effort shortens review time for new medical devices.

Three-Year Goals

- Provide technical support for the amendment of the FDA and international standards for lasers and sunlamp products. OSEL will serve as the lead office in the amendment of the FDA Performance Standard for Sunlamp Products.
- Represent FDA on numerous national and international consensus standards committees dealing with optical radiation-emitting/transmitting devices.
- Provide laboratory support for regulatory decisions related to the optical quality of IOLs as needed.
- Provide optical bench testing of the dioptric power of new IOL designs as needed by ODE.
- Provide ray tracing analysis of new IOL designs as needed by ODE.
  Develop and incorporate standard test methods for evaluating the optical power of IOLs in national and international standards.
- Complete development and incorporate standard test method for characterizing the potential for glare or unwanted images from new IOL designs in national and international standards.
- Develop and incorporate standard test method for characterizing the potential for glistenings with new IOL materials and designs in national and international standards.
- Develop and incorporate a standard test method for evaluating the dioptric power of new IOL designs and contact lenses in national and international standards.

Accomplishments

FY 2006 OTMNLab research and regulatory based activities were focused on developing, experimental testing and evaluating fundamental characteristics and features of alternative independent methods for the following:

- fiber-optic confocal laser testing optical properties of various positive and negative intraocular lenses (IOLs)

- ultra-high-resolution fiber-optic-based confocal microscopy beyond the diffraction limit in the nanometric scale
- all-hollow-waveguide laser delivery used for digital particle image velocimetry
- testing and characterizing the source of extraneous glare images from intraocular lens implants from point light sources

Research accomplished:

1) Developed, experimentally tested and filed a PCT International Pending Patent for a novel fiber-optic confocal laser test method for characterizing optical properties (i.e., dioptic power, transmission) of various positive and negative intraocular lenses.
2) Developed, experimentally tested and filed a PCT International Pending Patent for a novel method for ultra-high-resolution fiber-optic confocal microscopy beyond the diffraction limit in the nanometric scale.
3) Developed, experimentally tested and filed a PCT International Pending Patent for a novel method for delivery of high-power laser emission used in digital particle image velocimetry, which is based on an all-hollow-waveguide approach.
4) Developed and experimentally tested an alternative method for testing and characterizing the source of extraneous glare images from intraocular lens implants from point light sources. The haptic insertion in the optic of three-piece IOL's has been identified as a source of line glare images.
5) Designed, assembled and calibrated a fiber-optic confocal laser measurement system for *in-situ* testing (in balanced salt solution at 35 deg C) of IOL samples with various focal lengths in the range of 5-30 diopters.
6) Designed and experimentally tested alternative techniques for drawing nanobiosensor fiber probes with waveguide core sizes in the submicron and nanometric spatial range.
7) Developed experimental methods for testing and evaluating fundamental parameters and characteristics (i.e., geometrical parameters, transmission optical properties, numerical apertures, output intensity beam profile) of nanoscale size fiber sensor probes at various laser wavelengths
8) Developed methods for testing and evaluating fundamental laser beam parameters including 3-D intensity beam distribution, divergence, beam focal sizes, possible thermal lensing and defocusing effects, at laser beam propagation in single and multi-layered tissue samples.

Optical Diagnostics Laboratory **(Division of Physics)**

Scope

The rapid proliferation of medical devices employing minimally-invasive optical technology is revolutionizing modern health care. However, these devices also represent a significant new challenge to FDA. For many of these devices, guidance documents and reliable test methods are currently not available. Basic mechanism data is needed to facilitate the development of relevant evaluation criteria early in the regulatory process, thus enabling thorough and swift reviews of this cutting edge technology. The Optical Diagnostics laboratory program works to generate this data through studies of light-tissue interaction mechanisms, device performance and tissue safety for a variety of optical technologies. This program is located within the Division of Physics (DP).

Background

Prior to the formation of the Optical Diagnostics (OD) Laboratory, work on optics-based medical devices was performed by the Electro-Optics Branch (EOB) an entity that traces its history to the Bureau of Radiological Health (BRH). In the 1970s, EOB developed techniques for laser radiation measurement and contributed to the development of the Laser Product Performance Standard, which described performance requirements for a wide variety of laser-based devices. In the 1980s, EOB was incorporated into FDA and took on the task of performing research in preparation for regulatory reviews of laser-based therapeutic devices, such as laser angioplasty and surgical ablation lasers. As this effort progressed, it became apparent that there was a strong need for information on the fundamental mechanisms underlying light-tissue interaction. Therefore, EOB began to undertake studies on optical property determination, the influence of device probe design and test methods for device evaluation. In the 1990's, EOBs research focus began to shift once again, incorporating short pulsed laser ablation of corneal tissue and bioeffects of ultraviolet lasers as well as optical diagnostic approaches and the methods used to analyze detected optical spectra. These new areas of interest reflected both the approaches being developed in academic settings as well as topics of concern to ODE.

Since the 1990s, the most revolutionary optical technologies under investigation in academia and industry have been diagnostic ones, with the goal of enabling disease detection and physiological monitoring. In order to address these novel approaches, the OD laboratory was formed and began to incorporate more topics relating to light-based diagnostic devices. During the past 5 years, the laboratory has grown significantly, and now contains facilities for characterization of the basic optical properties of tissue; high precision fluorescence property measurements; a time-resolved fluorescence system; a fiberoptic-based reflectance spectroscopy systems, a portable fluorescence system, an optical coherence tomographic imaging system and facilities for computational modeling. Certain lines of research in the laboratory are more mature and have resulted in publications on basic light-tissue interaction mechanisms relevant to optical property determination and fluorescence spectroscopy. New projects which were started with MDUFMA funding 2 years ago are also beginning to produce significant results.

Research Program Description

Research in the OD laboratory is focused on generating knowledge that will enable CDRH staff to quickly and accurately evaluate the safety and efficacy of novel optical devices. By investigating the underlying light-tissue interaction mechanisms which affect device performance it is possible to develop a more thorough and accurate understanding of device behavior. Studies performed in this laboratory typically utilize both experimental and theoretical approaches to elucidate basic phenomena, develop test methods, and assess potential problems with optical devices.

Much of the research performed in the OD laboratory centers on fluorescence spectroscopy devices for neoplasia detection. Fluorescence-based techniques evolved steadily over the past 15 years and several fluorescence-based devices have been cleared by FDA. However, the majority of prior research has focused on application-oriented issues and clinical studies. As a result, many basic issues regarding light-tissue interaction remain poorly understood.

Characterization of the fundamental optical properties of biological tissue is one of the most fundamental and significant areas of research performed in the OD laboratory. Accurate data on optical properties can be critical to the validity of theoretical analyses. While the literature contains extensive data on tissue optical properties at certain visible and infrared wavelengths, data for ultraviolet and shorter visible wavelengths are uncommon. The literature contains even less data on *in vivo* measurements of tissue optical properties. Therefore, we have been investigating approaches for reflectance-based measurements of tissue optical properties at several important UV and visible wavelengths. The system uses a small fiberoptic probe which is suitable for *in situ* measurements. This project has required research on computational modeling of reflectance, tissue phantom construction, *in vitro* optical property validation, mathematical approaches for inverse modeling, and optical instrumentation issues. This research has already generated a number of insights into the measurement of fundamental tissue optical properties.

While fluorescence spectroscopy has proven an effective and popular technique, researchers are trying to obtain greater levels of accuracy in disease detection by exploring alternative fluorescence-based approaches. One of these is time-resolved fluorescence, which involves monitoring decays in emission intensity on the scale of nanoseconds. In order to gain experience with this promising technique and generate critical information on the mechanisms involved, the OD laboratory has performed experimental investigations to characterize a typical time-domain system and is currently performing preliminary investigations of components for multi-layer tissue phantoms.

The OD lab's efforts also extend to identifying and characterizing potential problems with novel optical techniques so as to provide needed data for consults with ODE and development of guidance documents. One issue is that confounding factors such as

exogenous fluorophores contained in intravenous drugs have the potential to interfere with endogenous fluorescence (autofluorescence) measurements. In order to assess this issue, the OD laboratory has characterized the fluorescence properties of drugs suspected to be strong fluorophores, using a high-precision spectrofluorometer. Several drugs such as fluoroquinolones have shown high quantum yields. Given the pharmacokinetics of these drugs and their distribution in biological tissues, results indicate that interference with fluorescence-based diagnostics has the potential to be significant.

High resolution optical imaging devices based on optical coherence tomography (OCT) represent another area of rapid growth over in the medical optics field. This technique has shown great promise for real time, fiberoptically delivered *in situ* imaging for detection of mucosal neoplasia, atherosclerotic vulnerable plaque detection, and ophthalmic diseases. The OD laboratory has recently started a research effort to elucidate the basic mechanisms of OCT and its performance characteristics. We have purchased and modified a novel type of OCT system and performed basic characterization of its imaging capabilities. We have an ongoing collaborative study with nanotechnology pioneers at Rice University (Professor R. Drezek) to investigate and characterize the performance of nanoparticle-based contrast agents for OCT. We have published initial results on the optical properties of nanoshells and will continue with more rigorous spectrophotometric measurements as well as a study of nanoshell-based tissue phantoms as a novel test method for evaluating the performance of OCT systems.

In general, the OD program addresses the current gap in scientific knowledge by conducting experimental and computational studies of optical diagnostic techniques, developing test methods and investigating potential problems with devices. Data generated in these studies are essential for reviews of novel devices which are being submitted to CDRH, and for development of guidance documents and standards which streamline the review of these products.

Relevance to FDA /CDRH Mission and the Public Health Impact

The OD laboratory performs research on novel optical device technologies that are critical to the FDA/CDRH mission of providing the public with safe and effective medical devices. This research will benefit public health both through facilitation of the regulatory pathway, and by providing information to researchers and device developers that will assist the development of optimal devices.

During the 5-year period ending in December 2002, 10% of PMA's and 7% of IDE's received by CDRH were in the area of minimally invasive optical technologies. The OD laboratory investigates these high priority optical technologies in order to assist Center reviewers in the timely assessment of manufacturer's submissions. We actively support ODE regulatory scientists in clinical fields such as gynecology, dentistry, gastroenterology, anesthesiology, urology and cardiology. OD scientists are also currently lending their

expertise to the development of a guidance document for optical-based detection of cervical neoplasia.

The technologies that the OD laboratory covers are critical to public health, such as fluorescence-based detection of mucosal neoplasia. Cancers of mucosal tissues such as those found in the cervix, colon and oral cavity represent some of the most prevalent and deadliest cancers. It may be possible to substantially reduce the mortality associated with these cancers through more effective screening and early detection. However, the current standard screening practices for these cancers are not ideal and frequently have low sensitivity, high cost, and long waiting times for diagnoses, which can result in missed follow-up exams. Light-based screening techniques currently under development may provide near-real-time results. These devices will improve clinical ability for early detection of mucosal cancers. The OD laboratory research is helping to facilitate the clearance of optical diagnostics devices which are effective in detecting cancers. Furthermore, many optical-based devices carry potential risks related to over-exposure by visible and ultraviolet radiation. Research and regulatory tasks performed by the OD laboratory help to ensure that devices which are cleared by FDA do no harm to patients when used in accordance with proper labeling.

Three-Year Goals

- Perform and publish high quality scientific studies on our core issues:
    - Fundamental mechanisms of novel optical diagnostic devices
    - Test methods for evaluating device performance
    - UV radiation safety of optical diagnostic devices

- Continue to improve our standing in the scientific community through conference attendance and participation in "professional development activities."

- Enhance our interaction with other offices within CDRH and other centers within FDA, as well as the quality of interaction with existing contacts so as to maximize our impact within the agency.

- Complete a guidance document on optical spectroscopy.

- Identify new high importance issues that arise in the field before they arrive at FDA as device submissions.

- Prepare for and execute a smooth, swift transition to the new laboratory at White Oak; develop the new laboratory into a state-of-the-art biomedical optics facility.

Accomplishments

Mechanisms of optical spectroscopy-based diagnostic devices for neoplasia detection

- Developed and calibrated a novel multi-wavelength optical property measurement system
- Performed initial validation of experimental system and control/acquisition/processing software routines.

Evaluation of the potential for medications to interfere with fluorescence diagnostics

Determined the fluorescence effective concentration for several biochemical constituents used in medications and used this data to evaluate potential for fluorescence interference under various conditions.

Data processing of time-resolved fluorescence measurements

- Developed a novel analytical tools for analyzing time-resolved fluorescence signals using biexponential iterative deconvoltion and a LaGuerre fitting approach.

- Evaluated the efficacy and robustness of the LaGuerre approach as well as several other standard techniques for analyzing time-resolved fluorescence signals.

Characterization of optical coherence tomography-based imaging approaches

Performed preliminary set of spectrophotometric and OCT-based measurements to (a) determine the attenuation and backscattering coefficients of gold nanoshells (b) evaluate the influence of polyethylene glycol (PEG) on nanoshells optical properties and (c) evaluate the accuracy of theoretical predictions.

Fluid Dynamics Laboratory **(Division of Solid and Fluid Mechanics)**

Scope

Fluid dynamics, as it applies to medical devices, can be broadly defined as the interaction of moving fluids with medical devices; both as the device affects the moving fluid and as the moving fluid affects the device. Often the moving fluid is blood, as in the flow of blood through a heart valve or through the filters and pumps of a renal dialysis apparatus. Damage to the flowing blood can result in serious clinical consequences, up to and including death. Damage to a device, such as might be caused by cavitation in a heart valve, can lead to catastrophic device failure causing death. Accordingly, the Laboratory of Fluid Dynamics, located in the Division of Solid and Fluid Mechanics, maintains a research program focused on the fundamental factors governing the interaction of flowing fluids with medical devices and the development of test methodologies to objectively characterize such interactions and their consequences.

Background

The interaction between biological fluids, especially blood, and medical devices is complicated in part because blood is not an ideal fluid. Rather, blood is a complex, living tissue consisting of deformable particulates (cells) suspended in a liquid phase (plasma) which itself has multiple constituents (ions, proteins, dissolved gases). Accordingly the "mechanical" characteristics that describe fluids (e.g., viscosity) are (nonlinear) functions of shear rate, hematocrit, and the like. As well, the extent to which the physiological functions (e.g., oxygen carrying capacity, ability to clot) of blood may be compromised by its passage through a medical device depend not only on physical factors describing the flow (e.g., shear rate) but also on time of exposure. Similarly, whether the function of a medical device will be compromised by its interaction with flowing blood (e.g., cavitation damage to a heart valve, flow reduction by clot formation in a blood pump) is a complex function of the flow dynamics within the device.

Therefore, to fulfill our functions as regulators and as scientists and engineers the Fluid Dynamics Laboratory continues to develop and to assess analytical (computational fluid dynamics) and measurement (flow visualization, hemolysis, platelet activation) techniques to better study the interaction of flowing fluids with medical devices.

Research Program Description

The Fluid Dynamics Laboratory can be conceptually viewed as having two broad areas of focus: one being oriented toward specific device types and the other being oriented toward methods and techniques that are applicable across device types.

As an example of the device type-specific focus, we have recently been a participating laboratory in a round-robin evaluation of the pulsatile flow characteristics of several specific prosthetic heart valves. This effort was driven by concerns expressed by industry and FDA that the results of such characterization were variable, and depended on the specific test equipment and test conditions utilized. Thus our laboratory, in collaboration with four manufacturers of prosthetic heart valves, characterized the pulsatile flow performance of particular heart valves under given sets of conditions. Our results indicate significant variability among laboratories, suggesting the need for tighter controls on standardized test equipment and protocols, and possible revisions to existing standards.

Other device-specific investigations have been directed at the pressure-flow characterization of cerebral-spinal shunts and at the flow patterns observed in vena cava filters.

As an example of the methods and techniques focus we have been developing skills in computational fluid dynamics, a mathematical modeling technique that allows us to predict flow patterns in and around complex medical devices. These skills have been applied to specific tasks, such as the modeling of flows in/around vena cava filters to investigate

factors that potentiate clot formation and the modeling of flow through vascular stents to investigate factors that affect the elution of drugs from the luminal surface.

Another methods and techniques effort is the investigation of different methods to quantitate damage to formed elements (e.g., red blood cells and platelets) as blood interacts with medical devices such as implanted and external blood pumps, vascular stents, and other such devices. Of note, we are bringing together multiple techniques (flow visualization, computational, and measurements of elevated physiological indicators of blood damage such as plasma free hemoglobin and platelet activation) to address this problem that is common to so many types of medical devices.

Relevance to FDA/CDRH Mission and the Public Health Impact

Work in this laboratory has been of value in both the pre-market and post-market arenas. Our skills with computational fluid dynamics have allowed us to assist staff in the Office of Device Evaluation (ODE) with their assessment of the safety of design changes proposed for complex, life-supporting mechanical circulatory support devices intended for long-term implant. Likewise, our expertise in blood damage has served the Office of Compliance (OC) in their assessment of adverse events observed with the use of renal hemodialysis equipment, and in the determination of the likely effectiveness of the "fix" proposed by the equipment manufacturer. Of note in this later case was our use of computational techniques to support the measurements of our blood damage group. In addition to our on-going support for ODE and OC, we are involved with multiple standards organizations; our staff have been instrumental in the development of national and international standards. Additionally, our attendance and presentations at professional meetings serves to make the results of our research available to the community, as do our multiple on-going collaborations with academic scientists and engineers.

Three-Year Goals

Based on our experience to date the Fluid Dynamics Laboratory proposes to expand its analytical capabilities by taking advantage of newly developed commercial software to allow computational modeling of "disturbed" flow; that is, flow in transition from laminar to turbulent; such flow is often encountered in medical devices. We also plan to increase the scope of our experimental techniques by extending our current flow visualization capabilities from two dimensional to three dimensional to accommodate the complex flow patterns seen in medical devices, most notably in mechanical circulatory assist devices. We currently have significant expertise in monitoring hemolysis; we will complement this by assessing multiple techniques to determine platelet activation, a prime factor in thrombogenesis. Finally, it is our intent to combine our analytical and experimental skills to allow us to investigate the relationships between physical factors that describe the dynamics of flowing blood and the resulting degradation of the physiological functions of blood.

Accomplishments

Flow visualization of vena cava filters

- Trapping efficiency of simulated clots was assessed. All tested filters demonstrated high capture efficiencies for medium and large sized simulated clots, and some demonstrated poor efficiency for small clots. Two-stage filters had higher capture efficiencies than the single stage designs. Two-stage filters caught the majority of clots in the proximal filter section, while the single stage filters caught the clots in the distal apex section of those conical filters. Final report is in preparation and will be submitted for peer review publication

Flow visualization studies of simulated clots were completed for selected filters. Computerized fluid dynamics (CFD) modeling results are being generated to compare with the experimental results. Preliminary results of the experimental data indicate that filter design may influence conditions that promote thrombus formation and occlusion.

Prosthetic heart valves (Bernoulli, and interlaboratory comparison, cavitation)

- Analyzed interlaboratory study data. Substantial site-to-site variability was encountered. Published abstract and presented poster at the Society for Heart Valve Disease, June 2005. Final report in preparation.

- Advanced the Bernoulli portion of interlaboratory study to include testing at Aachen, Germany.

- Completed data acquisition to evaluate the reliability of acoustic techniques to detect cavitation using a hyperbaric chamber in collaboration with NSF and Florida Atlantic University. Abstract and poster expected at the 2006 ASAIO.

Computational studies of fluid and chemical transport in vascular devices

- **Vena cava filters.** Computational studies of vena cava filters with and without clots have been validated by laboratory flow visualization experiments. Parametric computational studies of the effect of clot size and shape on important flow parameters (e.g., shear stress) are underway and almost complete. Methods for calculating and displaying shear stresses and recirculation times are being developed. A paper to disseminate the knowledge gained is in preliminary draft form.

- **Drug eluting stents.** A study of a coronary stent deployed into an artery, expanded, and then the drug delivered into the arterial tissue has been developed by industry colleagues, with FDA help. Parametric studies are planned for this model, to determine what variables are important in such computational models.

- ***In vivo* tissue engineered vascular grafts.** This collaborative study of the effects of vessel curvature on the blood-wall transport of cells and chemicals has been completed. A paper detailing the results is due to be published in the February 2006 issue of *Applied Biomaterials*.

Evaluation of blood damage caused by medical materials and devices

To assist in the preclinical hemocompatibility safety evaluation of medical devices, *in vitro* blood damage testing using animal blood is often conducted. However, the usefulness of the data in making regulatory decisions is limited due to biological variability of the blood, the lack of standardization in performing the testing, and uncertainty in interpreting the test results. In order to address these deficiencies, we developed two different models for *in vitro* blood damage testing which mimic blood flow in medical devices. It is important to note that the volume of blood needed with each model is small so that eventual comparisons between animal blood and human blood, which is more prone to damage, can be made. Model #1 is a single-pass model in which 2 mL of blood per test are forced through a small orifice. This model simulates the high damaging forces which may occur in medical devices when blood flows through constrictions (e.g., kinked hemodialysis blood tubing, obstructed heart valve leaflet). Model #2 incorporates a 1 mm inner diameter flow tube (30 mm long) and uses a recirculating flow loop design, which is often used to test medical devices on the bench. Model #1 is being used to assess how blood conditions which may alter red blood cell fragility (e.g. blood age, anticoagulant, glucose level, antibiotic, temperature) affect the reproducibility of the test results. Model #2 is being used to validate the results under lower shear stress conditions which are more representative of typical use. Blood damage results for the single-pass orifice model with bovine blood under standardized conditions showed high reproducibility over a range of flow rates (hemolysis varied by less than 5% between runs). To apply this research to predicting medical device safety, future *in vitro* blood damage experiments will be performed to compare the differences between animal and human blood.

- Two physical flow models were developed and used to perform standardized *in vitro* blood damage testing with bovine blood.
- To meet the program objective of correlating shear force exposure to actual blood cell damage (hemolysis and platelet activation), the geometries of the physical flow models were reproduced in a Computational Fluid Dynamic simulation program.
- Initiated the development of assays to evaluate platelet activation (based upon flow cytometry of fluorescently labeled cells, platelet aggregometry, enzyme-linked immunostaining methods, and particle cell counting).
- Initiated laboratory validation of the *in vitro* blood damage testing protocol written by OSEL for the new guidance document on hemodialysis blood access catheters.

Ultrasonics (Division of Solid and Fluid Mechanics)

Scope

Medical ultrasound spans a wide array of diagnostic, therapeutic, and surgical applications. An important part of establishing the safety and effectiveness of these devices is acquiring accurate and meaningful pre-clinical performance information. Therefore, to support the regulatory review of these products, the Ultrasonics Laboratory, located in the Division of Solid and Fluid Mechanics, maintains a research program devoted to exposure measurement and analysis, and guidance and standards development.

Background

In contrast to the early history of the medical uses of ionizing radiation, the initial applications of ultrasound for medical or biological purposes were therapeutic and surgical, so there was an awareness of a potential for risk associated with exposure to ultrasonic energy. This early concern for safety was heightened because of the prospect for widespread use of ultrasound imaging in obstetrics, an expectation that has been realized. Also, clinicians and scientists recognized that both the safety and effectiveness of applications in therapy and surgery were dependent on accurate assessment of the exposure levels. Unfortunately, acceptable instruments and methods for quantifying the acoustic field variables that define the extent of exposure were lacking. To assist in addressing this deficiency, and to fulfill our responsibilities under the Radiation Control for Health and Safety Act (RCHSA) and later the Medical Device Amendments, CDRH and its predecessors began an ultrasound regulatory research program in the early 1970's. This work has led to a number of advancements in the field, as well as a regulatory performance standard under the RCHSA and several national and international consensus standards now recognized by CDRH, along with related industry guidance documents.

The medical uses of ultrasound continue to expand. Applications now being performed or under clinical investigation or development include physiotherapy, diagnostic imaging and Doppler, extracorporeal shock wave therapy, low-frequency surgery, hyperthermia, focused ultrasound ablation, acoustic hemostasis, and ultrasound-mediated drug delivery. These new uses have been accompanied by new challenges in evaluating safety and effectiveness, such as characterizing devices used for high intensity focused ultrasound surgery. Increased knowledge about the potential for biological effects has bolstered the need for critical evaluation of these new devices. Therefore, current laboratory efforts include the development of new measurement and analysis methods. The results will be made available to the scientific and regulatory communities via symposia presentations and peer-reviewed publications, and they also will serve as input to guidance documents and consensus standards.

Research Program Description

Evaluating the safety and effectiveness of medical ultrasound transducers and systems entails several levels of activity. First, the temporal and spatial characteristics of the exposure field that are relevant to the potential for adverse biological effects need to be ascertained. Second, system characteristics that are germane to device performance and efficacious use must be identified and quantified. In performing these tasks, both theoretical modeling and *in vitro* or *in vivo* measurements are essential.

Ultrasonics Laboratory scientists and engineers are engaged in all of these activities. Previous accomplishments include the development and characterization of ultrasonic hydrophones and the calculation of steady-state and transient temperature rises under various ultrasound exposure conditions. Also, laboratory members have participated in developing industry guidance and FDA-recognized consensus standards for several medical ultrasound applications, including physiotherapy, extracorporeal shock wave lithotripsy, bone sonometry, and diagnostic ultrasound imaging.

Current and future work is being directed towards applications involving thermal therapy, new high intensity diagnostic modes, and ophthalmic imaging modes for which current safety models are inappropriate. In these cases the variable of ultimate interest is that of tissue temperature, as temperature profiles largely determine cell viability. Thermal injury is highly desirable for therapies intended to shrink or ablate tumors. However, injury is undesirable in the case of diagnostic imaging. Either way, the ability to predict the temperature-time response requires accurate knowledge of the ultrasound fields and how they are absorbed. Such knowledge becomes particularly important in the relatively new technology of using focused ultrasound to ablate selected regions of tissue, because energy levels are high and the targets may be deep within the body.

For focused ultrasound ablation, also known as high intensity focused ultrasound (HIFU) surgery, the primary mechanism in lesion formation is thermal. Therefore laboratory efforts are concentrating on methods of determining the focusing properties of the HIFU transducer and the spatial distribution of temperatures in tissue, because these factors along with the exposure time determine the lesion size. This effort is important to the regulatory evaluation of these devices, because at present standard methods are lacking to measure the acoustic output and spatial beam profiles of the transducers and transducer arrays that attempt to deliver therapeutic levels of ultrasound energy to precisely defined tissue locations, and to relate these measurements to the local tissue temperature. The absence of well-characterized standard techniques to obtain this information is a significant hurdle to the demonstration of safety and effectiveness that FDA is mandated to require of new technologies like HIFU.

With regard to ophthalmic and new higher intensity diagnostic applications, industry standards and FDA guidance use output limits for diagnostic ultrasound devices based on average tissue properties and steady-state temperature rise. The eye, having unique tissue characteristics, can have a temperature rise much higher than homogeneous soft tissue

when exposed to ultrasound. In new high output modes, the transient rather than steady-state temperature rise is most closely associated with risk, and current guidance to the industry is silent on this issue. Therefore, more realistic assessments of safety vs. exposure are being undertaken to ensure safe use while not restricting clinical utility.

Relevance to FDA /CDRH Mission and the Public Health Impact

This laboratory program helps to identify potential risks associated with exposures from existing and new applications of medical ultrasound. The test methods and models developed are used to characterize device safety, which in turn leads to recommendations for regulatory guidance to the industry, as well as input for consensus standards the Center can adopt in its regulatory review process. Also, symposia presentations and publications in the peer-review literature both publicize the research findings and enhance the reputation of Center laboratory efforts. Furthermore, project products provide important and practical input for appraising post-market performance and pinpointing potentially pernicious post-approval problems.

Three-Year Goals

The laboratory will concentrate on higher intensity applications of ultrasound that pose a greater potential for risk. With regard to focused ultrasound ablation, it is planned to develop and disseminate standard test methods for characterizing these surgical ultrasound systems, both through FDA guidance and international standards, thus allowing device safety and effectiveness to be assessed by the Center in a more methodical and scientifically rigorous manner. With regard to higher output diagnostic applications, or those such as ophthalmologic use for which current safety methodologies are insufficient, the goal is to develop and validate analytic models to determine steady-state and transient temperature rise for the relevant ultrasound beam, pulse regime, and tissue characteristics. This work will lead to standard test methods and guidance for safe use. Collaborations with industry, universities, and other government agencies are being explored in this effort.

Accomplishments

The project is divided into three tasks. The first task is to develop methods for assessing the acoustic output and beam profiles of therapeutic and diagnostic ultrasound devices. The second task is to develop mathematical models for calculating temperature profiles. In the third task, the output beam profiling and mathematical modeling results are validated via thermal test objects and other tissue-equivalent materials. Milestones accomplished in 2006 are discussed under each task.

Task 1: Acoustic output and beam profiling

- Completed development of a high-power calibration technique for high intensity focused ultrasound (HIFU) transducers using a radiation force balance system.

- Developed measurement protocol for characterizing acoustic intensity distribution from HIFU transducers at maximum power output using acoustic streaming/numerical inverse algorithm method. Presently validating accuracy of this method at maximum power as measured with standard radiation force balance method. Validated this new technique at low power levels with the hydrophone scanning system.

- Filed a joint (Epicor-St. Jude Medical and FDA) final non-provisional patent on 12/21/2006 entitled, "Optical Techniques and System For 3-D Characterization of Ultrasound Beams."

- Completed CRADA document between Epicor-St. Jude Medical and FDA. The CRADA is undergoing the FDA Centers' conflict of interest review; approval from the FDA CRADA Administrative Committee and sign-off by the Commissioner are expected sometime in January 2007.

Task 2: Mathematical models for calculating temperature profiles

- Developed analytical models of wave propagation across a fluid-solid interface, as well as models of propagation in linear elastic and linear viscoelastic solids. The analytical models have been used to begin validation of a three-dimensional wave propagation code (commercial) that will be used in conjunction with the experimental studies to evaluate the effects of bone on the heating patterns within tissue.

- Designed, implemented, and tested a fast algorithm for high-gain HIFU beams in a Gaussian approximation. This code solves the frequency-domain version of the KZK equation for HIFU propagation in biological tissue.

- Implemented a general frequency-domain KZK solver to compare with the fast algorithm described above.

- Implemented a bio-heat transfer equation integrator to compute heating in biological tissue subject to HIFU beam sonication.

- Continued development of analytical models to compute biomechanical effects due to ultrasound absorption. Derived asymptotic expressions for the tissue deformation and temperature rise due to the absorption of Gaussian beams. These analytic expressions elucidate the role that important operational parameters, such as transducer focal length and gain, play in tissue response to ultrasound absorption. The results will be useful in making rapid safety evaluations of ultrasound devices and procedures, and for establishing standards for quantifying ultrasound bioeffects.

- Completed computational analysis of how blood flow through large vessels influences procedures involving high intensity focused ultrasound. Finite-element calculations were performed that identified optimal conditions for performing various ablation procedures. Experiments in a tissue phantom were also performed to validate the heat-source model utilized in the computations.

Task 3: Validation of the beam output measurements and mathematical modeling results

- Completed development and testing of a new time delay spectrometry (TDS) system that employs digital processing to minimize hardware requirements. The laboratory uses TDS extensively for efficient characterization of the attenuation characteristics of ultrasound tissue mimicking materials (TMMs) used in the evaluation of HIFU systems.

- Continued development of tissue mimicking materials (TMMs) for the acoustic and thermal characterization of HIFU ablation devices. The TMMs are based on a hydrogel matrix embedded with dispersed aluminum oxide micro-spheres. Further developments included achieving a cavitation threshold similar to that of human soft tissue.

- Developed and characterized a blood-mimicking fluid (BMF) having viscosity, attenuation, and backscatter similar to that of human blood for the acoustic and thermal characterization of HIFU ablation devices.

- Initiated a project to predict the thermal field in the focal zone of an ultrasound beam, using temperature measurements acquired outside of the focal zone. A tissue phantom was constructed that contained a three-dimensional array of thermocouples distributed throughout the tissue volume. The phantom was sonicated inside the array using a HIFU transducer, and the transient temperature across the array was recorded. A mathematical model is being developed to back calculate the absorbed ultrasound energy giving rise to the observed temperature field on the array.

Mechanics Laboratory **(Division of Solid and Fluid Mechanics)**

Scope

The Solid Mechanics program is structured to help CDRH understand materials issues of concern in both pre-market evaluations and post-market reported adverse events. The materials of interest include synthetics like metals and polymers, materials of biological origin, and those used in tissue engineered medical products (TEMPs). We have the

capabilities to measure mechanical properties ranging from the tensile strength of sutures and medical glove materials, to the fatigue strength of total joint prostheses. Besides purely mechanical characterizations, our measurement capabilities for TEMPs constructs and scaffolds include quantification of phenotypic stability and the histomorphology of TEMPs relevant cell types. The combined output of this effort includes improved critical review of manufacturers' claims and data, test method development, material and methods standards development, and publications related to the public health impact of medical device materials design, fabrication, or failure.

Background

Medical device performance and safety requires reliable and safe use of materials. The synthesis, processing, and fabrication of materials affect the molecule structure, phases, and ultimately the physical, chemical, and mechanical properties, and biocompatibility of devices used in medical applications. Failure can result from improper material selection, inadequate stress analysis during device design, manufacturing errors, or misuse/abuse of devices. The Shiley heart valve weld failures, silicone breast implant membrane ruptures, and urethane pacemaker lead cracks are all examples of prominent material integrity issues. Degradation of materials can not only affect performance, it can also produce toxic substances which can cause serious injury or death to the patient. However, degradation is not always undesirable. It may be by design as with resorbables. Thus materials characterizations must always be done keeping the context of end use in mind.

Research Program Description

Activities in this program may be triggered within any phase of the product life cycle. In general, the activities of this group are directed not only towards resolving the specific issue that provided the trigger, but also in finding ways to apply the knowledge gained to future device problems. Since the inception of the FDA Medical Device program, this group has maintained a heavy involvement with voluntary device standards organizations, such as ASTM International. Their participation in these standards activities has leveraged Agency’s resources with industry and academia to create lasting consensus solutions to these regulatory issues once the laboratory studies have been completed. A few examples of these activities are provided in the following paragraphs. Compatibility issues involving magnetic resonance imaging (MRI) systems and implants or support equipment have existed since this imaging technology was introduced. CDRH has received reports of adverse events through its post-market monitoring system and the scientific literature describing deaths, burns, and other injuries from dislodged aneurysm clips, failed pacemakers, hurtling oxygen bottles, and brain stimulators.

In addition, pre-market clearance of devices likely to be exposed to MRI has been a continuing problem. Some implants can be used near the magnet but not in the magnet. Other implants cease to function temporarily in the magnet but restart when the device is

removed. Other devices fail completely in MRI. Other devices interfere with imaging but are immune from damage. And, in some cases the device can produce RF heating when placed within the MRI system, resulting in serious burns. In response, the mechanics laboratory has the lead in the development of five ASTM International standards on MRI compatibility that are now utilized in pre-market reviews. The mechanics laboratory has also done dome pilot laboratory studies on MR compatibility and has supported other laboratories, both within OSEL and extramural, in the conduct of laboratory work on MR compatibility.

As a result of the recent new healthcare industry practices to reuse single use devices (SUDs), OSEL scientists first evaluated the post-market device performance of balloon angioplasty catheters after single use at area cardiology centers. As a result of these and other studies, the issues of reuse have become an integral part of the pre-market review of reprocessed SUDs. Results of OSEL investigations provided vital information used in formulating Agency guidance on SUDs and opened but not used (OBNU) devices and has been used to develop training for field inspectors.

A potential problem was detected during pre-market review when an ODE reviewer observed that a plasma spray coating on total hip could be scraped off with a credit card. Because there were no reliable tests or acceptance criteria for abrasion resistance, all devices of this type were subjected to required post-market surveillance. Industry responded by improving the quality of the coatings. OSEL put together a research team which developed a test method, directed and participated in a round robin, and wrote an ASTM standard (F1978) for abrasion testing of thermal sprayed coatings. An OSEL, OSB, and ODE team was assembled to develop a guidance document for rescinding the required post-market surveillance. The companies used the method to document the improved abrasion resistance and the surveillances were rescinded. Pre-market concerns in ODE also recognized the need to standardize the characterization of the alginate, chitosan and collagen materials used in TEMPs as scaffolds. Staff in this program area led the standards development effort which, to date, has resulted in approval of three standards for characterizing these materials. This also has led to laboratory and standards development to characterize natural materials after exposure to cells.

As technology advances in the medical materials arena, it is critical for OSEL scientists and programs to maintain the expertise in these areas. TEMPs present a variety of material issues as well as cellular response issues. To address the broad scope of materials, we have also worked with other FDA Centers (CFSAN, CDER, and CBER) on a diverse range of products, such as blood filters, imaging agents, adhesives and packaging materials, as well as the decontamination of instruments that may have contacted Creutzfeldt-Jakob Disease (CJD). We are also piloting some laboratory work on the effects of repeated sterilization on resorbable polymers which we hope to develop in the near future into a full project.

Relevance to FDA's and CDRH's Mission, Program, and Public Health Impact
The broad-based nature of the mechanics and materials expertise has helped the Center in its mission in every phase of the TPLC. We have worked with ODE, OSB, and OC to develop guidance documents and a substantial number of standards. We have worked with OSB and OC in MDR, PMA inspection and Compliance actions. Numerous concerns raised in CDRH have been resolved by simply relying on laboratory experience of OSEL scientists. In other situations, consultations have led to longer duration laboratory studies. The horizontal nature of the program is such that work initiated to address the problems within one branch or division has often been extended to common problems within another. Mechanical and corrosion studies which were initiated by the ODE branch responsible for coronary stents have led to consults and guidance to ODE branches reviewing peripheral, endovascular, biliary and esophageal stents. In the TEMPs arena, products are currently in use for artificial skin for wound and burn repair and for regeneration of cartilage. Many more products and uses for products are under development for TEMPs and other medical devices.

This laboratory supports the Center's mission to assure the mechanical safety and effectiveness of medical devices. It develops new or improved techniques for measuring wear, abrasion, strength, degradation, and fatigue of materials, and durability of devices. The group works actively to identify biologically relevant parameters, to test and evaluate regulated devices, to assess established and proposed measurement protocols, and to participate in the development and support of voluntary consensus standards and guidance documents.

The laboratory has a broad spectrum of mechanical testing capabilities including corrosion testing, fatigue and abrasion testing, and metallography. It has uniaxial and biaxial (tension-torsion) servohydraulic testing machines as well as a collection of universal testing machines suitable for a wide range of load and displacement levels and rates. The laboratory also has the capability to perform a variety of morphological measurements using an array of instruments that include an analytical TEM microscope, SEM with EDAX, atomic force microscope, small angle X-ray scattering, fluorescent laser scanning confocal microscope, and a number of photomicroscopes.

Three-Year Goals
Prepare for challenges dealing with new materials and new technologies, such as nanophase composites, hydrogels, biointeractive surfaces and TEMPs that we expect to see in future new medical devices. In addition, challenges presented by custom designed components and the development of ever smaller-scale minimally invasive and nano-devices will create a need for more sensitive and miniaturized methods. The features that limit the usefulness of these materials in these applications need to be identified to prevent injuries, and also insure that post-market problems are handled correctly.

The mechanical quality of new device materials must be assured by the appropriate pre-market testing and post market surveillance. The appropriate test methods and measurements, and their limitations need to be identified. We need to incorporate these methods into national and international standards, which will result in the use of uniform, described and accepted methods, as well as to increase efficiency, quality and uniformity of product reviews. The goal of the mechanics of materials and structures program is to develop the regulatory science base to meet these new challenges.

Accomplishments

Development and validation of a proteomic kinase substrate array to evaluate chondrocyte based tissue engineered medical products (TEMPs)

Completed initial characterization of laminar flow fields in flow-cell chambers.

Fatigue testing of PMMA bone cement

- Phase 1 testing is finished. Test results were submitted to ASTM for their November 2006 committee week meetings. Results are being analyzed by ASTM who has indicated that they will be discussed at the May 2007 committee week meetings.
- Barium sulfate powders of a range of particle sizes have been obtained. Work is underway to determine techniques for mixing powders into PMMA and for determining particle size distribution in molded PMMA.

Development of guidelines for evaluating the appropriateness of vertebroplasty surgery for patients with osteoporosis

Project completed in 2006.

Mechanical Testing of Mesalamine Enema Bottles

- Designed and fabricated a holding fixture for nozzle bend tests of generic and proprietary enema bottles to examine differences in nozzle stiffness. Performed bend testing. Analyzed bend test data in collaboration with an OSB statistician; data from previously completed compression and tensile tests of the bottles were also analyzed. Compression results agreed with the referring patient's experience that a generic bottle required more force to compress during use than the proprietary bottle. Stiffness of the generic nozzles was also greater than that of the proprietary nozzles. Presented poster at the Biomedical Engineering Society Fall 2006 Meeting. A paper is in preparation for submission to a peer-reviewed journal.

Compatibility of Latex Gloves and Condoms with Lotions and Lubricants Applied by Consumers

- Participated in an ASTM interlaboratory study of a draft screening method for determining whether or not a consumer-applied lubricant has an effect on the

tensile properties of a thin-film latex medical device, e.g., gloves and condoms. Actively participated in the development of this draft standard.

Standards Management Staff

The Standards Management Staff (SMS) develops and manages the standards used for regulatory assessments. SMS staff facilitate the participation of CDRH and other FDA staff in the development of standards and ensure appropriate medical device standards are officially recognized and published in the *Federal Register*. This involves working closely with the Standards Developing Organizations (SDOs), advertising standards liaison representative positions, facilitating a Center recommendation to serve on a particular standards activity, and maintaining an appropriate standards database providing access to established standards to all CDRH staff, field inspectors, and industry.

SMS continually increases the recognition of voluntary consensus standards for medical devices and radiation-emitting electronic products. The Standards Program was created as a result of the Food and Drug Administration Modernization Act (FDAMA) of 1997. Although CDRH had been involved in the development of medical device standards for decades, FDAMA formalized the process. As part of this responsibility, the staff publishes lists of recognized standards annually and consistently increases the list of available standards.

Accomplishments

- **Recognized Standards for 2006**

  - **43 new standards**
  - **84 standards that were withdrawn and new versions were recognized**
  - **66 changes to the existing recognized standards**
  - **7 standards were withdrawn**

- **Continuous Glucose Monitoring.** As a result of the 2005 special meeting on the issue of standards development for non-invasive glucose meters, a new committee was formed with the Clinical Laboratory Standards Institute (CLSI) to write the first standard for these devices. This new standard was completed in 2006 and will be published in early 2007.

- **16th Annual AAMI/FDA International Conference on Medical Device Standards and Regulation**. As an annual co-sponsor of this important conference, Carol Herman, SMS Director, helped develop the agenda and identify appropriate

speakers. Of the 20 speakers, four were from FDA/CDRH. Nearly 200 participants attended the conference representing the medical device industry and FDA staff.

- **Global Harmonization Task Force (GHTF).** The Chairmanship of GHTF rotated to FDA after being held by the European Union for 3 years. FDA assumed the Chair of GHTF in late December 2006 and will hold the Chair until June 2008. FDA appointed Dr. Larry Kessler, Director of the Office and Science Engineering Laboratories, to be the Chair. In June 2006, as part of 10th Conference held in Lübeck, Germany, Dr. Kessler presented a portion of the Workshop entitled, Emerging Technology I: Clinical Expert Control Systems - Plug and Play. He led the ad hoc group that worked on the World Health Organization request to access the non-confidential part of vigilance data. Dr. Kessler and Mr. Brian Fitzgerald worked on the ad hoc software group, with Mr. Fitzgerald leading the group. The Software ad hoc group was formed and forwarded work items to the GHTF Steering Committee for approval in November 2006. The Software ad hoc group continues its work under Mr. Fitzgerald's leadership. Dr. Kessler leads the ad hoc group working on establishing the GHTF Training Institute. FDA (Jean Olson with David Racine and Stefan Gagne in OCER) continues to manage the GHTF website.

GHTF is an international voluntary group of representatives from national medical device regulatory authorities and the regulated industry. The United States is one of the five founding members of GHTF. Members are from the following three geographical areas: Asia, Europe, and North America.

The purpose of the GHTF is to encourage convergence in regulatory practices related to ensuring the safety, effectiveness, performance and quality of medical devices; and promoting technological innovation and facilitating international trade. The primary way in which this is accomplished is via the publication and dissemination of harmonized guidance documents on basic regulatory practices. The study groups are responsible for the drafting of the harmonized guidance documents.

APPENDIX A – OSEL Publications

January 1, 2006 – December 31, 2006

Journal Articles

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APPENDIX B – OSEL Presentations

January 1, 2006 – December 31, 2006

Agrawal A, Pfefer J, Lin A, Lee M, Drezek R. Optical properties of nanoshells for diagnostic imaging, OSA Biomedical Topical Meeting, Ft. Lauderdale, FL, March 19-22, 2006.

Agrawal A, Pfefer J. Optical properties of nanoshells for diagnostic imaging, FDA Science Forum, Washington, DC, 2006.

Agrawal A, Miller S, Matchette S, Pfefer J. Non-invasive estimation of sunscreen efficacy by diffuse reflectance spectroscopy. FDA Science Forum, Washington, DC, 2006.

Agrawal A, Pfefer J. Optical properties of gold nanoshells, SPIE Optical Imaging Workshop, National Institutes of Health, Bethesda, MD, September 25-27, 2006.

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Altiner A, Tock CL, Turner LR, Terunuma A, Miller SA, Beer JZ, Udey MC, Vogel JC. Identifying biosensor genes that quantify human epidermal response to UV radiation. Society for Investigational Dermatology, Philadelphia, PA, May, 2006.

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Benetatos NM. Investigating ionomer morphologies with STEM and SAXS: toward rigorous processing-structure-property relationships. Department of Physics, St. Joseph's University, Philadelphia, PA, October 25, 2006.

Benetatos NM, Winey KI. Quantitative reconciliation of STEM and SAXS data from ionomers. 2006 American Physics Society, Baltimore MD , (oral presentation), March 13-17, 2006.

Brown SA. The need for and use of standards by FDA in the regulation of medical devices, including those utilizing nanotechnology. ASTM E56/F04 workshop on Nanotech and Medical Devices, Atlanta, GA, November 14, 2006.

Chang IA, Luu H-MD, Hutter JC, Katzper M, Kim CS. Inter-Center Modeling Consortium, 12th Annual FDA Science Forum, Sigma Xi Poster Session, Washington Convention Center, Washington, D.C., April 18-20, 2006.

Chiesa, OA. Use of endoscopic serial tissue sampling techniques for pharmacokinetic studies in large animals: towards predictive modeling. Oral presentation at the 3rd Annual Scientific Meeting Veterinary Endoscopy Society at Keystone, Colorado, March 2006.

Chiesa, OA. Development of a new method to of accurately measure antimicrobials concentrations in intestinal mucosal secretions. Food and Drug Administration, Center for Veterinary Medicine, Rockville, MD May 2006.

Chiesa OA. Endoscopic serial sampling in large animals. Presented to the FDA Commissioner, Dr A. von Essenbach, Rockville, MD, July 2006.

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Godar D. Co-chair of symposium: Personal UV Dosimetry. 33rd Annual meeting of American Society of Photobiology, May 12, 2006.

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Goering PL. Development of an improved animal model of renal failure and improved biomarkers of nephrotoxicity. A research seminar to graduate students and faculty. University of Kansas School of Medicine, Department of Pharmacology and Toxicology, Kansas City, Kansas, January 20, 2006.

Goering PL. A career in health sciences at the Food and Drug Administrationz; a lecture to freshman students in Careers in Health Sciences, Purdue University School of Health Sciences, West Lafayette, Indiana, September 26, 2006.

Hitchins VM, AD Gantt, Jr. and JM Morris. FDA regulatory outlook: How to get a submission approved by the U.S. FDA. Invited talk at the Biofilm Conference at Montana State University, February 2-3, 2006.

Hitchins VM. Use of standards and guidance documents for submission of applications to CDRH. For the AAMI Webinar on “Reprocessing medical devices: current standards, guidances, and new developments in validating cleaning, disinfecting, and sterilization processes. December 5, 2006.

Horner M, Joshi S, Berry D, Dhruva V, Sett S, Stewart SF. Effects of deployment and tissue interaction on drug eluting stent performance. Biomedical Engineering Society Annual Meeting, Chicago, IL, October 2006.

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Ilev I. Fiber-optic biosensors and nanobiosensors: fundamentals. NATO Advance Science Institute (ASI) Symposium on "Optical Waveguide Sensing and Imaging in Medicine, Environment, Security and Defense" (invited lecture), Gatineau, Québec, Canada, October 11 – 14, 2006.

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Kaiser AD, McFarland RD, Dawisha SM, Leibenhaut S, Kaplan DS. Points to consider in the evaluation of articular cartilage repair or replacement products. International Cartilage Repair Society, San Diego, CA, January 2006.

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Karanian JW. FDA Overview: From Bench to Bedside. FDA Pre-conference, Association for Vascular Access, Indianapolis, IN, September 8, 2006.

Karanian JW, Pritchard WF. Kinetics and dynamics of peri-adventitial drug delivery in swine vasculature. Adventitia Research Interest Group Meeting, American Heart Association, Chicago, Illinois, November 12-14, 2006.

Katz E. TRC presentation to SPOC committee: Program in electrophysiology and electrical stimulation, implementation and safety of selective optical stimulation for the damaged nervous system, 2006.

Katz E. TATRC, U.S. Army presentation: Implementation and safety of selective optical stimulation for the damaged nervous system, 2006.

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Pritchard WF, Karanian JW. The FDA from bench to bedside. Association for Vascular Access, Pre-Conference Workshop Indianapolis, IN September 8, 2006.

Ranamukhaarachchi DG, Dalal R, Langone JJ, Kammula R, Sauberman H, Lababidi S, Tezak Z, Panguluri RK. Gene expression models for evaluating adverse effects due to nanoparticle exposure. FDA/CDRH Nanotechnology: Research and Regulatory Issues, Rockville, MD, October 6, 2006.

Rasooly A Biosensors technology at the AAPS conference, June 21, 2006. Boston, MA, June 21, 2006.

Rasooly A. Applications of biosensors technologies. The Gordon Conference on MEMS Technology & Biomedical Applications. Connecticut College, CT, June 28, 2006.

Regnault WF, Icenogle BT, Antonuccci JM (presenter), Liu DW, Skrtic D. Structure/property relationships in urethane dimethacrylate-based ACP composites. 31st Annual Meeting of the Society for Biomaterials, Pittsburgh, PA, April 26-29, 2006.

Richardson DC, Landry R, Ilev I, Faaland R. IOLs: methods development for preclinical testing. Biomedical Engineering Materials and Applications (BEMA) Roundtable and Workshop, Rockville, MD, May 31, 2006.

Salas-Vega S, Richardson DC. Vacuolar growth in foldable IOLs: toward a preclinical test," 12th Annual FDA Science Forum, Sigma Xi Poster Session, Washington Convention Center, Washington, D.C., April 18-20, 2006.

Saylor DM. Structure evolution and release behavior in controlled drug delivery devices. Computational Homology And Materials Science Workshop, Atlanta, GA, February 4, 2006.

Saylor DM, McDermott MK., Dair BJ., Kim CS, Toy J, Patwardhan DV, Warren JA. Micro structure development and release behavior in controlled drug delivery systems. 12th Annual FDA Science Forum, Sigma Xi Poster Session, poster G-13, page 93, Washington Convention Center, Washington, D.C., April 18-20, 2006.

Saylor DM, McDermott MK, Dair BJ., Toy J, Patwardhan DV., Warren JA. Effect of materials selection in controlled drug delivery systems: (Bio)degradable v. non-degradable polymers. 12th Annual FDA Science Forum, Sigma Xi Poster Session, poster G-14, page 93, Washington Convention Center, Washington, D.C., April 18-20, 2006.

Seidman S. The immunity of medical devices to continuous wave magnetic fields by immersion method. FDA Science Forum, Washington, DC, April 2006.

Sergeev N, Matviyenko A, Herold K, Rasooly A. Miniature PCR thermocycler for rapid detection of multiple microbial pathogens, FDA Science Forum, Washington, DC, April 2006.

Sergeev N, Matviyenko A , Herold K, Rasooly A. Rapid microbial pathogen DNA amplification using a battery-powered thin-film resistive heater thermocycler, FDA Science Forum, Washington, DC, April 2006.

Sergeev N, Rasooly A, Fortina P. Evaluation of biocompatibility of nanomaterials used in medical devices. "Nanotechnology - Research and Regulatory Issues." Rockville, MD , October 6, 2006.

Stratmeyer ME. Professor Floyd Dunn's contribution to understanding the biological effects of ultrasound. Acoustical Society of America 4th Joint Meeting, Honolulu, HI, November 28 - December 2, 2006 (invited presentation).

Tomazic-Jezic V. Umbreit TH, Stratmeyer MS. Evaluation of nanomaterial immunotoxicity: Example of Polystyrene Nanoparticles. Presented at the 1st International Nanotoxicology Meeting, Miami, FL, January 2006.

Tomazic-Jezic VJ, Umbreit TH, Stratmeyer ME. Evaluation of nanomaterials'inununotoxicity: example of polystyrene nanoparticles. FDA Science Forum, Washington, DC, April 2006.

Vorvolakos K, Das S, Patwardhan DV, Luu H-MD, Isayeva IS. Physical properties of abdominal adhesion barriers. 12th Annual FDA Science Forum, Sigma Xi Poster Session, Washington Convention Center, Washington, D.C., April 18-20, 2006.

Wagner RF. Bioinformatics, the multiple-biomarker classifier problem, complexity, and uncertainty. Annual Meeting of the American Association of Physicists in Medicine, Orlando, FL, July 2006.

Wear KA. The interaction between ultrasound and human cancellous bone," 4th Joint Meeting between the Acoustical Society of Japan and the Acoustical Society of America, Honolulu, HI, November 28 – December 6, 2006.

Wear KA. Attenuation, propagation and scattering of ultrasound in human cancellous bone. Ninth Western Pacific Acoustics Conference, Seoul, Korea, June 26-28, 2006.

Witters D. Radio frequency wireless medical devices and systems: addressing FDA concerns for electromagnetic compatibility (EMC). Coexistence and Data Integrity: poster presentation at the Conference on Distributed Diagnosis and Home Healthcare (D2H2 2006), Crystal City Marriott, VA, April 2-4, 2006.

Witters D. FDA perspective: recommendations for wireless medical devices. AAMI 2006 Conference and Expo, Washington DC, June 23, 2006.

Woods TO. Standards for safety of medical devices in MRI. Society for Medical Innovation and Technology 18th International Conference, SMIT 2006, Monterey, CA, May 11-14, 2006.

Wu D, Quiang R, Chen J, Seidman S, Kainz W. Possible non-compliance of one walk through metal detector for pregnant woman models as compared to ICNIRP Guidelines. BEMS 2006, 28th Annual Meeting, Cancun, Mexico, June 11-15, 2006.

Yen D, Woods TO. (Invited) Surgical robots and MRI safety: FDA Regulatory Perspective, 2006 IEEE International Conference on Robotics and Automation, Orlando, FL, May 15, 2006.

Youk H, Kang J, Khurgin J, Agrawal A, Ilev I, Waynant R. Surface-enhanced Raman glucose detection using gold nanoshells. LEOS/APS/OSA, Conference on Lasers and Electro Optics (CLEO 2006), Long Beach CA, May 21-26, 2006.

APPENDIX C – OSEL Academic Affiliations

January 1, 2006 – December 31, 2006

Agrawal, Anant	Virginia State University Department of Mathematics and Computer Science Member, Master's thesis committee
Badano, Aldo, Ph.D.	University of Michigan College of Engineering Department of Electrical Engineering and Computer Science Visiting Research Scientist
Bassen, Howard I.	University of Maryland College of Engineering Lecturer
Chang, Isaac A. Ph.D.	Catholic University of America Department of Biomedical Engineering Assistant Professor
Das, Srilekha S., Ph.D.	Henry M. Jackson Foundation for the Advancement of Military Medicine Guest Scientist
Goering, Peter L., Ph.D.	University of Maryland School of Medicine Graduate Program in Toxicology Adjunct Professor George Washington University Department of Biological Sciences Adjunct Associate Professor
Hilbert, Stephen L., M.D., Ph.D.	Brown University School of Medicine Department of Surgery Division of Cardiothoracic Surgery Adjunct Professor of Surgery (Research)
Kainz Wolfgang, Ph.D.	University of Houston

	Department of Electrical and Computer Engineering Member, Doctoral thesis committee
Krauthamer, Victor, Ph.D.	Uniformed Services University of the Health Sciences Department of Anatomy, Physiology and Genetics Adjunct Assistant Professor American University Department of Biology Adjunct Associate Professor George Washington University Department of Biology Adjunct Associate Professor
Myers, Kyle J., Ph.D.	Georgetown University Medical Center Department of Radiology Adjunct Associate Professor University of Arizona Optical Sciences Center Adjunct Associate Professor
Myklebust, Joel, Ph.D.	George Washington University Department of Electrical and Computer Engineering Adjunct Assistant Professor
O'Hara, Michael D., Ph.D.	Thomas Jefferson University Department of Radiation Oncology Adjunct Assistant Professor
Patwardhan, Dinesh V, Ph.D.	Pennsylvania State University Department of Chemical Engineering Adjunct Professor
Petrick, Nicholas, Ph.D.	University of Michigan Department of Radiology

	Adjunct Assistant Professor
Pfefer, T. Josh, Ph.D.	Rice University Department of Bioengineering Doctoral thesis committee
Pollack, Steven, Ph.D.	University of Maryland, College Park College of Chemical and Life Sciences Department of Chemistry and Biochemistry Adjunct Professor
Rasooly Avraham, Ph.D.	Program Director, Cancer Diagnosis Program National Cancer Institute National Institutes of Health
Spees, William, Ph.D.	University of Phoenix Adjunct Practitioner faculty member
Waynant, Ronald W., Ph.D.	Catholic University of America Electrical Engineering Department Adjunct Associate Professor Uniformed Services University of the Health Sciences Adjunct Professor
Wear, Keith A., Ph.D.	Georgetown University Department of Radiology Adjunct Professor Henry M. Jackson Foundation for the Advancement of Military Medicine Guest Scientist
Weininger, Sandy, Ph.D.	Drexel University School of Biomedical Engineering Visiting Lecturer

APPENDIX D – OSEL Patents

January 1, 2006 – September 30, 2006

Anders J, Romanczyk T, Waynant R, Ilev I. Light as a replacement for mitogenic factors on progenitor cells. PCT International Patent No. PCT/US06/11573, March 30, 2006.

Ilev I. Confocal fiber-optic laser device and method for intraocular lens power measurement. PCT International Patent No. PCT/US2006/007474, March 03, 2006.

Ilev I, Robinson R, Waynant RW. Particle image velocimetry system having and improved hollow-waveguide-based laser illumination system. U.S. Non-Provisional Patent No. 11/589,310, October 30, 2006.

Ilev I, Waynant RW, Gannot I, Gandjbakhche A. Ultrahigh-resolution fiber-optic confocal microscope and method of use. PCT International Patent No. PCT/US2006/014162, April 14, 2006.

Ilev IK, Robinson RA, Waynant RW. Final non-provisional patent DHHS # E-015-2006/0-US-03 titled: All-hollow-waveguide laser delivery system for digital particle image velocimetry. Filed with Patent Office by NIH on October 28, 2006.

Passaro LC, Pollack SK.. Process for the preparation of 2-furyl-N-pentylketone and longer chain analogs, US Patent No. 7,129,234, October 31, 2006.

Sliwa J, Hariharan P, Robinson R, Myers M, Maruvada S, Banerjee R, Harris GR. Final non-provisional patent (Attorney Docket No. OE-040501US/82410-0163): Optical techniques and system for 3D characterization of ultrasonic beams. Filed with Patent Office by Epicor Medical on December 21, 2006.

APPENDIX E – OSEL-Sponsored Seminars

January 1, 2006 – December 31, 2006

Dr. Harrison H. Barrett, Optical Sciences Center and the Department of Radiology, University of Arizona. New approaches to adaptive optics, wavefront sensing and 3D microscopy. FDA/CDRH, Maryland, January 8, 2006.

Dr. Guy Besson, ForeVision Technologies Corporation, Lafayette, Colorado. SBIR medical imaging research at ForeVision. FDA/CDRH, Rockville, MD, September 12, 2006.

Dr. Heang-Ping Chan, Dr. Berkman Sahiner, University of Michigan, Department of Radiology and Dr. Charles Metz, University of Chicago. Joint working meetings on breast imaging and CAD. FDA/CDRH, Rockville, MD, January 4-6, 2006.

Dr. Eric Clarkson, Optical Sciences Center and Department of Radiology, University of Arizona. Some recent work on the Hotelling observer and an introduction to the estimation ROC curve (EROC), CDRH, Rockville, MD, July 11, 2006.

Stan Farnsworth, Nanotechnologies, Inc. Synthesis, characterization, and antimicrobial applications for nano-particulate silver. CDRH Science Seminar, Rockville, MD, June 7, 2006.

Melanie Freed, M.S., University of Arizona. Designing, building, and testing an adaptive SPECT small-animal imager. CDRH, Maryland, May 18, 2006.

Dr. Andreas Hielscher, Columbia University. Optical tomography: potential and limits of an emerging imaging modality. April 6, 2006.

Dr. Wolfgang Kainz, FDA/CDRH/OSEL Dr. Niels Kuster, IT'IS - Foundation for Research on Information Technologies in Society. Numerical models and tools - the virtual family. Zurich, Switzerland, July 6, 2006.

Dr. AD Lucas, Dr. D Wray-Cahen, Dr. RP Brown, Dr. SK Lappalainen. Mild hyperthermic incubation can potentiate the cytotoxicity of exogenous compounds and medical device extracts. CDRH, FDA Silver Spring, MD.

Dr. George Mills, Director, Medical Imaging and Radiopharmaceutical Drug Products. Use of imaging in drugs/biologics approval studies, FDA/CDER, Maryland, January 26, 2006.

Dr. Gene Pennello. Diagnostic imaging procedures: defining and analyzing test results to account for unknown disease loci. CDRH/OSB, October 11, 2006.

Dr. Lorenzo Pesce, University of Chicago. PROPROC: the proper binormal ROC model and its applications. June 6, 2006.

Dr. Etta D. Pisano. The University of North Carolina at Chapel Hill. The digital mammographic imaging screening trial (DMIST), Maryland, January 17, 2006.

S. Kim, R. Dalal, DG Ranamukhaarachchi. Toxicological impacts of quantum dots (QD) on human mesenchymal cells. Office of Science and Engineering Laboratories, Center for Devices and Radiological Health, FDA. Silver Spring, MD, August 16, 2006.

Dr. Stephen Rudin, University at Buffalo (SUNY). High-resolution ROI and ROI-CT x-ray detectors and image-guided neurovascular interventional devices for blood flow modification in the endovascular treatment of cerebral aneurysms. Rockville, MD, February 24, 2006.

Dr. N Sergeev, Dr. A Rasooly, P Fortina. Evaluation of biocompatibility of nanomaterials used in medical devices, Staff College and OSEL Presentations on "Nanotechnology - Research and Regulatory Issues" Center for Devices and Radiological Health, FDA, Rockville, MD, October 6, 2006.

Dr. James Staudenmeier, Clinical Practice of Electroconvulsive Therapy, December 2006.

Dr. Hemant D. Tagare, Yale University. A geometric theory of non-rigid registration and correspondence. CDRH, November 15, 2006.

Dr. Daniel Weinreich, University of Maryland. A calcium regulation in individual peripheral sensory nerve terminals of the cornea. August 30, 2006.

Dr. Paul Williams, National Institute of Standards and Technology (Boulder). Measurement support for optical coherence tomography at NIST Boulder, October 13, 2006.

APPENDIX F – Interagency Agreements and Cooperative Research and Development Agreements

FY 2006 Reimbursable IAG's

Air Force Office of Scientific Research (AFOSR) (IAG #224-98-6005). Renewal light therapy mechanisms

Defense Advanced Research Projects Agency (DARPA) (IAG#224-98-6005). Test bed development for deep bleeder acoustic coagulation program

Defense Advanced Research Projects Agency (DARPA) (IAG #224-05-8093). Collaboration on innovative medical technology

National Cancer Institute (NCI) (IAG #224-04-6058). Assessment of computer-aided diagnostics

National Institute for Biomedical Imaging and Bioengineering (NIBIB) (IAG #224-05-6014). Assessment of computer-aided diagnostics

National Institute for Biomedical Imaging and Bioengineering (NIBIB) (IAG #224-04-6055). Laboratory for the Assessment of medical imaging systems

National Institute on Disability and Rehabilitation Research (NIDRR) (IAG #224-06-6059).

National Institutes of Health (NIH) (IAG #224-04-6070). Image-guided interventional therapeutics

Telemedicine and Advanced Technology Research Center (TATRC) (IAG #224-06-6063). Design verification and validation of software systems using formal methods

Telemedicine and Advanced Technology Research Center (TATRC) (IAG #224-06-6066). Implementation and safety of selective optical stimulation for the damaged nervous system

Transportation Safety Administration (TSA) (IAG #224-05-6002). Assessment of X-ray security systems for conformance with radiological safety standards

FY 2006 CRADAs

CTIA (#43-00)

Mobile Manufacturers (MMF) (#6403)

Biophan (#114-06). Measurements and computer modeling to evaluate the safety of medical implants by examining leads of cardiac rhythm management and neurostimulation devices in the presence of electromagnetic fields from magnetic resonance imaging

Nanosonic (#86-05)

University of Pennsylvania (U-PA) (#8705)

Foundation for Research on Information Technologies in Society (IT'IS) (#104-05). MMF dosimetery program

APPENDIX G - OSEL Laboratories and Laboratory Leaders

Division of Biology

Toxicology (biocompatibility): *Peter Goering, Ph.D. (301.796.0253) or peter.goering@fda.hhs.gov*

Laboratory of Cardiovascular and Interventional Therapeutics:
John Karanian (301.210.4247)or john.karanian@fda.hhs.gov

Biological Risk Assessment (infection control): *Ronald Brown (301.796.0252) or ronald.brown1@fda.hhs.gov*

Radiation Biology (photosciences): *Howard Cyr Ph.D. (301.796.0297) or howard.cyr@fda.hhs.gov*

Biomolecular Mechanisms (molecular biology, immunology, allergy, cell biology, genomics/genetics): *TBD - contact Marilyn Lightfoote, Director DB (301.796.0235) or marilyn.lightfoote@fda.hhs.gov*

Biotechnology (biosensors, nanotechnology): *John Langone, Ph.D. (301.796.0245) or john.langone@fda.hhs.gov*

Division of Chemistry and Materials Science

Materials Chemistry: *Joyce Whang, Ph.D. (301.796.2475) or joyce.whang@fda.hhs.gov*

Experimental Pathology: *Steve Hilbert, MD (301.796.2607) or stephen.hilbert@fda.hhs.gov*

Active Materials: *Dinesh Patwardhan, Ph.D. dinesh.patwardhan@fda.hhs.gov*

Division of Electrical and Software Engineering

Software: *Joseph Jorgens (301.796.2588) or joseph.jorgens@fda.hhs.gov*

Electrical Engineering: *Al Taylor, Director DESE (301-796-2583) or alford.taylor@fda.hhs.gov*

System Engineering: *Al Taylor (acting), Director DESE (301.796.2583) or alford.taylor@fda.hhs.gov*

Division of Imaging and Applied Mathematics

Imaging Analysis: *Nicholas Petrick,, Ph.D. (301.796.2563) or nicholas.petrick@fda.hhs.gov*

Imaging Physics: *Aldo Badano, Ph.D. (301.796.2534) or aldo.badano@fda.hhs.gov*

Ionizing Radiation Metrology: *Mary Walker (301.796.2558) or mary.walker@fda.hhs.gov*

Division of Physics

Electro-physiology and Electrical Stimulation: *Victor Krauthamer, Ph.D. (301.796.2474) or victor.krauthamer@fda.hhs.gov*

Electromagnetic and Wireless Technology: *Howard Bassen (301.796.2472) or howard.bassen@fda.hhs.gov*

Optical Diagnostics and Therapeutics: *Joshua Pfefer, Ph.D. (301.796.2494) or joshua.pfefer@fda.hhs.gov*

Optical Therapeutics and Medical Nanophotonics: *Ilko Ilev, Ph.D. (301.796.2489) or ilko.ilev@fda.hhs.gov*

Division of Solid and Fluid Mechanics

Fluid Dynamics: *Michael Berman, PhD (301.796.2504) or michael.berman@fda.hhs.gov*

Mechanics: *Terry Woods,, PhD (301.796.2503) or terry.woods@fda.hhs.gov*

Ultrasonics: *Gerald Harris, Ph.D (301.796.2508) or gerald.harris@fda.hhs.gov*

OFFICE OF SCIENCE AND ENGINEERING LABORATORIES

as of 4/30/07