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), one of seven Offices within the Center for Devices and Radiological Health (CDRH), contributes to accomplishing the Center's mission. 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 newly reorganized 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 are expected to move to the White Oak facilities in 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 in the Office and effectively removed all designated branches.

This reorganization has taken place at a crucial time. 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 provides OSEL management an excellent opportunity to increase collaboration with other components of CDRH. Finally, with the recent move of the life

sciences staff to White Oak and the impending construction of the engineering and physics building, the prospects for OSEL are promising.

OSEL long-term goals focus on the following:

- Chart a course to becoming an exciting and dynamic organization for cutting-edge regulatory research in medical devices.

- Integrate the structure and work of OSEL with the mission and function of CDRH.

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 abstracts of research projects as well as their accomplishments. This report also summarizes 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 301.827.4777.

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Director
Office of Science and Engineering Laboratories

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 challenges and anticipating future regulatory challenges, and
2. Provide technical consults in support of the Center's pre-market and post-market activities.

Both activities are coordinated within OSEL in an effective manner so as to best meet the Center's regulatory and 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 the device performance or test procedures to enable the Center and device manufacturers to gain an improved understanding of issues related to the safety and efficacy. In general, though the research is directed toward issues identified at the pre-market approval level, in reality, 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 consults that OSEL provides to Center's offices in 2005:

Number of consults to pre-market issues:	1023
Number of consults to post-market issues:	173
Number of consults to other Centers and agencies:	60
Number of activities related to standards	116

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,
- 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 may 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:

- Scientific and engineering reviews and analyses
- Laboratory investigations of product performance
- Participation in inspections of medical device establishments
- Forensic reviews and investigations
- Identify device safety and performance issues
- Provide training to FDA and industry
- Contributions 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 is an illustration from the past of a regulatory support activity in which OSEL participated. A few years ago, the reuse of single use devices was a major issue. OSEL established a major research project on this issue in response to a request from the Office of Compliance and Office of Surveillance and Biometrics to address issues related to reuse of single use devices. OSEL researchers organized a team and initiated a preliminary study to determine the effects of a variety of disinfection and sterilization methods on variety of generic materials. The team worked with other Center Offices to set up a retrieval program of cardiac catheters after single use at two local hospitals. These

catheters were marketed for single use only but were reprocessed for reuse in many hospitals and third party facilities. To identify the nature and scope of potential problems with reuse of these devices, the team identified key performance characteristics and developed laboratory test methods to study the effects of use and simulated reuse on these characteristics. OSEL also developed methods for simulating reuse. The laboratory data demonstrated that the performance of some devices does not meet manufacturers' specifications after a single use, and that these properties are further altered after simulated reuse, re-cleaning or resterilization. These laboratory data have had a major impact on the Center's deliberations on the subject as well as incorporation of the data in standards development.

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

1. Computational fluid dynamics of left ventricular assist device

OSEL laboratory expertise in experimental and computation fluid dynamics was recently utilized to aid in the evaluation of a post-approval study change for a pediatric left ventricular assist device (LVAD). The sponsor proposed to make a change to the blood flow path within the pump that could have adversely affected hemolysis and thrombogenesis in the pump such that patient safety and/or device efficacy could have been compromised. It would have been extremely difficult, if not impossible, to validate the design changes using animal or human data. After discussions and a meeting with FDA staff, the sponsor agreed to provide experimental (flow visualization, hemolysis) and analytical (computational fluid dynamics [CFD]) testing to support the design changes. CDRH experts recommended appropriate CFD models to the sponsors and analyzed the results. In this instance, our efforts eliminated the need for the sponsor to perform expensive and time-consuming animal testing and/or clinical testing. The proposed design changes were approved, thus expediting the availability of this innovative device.

2. Computer-assisted diagnostic systems

OSEL scientists have also played a leading role in the development of new models and methods for the assessment of computer-assisted diagnostic systems. The techniques were first developed during our review of digital mammography systems, and have since been extended to the development of systems for breast cancer screening, lung cancer screening, and CT colonoscopy. CDRH scientists who have developed these methods have played an important role on the review team for applications for these devices. Having these tools and methods available has greatly assisted developers of these innovative imaging and CAD-assist devices.

3. Performance testing of pulse oximeters

CDRH scientists and engineers have developed test methods for a range of non-invasive monitoring devices. CDRH laboratory studies on pulse oximeter performance, for example, enabled substantial improvements in the ISO/IEC standard and the CDRH Guidance Document. This testing facilitated the development of a single test protocol for SpO2 accuracy studies, which simplified the pre-market evaluation process by unifying the basis for establishing substantial equivalence. The work has established the groundwork to enable the extensions of claims being made for perfusion measurements and established acceptable performance criteria. In a related initiative, CDRH laboratory work on surface temperature properties was central in defining the limits for the General Standard for Electromedical Safety, 3rd edition of IEC 60601-1, and for the particular standard for the safety and essential performance of pulse oximeters, ISO/IEC 9919. CDRH laboratory scientists, working with industry experts, provided computational models and relevant literature that established that the existing limit could be relaxed by 2°C, making possible new device types and extending applications of existing devices. CDRH laboratory efforts were also instrumental in the establishment of a reliable test method for validating the design of pulse oximeter cables. This work is being incorporated in the next revision of the ISO/IEC standard.

4. 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, in a device for the ablation of uterine fibroids, CDRH-developed computational modeling was used to predict the performance of the device under conditions that would have been difficult to investigate experimentally, thus shortening the review time. CDRH laboratory staff members are now collaborating with outside research institutions and the affected industry to develop standard measurement and analysis methods as input to international standards for HIFU that will be used to facilitate the regulatory review process.

5. Guidance for extracorporeal shock wave lithotripsy

Extracorporeal shock wave lithotripsy is a minimally invasive technology that employs focused, high pressure ultrasonic waves for fragmentation of kidney and ureteral calculi. When first introduced, these devices were deemed Class III because of the new intended use coupled with the potential for serious collateral damage to non-targeted tissue. At the time there were no accepted means for measuring the very high pressures produced by these devices, which complicated the regulatory reviews. Based on CDRH laboratory efforts, performance requirements for measurement instruments and appropriate measurement procedures were developed and documented in a pre-clinical testing guidance for the industry. This guidance eventually led to two international consensus standards, which in turn were instrumental in allowing CDRH to down-classify these devices to Class II, thus saving the industry from lengthy human clinical trials.

6. Expediting intraocular lens evaluations

OSEL laboratory scientists have played a leading role in the development of new test methods for measuring the optical parameters of intraocular lens implants (IOLs). An estimated 20 million Americans over the age of 40 have cataracts in at least one eye, most of which can be corrected through the implantation of IOLs. The focal length (or dioptic power) is a fundamental parameter whose precise measurement is of critical importance for evaluating the safety and effectiveness of IOLs. Testing the dioptic power of IOLs has been difficult because conventionally used test methods are limited in terms of accuracy and the dynamic range over which measurements can be performed. To overcome these problems, CDRH laboratory scientists developed a novel confocal fiber-optic laser method (CFOLM) for precise measurement of IOL dioptic power which provides high accuracy (exceeding 1 um) in spatially locating the focal point and in measuring the IOL dioptic power. Such accurate measurements have not been achievable previously. The new CFOLM measurement system has been used to evaluate the dioptic power of a variety of new IOL designs from several different manufacturers, and to resolve questions about the accuracy of the labeled dioptic power, expediting decision making by facilitating agreement between industry and CDRH. This new test method will be considered for incorporation in international product performance standards for testing IOLs.

In addition, experimental and theoretical work in the laboratories on the mechanism of formation of vacuoles in foldable, hydrophobic intraocular lenses (IOLs) has led to an understanding of differential osmotic forces as the root cause of these artifacts. Characterization of the kinetics of vacuole formation revealed that changes in the lens environment (both thermal and chemical) can modulate the size and number of vacuoles. These observations allowed for the rapid acceptance of changes in the storage solutions proposed by the sponsors of a new class of hydrophobic IOL materials. The computational and experimental tools developed in these studies will allow for rapid evaluation of optical stability of future classes of IOL materials.

7. Spinal implant evaluation

FDA has received a dramatic increase in the number of submissions for new spinal implants, a sector of the orthopedic medical device industry whose revenues were estimated at $3.6 billion in 2005, signifying an increase of 17% over the previous year. Motion-preserving devices and novel concepts such as minimally invasive fracture repair strategies have been responsible for much of this growth. Under the auspices of MDUFMA, CDRH laboratories initiated a research program into vertebroplasty, a minimally invasive procedure for treatment of spinal compression fractures, with the goal of providing reviewers with better scientific information on the mechanical benefits of the treatment in order to accelerate and improve reviews of product safety and labeling. This laboratory initiative resulted in developing information clarifying the mechanical stability of the spine after this treatment which has substantially assisted CDRH's scientific review staff, enabling more efficient interactions with manufacturers and expediting the review process. CDRH laboratory staff have also become active participants on CDRH's spine review team as well as an international standards organization that writes standard testing methods for medical implants, ASTM F04 Medical & Surgical Materials and Devices. In fact, CDRH laboratory staff have assumed the chairmanship of the ASTM subcommittee F04.25 on spinal devices. In addition, CDRH laboratory scientists have provided the device reviewers in CDRH's Office of Device Evaluation with information on the use of these testing standards which, complemented with physical models of testing fixtures, has enabled improved understanding of how standard test methods are being used by device companies. This understanding has greatly facilitated their reviews of new products.

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

- Materials Characterization
- Experimental Pathology

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

- Medical Imaging and Diagnostics
- 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 Radiation Safety and Devices
- Optical Diagnostics and Therapeutics

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
- Solid 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 (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 support risk management decision-making in the Center. Research is focused in three areas:

Development of clinically relevant biomarkers and preclinical animal models: Research in this was identified as being central to the FDA Critical Path Initiative (http:// www.fda.gov/cdrh/present/criticalpath and (http://www.fda.gov/oc/speeches/2005/ddtd0810.html).

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.

Bioeffects of ultrasound and ultrasound contrast agents: 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). The hazard identification stage of risk assessment requires that we have the necessary tools to detect the effects produced by compounds or infectious agents released from medical devices. Consistent with the Critical Path objectives, these new tools include clinically relevant biomarkers and preclinical models to detect adverse effects at the earliest stages. Toxicity studies used for the risk assessment of compounds released from medical devices are almost always conducted using healthy animals; however, patients exposed to these compounds may be critically ill or injured. A number of studies have demonstrated that the potency of some

compounds is potentiated by conditions such as renal failure, liver failure, and sepsis. To address this broad issue, animal and *in vitro* (cell culture) models of compromised health are being developed in the laboratory and will be used to examine whether the potency of compounds is increased in experimental animals with compromised health or injured cells compared to healthy animals and cells. Animal models of compromised health are also being used to assess the impact of ultrasound contrast agents on the vascular endothelium and to develop new devices that can be used to assess tissue damage and functional changes in diabetic patients.

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.

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

- Develop and validate clinically relevant biomarkers and preclinical models
- Use these biomarkers and preclinical models to address issues of regulatory importance to CDRH
- Conduct risk assessments to support the regulatory decision-making process in CDRH
- Determine the effectiveness of various cleaning/disinfection strategies to remove bio-burden on reprocessed devices.
- Determine the effect of ultrasound contrast agents on vascular tissue
- Initiate and/or maintain collaborations with other FDA Centers, other Federal government agencies (e.g., USDA, USUHS) and academia.

Accomplishments

- Determined the amount of residual proteins on two single use devices (GI biopsy forceps, cardiac electrophysiology catheters) following cleaning and disinfection. The data obtained are used by ODE for reviewing supplemental validation submissions for reprocessing single use devices by third party reprocessors, and for OC inspectors when they are inspecting third party reprocessors at their facilities.
- Assessed the risk of iatrogenic vCJD transmission from reprocessed neurosurgical instruments and presented the results to the General Hospital and Personal Use Devices Panel of the Medical Devices Advisory Committee.
- Developed an *in vitro* method using hemolysis as a rapid bioindicator of residual disinfectants on reprocessed medical device materials.
- Compared the relative sensitivity of L929 fibroblasts, RAW 264.7 macrophages, and erythrocytes to disinfectants to determine the most sensitive assay for determination of the cytotoxicity of residual disinfectants on medical devices.
- Developed a survivable *in vivo* (pig) inflammation model for testing the impact of inflammation on host responses to devices and device residues and conducted time-

course studies of LPS-induced inflammation in newborn pigs (in collaboration with USDA and University of Pennsylvania).

- Determined the *in vitro* toxicity of extracts from ethylene oxide-sterilized devices to support revision of the ISO 10993-7 standard.

- Conducted a study of the acute hemodynamic and hemolytic effect of intravenously administered ethylene glycol in the pig to support revision of the ISO 10993-7 standard.

- OSEL scientists collaborated with research scientists from CDER and Harvard University to validate a new biomarker of renal injury and disease that can be detected in urine samples of patients and animals in preclinical safety evaluations. The utility of the new biomarker was evaluated in experiments designed to expose laboratory rodents to low doses of prototypic nephrotoxicants. The new biomarker appears to be more sensitive and predictive that currently used preclinical and clinical markers of renal damage.

- OSEL scientists continued to validate the animal model of subclinical renal injury with the goal to improve the model for targeted use in biocompatibility and preclinical testing of medical devices materials and residues. The model is easy to produce in laboratory rodents and inexpensive, and appears to be better and have advantages over several existing models that are used. The model is used to identify potentially nephrotoxic materials and residues at clinically relevant exposures that were not nephrotoxic in healthy subjects. The model may find utility as a special adjunct test in preclinical biocompatibility testing when a residue is suspected of being nephrotoxic and/or when a device is intended for use in a critical care patient population.

- Initiated a study to investigate the pharmacokinetic behavior in pigs of fentanyl released from a combination device (collaboration with CDER).

- 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 **(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 radiofrequency 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 to 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.
- Laboratory research gives our staff the scientific credibility needed to help with devices reviews and development of international standards and guidelines.
- Serves as a radiobiology resource for homeland security issues.

Three-Year Goals

- The first project under the FDA-CTIA CRADA investigating the possible genotoxic effects of exposure to radiofrequency radiation is now complete. The second project under the CRADA, to investigate the factors that characterize a good exposure assessment for an epidemiology study, will be completed in FY 06. The third project under the CRADA will identify any gaps in the scientific evidence and prioritize future research needs. This will begin in FY 06.
- 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

Radiofrequency studies and oversight of CRADA on cell phones

- Authored section on standards affecting cell phone use for Commissioner's report on "Global Harmonization Efforts."

- Provided oversight of Phase 1 of the Cell Phone CRADA monitoring publications from two of three investigators who reported no increases in micronuclei following exposures to radiofrequency radiation. The third investigator has completed project but has not submitted final report.

- Conducted site visits to laboratories performing research on important factors in determining the amount of human exposures to radiofrequency radiation during typical cell phone usage.

- Prepared a Memorandum of Needs document that is being used by FDA contracting office to solicit contractors to conduct Phase 3 of the Cell Phone CRADA which will investigate the state of current knowledge on the possible health effects and highlights deficiencies in that knowledge that could be addressed by further research.

- 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 standard is now complete and will be published in the immediate future.

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

- Using preliminary hyperthermia data obtained in the laboratory, initiated a project to look at the effects of hyperthermia in sensitizing cells to low LET x-ray therapeutic doses.

Human Photosciences Research

- Completed collection of data on histological and molecular changes induced by UV exposure in three U.S. population groups. Analyses of these data show that the differences in susceptibility to UV-induced cutaneous malignant melanoma and non-melanoma skin cancers may depend not only on the extent of DNA damage but also on its distribution (in dark skin, the damage is restricted to the superficial layers of the epidermis).

- In collaboration with the J&J Materials and Models team, we developed methodology for determination of the blood and melanin content in human skin of different color. This non-invasive methodology makes it possible to measure the erythemal component of the UV-induced skin color change. This, in turn makes it possible to minimize erythema during UV procedures. Erythema links to melanoma induction are indicated by epidemiological studies.

- Developed models for relationships between melanin content and susceptibility to erythema and DNA damage in the skin of different color. Analyses of these models based on our experimental data allowed us to propose further improvements in modeling of human UV response that eventually may predict UV responses of individual humans as a part of the personalized medicine approach.

- Demonstrated and investigated the UV-induced redistribution of melanin as an element of post-UV-exposure skin color change and as a defensive mechanism that may reduce carcinogenesis. These observations should be followed by a search for factors that may accelerate such redistribution. This would reduce risks of repeated exposures.

- Served as one of two U.S. representatives on the IEC TC 61 MT 16 committee for sunlamps. As chairperson of the sub-committee on exposure schedules, prepared proposal and attended annual meeting to discuss options for including recommended exposure schedules in this international standard. Prepared a concept paper which proposes specific amendments to the FDA Performance Standard for Sunlamp Products. In addition, served as FDA's liaison to the International Standards Organization (ISO) committee on optics and ophthalmic instruments.

- Completed study of 46 human subjects to explore improvements to the current FDA recommendations for exposure schedules for sunlamp products. Found that cumulative UV dose to indoor tanners could be significantly reduced.

- Worked on team to update the guidance document (intended for sponsors of clinical studies) for optical diagnostic devices intended to detect cervical cancer and its precursors.

Biotechnology (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. The laboratory's main research projects are focused 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.

Research Program Description
The laboratory is working on six major research projects related to detection and analysis of microbial pathogens funded in part by the FDA's Office of Science and Health Communication 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: This bioengineering project was supported in part by University of Maryland.

- Staphylococcal pathogenesis: This bacterial species is the one most commonly associated with catheter colonization. The project was funded by the FDA's Office of Science and Health Communication.

- Bioinformatics tools for microarray development: New tools are being developed with funding from the USDA.

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 as bioweapons all add to the need for better microbial detection and diagnostics for medical devices.

Three-Year Goals

- Improving the prototype of the portable PCR thermocycler for regulatory and biodefense applications. We plan to optimize of the wiring, design a holder for the capillaries, and develop an electro-optical detection module and a PDA-based controller.

- Developing 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.
- Developing whole genome amplification methods for microarray analysis of microbial contaminants.
- Improving the assembly of our microfluidics device for use in detection of microbial pathogens.
- Studying Staphylococcus colonization of catheters and biofilms formation.

Accomplishments

- Development of 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.

- Analysis of *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.

- Development of 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.

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

Development of a hand-held microfluidics multi-channel biosensor for detection of microbial pathogens: The biosensor consists of a three-layer plastic cartridge assembled with a thermal press. Samples and reagents for the sandwich assay are delivered to the membrane through microcapillaries using a miniature built-in manual vacuum pump. A prototype immunosensor was tested for detection of detection of staphylococcal Toxic Shock Syndrome Toxin (TSST), a women health concern.

- Development of bioinformatics tools: New software was developed and tested that automates the selection of oligonucleotides for microarrays.

Cardiovascular and Interventional Therapeutics (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

Participated in Agency Outreach with Professional Organizations, and Agency Cardiovascular Web Site

Developed facilities and content for new 6-hour course with FDA/CDRH Staff College: "Emerging Technology: Preclinical Animal Models, Studies and Data Evaluation." Course began in May 2005 and is ongoing.

Designed a series of on-line training programs with Staff College in parallel with the above-listed course.

Developed several funding/extramural collaborations and/or Material Transfer Agreements with University Of Pennsylvania, NIH, Diagnostic Radiology Department and NIH Clinical Center, Interventional Therapeutics, EndobionicsBiopal, Lenox Hospital, Hartford Hospital, and Sonus Pharmaceutical.

Developed significant number of current Animal Use Protocols, including Models of therapeutic intervention for vascular disease, biomechanics and genomics of vascular dysfunction, congenital and acquired cardiovascular abnormalities, intravascular radiofrequency ablation for hemostasis: preclinical study, intravascular radiofrequency ablation for hemostasis, and biomechanics and genomics of vascular dysfunction.

Toxicology (Division of Biology)

Scope

The Laboratory of Toxicology, located in the Division of Biology, 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.

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

- Evaluate currently used or develop new test methods to examine the potential immunotoxic, inflammatory, and proliferative effects of nanoparticles (collaboration with the National Cancer Institute – Nanotechnology Characterization Laboratory).
- Study the transport of nanoparticles across the placenta and resulting effects on the developing fetus (collaboration with George Washington University). Excellent leveraging opportunity – GWU will provide a PhD student for this project with no stipend or personnel cost to FDA.

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.

In mid-2005, the laboratory terminated a multi-year research project devoted to understanding potential hormone disrupting effects of bisphenol A, an estrogen-mimicking chemical that migrates out of medical plastics. The highly successful project produced 6 peer-reviewed publications and numerous presentations at national and international scientific meetings. Expertise gained was useful for OSEL scientist to participate in the OSTP Inter-Agency Workgroup on Endocrine Disruptors.

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 R&D 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 Objectives

- 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

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.

- Ethylene oxide and ethylene glycol levels were quantified in solutions used to conduct *in vitro* and *in vivo* biological testing of these compounds. The results of this effort were used to directly support the revision of the ISO 10993-7 standard.

- DEHP, a plasticizer released from many PVC medical devices, was quantified in solutions administered to pigs in a study to determine the effect of endotoxemia on DEHP-induced toxicity.

Two related studies were conducted under the Laboratory goal to develop test methods to evaluate adverse effects of medical devices and device materials, including nanoparticles.

- Studies were conducted to understand the effects of polystyrene nanoparticles (50-nm) and larger polystyrene particles (500-nm) on immune responses in mice and the effect of particles as antigen carriers on host immune response. Data indicated that particles of both sizes used as antigen carriers can enhance IgG immune responses. In contrast, the smaller 50-nm particles also increased the IgE antibody level, thus enhancing the potential for sensitization.

- A second study was conducted exposing mice to fluorescent-tagged polystyrene nanoparticles in order to evaluate translocation of particles from the site of injection, cytokine production, and histopathology.

Biomolecular Mechanisms **(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.

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.

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.

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. In addition, collaborations within FDA, with other government organizations, academia and industry have provided ample opportunity for significant leveraging of resources and expertise.

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)
- Utilization of 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

Accomplishments

1. Prioritizing Variables in Genomic Microarray Data
    - CDRH has the lead in organizing and coordinating the project. Four FDA Centers are involved and have implemented a series of comparative experiments under the OSHC Inter-Center Project
    - Large scale preparation and QC testing of cells and RNA for genomic microarray experiments (gamma irradiated cells and controls).
    - Design of our own microarray and all of the ~200 probes.
    - Streamlined experimental design testing inter-lab and intra-lab technical variables, based on input from the four participating FDA genomics labs.

- Discovered novel approaches to microarray QC, including the use of random 9-mer hybridization mixes to differentiate probe mobilization from probe hybridization variables.

2. Latex allergy genomics project (initiated via funding from Office of Women's Health). Results this year include:
   - Identification by DNA sequencing of differentially expressed gene fragments.
   - Data analysis on inflammatory response genes differentially expressed in latex allergic subjects compared with non-allergic controls.
   - The identification of a set of genes from which a diagnostic microarray for latex allergy could be created.
   - IRB approval, identification of new subjects, and coordination with a CDRH epidemiologist for the beta testing of our genomic microarray.
   - IAG between the Federal Occupational Health agency and CDRH for blood drawing with new subjects.

3. Identification of medical device-related pathogens using microarrays and RT-PCR.
   - Microarray aspects for the identification of six FDA relevant bacteria (*S.aureus, E.coli, Salmonella, Shigella, Listeria* and *Streptococcus*) pathogens have been fulfilled. This includes designing and synthesis of probes, printing microarrays and DNA hybridization. Developing internal controls for a diagnostic pathogen detection microarray is under evaluation.
   - Designed and developed PCR primers for real-time PCR detection of above pathogens.
   - Rapid detection procedures using real-time PCR for above pathogens except *Listeria* spp. have been developed.

4. Genetic testing microarray development
   - In this project, the identification of 8 single base pair hotspots in a tumor suppressor gene was optimized. The results will be used to improve or critique genetic testing methodologies, including those in diagnostic genetic tests.

Electronics (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

Electronics 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 Electronics 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 Electronics 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

***Postmarket 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.

This work often required gathering information from sources that were less than completely candid. We had to make reasonable inferences about the nature and likely causes of the problem, then work cooperatively with other Center experts to understand the public health implications of our findings. In a number of these cases, our analyses led the manufacturers in question to expand the scope of the recall and/or undertake a more comprehensive corrective action than was originally proposed. The cases involved a range of issues such as microprocessor circuit design, basic electrical safety, battery and charging circuitry performance, software functional errors, and user interface designs that were flawed from a human factors standpoint.

Software (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 Objectives

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 2007 and 2007.

Accomplishments

Software Forensic Laboratory. In FY2005, DESE engineers took the first concrete steps toward implementing a new generation of software forensic laboratories.

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.

- DESE software engineering research has been exploring tools for analytically proving the correctness of software programs and strengthening the linkage between natural language requirements, the resultant software code, and "safety cases" that document the rationale for a manufacturer's claim that a given design is acceptably safe. These tools were originally envisioned as being useful for software developers on the front end of a product design, ultimately permitting the manufacturer to certify the correctness of those designs. Gradually, it became apparent that some of these tools could also be applied to software code after an adverse event has occurred, enabling FDA analysts to quickly understand what might have gone wrong and pointing to the most appropriate corrective action. We could also conceivably use these tools to quickly check the integrity of a given software design during a pre-market review.

- DESE researchers visited the FBI's software forensics laboratory, confirming the validity of this approach. We found that the FBI's laboratory capabilities are attuned to the national security threats and unlawful business practices that form the bulk of their caseload. Our focus on embedded medical device software is complementary to their approach. Thus encouraged, in FY 2005 we began detailed planning for a software forensics lab that could be used for pre-market review as well as post-market investigations. The first tools were acquired late in the year

and, at press time, have just been put to their first use in a post-market investigation. We anticipate that the laboratory will evolve considerably in FY 2006.

Systems Engineering (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 in three 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 the development of 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 healthcare facilities.

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. Finally, 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.

Accomplishments

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

- In 2003 computer viruses found in medical devices were causing significant disruptions to hospital networks. Healthcare organizations were looking to FDA for solutions. A cross-Center team, led by DESE, took responsibility for consulting with all stakeholders and developing a comprehensive solution.

- 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.

- Scientists have long used a formalized process of risk assessment to assess and mitigate risk arising from environmental threats as well as hazardous materials and substances used in products. Now, the medical device community has embraced a similar engineering process intended to manage risks arising from the design of medical devices. This process exploits the many opportunities to improve product safety, both during the product design phase and throughout the product life cycle, by systematically analyzing risks, introducing appropriate control measures, and measuring/monitoring their effectiveness.

- DESE engineers played a key role in development of 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 Chemistry **(Division of Chemistry and Materials Science)**

Scope

This program conducts research and testing in support of the Center's mission related to materials characterization, degradation, and materials-tissue interactions as they affect medical devices, in both pre-market evaluations and post-market surveillance. The program was established to provide CDRH and other FDA Centers the scientific and engineering capability to test and evaluate medical device materials safety and effectiveness in the total product life cycle (TPLC). The testing and evaluation services include development of instrumentation and testing protocols, procurement of appropriate

research and regulatory device/materials samples and providing recommendations for the product performance criteria, accuracy, precision, and safety of medical devices.

Background

The laboratory's testing and evaluation activities contribute to evaluating medical device materials safety and effectiveness in TPLC. These activities are directed not only toward solving the specific device-related regulatory issues, but also in finding ways to apply the knowledge gained to publish in medical device peer-reviewed journals.

Research Program Description

The program addresses materials synthesis, processing, and fabrication as they influence medical device performance. These processes are affected by the molecular structure, phase, and ultimately the physical-chemical interactions in materials. The research includes characterization of residue and contamination analysis, purity, chemical structure and formulations, thermal stability, phase stability and transformation, transport and thermodynamic properties, and viscoelastic and adhesive properties.

The laboratories are capable of testing the performance of physical and chemical processes of importance to medical devices, such as mass transfer through membranes used in dialysis and manufacturing processes used to fabricate materials. This program provides the Center with independent data as well as intramural knowledge and experience concerning the use of preclinical/post-market studies for the evaluation of medical device materials safety and performance. Additionally, the program evaluates the degradation of materials in storage or use *in vivo* or *ex vivo*, identifying potential materials issues related to failure modes, and also contributes to the development of regulatory guidance and test methods to ensure the safety and effectiveness of medical devices and their material components.

Materials characterization focuses on surface and interface chemistry, bulk and surface morphology, bulk composition, and chemical/physical parameters for structure determination. The materials degradation area evaluates the chemical, thermal, and environmental degradation of materials and the affect of degradation on medical device performance and safety. The polymer/materials degradation area focuses on materials integrity, materials interactions; chemical, physical, and thermal degradation; *in-vitro* and *in-vivo* studies for medical device/materials; and shelf and service-life. This work includes post-market evaluations of device failures and forensic investigations such as unidentified particles in PVC blood bags, defective IV set fabrication, adhesion barriers, and counterfeit hernia repair mesh.

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. The materials characterization, polymer degradation, materials-tissue interactions programs play a pivotal role in pre-market evaluation, and post-market monitoring activities. Materials will continue to be an essential component of medical devices, and OSEL's laboratory capability to evaluate materials will help the Agency make regulatory decisions based on the best available expertise and independent scientific information. It is anticipated that a focused program in which the materials characterization, degradation, and tissue-materials interactions laboratories will help determine product performance criteria, accuracy, precision, reliability and safety of medical devices which will help the Center in its mission in every phase of TPLC. This program's activities will help ODE, OC, OSB and other FDA Centers to develop guidance documents and a substantial number of standards.

Three-Year Goals

- Develop test methods to ensure the safety and effectiveness of new device technologies.
- Increase peer-reviewed publications, presentations, and test methods developed in support of guidance and standards.
- Provide independent laboratory data on materials failures to improve the pre-market evaluation and post-market issues.

Accomplishments

Assessment of Calcium Phosphate Deposition Mechanisms in Dental, Orthopedic and Cardiovascular Device Applications

- Developed a reliable method for forming model systems based on amorphous calcium phosphate (ACP) and photo-cured polymers. Used these constructs to observe conversion of ACP to calcium hydroxyapatite as a model for calcification of medical plastics.

Characterizing Cross-linked Viscous Abdominal-Pelvic Adhesion Barriers

- Identified new dynamic mechanic methods for characterizing physically ionically cross-linked gels used in adhesion barrier materials.

- Investigated issues related to the reliable and reproducible manufacturability of hydrogel barrier materials. These included understanding impact of process variables on inclusion formation and viscosity.

Vacuolar Behavior and Morphology in `Glistened' Intraocular Lenses

- Developed simple protocols for accelerated development of vacuoles in hydrophobic acrylic IOL materials. Differences in materials behavior in a variety of media has led to a correlation between vacuole formation and ionic strength.

- Identified quantitative methods for relating Clinical Grade (glistening density) to a numerically quantifiable optical parameter for further analysis.

- Identified that via cyclic hydration/dehydration of hydrophobic acrylic IOL materials that materials do not "heal" and that vacuole formation creates (or enlarges) a permanent defect in the lens.

Experimental Pathology **(Division Of Chemistry And Materials Science)**

Scope
The laboratory is research-based and is intended to provide the Center with independent data as well as intramural knowledge and experience concerning the use of preclinical *in vitro* and *in vivo* studies for the evaluation of medical device materials safety and performance. The major output of the laboratory specialty areas include independent assessment of manufacturers' claims and data, test methods, standards, regulatory guidance, and publications related to the public health impact of medical device materials design and safety.

Background
The program's research activities contribute to evaluating medical device materials safety and effectiveness in TPLC. These activities are directed not only toward solving the specific device-related regulatory issues, but also in finding ways to apply the knowledge gained to publish in medical device peer-reviewed journals. Research efforts have been focused on the development of *in vitro* science and engineering studies suitable for the characterization, degradation, and biomaterials applications.

Research Program Description
This program's experimental pathology laboratory is designed to evaluate the explant pathology of medical devices utilizing gross pathology, histopathology, immunohistochemical staining and molecular pathology studies. This research program has provided independent data identifying heart valve failure modes associated with emerging polymeric and tissue-derived materials as well as identifying a mechanism for the loss of cuspal cells in viable allograft heart valves following implantation. The research results have supported the regulatory decisions and recommendations made concerning four generations of replacement valves.

The materials-tissue interactions area conducts experimental research in support of pre-clinical models for evaluating dental, orthopedic, and cardiovascular device applications with respect to calcification and other phenomena. There is new focus is on materials processing, and materials science-related issues relevant to *in-vitro* diagnostic devices. The research is directed toward developing and establishing the *in vitro* and *in vivo* studies and models suitable for evaluating materials-tissue interactions, failure modes and effects analysis, the assessment of medical device-related pathology, peer-reviewed basis for regulatory guidance recommendations and standards development.

Relevance to FDA's and CDRH's Mission, Program, and the Public Health Impact
The research in this program area is directed toward the development and establishment of *in-vitro* and *in-vivo* studies and models suitable for the evaluation of medical device materials safety. The peer-reviewed findings of these research projects serve as the

scientific basis for regulatory guidance recommendations and standard development. The quality of new device materials must be assured by the appropriate pre-market testing and post-market surveillance. The goal is to develop the quality regulatory science base to meet the new challenges.

Three-Year Goals

- Contribute to the missions and functions of CDRH and other FDA centers by solving interdisciplinary problems involving materials;
- Enhance active participation with external partners including governmental partners, academia, and industry; and
- Provide independent data based on *in vivo* preclinical studies evaluating the next generation of replacement materials in devices such as stents, heart valve, and cardiovascular device materials.

Accomplishments

Controlled R_x Delivery

- Developed comprehensive theory based on classical materials physics for structural evolution of drug-polymer-solvent systems (in collaboration with NIST). This model was tested to "real-world" polymer/drug systems and typical processing conditions.

- Developed methods, including a motor controlled spray coater apparatus with temperature and gas environmental control, to fabricate reproducible drug/polymer constructs for use as substrates in elution studies.

- Developed optical and probe microscopic analyses for characterizing drug/polymer constructs. Surface spectroscopy (TOF-SIMS, done in collaboration with NIST) has also been used to characterize 3-D drug distribution in these constructs.

Assessing the Stability of Nano-scale Constructs

- Developed first-principles mathematical models for predicting the formation of drug nanoparticles and their size stability in polymer matrices. These methods allow for the prediction of drug elution rates for a variety of polymer/drug morphologies and polymer/drug physical characteristics (e.g. solubility, thermodynamic stability)

- Evaluated with Carnegie Mellon University scanning probe microscopy (SPM) techniques as tools to characterize the structure of organic nano-constructs as a model for drug releasing polymeric coatings.

Medical Imaging and Diagnostics (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 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 novel soft-copy display devices for viewing medical images.

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 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 here 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.

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 imaging and CAD systems. A multivariate approach is needed for several reasons, including the great reader variability that has been demonstrated in recent years. Current work includes the development of software for clinical trial design and analysis.

Contemporary in-house programs address measurement methodology for the assessment of many new technologies for digital image capture and display; novel ultrasonic methods for *in-vivo* tissue characterization and bone densitometry; statistical analysis of neural-network decision-assist tools; and the emerging field of DNA micro-arrays.

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.

These investigations inform the Center's regulatory decision-making on new digital image 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 Sonometer PMA Applications: Final Guidance for Industry and FDA." OSEL scientists have applied their expertise to the development of a CDRH web site on CT, the development of amendments to the diagnostic x-ray equipment performance standard, and the development of an advisory pertaining to pediatric CT exposures. Recently OSEL staff, along with OCER staff, assisted in the joint planning of a consensus development conference on CT with NIH, and made presentations at that conference.

Improved knowledge of the fundamental imaging mechanisms will lead to an understanding of the sources of variability in imaging data. Having that, inter-machine and inter-institute 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 developing new equipment performance standards as digital mammography develops, special procedures and test equipment for MQSA, and will be used to inform decisions on marketing clearance for new products and in compliance actions.

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.

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 radiographic imaging systems, the development of amendments to the diagnostic x-ray performance standard, the development of an advisory pertaining to pediatric CT exposures, and participation in the planning and presentation of materials to consensus development conferences. The x-ray spectral measurements program provides a source of otherwise unavailable data to the entire mammography research community. Finally, investigations of computer-assisted diagnosis devices provide the Center with the scientific basis to effectively regulate this fast growing field.

Three-Year Goals

Future efforts in the Medical Imaging and Diagnostics 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 performance measures, optimizing overall system performance 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 volume imaging of the human anatomy including cone beam computed tomography 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, and the use of ultrasonic measurements in pattern recognition systems. While DIAM continues to work in the area of ultrasound, the largest activity for this year involves high-intensity focused ultrasound, and this is described in the program description for Fluid Dynamics and Ultrasonics.

The Medical Imaging and Diagnostics program has made fundamental contributions to the field of statistical analysis of diagnostic imaging and systems for computer-aided diagnosis. We would like to exploit this work and validate its range of utility through extensive computer simulations. In the process, we would be 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). Development of such a system would address one of the most difficult yet most common assessment problems in the field of diagnostic medicine. 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

- Scientific research on diagnostic medical ultrasound being conducted in DIAM has led to a number of significant publications and presentations in 2005, and contributed to the successful development of documentation required for the reclassification of ultrasound bone sonometers. The reclassification of these devices was completed in 2005.

- 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." 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.

- A high-resolution laboratory cone-beam CT system has been built which can perform fully automated CT scans of small animals, phantoms, or tissue samples with high resolution. Investigations are underway to fully characterize the 3D imaging properties of our system; this information will be useful in novel image-reconstruction algorithms. We have also developed a gender-specific statistical model of pathological coronary arteries which will be used for generating simulated angiograms. These efforts will be reported at the upcoming SPIE Medical Imaging Symposium in February 2006.

- Our Monte Carlo computer simulation activity has been greatly extended via the incorporation of the PENELOPE code, through collaboration with one of the developers of this code, Dr. Josep Sempau of the Institut de Tecniques Energetiques, Universitat Politecnica de Catalunya in Barcelona, Spain. This accomplishment enables the combined x-ray/electron/optical simulation of radiation detection at the full energy range of interest in radiological imaging.

These advancements were reported at the 2005 SPIE Medical Imaging Symposium. One DIAM investigator has organized a short course on Monte Carlo simulation of imaging systems for the upcoming 2006 SPIE Medical Imaging Symposium, at which time a public release of the combined code, called MANTIS, will be made available.

- DIAM researchers have developed methods for the automated, quantitative evaluation of imaging phantoms for use in the objective assessment methods for digital radiography. These methods were validated using both a laboratory imaging system in DIAM as well as a clinical mammography unit at USUHS. This work was accepted for publication in Medical Physics and should appear in print in early 2006.

- In the area of display evaluation, we have performed testing to characterize color monitors by determining the uniformity and color difference using various standards including ISO, VESA, TCO, SPWG, and TG-18 guidelines on measurements. In addition, DIAM scientists are developing new approaches for the determination of the temporal response for monitors for use in the evaluation of display devices that will be used for dynamic viewing of 3D imaging.

- In the area of computer-aided diagnosis (CAD) : a)developed a method for the alignment of full and partial CT thoracic scans using bony structures that enables the automatic matching of lung nodules in temporal CT scans for treatment monitoring in lung cancer; b) investigated the use of image pairs (contralateral images) in mammography for false-positive reduction in breast CAD; and c) reported on the influence of panel size and expert skill on truth panel performance when combining expert ratings. This work has relevance to device assessment approaches that use a panel of experts to determine truth in the absence of a gold standard.

- Discovered an unbiased nonparametric method for estimating the multi-reader, multi-case variance of the empirical area under the ROC curve (AUC) that does not employ resampling methods. He presented this material at the 2005 Medical Imaging and Perception Society Conference, and the corresponding manuscript "One-shot estimate of MRMC Variance: AUC" has been accepted for publication in *Academic Radiology* and will appear very soon in 2006. This work was the result of collaboration with the University of Arizona and, thanks to the conference presentation, has spawned a new collaboration with the University of Pittsburgh. The work has also contributed significantly to a new understanding of the performance behaviors and limitations of parametric and nonparametric approaches to MRMC confidence intervals.

- There has been a major advance that allows the estimation not only of the performance of the diagnostic test, but also the uncertainties in this estimation that are due to the finite size of the training set and the finite size of the test set. The dissertation of another DIAM researcher presented approaches to estimation of the entire receiver operating characteristic (ROC) curve. Current efforts are directed toward the use of the partial area measure that may be more suited to particular screening or diagnostic settings, depending on the disease prevalence in the population of interest.

Ionizing Radiation Metrology (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

The IRML's calibration program was designed to economically provide a large volume of high quality calibrations for a nationwide network of inspectors. Each year FDA is responsible for the inspections of over 11,000 mammography facilities under the Mammography Quality Standards Act (MQSA). In addition, about 1,600 installations of general radiographic equipment are inspected against the mandatory performance standards established under the Radiation Control for Health and Safety Act (RCHSA). FDA also tests a number of non-medical x-ray installations each year. These inspection and testing programs involve measurements of ionizing radiation. IRML supplies the CDRH Office of Communication Education and Radiation Programs (OCER), the FDA Office of Regulatory Affairs (ORA), and partnership States with the following: 1) calibrated x-ray instruments and supplies for the various compliance inspection programs, 2) support for special measurements as needed, such as measuring the ionizing radiation output from products such as personnel security scanners and night vision devices, and 3) technical consultation on industry submissions and measurement issues. Traceability of measurements is achieved through the operation of a secondary standard laboratory accredited by NVLAP. The laboratory's services are used for leveraging state agencies to test newly installed radiological equipment against FDA requirements, resulting in hundreds of additional inspections per year.

The IRML staff contribute to the development of new measurement standards. For example, laboratory staff have been instrumental in establishing the national standard for mammography x-ray calibrations and continue to work closely with NIST. The Laboratory also participates in the development of consensus standards on radiation safety of x-ray products.

Relevance to FDA and CDRH Mission and the Public Health Impact

This laboratory allows the CDRH to fulfill its responsibilities for monitoring the safety of electronic products that emit potentially hazardous levels of radiation. For example, inspection of mammography facilities mandated by MQSA, as well as of medical diagnostic radiographic equipment, requires the use of calibrated radiation monitoring equipment provided by this program. 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 5 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 work with outside agencies and institutions on voluntary standards and guidance, particularly in the area of non-medical x-ray safety. The laboratory will continue to seek collaborative agreements with other federal agencies for the purpose of evaluating radiation hazards from new security screening technologies. 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 5 years are predictable at this time. For example, the laboratory will have to reassess the need for continuing to seek NVLAP accreditation based on the new environment.

Accomplishments

- Provided instrumentation and logistics support to FDA and Agreement-State inspectors for compliance testing of about 1,500 general radiography installations, over 10,000 mammography machines, and voluntary surveys under the Nationwide Evaluation of X-ray Trends (NEXT) program.
- Operated the CDRH X-ray Calibration Laboratory accredited by the National Voluntary Accreditation Program (NVLAP). The laboratory provided 1,040 radiation calibrations of general diagnostic instruments, 330 radiation calibrations of mammographic instruments, 650 electrical calibrations of radiation monitors, and 104 calibrations of non-invasive kVp meters.
- Updated the calibration laboratory's automation and data collection systems. This included the completion of a new Labview program to control the calibration process.
- Began a comprehensive performance evaluation of commercially-available instruments for diagnostic x-ray measurements and quality control.
- Contributed to the development of consensus standards for radiation safety by providing a representative to the following standards committees: ANSI/HPS N43

Standards Committee on Equipment for Non-medical Ionizing Radiation Applications; ANSI/HPS N43.16 Subcommittee on Radiation Safety of Cargo Security Screening Systems; and ANSI/HPS N43.17 Subcommittee on Personnel Security Screening Systems.

- Provided extensive testing, under an interagency agreement with the Transportation Security Administration, of the radiation safety characteristics of two prototype x-ray systems for security screening of passengers.
- Working with other federal agencies and the Interagency Steering Committee on Radiation Standards (ISCORS), initiated work to draft guidance to federal agencies on the use of ionizing radiation for security screening of humans.

Electrophysiology and Electrical Stimulation (Division of Physics)

Scope

Medical devices that rely on electrophysiology and electrical stimulation for safety and efficacy cut across all medical specialties. The obvious examples are devices that work in the nervous system and heart including: cardiac pacemakers, defibrillators, heart monitors, brain stimulators (for Parkinson's disease, pain, motor function, hearing), electroconvulsive therapy, visual prosthetics that stimulate the retina or brain, cochlear implants, middle ear hearing devices, spinal cord stimulators, electroencephalography, vagus nerve stimulators, peripheral nerve stimulators (including those for locomotion, breathing, bladder and bowel control) and magnetic nerve stimulators. 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.

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 to electrical stimulation has increased. As a result, five personnel appointments have been made in electrophysiology since September 2003. Three cardiac physiologists/biomedical engineers are now on staff as is a visual physiologist and a general biomedical engineer. These appointments are all shared with other offices in CDRH (in ODE: DRARD, DOED and DCD, in OSB: DPS). The need in the Center divisions for scientific skills in these

areas is substantial, and we emphasize both our laboratory research and direct regulatory involvement in sister divisions.

Our largest emphasis is on research related to cardiac devices. This is due to new regulatory challenges caused by innovations and because of the high impact of these devices on human life. Concerning defibrillators, the American College of Cardiology recently advised a large expansion of the patient population to be implanted with automatic defibrillators, and this has been followed by the Center for Medicare and Medicaid Services greatly expanding the reimbursable uses for these devices. There is also a host of new cardiac electrical stimulation device applications being submitted for approval, these include over-the-counter automatic external cardiac defibrillators and stimulation devices for the treatment of congestive heart failure. We also anticipate cardiac stimulation devices that will take advantage of chaotic properties of pathological states for therapy that uses considerably less energy than cardioversion or defibrillation. In ophthalmics, retinal stimulators have become devices of major public interest because of their potential to treat the blindness afflicting millions of Americans. In otolaryngology, high-rate stimulation is being implemented in cochlear implants, and middle ear implants are used to treat deafness. We anticipate combination mechanical and electric-stimulation devices for deafness. In urology electrical stimulation devices that work on the lower spinal cord or in muscle are being evaluated for urological conditions. In radiology, devices that apply electric current and make electrical measurements are being evaluated for the diagnosis of breast cancer. In neurology, our work supports the regulatory efforts are a host of brain and nerve stimulators along with the long-standing need for a guidance document for electroconvulsive therapy. Our work with post-market surveillance is related to recent recalls and publicized adverse events with implantable cardioverter defibrillators.

The diversity of the devices and the large number of regulatory applications has 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 provide the basis for guiding clinical trials and guidance documents, they are useful as part of the approach that assists firms with the least burdensome route to approval, they generate publications that draw the attention of the scientific community to issues of safety. With the current staff we perform in-house laboratory studies encompassing cardiac electrophysiology, neurophysiology, cardiac electrophysiology, and visual and hearing science.

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, guidance documents that speed device approvals, and industry safety standards for electrical stimulation. Specific

areas of investigation include the cellular basis of electrical stimulation safety, cardiac electrophysiology and defibrillation, and retinal electrophysiology and stimulation. These areas map onto the anticipated regulatory needs of the Center in this broad area of medical devices. Current projects, each led by a principal investigator, fall into broad and overlapping areas of investigation. The major areas:

Cellular Studies of the Safety of Electrical Stimulation – Many neurological and cardiac devices employ electrical stimulation to affect or replace neural function. Our initial studies defined the possible dangers of electrical stimulation, and the related stimulus parameters. These studies showed that for most neurological devices the primary safety concern (at the cellular level) is that electrical stimulation can cause metabolic fatigue, and for cardiac defibrillation the concern is for cell membrane damage and ion channel changes. For neurological devices, including cochlear implants and deep brain stimulators, our present studies are focusing on effects of high-frequency stimulation. The results demonstrate that high-frequency stimulation is likely to fatigue nerve and produce conduction block. This work complements the specific studies of retinal stimulation (see below).

In the area of cardiac electrical stimulation, we are technically unique in our combination of intracellular electrical recording and high-time-resolution optical recording. The work is examining the safety basis for effective cardiac defibrillation and pacing to improve cardiac function. We have been investigating how the defibrillation shock interacts with cardiac tissue, to the improvement of safety and patient outcome. We are studying the fundamental basis of arrhythmia generation, both before and during cardiac pacing. We are also examining how electric shocks (from pacemakers or defibrillators) affect remodeling and communication between heart cells. Our initial studies showed the relationship between shock strength, waveform, and duration on the arrest time and intracellular calcium dynamics in tissue cultured heart cells. Our present studies are examining the basis of arrhythmia generation, pharmacology of electrical stimulation related to the interaction between certain cardiovascular medications and defibrillator shocks, and cardiac remodeling after treatment. This work feeds into our studies of integrated cardiac electrophysiology.

Integrated Cardiac Electrophysiology – This program area integrates cellular studies, organ physiology of the heart, anatomy and the known properties of electric current flow to develop a verified human model to test cardiac electrical stimulation devices. OSEL researchers are performing the studies that form the basis of the cardiac pathology used in the model. These include experimental studies on how arrhythmias are generated and how remodeling of intercellular occurs after therapy. Heart disease remains the primary killer in the U.S. This integrated program is developing a computational model test method for cardiac stimulation devices. It is also being used to understand the adverse events reported in the post-market arena. The knowledge gained from this study will be used to assist in the planning clinical in the most strategic and least-burdensome way. This work would

provide the scientific basis for establishing the "substantial equivalence" for device approvals without the need for clinical trials. The impact on public health will be the more rapid introduction of highly effective cardiac electrophysiological devices.

Safety of Stimulation in the Retina – With over one million Americans suffering blindness from retinal disease and dysfunction and a new technology that seeks to replace sensory elements of the retina, a directed effort has been undertaken to examine the safety and efficacy limits of such devices. This work will support the Center's regulatory efforts in assuring the safety and efficacy of visual prosthetic devices implanted in the eye. The elements of the studies include the cellular electrophysiology of the retina and the flow of applied current in the retina. The work will predict the spatial resolution attainable by electrical stimulation, and the possible toxic effects of stimulation. The knowledge gained by this work will establish the safety and efficacy limits of stimulation, specifically for the retina. It will be the basis of the formal guidance to industry and reviewers that will improve the design and trials for these high-profile devices.

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

Laboratories are defining the safety and efficacy concerns regarding electrical stimulation in the nervous system and heart. The application of FDA laboratory work has been instrumental in regulatory reviews of a number of medical implants. The research results are also used in the formulation of guidance documents and industry standards.

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. The investigations center on clarifying the mechanisms of interaction of the technology with the body and on developing meaningful performance assessment procedures.

The specific value added to FDA and public health by the expertise developed in this work permits CDRH 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. Such initiatives are substantial contributions to CDRH's commitment to "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 the development of research that will have

general applicability to the regulatory process including providing the scientific expertise for reviews, guidance document development and contributions to industry standards. The program will continue to examine new devices and technologies for safety and effectiveness. This information will be obtained from independent laboratory studies, and in-house research that is conducted to anticipate new directions of this technology and will be disseminated in the form of peer-reviewed publications, consultative reviews, and guidance documents. It will assist in expediting movement of safe and effective medical devices to the market that benefit the U.S. public.

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

Computational human model to test cardiac electrophysiology devices: We will use advanced computer models of heart as a means of establishing realistic human models for device testing that will supplement present animal and *in vitro* models.
Investigations of basis of arrhythmia generation in heart: 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.

Remodeling of electrical of cardiac tissue: This work will examine the plastic changes in heart tissue that result from various forms of therapy, including ablation and new pacing modalities. This work is directly related to the remodeling effects of new devices for dual chamber pacing with specific studies in which cardiac pacing is out-of-phase with mechanical activation.

Safety and efficacy limits of retinal prosthetics: The research that determines physiological limits of stimulation will be written into a guidance document to assist device sponsors and used for the development of industry standards.
Electroconvulsive Therapy Submission Criteria: This guidance document is of immediate need; it is to guide the information necessary to assure the safety and effectiveness of electroconvulsive therapy devices.

Accomplishments

- Completed an analysis completed from the published literature of various forms of biological interfaces for visual prosthetics. This information is being developed for an FDA guidance document for studies of the safety and effectiveness of visual prosthetics.

- Completed work on electrophysiological modeling of different retinal ganglion cells, based on patch-clamp measurements of calcium channel behavior. The model accurately predicts the different responses to light, and it will enable prediction of selective responses to electrical stimulation devices. This work was done in collaboration with the University of Minnesota.
- A model is being implemented for two types of cat retinal ganglion cells based on anatomical measurements and patch-clamp recordings. The model is intended to predict action potential firing patterns, and it may be useful for understanding responses to stimulation from medical devices.
- Completed a study on the effects of high-rate neural stimulation. It demonstrated that neuronal action potential can be blocked by high-rate electrical stimulation and that axon diameter is not a factor in differential block. This work is relevant to a host of new devices that employ high-rate electrical stimulation to block nerve activity.
- A study was completed on anatomical and physiological changes that occur to heart cells when grown in tissue culture in organotypic aggregates. The study showed that chicken embryo heart cells retain their characteristic *in vivo* features when they are grown *in vitro* in the form of aggregate spheres. The study also demonstrated a method for cryopreservation of the spheres of heart cells. These spheres are suitable candidates for cell-based biosensors from which electrical, optical and mechanical information can be obtained.
- A study is near completion on effects of electric defibrillation on human blood. The study is being performed in collaboration with CBER, and it focuses on effects of shocks upon hemolysis and platelet activation.
- Work was initiated in collaboration with the Division of Cardiology at the Uniformed Services University of the Health Sciences (USUHS) to study the physiological changes that occur in heart cells during congestive heart failure. The USUHS animal model for heart failure displays a similar gender difference in mortality as in humans. We are comparing the intracellular calcium responses of heart failure cells to normal cells. Specifically, we are examining the responses to electrophysiological devices used during the treatment of heart failure.
- We completed the design and construction of an optical mapping system capable of mapping electrical activity from isolated tissue, whole heart, and cell culture preparations. This will be used for verification and refinement of an advanced bidomain model of cardiac pathology and electrophysiological device treatments.
- We obtained our first optical propagation maps from cultured embryonic chick cardiomyocytes. The signal-to-noise-ratio from these voltage-sensitive-dye recordings were favorable, even without the use of signal-conditioning amplifiers or signal averaging.
- The design and construction are underway of experimental apparatuses to determine the effects of Cardiac Resynchronization on the passive electrical properties of cardiac muscle. The present apparatus is capable of applying

mechanical stretch to sheets of cultured heart cells while pacing pulses can be applied at any time during the stretch cycle.

- Completed a study on the effects of high-rate neural stimulation. It demonstrated that neuronal action potential can be blocked by high-rate electrical stimulation and that axon diameter is not a factor in differential block. This work is relevant to a host of new devices that employ high-rate electrical stimulation to block nerve activity.

Electromagnetics and Wireless Technology (Division of Physics)

Scope

This laboratory is in the Division of Physics (DP), and focuses on the several needs associated with medical devices that utilize or are affected by electro-magnetic (EM) fields. One need to address is 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 measuring and evaluating EM heating and evaluating devices used intentionally to heat body tissues. A principle goal of this effort is to develop standard techniques for measuring and evaluating 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 implants, attached electrodes, and other medical devices, are being imaged by MRI. 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 coming to FDA to seek approval of their implanted and other devices as MRI heating compatible.

CDRH has the responsibility to study and assess the risks of exposure to humans from electromagnetic non-ionizing radiation from radiofrequency and microwave emitting electronic products. This is a complex and challenging field. The Electromagnetics and Wireless Laboratory works continually with other government agencies and professional societies such as the IEEE International Committee on Electromagnetic Safety (ICES) to attempt to stay abreast of the many hundreds of papers produced annually on this subject. EPB performs measurements and dosimetry to evaluate the most common emitters of EM fields, e.g., cellular phones and MRI devices.

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 CDRH Director's office to lead the Electromagnetic Compatibility (EMC) working group that develops Center-wide solutions for medical device EMI problems. Interference from metal detectors has caused many injuries to patients with implanted spinal stimulators.

Electromagnetic Radiation Safety of Personnel: 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. In addition, 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. In addition, 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).

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, multi-step 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. Our present effort is aimed 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 the 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) to assess the exposures and adequacy of existing medical device EMC design and testing criteria from appropriate standards. In addition, many medical device standards do not address EMC or the use of wireless technology in or around the devices. The Division of Physics also performs computations and measurements of the EM fields received by victim medical

devices. OSEL must therefore develop the testing methods for devices 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 guidances, 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, the Division 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 making 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. To assess the measurement problems with fiber optic probes observed by DP and others, we will continue collaboration with Dr. Anthony Kam, who has performed proton resonance frequency shift (PRFS) thermometry with several NIH clinical MRI systems. PRFS thermometry allows temperature to be measured by the MRI system itself, without any external thermal probes.

Computational Modeling of Thermal Effects from RF and Microwave Medical Devices: Our work will focus on computational model development, computational efficiency, and experimental measurement of the temperature-dependent properties of tissues. The goal of this computational modeling 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 effort focuses on the development of models that simulate the response of tissues to thermal injury.

When solving computational models that involve large blood vessels, the efficiency is significantly reduced due to the need to solve fluid dynamic and heat transfer equations within blood vessels. To date, a complete theory for predicting lumped parameter heat transfer and convection coefficients has not been developed. With these parameters, it is theoretically possible to speed up computational efficiency by a factor of 400-500%; thus, making it possible to simulate more complex (and realistic) problems. We have derived a robust theory that predicts transitional flows in conduits.

Experimental measurement of temperature-dependent properties of tissues will be performed. The accuracy of computational models for radiofrequency and microwave medical devices is directly related to the tissue parameters that are inserted in the model. A severe limitation for many of these models is the assumption that these tissue parameters remain constant throughout the heating process. To date, there have been no formal studies to systematically determine how tissue properties change with temperature. In FY 2004, we demonstrated that temperature-dependent phenomena account for as much as 20-30% error in many electromagnetic-thermally coupled problems (i.e., ablation of body tissues.) We made preliminary measurements of the dielectric properties of tissues and found a complex hysteresis response that is a crucial part in modeling problems where multiple treatments are applied to the same area of tissue. We plan to develop numerical descriptions of our experimental data and implement the non-linear behavior into future

computational models. Through this research, we will be able to identify key parameters that effect the growth of lesion size, which will guide CDRH in determine the amount of emphasis that should be placed on the various bench and clinical tests submitted by manufacturers.

Relevance to FDA /CDRH Mission and the Public Health Impact

Medical Device EMC - Hundreds of thousands of implants are prescribed per year. All of the patients with 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 implant manufacturers, and thus protect patients. In addition, 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 cell phone 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 result in lethal tumors and other serious conditions going undetected, even if they are imaged by other, less sensitive modalities. Without MRI, 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. This project supports ODE staff in the quality and timeliness of their review and will improve the development of guidance documents; improve computational analysis tools that identify key safety issues; and improve 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 - More than 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 menorrhagia. All of these conditions are treatable with radiofrequency ablation. 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.

Three-Year Goals

Wireless Technology and Electromagnetic Compatibility (EMC) For Medical Devices - 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 perform computations and measurements of the EM fields received by victim medical devices by selected, worst case emitters of EM fields. These will include high frequency emitters such as wireless local are network transmitters (Bluetooth, 802.11) and low frequency emitters such metal detectors. DP will 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. This compliments the DP projects for EMC of implanted medical devices exposed to fields from wireless devices and 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 proposes 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. 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 laboratories to determine MRI-induced heating. DP will develop efficient methods to verify medical device manufacturers' claims of limited MRI heating. 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 of medical devices

- Performed research and laboratory evaluations to evaluate metal detector effect on medical implants, including spinal and brain stimulators and pacemakers.
- Developed new EMC simulators to enable, for the first time, testing new ISO standards for magnetic field susceptibility of medial implants below 30 MHz
- Completed the first major CDRH project to develop original techniques to evaluate coexistence and EMC of medical devices using Bluetooth and 802.11 wireless networks
- Developed test methods, set up systems and obtained commercial devices to study the effects of to radiofrequency identification (RFID) systems on active implantable medical devices such as pacemakers and defibrillators.

Safety of exposure to Electromagnetic Fields

- Designed and lead a major international intercomparison of measurements and computations of cellular phone energy delivered to realistic models of the human head. Performed in-house studies on the results of the group studies.
- Developed computer models of a pregnant woman with fetus and used them to evaluate the safety of exposures to metal detectors.
- Developed a new class of detailed, object-based anatomical computer models of adults and children for use in numerical dosimetry and evaluations of EM effects on medical devices.
- Performed analysis and published results of heating and EM field induced in selected pharmaceuticals exposed to radiofrequency identification systems. Developed a protocol for a study of the effects RFID on drugs in collaboration with FDA Center for Drug Evaluation and Research.

MRI safety

- Performed studies and computer modeling of the heating of metallic implants during exposures to MRI. Studies included heating of cardiac stents and pacemaker leads in support of the CDRH Office of Device Evaluation.
- Developed a new technique to perform real time imaging of implant heating in a clinical MRI system throughout a phantom. Performed this work in collaboration with U.S. National Institutes of Health.
- Developed a protocol and led the first phase of an international intercomparison of the accuracy of heating measurements of metallic implants during exposures to MRI.

Medical applications of electromagnetic energy and ablation

- Developed new techniques and performed computational modeling to assess intended and unintended tissue damage induced by RF and other ablation modalities.

- Performed computer modeling studies in support of CDRH Office of Device Evaluation to assess the effectiveness of body-fat analyzers
- Developed a cryoablation test system to perform laboratory studies of this ablation modality.
- Supported the Electrosurgical Unit Burn Postmarket Issue Action Team by performing computer analysis and experiments.

Optical Radiation Safety and Devices (Division of Physics)

Scope

To provide state-of-the-art measurement capability and support to other CDRH Offices and FDA Centers related to optical radiation-emitting or transmitting devices by conducting focused research to address specific questions/problems. This program will also provide optical engineering/physics expertise to the review of medical devices and consumer products, the development of national and international voluntary standards, and educational materials targeted to consumers.

Background

Optical Radiation-Emitting Devices

CDRH has the responsibility for enforcing three optical radiation performance standards for Lasers, Sunlamps, and Mercury Vapor Lamps under the Radiation Control for Health and Safety Act. In support of this activity, OSEL maintains FDA's primary instrumentation, with calibrations traceable to NIST, for measurements of the wide variety of laser products on the market today. OSEL also maintains FDA's instrumentation and standards for measurements of non-coherent optical sources. OSEL calibrates laser measurement instruments, maintains laser field instrumentation kits used by FDA inspectors, tests regulated products, and provides technical consultation and measurement support for enforcement activities. Optical radiation measurements are used to support risk assessments and to evaluate potential adverse effects of optical radiation-emitting medical devices (e.g., ophthalmic instruments and optical diagnostic devices) and consumer products (laser pointers, sunlamps and high-intensity light sources). More recent efforts have focused on the development of voluntary (as opposed to mandatory) national and international standards for optical radiation-emitting devices.

Voluntary national and international standards have been developed and continue to be developed for the optical radiation safety of medical devices and radiologic products which emit optical radiation under ANSI Z311, Z136, IEC 60335-2-27 and ISO TC 172 SC 7 and SC 9. The international standards for laser products (IEC 60825-1) and sunlamp products

(IEC 60335-2-27) have been revised and CDRH continues to move forward in the harmonization of the FDA performance standards with the international standards for these products. OSEL efforts have led to the development/publication of over 30 standards (see Appendix I).

Optical Radiation-Transmitting Devices

Approximately 1.5 million intraocular lenses (IOLs) are implanted each year in the U.S. alone with an annual cost on the order of 3 billion dollars. Thus, a small percentage of problems with IOLs can result in a significant number of visually impaired patients and in significant costs. There are several complications of IOLs that result in the need for a second surgery to explant and replace IOLs or that result in a reduced quality of vision. These device-related complications include: incorrect dioptric power; bubbles (glistenings) in the IOL optic; calcification on the IOL surfaces; opacification in the IOL optic; "snowflake" or crystalline calcifications in IOL optics; and reflected glare from IOLs New types of IOLs and materials are being developed for the correction of vision (phakic or aphakic, accommodative or toric). ODE makes decisions on a large number of IDEs and PMAs for various types of IOLs (monofocal, multifocal, and phakic). The data obtained from this laboratory will be used in national and international standards which are currently used in the ODE review process for IOLs.

OSEL scientists have provided optical engineering expertise for the evaluation of the optical quality of IOLs over the past 10 years. This includes participation in developing national and international performance standards, optical bench testing of the optical quality of IOLs as needed by ODE, and, providing ray tracing analysis of new IOL designs as needed by ODE. More recently, a novel fiber optic confocal-based optical system was developed to measure the dioptric power of IOLs. This new system overcomes significant problems associated with testing the dioptric power of IOLs. The new system provides high accuracy in measuring the IOL dioptric power. Most importantly, this method provides FDA and the medical device community with a means for the accurate measurement of a wide range of both positive and negative powers including high-magnification IOL's with power greater than ± 20 diopters. Such accurate measurements are not achievable with present day methods. The new optical power measurement system was used to evaluate the dioptric power of regulatory samples of new IOL designs and has been used to evaluate official samples of IOLs on regulatory hold for questions about the accuracy of the labeled dioptric power. A patent application was filed for the new test method. The new test method has been proposed as a standard test method for national and international performance standards.

Research Program Description

High precision optical radiation measurement laboratory

This laboratory supports risk assessments for optical radiation-emitting products for which the FDA has regulatory authority. Measurements made with this equipment are traceable to NIST primary measurement standards, and as such, can provide reliable and accurate results of any testing that is done. In addition, the measurement expertise and capabilities of this laboratory enable OSEL to provide input for the development and/or improvement of national and international voluntary standards. CDRH benefits from the development of these standards because manufacturers can declare conformance of their devices to such standards that are recognized by FDA. This shortens review time for new medical device applications.

This facility provides the capability to perform optical radiation evaluations of products at both the pre- and post-market stage, thereby providing independent information to identify potentially hazardous products and thereby decrease the exposure of the general public to unnecessary optical radiation. OSEL perform intercomparisons with NIST, NCTR, and our field laboratory at WEAC. These interactions provide an opportunity for collaborations with others and maintaining information flow between these organizations.

Specifically, OSEL provides spectral dosimetry measurements and consultation to:

- WEAC for spectral measurements of light-emitting products
- NCTR to assist them in maintaining an FDA-wide phototoxicity testing center
- CDER to assist in the development of the Final Monograph for Sunscreen Testing and the Test Method for determining the UVA Protection of OTC Sunscreen Products
- CFSAN to assist in phototoxicity and photocarcinogenicity testing of cosmeceuticals.
- ODE for hazard analysis in the approval of innovative medical devices which use optical diagnostic techniques.

Additionally, OSEL provides measurement and optical engineering assistance to several multi-center human Photosciences Projects.

<u>Intra-ocular/contact lens power and optical quality assessment laboratory</u>
This laboratory provides engineering support for the regulation of intraocular lenses (IOLs). This includes participation in the development of national and international performance standards, optical bench testing of the optical quality of IOLs as needed by ODE, and, providing ray tracing analysis of new IOL designs as needed by ODE. In summary, this laboratory serves to develop standard test methods to evaluate the optical quality of IOLs and contact lenses.

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 the 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 evaluating the dioptric power of new IOL designs 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 contact lenses in national and international standards.

Accomplishments

IOL Program

- Developed, experimentally tested and pending patent filed of a Novel Standard Test Method for Evaluating Dioptric Power of IOLs and Contact Lenses and used to support ODE/DOED regulatory decisions. A new confocal fiber-optic based laser method for measuring the dioptric power of monofocal IOLs and contact lenses (both positive and negative power lenses) was developed.

- Developed Standard Test Method for Evaluating Unwanted Glare Images from IOLs to obtain data to address ODE/DOED concerns which showed that the source of an unwanted line image from point light sources is a reflection from the haptic in the optic of a three-piece IOL. A fiber-optic based laser method for characterizing glare/unwanted images from IOLs was developed. It is intended that this new test method for characterizing potential glare images from IOL's is to be incorporated in international standards for these devices.

- Developed Standard Test Method for Evaluating the Optical Quality of Glistenings in IOLs (bubble-like optical defects that range from ~ 5-20 microns).

- Designed, assembled and calibrated an IOL dioptric power testing setup, and performed measurements of the dioptric power of various types of IOLs (phakic, aphakic, toric, positive and negative power) in support of ODE/DOED reviews.

- Continued active participation in national and international standards bodies. We anticipate that OSEL-developed test methods will be proposed for incorporation into standards. Once recognized, these standards will assist ODE/DOED in the review of IDE's, and PMA's for IOLs.

Optical Radiation Safety

- Served as leader for development of Guidance document for dental curing lights for ODE. This Guidance document will facilitate the submission and FDA review of pre-market applications for these devices.

- Continued active participation in national and international standards bodies. Developed international standards for ophthalmic instruments. These instruments direct optical radiation into the eye during ophthalmic examinations and retinal surgery. These standards will provide for safer instruments and will facilitate the submission and FDA review of pre-market applications for 510K's, IDE's, and PMA's for these devices.

- Participated in multi-office working group assessing radiation-related issues of an ophthalmic laser used for photorefractive surgery. Chaired the engineering/physics sub-group which discussed and resolved technical issues related to testing protocol.

- Communicated risk/benefit information related to optical radiation safety of ophthalmic instruments to manufacturers and the ophthalmologist community by co-authoring book chapter, "Light Hazards", in the Book, Fundamentals and Principals of Ophthalmology, Section 2, Basic and Clinical Science Course published by the American Academy of Ophthalmology in April 2005.

- Provided scientific input into article for FDA Consumer on the dangers of indoor tanning.

- Communicated risks of UV radiation exposure from the sun and from indoor tanning via preparation of lesson material for secondary students. This is available on the FDA website, 'FDA and You'.

Other

- Served as one of two US representatives on the IEC TC 61 MT 16 committee for sunlamps. Prepared a concept paper which proposes specific amendments to the FDA Performance Standard for Sunlamp Products.

- Completed study of 46 human subjects to explore improvements to the current FDA recommendations for exposure schedules for sunlamp products. Found that cumulative UV dose to indoor tanners could be significantly reduced.

- Worked on team to update the guidance document (intended for sponsors of clinical studies) for optical diagnostic devices intended to detect cervical cancer and its precursors.

Optical Diagnostics and Therapeutics **(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 and Therapeutics 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 and Therapeutics (ODT) 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 ODT 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 ODT 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 ODT 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 and the role of various parameters remain poorly understood.

One of these issues is the role of illumination and collection design parameters. Since there is little standardization in optical device design, a wide range of fiberoptic probe geometries have been implemented in research and commercial devices. While limited data suggests that probe design influences the depth of the tissue region interrogated, this data was not sufficient to enable researchers to estimate the influence of changes in specific design parameters, or how to optimize a device to interrogate a specific tissue layer. The ODT laboratory is studying the effect of device design with experimental and computational approaches. Computational modeling is a powerful tool for predicting the behavior of optical-based medical device and is particularly useful for measuring in tissue. ODT researchers have worked to develop new computational models based on the well-established Monte Carlo approach and implement these models to answer questions about device design. This technique is particularly useful for investigating a range of fiberoptic probe geometries and tissue optical properties. Experimental approaches have been used to provide validation of modeling results and identify effects that are not easily apparent with simulations. Such an approach also allows ODT researchers to identify tissue phantoms that are appropriate for studying the performance of optical devices. By performing computational and experimental research, it is possible to provide a range of insights that are useful for evaluating the mechanism of action and source of contrast for specific devices.

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 ODT 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 ODT 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 ODT laboratory is characterizing the fluorescence properties of drugs suspected to be strong fluorophores, using a high-precision spectrofluorometer. While this study is ongoing, several drugs such as fluoroquinolones have shown high quantum yields. Further analysis will require studying the pharmacokinetics of these drugs and their distribution in tissues that might be interrogated by fluorescence-based devices.

Characterization of the fundamental optical properties of biological tissue is one of the most fundamental and significant areas of research performed in the ODT 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 in the 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.

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 ODT 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. Recently, we have embarked on a collaborative study with nanotechnology pioneers at Rice University (Professor R. Drezek) to investigate and characterize the performance of nanoparticle-based contrast agents for OCT.

In general, the ODT 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 ODT 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 ODT 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 and cardiology. ODT 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 ODT 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 ODT 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 ODT 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 guidance documents on optical spectroscopy and optical coherence tomography.
- 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

Measurements of drugs with the potential to interfere with fluorescence-based diagnostic devices

- Performed measurements of tissue phantoms and *ex vivo* animal tissue with optical property measurement system, and compared results to gold standard values obtained via spectrophotometry.
- Developed in house capability for steady state quantum yield measurements.
- Identified class of antibiotics likely to interfere in UV/VIS optical diagnostic devices.
- Described "fluorescence effective concentration" concept to use to identify potentially interfering drugs.

UV-VIS optical property measurements

- Performed measurements of tissue phantoms and *ex vivo* animal tissue with optical property measurement system, and compared results to gold standard values obtained via spectrophotometry and inverse adding-doubling.
- Set up new instrumentation for optical property measurement system, including a fiber switcher and portable spectrometer/CCD.

Device-tissue interface effects on time-resolved fluorescence measurements

- Set up new instrumentation for optical property measurement system, including a fiber switcher for multiple wavelength operation.
- Developed novel Monte Carlo model for time-resolved fluorescence in layered tissue capable of implementing experimentally-measured instrument response function.

- Performed simulations to evaluate effect of fiberoptic probe geometry on detection of neoplasia-induced changes in tissue morphology and accuracy of fluorescence lifetime estimates.
- Developed novel tissue phantom constructs, including silicone-based solid phantoms, and performed time-resolved fluorescence measurements of these phantoms.
- Developed a specialized experimental apparatus which allows for investigation of various fiber-optic probe geometries, including those with angled fibers.

Characterization of optical coherence tomography-based imaging approaches

- Completed first round of experiments which quantify the effects of gold nanoshells on OCT signal enhancement.
- Established accurate and precise method for determining concentrations of nanoshell suspensions.
- Compared theoretical predictions of nanoshell extinction coefficients to experimental measurements obtained via spectrophotometry.
- Obtained initial estimates of backscattering coefficients of nanoshells with calibrated OCT measurements.

Nanobiosensors

- Developed, experimentally tested and pending patent filed of a novel method for ultrahigh-resolution fiber-optic confocal microscopy beyond the diffraction limit in the nanometric scale.
- Developed, experimentally tested, and pending patent filed of a novel all-hollow-waveguide laser delivery system for digital particle image velocimetry (DPIV).
- Designed and experimentally investigated alternative techniques for drawing nanobiosensor fiber probes with waveguide core sizes in the submicron and nanometric spatial range.
- 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.
- Developed methods for testing and evaluating fundamental laser beam parameters (such as intensity beam distribution, divergence, beam focal sizes, possible thermal lensing and defocusing effects) at laser beam propagation in single and multi-layered tissue samples.
- Designed experimental fiber-optic-based systems for both direct 3-D intensity imaging and mid-IR thermal monitoring of laser beam propagation through turbid tissue.

Fluid Dynamics (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

In response to reports to the FDA of life-threatening damage to red blood cells (hemolysis) in hemodialysis patients, a research project was initiated to investigate whether kinked tubing could have contributed to the adverse patient events.

- Laboratory analysis using bovine blood with a hemodialysis machine determined that tube kinking in the post-pump region of the circuit could occur without being detected by the machine's pressure monitoring safety system.

- Other aspects of the investigation included a computational fluid dynamic model of blood flow through hemodialysis needles and an evaluation of the clinical pressure traces for patients who experienced hemolysis. Publication of the results of this research will help to promote patient safety in the hemodialysis clinic.

Another area of research for this project includes the study of blood damage due to electrical shocks from implantable cardioverter-defibrillators. Preliminary *in vitro* testing using human and bovine blood in electroporation vials demonstrated that changes to red blood cells and platelets occurred as the current density of the shocks was increased to near

the maximum clinical levels. This research may provide a new *in vitro* method to evaluate blood damage caused by electroshock medical devices.

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 Objectives

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

- Developed a protocol for high-power calibration of high intensity focused ultrasound (HIFU) transducers using a radiation force balance system. A presentation was made at a scientific conference and a proceedings paper was prepared that describes this technique.

- Began development and characterization 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 oil droplets and/or low density polyethylene micro-spheres. For each TMM a broad range of ultrasonic parameters, including attenuation coefficient, speed of sound, acoustical impedance, nonlinear parameter B/A, backscatter coefficient, and thermal properties are being characterized as a function of different phantom constituents and temperatures. A paper is being prepared for submission to a peer-reviewed journal.

- Developed and tested a new time delay spectrometry (TDS) system that employs digital processing to minimize hardware requirements. The lab uses TDS extensively for efficient characterization of the attenuation characteristics of ultrasound tissue mimicking materials (TMMs) used in the evaluation of HIFU systems. A presentation was made at an engineering conference and a proceedings paper was prepared that describes this system.

- Developed a digital particle image velocimetry (DPIV) system for measurements of acoustic streaming properties of HIFU transducers to non-invasively characterize the intensity field of these transducers at high outputs. Preliminary results on two HIFU transducers showed good agreement between numerical modeling data and experimental DPIV data. A provisional patent application was prepared.

- Extended a previous analytical model for predicting temperature rise at a bone/soft-tissue interface to study the role played by the characteristics of the ultrasound pulse train. The model was able to quantify how much standard calculations using only the time-averaged intensity of the pulse train underestimate the risk associated with the procedure. A peer-reviewed paper was published in a scientific journal.

- Developed a computational model for assessing the effect of blood flow through large vessels on the efficacy of HIFU ablation procedures targeted near the vessel wall. The model was used to identify optimal amounts of focusing for a given procedure, i.e., levels of focusing that will produce adequate cell death and minimize treatment time. A paper is being prepared for submission to a peer-reviewed journal.

Mechanics **(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 Objectives

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)

- Chondrocytes from human and bovine cartilage have successfully been propagated and passaged as monolayer cultures for at least one month. Extended passage induced phenotypic changes from production of type II collagen to type I and from high to low molecular weight proteoglycans.

- Chondrocytes have been seeded onto bovine type I microcarriers and propagated in mechanically active bioreactors. We are in the process of characterizing the growth rates and phenotype expression in these different *in vitro* models. Preliminary results confirm that chondrocytes propagated in microcarrier bioreactor system proliferate and continue production of type II collagen and aggrecan.

Fatigue testing of PMMA bone cement

- Round robin test protocol and cement samples received, and work in progress to make test samples.
- Faxitron procedure tested and operational

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

- 15 cadaver spines received, analyzed for bone density.
- 130 vertebral bodies dissected, machined into test specimens, treated with vertebroplasty procedure. All specimens mechanically tested for stiffness and strength. Data currently being analyzed with help from OSB statistician.

Standards Management Staff

The Standards Management Staff develops and manages the standards used for regulatory assessments. Staff facilitate the participation of CDRH and other FDA staff in developing standards. 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 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.

Accomplishments

- **Recognized Standards for 2005**

  - **48 new standards**
  - **110 standards that were withdrawn and new versions were recognized**
  - **98 changes to the existing recognized standards**
  - **14 standards were withdrawn**

- **Continuous Glucose Monitoring.** At the Fifth Annual Diabetes Technology Meeting in San Francisco, November 2005, Carol Herman, Director of the Standards Management Staff, served as the facilitator for a special meeting on the issue of standards development for non-invasive glucose meters. Ms. Herman moderated a panel composed of disparate scientists from government, industry and academia to arrive at a focused and concrete project proposal for determining accuracy for non-invasive glucose meters.

- **Hosted a Global Harmonization Task Force (GHTF) Joint Study Group meeting.** In September 2005, FDA hosted a GHTF Joint Study Group Meeting. A Joint Study Group Meeting was held to facilitate cross-consultation and joint consideration of issues by the study groups and to provide a forum to update the members on the activities of all of the study groups.

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.

- **Facilitated a secondary tract for the development of guidances.**
  Recent internal studies concluded that standards in combination with guidance provide the most valuable tool to industry. Consequently, SMS implemented a science resource-sharing Center initiative to facilitate a secondary tract for the development of guidances. As a result, we were able to complete additional guidances.

APPENDIX A – OSEL Publications

January 1, 2005 – December 31, 2005

Journal Articles

Amat A, Rigau J, Waynant R, Ilev I, Tomas J, Anders J. Modification of the intrinsic fluorescence and the biochemical behavior of ATP after irradiation with visible and near-infrared laser light. *Journal of Photochemistry and Photobiology B: Biology* **81:**26-32, 2005.

Amat A, Rigau J, Waynant R., Ilev I, Anders J. The electric field induced by light can explain cellular responses to electromagnetic energy: a hypothesis of mechanism. *Journal of Photochemistry and Photobiology B: Biology* **82**, 2005.

Amat A, Rigau J, Waynant R, Ilev I, Anders J. Adenosine triphosphate ATP, a cellular key molecule, is affected by non-resonant optical frequencies. *Lecture Series on Computer and Computational Sciences* **4:**223-226, 2005.

Baker SC,.....Elespuru RK et al. The External RNA Controls Consortium: a progress report. *Nature Methods* **2**:731-734, 2005.

Bassen HI. Liquid pharmaceuticals and 915 MHz radiofrequency identification systems - worst-case heating and induced electric fields. RFID Journal, White Paper Library, September 2005, http://www.rfidjournal.com/whitepapers/7

Bassen HI, Schaefer DJ, Zaremba L, Bushberg J, Ziskin M, Foster KR. Exposure of medical personnel to electromagnetic fields from open magnetic resonance imaging systems. *Health Physics* **89(6):**685-690, December 2005.

Brown SA, Merritt K, Woods TO, Busick DN. The effects on the instruments of the WHO recommended protocols for decontamination after possible exposure to TSE contaminated tissue. *Journal of Biomedical Materials Research., Part B Applied Biomaterials* **72B:**186-190, 2005.

Brown SA, Merritt K, Woods TO, Busick DN. Effects on instruments of the World Health Organization-recommended protocols for decontamination after possible exposure to transmissible spongiform encephalopathy-contaminated tissue. *Journal of Biomedical Materials Research Part B: Applied Biomaterials* **72B:**186-190, 2005.

Chen Y, Kittles R, Zhou J, Chen G, Adeyemo A, Panguluri RK, Chen W, Amoah A, Opoku V, Acheampong J, Agyenim-Boateng K, Eghan BA Jr, Nyantaki A, Oli J, Okafor G, Ofoegbu E, Osotimehin B, Abbiyesuku F, Johnson T, Fasanmade O, Rufus T, Furbert-Harris P, Daniel HI, Berg KA, Collins FS, Dunston GM, Rotimi CN. Calpain-10 gene polymorphisms and type 2 diabetes in West Africans: the Africa America Diabetes Mellitus (AADM) Study. *Annals of Epidemiol*ogy **15(2):**153-9, February 2005.

Coelho SG, Miller SA, Beer JZ. Quantification of UV-based erythema and pigmentation using computer assisted digital image evaluation (CADIE). *Pigment Cell Research* **18 (Supplement 1):**73, 2005.

Cohen ED, Chan DD. Development of a mammalian retinal ganglion cell model of electrical stimulation. 2005 FDA Science Forum: Advancing Public Health through Innovative Science, Washington, DC, April 27-28, 2005.

Elespuru RK. Integrating new technologies into the monitoring of heritable genetic effects. *Mutation Research* **577S:** e162, 2005.

Faris O, Chen E, Berman M, Moynahan M, Zuckerman B. A U.S. Food and Drug Administration perspective on cardiac resynchronization and ventricular assist device trials. *Journal of Congestive Heart Failure* **11:**207-211, 2005.

Godar DE. UV doses worldwide. *Photochemistry and Photobiology* **81:**736-749, 2005.

Godar DE, Lucas AD. UVA1 mediated receptor and cytokine changes of transformed lymphocytes. *Photodermatology, Photoimmunology, and Photomedicine*, **20:**1-9, 2005.

Harris GR. Progress in medical ultrasound exposimetry. *IEEE Transactions in Ultrasonics, Ferroelectrics, and Frequency Control* **52(5):**717-736, 2005.

Heller D, Smith M, Chiesa OA. Detection of penicillin residues in bovine oral fluid (saliva) by liquid chromatography/tandem mass spectrometry. *Rapid Commun Mass Spectrom* **20(2):**321-324, December 13, 2005

Heller D, Smith M, Chiesa OA. LC/MS/MS measurement of penicillin g in bovine plasma, urine, and biopsy samples taken from kidneys of standing animals. *Journal of Chromatography B* **830(1):**91-99, 2005.

Heller D, Peggins J, Nochetto C, Smith M, Chiesa OA, Moulton K. LC/MS/MS measurement of gentamicin in bovine plasma, urine, milk, and biopsy samples taken from kidneys of standing animals. *Journal of Chromatography B* **821:** 22-30, 2005.

Hutter JC, Luu, HD and Kim CS. A dynamic simulation of bisphenol A dosimetry in neuroendocrine organs. *Toxicology and Industrial Health* **20:**29-40, late 2004.

Icenogle TB, Regnault WF, Antonucci JM, Skrtic D. Physical and chemical characterization of bioactive polymer composites. *Polymer Preprints* **46:**693, 2005.

Kainz W, Christ A, Kellom T, Seidman S, Nikoloski N, Beard BB, Kuster N. Dosimetric comparison of the specific anthropomorphic mannequin (SAM) to 14 anatomical head models using a novel definition for the mobile phone positioning. *Physics in Medicine and Biology* **50:**3423-3445, July 2005.

Kainz W, Casamento J, Ruggera P, Chan D, Witters D. Implantable cardiac pacemaker electromagnetic compatibility testing in a novel security system simulator. *IEEE Transactions on Biomedical Engineering* **52(3):**520–530, March 2005.

Kim CS, Sapienza PP, Ross IA, Johnson JD Luu, HD, Hutter J. Distribution of bisphenol A in the neuroendocrine organs of female rats. *Toxicology and Industrial Health* **20:**41-50, late 2004.

Myers MR. Effect of pulse characteristics on temperature rise due to ultrasound absorption at a bone/soft-tissue interface. *Journal of the Acoustical Society of America* **117(5):** 3281-3287, May 2005.

Newton KM, Buist DS, Miglioretti DL, Beverly K, Hartsfield CL, Chan KA, Andrade SE, Wei F, Connelly MT, Kessler L. The impact of co-morbidities on hormone use after the 2000 release of the Women's Health Initiative. *Journal of General and Internal Medicine* **20(4):**350-6, April 2005.

Passerini AG, Shi C, Francesco NM, Chuan P, Manduchi E, Grant GR, Stoeckert Jr CJ, Karanian JW, Wray-Cahen D, Pritchard WF, Davies PF. Regional determinants of arterial endothelial phenotype dominate the impact of gender or short-term exposure to a high-fat diet. *Biochemical and Biophysical Research Communications* **332(1):**142-148, June 24, 2005.

Pfefer TJ, Agrawal A, Drezek RA. Oblique-incidence illumination and collection for depth-selective fluorescence spectroscopy. *Journal of Biomedical Optics* **10(4):**044016:1-9, 2005.

Qiang R., Wu D, Chen J, Wilton D, Kainz W. An efficient two-dimensional FDTD method for bio-electromagnetic applications. *IEEE Transaction on Magnetics (Compumag 2005)*.

Ranamukhaarachchi DG, Unger ER, Vernon SD, Lee D, Rajeevan MS. Gene expression profiling of dysplastic differentiation in cervical epithelial cells harboring human papillomavirus 16. *Genomics* **85(6)**:727-38, June 2005**.**

Rasooly A. Biosensor technologies. *Methods* **37(1):**1-3, September 2005. E-pub, September 30, 2005.

Reid L, Ranamukhaarachchi D, Elespuru RK, et al. Proposed methods for testing and selecting the ERCC external RNA controls. *BMC Genomics* **6:**150, 2005.

Rinaldi JE, Chen EA, Berman MR. Pediatric circulatory support: an FDA perspective. *ASAIO J* **51(5):**533-535, September-October 2005.

Samei E, Badano A, Chakraborty D., Compton D, Cornelius C, Corrigan K, Flynn MJ, Hemminger B, Hangiandreou N., Johnson J, Moxley M, Pavlicek W, Roehrig H, Rutz L, Shepard J, Uzenoff R, Wang J, Willis C. Assessment of display performance for medical imaging systems: executive summary of AAPM TG18 report. *Medical Physics* **32(4):** 1205-1225, 2005.

Sergeev N, Rasooly A, Herold KE , Oligonucleotide design for PCR Primers and Microarray Probes. *Encyclopedia of Medical Genomics & Proteomics (EMGP)* 938-942, 2005.

Sergeev N, Distler M, Vargas M, Chizhikov V, Herold KE, Rasooly A. Microarray analysis of *Bacillus cereus* group virulence factors. *Journal of Microbiological Methods* October 19, 2005.

Sharma U, Chen G, Kang J, Ilev I, Waynant R. Fiber optic confocal laser Doppler velocimeter using an all-fiber laser source for high resolution measurements. *Optics Express* **13:**6250-6258, 2005.

Sliney DH, Aron-Rosa D, Frankhauser F, Landry RJ, Mainster MA, Marshall J, Rassow B, Stuck B, Trokel S, Wolffe M. Adjustment of guidelines for exposure of the eye to optical radiation from ocular instruments. Statement from a task group of the International Commission on Non-Ionizing Radiation Protection (ICNIRP), *Applied Optics* **44(11):**2162-2176, April 10, 2005.

Tadokoro T, Yamaguchi Y, Batzer J, Coelho SG, Zmudzka BZ, Miller SA, Wolber R, Beer JZ, Hearing VJ. Mechanisms of skin tanning in different racial/ethnic groups in response to ultraviolet radiation. *Journal of Investigative Dermatol*ogy **124:**1326-1332, 2005.

Tang X, Morris SL, Langone JJ, and Bockstahler LE. Microarray and allele specific PCR detection of point mutations in Mycobacterium tuberculosis genes associated with drug resistance. *Journal of Microbiological Methods* **63:**318-330, 2005.

Tomazic-Jezic VJ, Sanchez BA. Allergen profiles of natural rubber latex (NRL) proteins on gloves and glove powder. *Journal of Long Term Effects of Medical Implants* **15:**115-124, 2005.

Wang AMJ, Bender JE, Pfefer J, Utzinger U, Drezek RA. Depth-sensitive reflectance measurements using obliquely oriented fiber probes. *Journal of Biomedical Optics* **10(4):**044017:1-17, 2005.

Wear KA, Laib A, Stuber AP, Reynolds JC. Comparison of measurements of phase velocity in human calcaneus to Biot theory. *Journal of the Acoustical Society of America* **117(5):**3319-3324, May 2005.

Wear KA. The dependences of phase velocity and dispersion on trabecular thickness and spacing in trabecular bone-mimicking phantoms. *Journal of the Acoustical Society of America* **118(2):**1186-1192, August 2005.

Wear KA, Stiles TA, Frank GR, Madsen EL, Cheng F, Feleppa EJ, Hall CS, Kim BS, Lee P, O'Brien WD, Oelze ML, Raju BI, Shung KK, Wilson TA, Yuan JR. Interlaboratory comparison of ultrasonic backscatter coefficient measurements from 2 to 9 MHz. *Journal of the Acoustical Society of America* **24(9):**1235-1250, September 2005.

Wei J, Sahiner B, Hadjiiski LM, Chan HP, Petrick N, Helvie MA, Roubidoux MA, Ge J, Zhou C. Computer aided detection of breast masses on full field digital mammograms. *Medical Physics* **32(9):**2827-2838, 2005.

Wood SC, Bushar G, Tesfamariam B. Inhibition of mammalian target of rapamycin modulates expression of cell adhesion molecules and diapedesis in endothelial cells. *Toxicology Letters* December 2005.

Wray-Cahen D, Pritchard W, Ashby A, Russek-Cohen E, Vossoughi J, Karanian J. Gender, age, and hormonal status affect recovery time from general anesthesia in pigs. *Journal of Animal Sci*ence **83 (Suppl. 1):**260, 2005.

Yousef WA, Wagner RF, Loew MH. Estimating the uncertainty in the estimated mean area under the ROC curve of a classifier. *Pattern Recognition Letters* **26:**2600-2610, 2005.

Books

Thrombosis Research and Treatment: Bench to Bedside. J Vossoughi, J Fareed, SA Mousa, JW Karanian, eds, 2004.

Emergency Revascularization: Bench to Bedside. J Vossoughi, E Topaz, A Sasahara, JW Karanian, eds, 2005.

Book Chapters

Chan HP, Sahiner B, Hadjiiski LM, Petrick N. Computer-aided diagnosis of breast cancer. In: Applied Medical Image Analysis Methods , Costaridou L (ed.) CRC Taylor and Francis Group, pp. 1-49, 2005.

Cibis G, Landry RJ, Mainster M, Sliney DH, Stuck B, Wolffe M. Light hazards. In: American Academy of Ophthalmology Study Manual, Section 2 - Cibis, G (ed.), American Academy of Ophthalmology, 2005, pp 459-465.

Gammell PM, Maruvada S, Harris GR. A simplified ultrasonic time-delay spectrometry (TDS) system employing digital processing to minimize hardware requirements. In: Review of Quantitative Nondestructive Evaluation, D.O. Thompson and D.E. Chimenti (eds.) American Institute of Physics, New York, 2005.

Ilev I, Gannot I. Fiber Optic Biosensors. In: Encyclopedia on Biomaterials and Biomedical Engineering (EBBE). Wnek G. and Bowlin, G. (eds.) Marcel Dekker, New York, 2005.

Ilev I, Waynant R. Mid-infrared biomedical applications. In: Mid-Infrared Semiconductor Optoelectronics. Editor: Krier, A. (Springer, London, 2005).

Schroeder LW, Walsh DL, Schwerin MR, Richardson DC, Kisielewski RW, Cyr WH. Standard quality control testing, virus penetration and glove durability. In: Protective Gloves for Occupational Use [2nd ed.], A Boman, T Estlander, JE Wahlber and HI Maibach (Eds.), CRC Press, Boca Raton, FL, chapter 8, pp.89-109, 2005.

Stratmeyer ME. Book review: Biological safety & European medical device regulations. In: Journal of Medical Device Regulation, pp. 75-76, November 2004.

Sergeev N, Rasooly A, Herold KE. Oligonucleotide design for PCR primers and microarray probes. In: Encyclopedia of Medical Genomics and Proteomics, Marcel Dekker, 2005.

Tianhong C, Small DA, McDermott MK, Bentley, WE, Payne GF. Biomimetic approach to biomaterials: amino acid-residue-specific enzymes for protein grafting and crosslinking. In: Polymer Biocatalysis and Biomaterials, chapter 8, pp.107-118, American Chemical Society (publisher), 2005.

Woods TO. MRI safety: device compatibility considerations. John Wiley Encyclopedia of Biomedical Engineering, December 2005.

Proceedings, Abstracts, Letters, Book Reviews, etc.

Agrawal A, Huang ST, Pfefer J, Lee M-H, Drezek R. Quantitative evaluation of nanoshells as a contrast agent for optical coherence tomography. European Conferences on Biomedical Optics, Optical Society of America/SPIE, Munich, Germany, June 12-16, 2005.

Agrawal A, Huang S, Pfefer TJ, Lee, M-H, Drezek, R. Quantitative evaluation of nanoshells as a contrast agent for optical coherence tomography. Conference on Lasers and Electro-Optics (CLEO), Optical Society of America, Baltimore, MD, May 22-27, 2005.

Alderson N, Ali SN, Elkins C, Fahmy RM, Gobburu JVS, Grant M, Johannessen J, Kulka M, Major M, Manjanatha M, Stern S, Trinh H, Uppor R, Ward J, Wood G, Woods TO. Committee for the Advancement of FDA Science (CAFDAS): the FDA scientist's liaison to the Commissioner's Office, 2005 FDA Science Forum – Advancing Public Health Through Innovative Science, Washington, DC, April 27-28, 2005, p. 142.

Amat A, Rigau J, Waynant R, Ilev I, Anders J. Electromagnetic interaction between laser light and ATP: a non-absorptive mechanism. *Lasers in Surgery and Medicine* **36:**S17, p. 10, 2005.

Badano A, Sempau J, Boswell JS. Combined x-ray/electron/optical Monte Carlo code based on PENELOPE and DETECCT-II and statistics of the scintillation output using a combined x-ray/electron/optical Monte Carlo method. Proceedings of the International Society for Optical Engineering (SPIE), **5745:**870-876, 2005.

Badano A, Sempau J, Jennings RJ. Statistics of the scintillation output using a combined x-ray/electron/optical Monte Carlo method. Proceedings of the International Symposium on Medical Imaging (SPIE), **5745:**361-365, 2005.

Badano AG, Gallas BD, Fifadara DH. Visual detection with non-Lambertian displays: model and human observer results. Proceedings of the International Society for Optical Engineering (SPIE), 5744: 271-278, 2005.

Badano A, Liang H, Gallas BD. Current challenges in medical displays. Proceedings of the Conference on American Display Engineering and Applications II:154–157, 2005. *(Invited paper)*

Badano A. Viewing angle comparison of IPS and VA medical AMLCDs. Proceedings of the Society of Information Display **36:**192–195, 2005.

Baskar HS, Lappalainen SK, Hitchins VM. 2005. Cytotoxicity of residual cleaning agents used in reprocessing medical devices. FDA Science Forum, J-23 (p. 105), 2005.

Beer JZ, Yamaguchi Y, Tadokoro T, Batzer J, Coelho SG, Zmudzka BZ, Miller SA, Wobler R, Hearing VJ. UV-induced redistribution of epidermal melanin in different races – a defensive response. *Journal of Investigative Dermatology* **124 (Supplement 1):**808, 2005.

Beer JZ, Zmudzka BZ, Bushar HF, Miller SA, Yamaguchi Y, Tadokoro T, Coelho SG, Hearing VJ. Melanin, race and UV responses. *Pigment Cell Research* **18 (Supplement 1):**83, 2005.

Chen ET, Richardson DC. *In vitro* clustering of microvacuoles in foldable intraocular lenses. FDA Science Forum, Washington, DC, April 27-28, 2005.

Chiesa OA, Heller D, Smith M, Nochetto C, Karanian J, Pritchard W, von Bredow J. Development and application of serial endoscopic tissue sampling techniques for pharmacokinetic and

pharmacodynamic studies in large animal models of disease and intervention. Veterinary Endoscopy Society, Keystone, CO, March 13-15, 2005.

Chiesa OA., Heller DN, Smith M, Condon R, von Bredow JD, Thomas MH. Correlation of penicillin concentrations in kidney tissue with penicillin levels in urine and plasma. In: (Ed.), 14th Biennial Symposium of the American Academy of Veterinary Pharmacology and Therapeutics - May 16-18, 2005, Washington, DC, USA. Ithaca: International Veterinary Information Service (www.ivis.org), Document No. P1841.0505, 2005

Chiesa OA, von Bredow J, Heller DN, Smith M, Thomas M. One-port laparoscopy assisted kidney biopsy in standing steers. Academy of Surgical Research. 21st Annual Convention. Philadelphia, Pennsylvania, September 15-17, 2005.

Chiesa OA, Heller DN, Smith M, Condon R, von Bredow J, Thomas M. Plasma and/or urine penicillin concentrations predict kidney tissue tolerance level. FDA Science Forum, Washington, DC, April 27-28, 2005.

Chiesa OA, Pritchard WF, Murray TL, Shah AD, Karanian JW. Minimally invasive endoscopic techniques allow serial tissue visualization and sampling for pharmacokinetics and safety studies in large animal models of vascular disease and intervention. FDA Science Forum, Washington, DC, April 27-28, 2005.

Coelho SG, Miller SA, Beer JZ. Quantification of UV-induced erythema and pigmentation using computer-assisted digital image evaluation (CADIE). 19th International Pigment Cell Conference (IPCC), National Institutes of Health, Reston, VA, September 18-22, 2005

Dair BJ, Patwardhan DV, Saylor DM, Schroeder LW, Richardson DC. Observations on the morphology and growth of microvacuoles in foldable intraocular lenses. FDA Science Forum, April 27-28, 2005.

Gammell PM, Maruvada S, Harris GR. A simplified ultrasonic time-delay spectrometry (TDS) system employing digital processing to minimize hardware requirements. 32nd Annual Review of Progress in Quantitative Nondestructive Evaluation (QNDE), Brunswick, ME, July 31-August 5, 2005 (conference proceedings).

Godar DE, Coelho SG, Landry RJ, van der Leun JC. A melanoma hypothesis: the paradox of outdoor and indoor solar UV exposures. Perspectives in melanoma IX, ECOG Fall Meeting, Tampa, FL, November 17-21, 2005.

Godar DE, Dowdy JC, Coelho SG, Landry RJ, Sayre RM, van der Leun JC. A melanoma hypothesis: the paradox of outdoor and indoor solar UV contributions toward skin cancer. 2005 FDA Science Forum: Advancing Public Health through Innovative Science, Washington, DC, April 27-28, 2005.

Godar DE, Lucas AD. UVA1-mediated receptor and cytokine changes of transformed lymphocytes. 11th Annual FDA Science Forum, Washington, DC, April 27-28, 2005.

Goering PL, Madden EF, Brown RP, Rosenzweig BA, Thompson KL. A subclinical renal injury model in rats for detection of nephrotoxic compounds. FDA Science Forum, Washington, DC, April 27-28, 2005.

Harris GR. The FDA perspective on pre-clinical testing for high intensity focused ultrasound devices. (Invited), 5th International Symposium on Therapeutic Ultrasound, Boston, MA, October 2005.

Harris GR. Regulation of high intensity focused ultrasound devices at the U.S. FDA. (Invited) 34th Ultrasonic Industry Association Symposium, Las Vegas, NV, March 2005.

Huang S, Agrawal A, Pfefer JT. Nanoshells enhance optical coherence tomography images of tissues phantoms. 2005 FDA Science Forum: Advancing Public Health through Innovative Science, Washington, DC, April 27-28, 2005.

Icenogle TB, Regnault WF, Antonucci JM, Skrtic D. Physical and chemical characterization of bioactive polymer composites. Polymer Preprints **46:**693, 2005.

Ilev IK, Faaland RW, Landry RJ, Waynant RW, Calogero DX. Novel confocal laser method for intraocular lens power testing: how a laboratory born invention goes through the path from bench to independent clinical sample testing. 2005 FDA Science Forum: Advancing Public Health through Innovative Science, Washington, DC, April 27-28, 2005.

Ilev IK, Waynant RW, Amat A, Royston DD, Weiblinger R., Romanczyk T, Anders J, Gandjbakhche A. Continuous-wave vs. ultrashort (pico- and femtosecond) pulsed laser beam propagation through turbid tissue in minimally invasive laser medical devices. 2005 FDA Science Forum: Advancing Public Health through Innovative Science, April 27-28, 2005.

Ilev I, Waynant RW. Confocal fiber-optic nanobiosensing. LEOS 2004 - Annual Meeting of the IEEE Lasers and Electro-Optics Society, Sydney, Australia, October 23-27, 2005.

Kaczmarek RG, Pressly NA, Woods TO, Bassen HI, Eudy M, Ferriter AM, Hazes MJ, Kainz W, Lange S, Malli SM, Ruggera PS, Scott WL, Zaremba L. Neurological implants with lead systems and magnetic resonance imaging: adverse events and prevention. 2005 FDA Science Forum – Advancing Public Health Through Innovative Science, Washington, DC, April 27-28, 2005, p. 143.

Kainz W, Christ A, Chen J. Current and future needs for computational methods for medical applications. URSIGA 2005, XXVIII General Assembly of International Union of Radio Science, New Delhi, India, October 23-29, 2005.

Kainz W, Christ A, Kellom T, Seidman S, Nikoloski N, Beard BB, Kuster N. The specific anthropomorphic mannequin (SAM) compared to 14 anatomical head models using a novel definition for the mobile phone positioning. BioEM 2005, The Bioelectromagnetics Society (BEMS), University College of Dublin, Dublin, Ireland, June 19-24, 2005.

Kainz W, Kellom T, Qiang R, Chen J. Development of pregnant woman models for nine gestational ages and calculation of fetus heating during magnetic resonance imaging (MRI). BioEM 2005, The Bioelectromagnetics Society (BEMS), University College of Dublin, Dublin, Ireland, June 19-24, 2005.

Kainz W, Seidman S, Qiang R, Chen J, Bassen HI. The future of anatomical models - anatomical CAD models for numerical dosimetry and implant evaluations. BioEM 2005, the Bioelectromagnetics Society (BEMS), University College of Dublin, Dublin, Ireland, June 19-24, 2005.

Kaplan DS, Hitchins VM. Role and use of guidance documents and standards for submission of applications for combination and human cell, tissue, and cellular and tissue-based products to the Food and Drug Administration. FDA Science Forum, Q-07 (p. 143), 2005.

Krauthamer V, Malinauskas RA, Mitrojorgji E, Stratton M, Higginson K, Zivny J, Vostal J. Effects of implantable cardioverter-defibrillator (ICD) shocks upon human blood. FDA 2005 Science Forum - Advancing Public Health Through Innovative Science, Washington, DC, April 27-28, 2005, Abstract A-31.

Kyprianou IS, Ganguly A, Rudin S, Bednarek DR, Gallas BD, Myers KJ. Efficiency of the human observer compared to an ideal observer based on a generalized NEQ which incorporates scatter and geometric unsharpness: evaluation with a 2AFC experiment. Proceedings of the International Symposium on Medical Imaging (SPIE) **5749:** 251-262, 2005.

Lappalainen SK, Baskar HS, Hitchins VM. Residual total protein levels on reprocessed gastrointestinal (GI) biopsy forceps. FDA Science Forum, J-22 (p. 105), 2005.

Leeper DB, Burd R, Pollard MD, Canter RJ, Zhou R, Kesmodel SB, Glickson JD, O'Hara MD, Fraker DL. Melanoma xenografts are sensitized to melphalan by mibg and hyperglycemia suggesting therapeutic gain. 6th World Congress on Melanoma, Vancouver, British Columbia, Canada, September 2005

Lucas A, Brown R. Release of the plasticizer di-2-ethylhexyl phthalate (DEHP) into normal saline stored in heated and nonheated PVC bags, 11th Annual FDA Science Forum, Washington, DC, April 27-28, 2005.

Luu HMD, Isayeva IS, Vorvolakos K, Patwardhan DV, Das SS. Materials issues in the post-market evaluation of bioresorbable iron cross-linked hyaluronic acid-based adhesion prevention solution (Fe-HA). Abstract and poster presentation at the FDA Science Forum, Washington, DC, April 27-28, 2005.

Lyle DB, Shallcross JC, Hitchins VM, Langone JJ. 2005. Testing biomaterials for stimulation of major inflammatory pathways. Proceedings of the FDA Science Forum, Washington, DC, April 27-28, 2005, p 33.

Lyle DB, Shallcross JC, Hitchins VM, Durfor CN, Langone JJ. An *in vitro* test for inflammatory potential of hyaluronic acid preparations. Proceedings, FDA Science Forum, Washington, DC, April 27-28, 2005, p 34.

Madden EF, Brown RP, Goering PL. Utility of a subclinical renal injury model in rats for detection of increased sensitivity to site-specific nephrotoxic metals. Society of Toxicology, 44th Annual Meeting, New Orleans, LA. *Toxicological Science* 84 (S-1), 2005.

Maruvada S, Harris GR, Herman BA, King RL. Analysis of a protocol for measuring ultrasonic power from focused therapeutic ultrasound transducers using radiation force. 5th International Symposium on Therapeutic Ultrasound, Boston, MA, October 2005. (Conference proceedings)

Maruvada S, Harris GR. Acoustic regulation of extracorporeal shock wave (ESW) therapy devices in the U.S. (Invited) 149th Meeting of the Acoustical Society of America, Vancouver, Canada, May 2005.

Matchette LS, Agrawal A, Pfefer TJ. Quantum yield measurements of drugs with the potential to interfere with flourescence-based diagnostic devices. 2005 FDA Science Forum: Advancing Public Health through Innovative Science, April 27-28, 2005.

McDermott MK, Saylor DM, Witkowski CN, Williams CM, Thomas TM, Lee AS, Hutter JC. Breakage of blood bags used off-label to store hematopoietic stem cells. 11th Annual FDA Science Forum, Sigma Xi Poster Session, poster G-14, page 70, Washington, DC, April 27-28, 2005. (Winner of both the "Sigma Xi Poster Winner Award" and "Clear Science Communication Award".)

McDermott MK, Williams CM, Thomas TM, Lee AS, Witkowski CN, Saylor DM, Hutter JC. Fabrication variability and consistency of controlled release technologies. 11th Annual FDA Science Forum, Sigma Xi Poster Session, poster G-15, page 70, Washington, DC, April 27-28, 2005.

McDermott MK, Lee AS, Thomas TM, Isayeva IS, Lucas AD, Witkowski CN, Hutter JC. Characterization of the structure and properties of authentic and "suspect counterfeit" polypropylene surgical meshes. 11th Annual Science Forum, Sigma Xi Poster Session, poster G-16, page 71, Washington, DC, April 27-28, 2005. (Winner of the "Clear Science Communication Award".)

Mendoza GG, Witters DM, Bassen HI. Electromagnetic compatibility (EMC) of active medical devices exposed to wireless personal digital assistants (PDAs). 2005 FDA Science Forum: Advancing Public Health through Innovative Science, Washington, DC, April 27-28, 2005.

Miller SA, Zmudzka BZ, Coelho SG, Beer JZ. Comparison of different UV exposure regimens for cosmetic tanning. *Journal of Investigative Dermatology* **124:**818, 2005.

Miller SA, Coelho SG, Zmudzka BZ, Bushar HF, Beer JZ. Recommended exposure schedules for indoor tanning: explorations to improve current FDA guidance. 11th Annual FDA Science Forum, p. 136, 2005.

Miller SA, Coelho SG, Zmudzka BZ, Bushar HF, Beer JZ. Recommended exposure schedules for indoor tanning: explorations to improve current FDA guidance. *Journal of Investigative Dermatology* **124**, April 2005.

O'Hara MD, Pollard MD, Pocceschi M, Leeper DB. MIBG plus hyperglycemia sensitizes bone marrow cfu-f but not cfu-c to cs-137 irradiation *in situ*. Radiation Research Society and ASTRO meeting, Denver, CO, October 2005.

OSEL/Division of Solid and Fluid Mechanics, ODE/Division of Cardiovascular Devices/Interventional Cardiology Devices Branch & Peripheral Vascular Devices Branch. Non-clinical tests and recommended labeling for intravascular stents and associated delivery systems. 2005 FDA Science Forum – Advancing Public Health Through Innovative Science, Washington, DC, April 27-28, 2005, p. 133.

Park S, Clarkson EA, Kupinski M.A, Barrett HH. Efficiency of human and model observers for signal-detection tasks in non-Gaussian distributed lumpy backgrounds. Proceedings of the International Symposium on Medical Imaging (SPIE) **5749:**138-149, 2005.

Passerini A, Manduchi E, Grant G, Pritchard WF, Davies PF. Genomic studies of atherosusceptibility *in vivo*: probing the flow-correlated regional determinants of arterial endothelial phenotype. Vascular Biology and Medicine 2005: From Molecules to Man, Chicago, IL, June 16-19, 2005.

Petrick N, Gallas BD, Samuelson FW, Wagner RF, Myers K.J. Influence of panel size and expert skill on truth panel performance when combining expert ratings. Proceedings of the International Society for Optical Engineering (SPIE), **5749:**49-57, 2005.

Pfefer TJ, Sharma D, Agrawal A, Matchette S. Evaluation of a fiber-optic-based system for optical property measurement in highly attenuating turbid media. Proceedings of the SPIE 5691:163-171, 2005.

Pfefer TJ, Agrawal A, Drezek RA. Simulation of oblique-incidence probe geometries for depth-resolved fluorescence spectroscopy. European Conferences on Biomedical Optics, Optical Society of America/SPIE, Munich, Germany, June 12-16, 2005.

Pritchard WF, Passerini AG, Shi C, Francesco NM, Chuan P, Manduchi E, Grant GR, Stoeckert CJ, Wray-Cahen D, Karanian JW, Davies PF. Blood flow and artery type are key determinants of endothelial cell gene expression and the development of vascular disease. FDA Science Forum, Washington, DC, April 27-28, 2005.

Qiang R., Wu D., Chen JI Wilton D, Kainz W. An efficient two-dimensional FDTD method for bio-electromagnetic applications", IEEE Transaction on Magnetics (Compumag 2005), 15th Conference on the Computation of Electromagnetic Fields, Shenyang, Liaoning, China, June 26 - 30, 2005.

Quinn JB, Regnault WF, Antonucci JM, Skrtic D. Fractographic analysis of amorphous calcium phosphate/urethane composites. 83rd General Session of the International Association for Dental Research, Baltimore, MD, March 9-12, 2005.

Ranamukhaarachchi D, Puri R., Fuscoe J, Morris S, Pennello R, Han J, Han T, Simon K, Wang S-J, Mendrick D, Martinsky T, Simon K, Frueh F, Nandanie D, Elespuru R. Prioritizing sources of variability in genomic profiling data for standards and guidance development. FDA Science Forum, Washington DC, April 27, 2005.

Regnault WF, Antonucci JM, Skrtic D, Quinn JB. Environmental effects on the mechanical strength of amorphous calcium phosphate polymeric composites. 83rd General Session of the International Association for Dental Research, Baltimore, MD, March 9-12, 2005.

Robinson RA, Ilev IK. High-peak-power fiber-optic laser delivery for digital particle image velocimetry. SPIE-BIOPHOTONICS, BiOS 2005, San Jose, CA, January 22-28, 2005.

Robinson RA, Ilev IK. All-hollow-waveguide laser delivery: a novel approach for high-peak power and homogeneous laser delivery in DPIV systems. 6th International PIV Convergence, California Institute of Technology, September 21-23, 2005.

Robinson RA, Ilev IK. All-hollow-waveguide laser delivery: a novel approach for high-peak and homogeneous laser delivery in DPIV systems. PIV 05 Conference, Pasadena, CA, September 21-23, 2005.

Samuelson FW, Wagner RF. Contemporary issues in the MRMC ROC paradigm. Proceedings of the International Symposium on Medical Imaging (SPIE) **5749:**15-20, 2005.

Saylor DM, Warren J, Wanner T. Structure evolution and release behavior in controlled drug delivery systems. *Materials Science and Technology*, Pittsburgh, PA, Sept. 2005.

Saylor DM, Warren J, Wanner T. Pattern classification in controlled drug delivery systems. SIAM Conference on Applications of Dynamical Systems, Snowbird, UT, May 2005.

Schwerin MR, Busick DN, Cash LD, Morrisson AE. Accidental disconnection of luer locks. 2005 FDA Science Forum – Advancing Public Health Through Innovative Science, Washington, DC, April 27-28, 2005.

Spees WS, Jones PL. Adding flight data recording technology to medical device systems. 12th International Conference on Biomedical Engineering, Singapore, Malaysia, December 7-10, 2005.

Sharma D, Agrawal A, Matchette LS, Pfefer J. Techniques for reflectance-based determination of optical properties in highly attentuating turbid media. Conference on Lasers and Electro-optics, Optical Society of America, Baltimore, MD, May 22-27, 2005.

Takahashi K, Yamaguchi Y, Hoashi T, Zmudzka BZ, Miller SA, Beer JZ, Hearing VJ. Effects of ultraviolet radiation on signaling proteins of the melanogencic system. 19th International Pigment Cell Conference, Reston, VA, September 18-22, 2005, *Pigment Cell Research* **18 (Supplement 1):**83.

Tock CL, Turner LR, Batra P, Coelho S, Miller SA, Beer JZ, Radonovich M, Brady JN, Turner ML, Vogel JC. Transcriptional profiling of the epidermal response to ultraviolet radiation. Society for Investigative Dermatology, St. Louis, MO, May 4-7, 2005.

Vorvolakos K, editor. Proceedings of the 28th Annual Meeting of the Adhesion Society, Mobile AL, February 13-16, 2005.

Wang A, Bender JE, Pfefer TJ, Utzinger U, Drezek R. Depth-sensitive reflectance measurements using obliquely oriented fiber probes. Proceedings of the SPIE 5691:54-65, 2005.

Waynant RW, Ilev IK. Confocal fiber-optic nanobiosensing. LEOS 2004 - Annual Meeting of the IEEE Lasers and Electro-Optics Society, Sydney, Australia, October 23-27, 2005.

Waynant RW, Ilev IK, Gorman E. New fibers for mid-infrared delivery: measurements and evaluation. Annual General Meeting of the Air Force Office of Scientific Research (AFOSR), Palo Alto, CA, September 12-15, 2005.

Waynant R, Ilev I, Amat A. Laser therapy – still a lot of explaining to do. *Lasers in Surgery and Medicine*, v. 36, S17, p. 56, 2005.

Wear KA. Dependence of sound speed on porosity in human calcaneus: theory and experiment. Annual Conference of the American Institute of Ultrasound in Medicine, Orlando, FL, June 19-22, Journal of Ultrasound in Medicine **24(6)** (suppl.):S20, June, 2005.

Wear KA. Relationship between phase velocity and porosity in bone-mimicking phantoms and human calcaneus: theory and experiment. 30th Annual Conference on Ultrasonic Imaging, Arlington, VA, May 25, 2005.

Wear KA. Ultrasonic wave propagation and scattering in cancellous bone. Acoustical Society of America Annual Conference, San Diego, CA, November 15, 2004.

Wei J, Sahiner B, Hadjiiski LM, Chan HP, Helvie MA, Roubidoux MA, Petrick N, Ge J, Zhou C. Computer-aided detection of breast masses on mammograms: performance improvement using a dual system. Proceedings of the International Society for Optical Engineering (SPIE) **5747:**9-15, 2005.

Weininger S, Pfefer J, Chang IA. Factors to consider in a risk analysis for safe surface temperature. Product Safety Engineering Society, IEEE, Chicago, IL, October 3-4, 2005.

Witters DM. Wireless technology in and around medical devices: addressing electromagnetic compatibility (EMC) and data integrity concerns. 2nd Operating Room of the Future Medical Device Plug-and-Play meeting, Center for Devices and Radiological Health, FDA, Rockville, MD, November 15-16, 2004.

Witters DM. Wireless technology in and around medical devices: addressing FDA concerns for electromagnetic compatibility (EMC) and data integrity. AAMI 2005 Conference and Expo, May 14-17, 2005.

Witters DM, Buzduga V, Seidman S, Kainz W, Casamento JP, Ruggera PS. Hand-held metal detectors and medical devices: measurements and testing for electromagnetic compatibility. IEEE International Carnahan Conference on Security Technology, 39th Annual Conference, Las Palmas De Gran Canaria, Spain, October 11-14, 2005.

Witters DM, Buzduga V, Seidman S, Kainz W, Casamento JP, Ruggera PS. Hand-held metal detectors and medical devices: measurements and testing for electromagnetic compatibility. 2005 IEEE Carnahan Conference on Security Technology, IEEE (conference proceedings), Las Palmas Dr Gran Canaria, Spain, October 11-14, 2005.

Wokovitch AM, Brown SA. *In-vitro* test method development for determining transdermal drug delivery systems (TDDS) adhesion. Abstract G25, 2005 FDA Science Forum, Washington, DC, April 27-28, 2005.

Wood SC, Brown RP, Chen J, Gordon EA, Harris GR, Hitchins VM, Maruvada S, Mtungwa AR, Stratmeyer ME. Bioeffects of ultrasound and ultrasound microcontrast agent on three mammalian cell lines. FDA Science Forum, Washington, DC, J-46 (p. 111) April 2005.

Wray-Cahen D, Pritchard W, Ashby A, Russek-Cohen E, Vossoughi J, Karanian J. Gender, age, and hormonal status affect recovery time from general anesthesia in pigs. American Society of Animal Science Meeting, Cincinnati, OH, July 25-28, 2005.

Wu D, Qiang R., Chen Ji, Kainz W, Seidman S. Safety evaluation of walk-through metal detectors. International Symposium on Electromagnetic Compatibility 2005, Chicago, IL, August 8-12 2005, vol., pp. 796- 800.

Yamaguchi Y, Takashi K, Tadokoro T, Zmudzka BZ, Kornhauser A, Miller SA, Berens W, Beer JZ, Hearing VJ. Human skin responses to UV radiation: pigment in the upper epidermis protects against dna damage in the lower epidermis and facilitates apoptosis. *Pigment Cell Research* **18 (Supplement 1):**32–33, 2005.

Yamaguchi Y, Takahashi K, Zmudzka BZ, Kornhauser A, Miller SA, Tadokoro T, Berens W, Itami S, Katayama I, Beer JZ, Hearing VJ. Melanin in the upper epidermis not only protects against UV-induced DNA damage but also facilitates apoptosis in its vicinity. *Journal of Investigative Dermatology* **124:**830, 2005.

Letters to the Editor

Sadrieh N, Brown SA. Therapies require teamwork among FDA and developers. Small Times Magazine **5(8):**22-23, 2005.

APPENDIX B – OSEL Presentations

January 1, 2005 – December 31, 2005

Badano A. Display technologies. Update course - Advances in digital radiography: digital radiographic display considerations. Annual Meeting of the Radiological Society of North America (RSNA), Chicago, IL, November 28-December 1, 2005.

Beer JZ, Tadokoro T, Yamaguchi Y, Batzer J, Coelho S, Zmudzka BZ, Miller SA, Wolber R, Hearing V. UV-induced redistribution of epidermal melanin in different races - a defensive response? 66th Annual Meeting of the Society of Investigative Dermatology, St. Louis, MO, May 4-7, 2005.

Beer JZ, Zmudzka BZ, Bushar HF, Miller SA, Yamaguchi Y, Tadokoro T, Coelho SG, Hearing VJ. Melanin, race and UV responses. 19th International Pigment Cell Conference, Satellite Meeting on the Photobiology of Melanocytes and Melanoma, Reston, VA, September 2005.

Bhat S, Paquerault SO, Petrick N. Graphical user interface (GUI) for mammography review and CAD development. FDA Science Forum, Washington, DC, April 27-28, 2005 (poster).

Brown R, Goering P. Animal models of compromised health and improved biomarkers of toxicity for biocompatibility and risk assessment. ODE-DGRND Clinical Rounds, Rockville, MD, November 30, 2005.

Brown RP. Animal models of compromised health: sepsis. OSEL Science Review, Rockville, MD, February 22, 2005.

Brown RP. Use of animal models of disease for preclinical evaluation of safety and efficacy. 2005 FDA Science Forum, Washington, DC, April 27, 2005.

Brown R, Wray-Cahen D, Stratmeyer M. Acute hemodynamic and hemolytic effects of intravenously administered ethylene glycol in the pig: Implications for ethylene oxide sterilization residues standard (ISO 10993-7). FDA Science Forum, Washington, DC, April 27-28, 2005.

Brown RP. Iatrogenic CJD risk from reprocessed neurosurgical instruments. General Hospital and Personal Use Devices Panel of the Medical Devices Advisory Committee, Gaithersburg, MD, September 27, 2005.

Brown RP, Goering PL. Risk assessment for compounds released from medical device materials. ODE-DGRND Clinical Rounds, Rockville, MD, November 9, 2005.

Chen ET, Richardson DC. *In vitro* clustering of microvacuoles in foldable intraocular lenses. FDA Science Forum, Washington, DC, April 27-28, 2005.

Chiesa OA, Heller D, Smith M, Karanian JW, Pritchard WF, von Bredow J. Development and application of serial endoscopic tissue sampling techniques for pharmacokinetic and pharmacodynamic studies in large animal models of disease and intervention. 2nd Annual Scientific Meeting Veterinary Endoscopy Society, Keystone, CO, March 13-16, 2005.

Coelho SG, Miller SA, Beer JZ. Quantification of UV-based erythema and pigmentation using computer assisted digital image evaluation (CADIE). 19th International Pigment Cell Conference, Reston, VA, September 2005.

Cohen ED. New designs for visual prostheses. Interdisciplinary Club for Biomaterials and Regenerative Medicine, Rockville, MD, April 15, 2005.

Dair BJ, Patwardhan DV, Saylor DM, Schroeder LW, Richardson DC. Observations on the morphology and growth of microvacuoles in foldable intraocular lenses. FDA Science Forum, April 27-28, 2005.

Desta AB, Ettore Majorana Foundation and Centre for Scientific Culture International School of Biolelectromagnetics 2nd course on "Electromagnetic Fields and Genotoxicity," Gene Toxicity Studies funded through a CRADA between FDA and CTIA, Erice, Italy, October 9, 2005.

Desta AB, Science Prioritization Process lecture: Electromagnetic Field Research, Rockville, MD, October 25, 2005.

Desta AB. U.S. FDA efforts to better understand risks associated with the use of wireless devices. International Workshop on Mobile Telephony and Health, Seoul, Korea, November 7, 2005.

Elespuru RK. OSEL Project Updates: Prioritizing sources of variability in genomic profiling data (OSHC). FDA Center for Devices and Radiological Health, Rockville, MD, February 22, 2005.

Elespuru RK. Cancer projects at CDRH. National Cancer Institute, Bethesda, MD, June 23, 2005.

Elespuru RK. Integrating new technologies into the assessment of heritable genetic effects. International Conference on Environmental Mutagens, San Francisco, CA, September 6, 2005.

Elespuru RK. Prioritizing sources of variability in genomic profiling data for standards and guidance development: OSHC project implementation. National Institute of Standards and Technology, Gaithersburg, MD, September 20, 2005.

Eloff BC. Use of ECG databases in device evaluation. Cardiac Safety and the Critical Path Initiative Think Tank, Bethesda, MD, October 11, 2005.

Fitzgerald BJ. FDA cybersecurity guidance. American College of Clinical Engineering, Tampa, FL, May 12, 2005.

Fitzgerald BJ. FDA cybersecurity guidance. Association for the Advancement of Medical Instrumentation, Tampa, FL, May 16, 2005.

Gallas BD. One-shot estimate of MRMC variance. MIPS XI, Medical Imaging Perception Society, Windermere, UK, September 27-30, 2005.

Gavrielides MA. Algorithms for automated analysis in microscopy imaging: applications to immunohistochemistry and fluorescence in situ hybridization. FDA/CDRH/OIVD Staff College: Lecture on Computer-Assisted Image Analysis, Rockville, MD, July 11, 2005.

Godar DE, Lucas AD. UVA1-mediated receptor and cytokine changes of transformed lymphocytes. 11th Annual FDA Science Forum, Washington, DC, April 27-28, 2005.

Goering P. A career in Health Sciences at the Food and Drug Administration lecture for freshman level course at Purdue University School of Health Sciences. West Lafayette, Indiana, September 20, 2005.

Goering P. Development of an improved animal model of renal failure and improved biomarkers of nephrotoxicity. Seminar for graduate students and faculty, Purdue University School of Health Sciences, West Lafayette, Indiana, September 20, 2005.

Goering P. Mechanisms of metal toxicity. American Chemical Society continuing education course lecture, Philadelphia, PA, October 20-21, 2005.

Goering PL, Madden EF, Brown RP, Rosenzweig BA, Thompson KL. A subclinical renal injury model in rats for detection of nephrotoxic compounds. FDA Science Forum, Washington, DC, April 27-28, 2005.

Goering PL. Animal models of compromised health – research update on a renal injury model in rats. OSEL/DB Research Update series, Rockville, MD, March 1, 2005.

Ilev IK. Modern nanophotonics technologies. CEATEC' 2005, Tokyo, Japan, October 7, 2005.

Ilev IK. Novel biophontonics delivery, nanosensing and nanoimaging techniques. The Institute of Physical and Chemical Research (RIKEN), Tokyo, Japan, October 3, 2005.

Ilev IK. Precise confocal laser method for intraocular lens power measurement. ICBRO 2005, FDA/CDRH/ODE-OSEL, Rockville, MD, April 15, 2005.

Ilev IK. Ultrahigh-resolution confocal nanbioimaging and sensing beyond the diffraction barrier in the nanoscale range. Tokyo Tamagawa University, Tokyo, Japan, October 8, 2005.

Ilev IK. Confocal fiber-optic nanobiosensing and imaging beyond diffraction barrier. National Institute of Health/ NIH Functional and Molecular Optical Imaging Seminar, Bethesda, MD, July 13, 2005.

Ilev I. Confocal nanoscopy and nanobiosensing. George Washington University/Institute of Biomedical Engineering Seminar, Washington DC, November 18, 2005.

Jones PL. Software risk management purpose and scope. AAMI 15th Annual Standards Conference AAMI TIR32:2005, McLean, VA, March 23, 2005.

Kainz W, Christ A, Chen J. Current and future needs for computational methods for medical applications. URSIGA 2005, General Assembly of International Union of Radio Science, New Delhi, India, October 23-29, 2005.

Kainz W, Christ A, Kellom T, Seidman S, Nikoloski N, Beard BB, Kuster N. The specific anthropomorphic mannequin (SAM) compared to 14 anatomical head models using a novel definition for the mobile phone positioning (conference poster). BioEM 2005, the Bioelectromagnetics Society (BEMS), Dublin, Ireland, June 19-24, 2005.

Kainz W, Kellom T, Qiang R, Chen J. Development of pregnant woman models for nine gestational ages and calculation of fetus heating during magnetic resonance imaging (MRI). BioEM 2005, the Bioelectromagnetics Society (BEMS) Dublin, Ireland, June 19-24, 2005.

Kainz W, Seidman S, Qiang R, Bassen HI. The future of anatomical models - anatomical CAD models for numerical dosimetry and implant evaluations (conference poster). BioEM 2005, the Bioelectromagnetics Society (BEMS), Dublin, Ireland, June 19-24, 2005.

Kalb SS. Biomedical Engineering Seminar I Guest Lecture: Biomedical Engineers at FDA/CDRH. Department of Electrical and Computer Engineering, George Washington University, November 11, 2005.

Karanian JW, Pritchard WF. Emerging interventional therapeutics to treat vascular disease and cancer: bench to bedside. (Invited) CAFDAS seminar, Office of the Commissioner, FDA, Rockville, MD, November 19, 2004.

Keith EI, Woods TO. An FDA perspective: GMP requirements and cleanliness of newly machined implants. ASTM Symposium on Cleanliness of Implants, Reno, NV, May 18, 2005.

Kessler LG. Guidance and standards: two sides of the same coin. AdvaMed, February 2005.

Kessler LG. CDRH current challenges. University of Minnesota, February 2005.

Kessler LG. Developing FDA guideline for medical devices. AAMI, March 2005.

Kessler LG. Using risk management principles at the Center for Medical Devices. Risk Management Conference, Lubeck, Germany, June 2005.

Kessler LG. Hearing aid compatibility with cell phones: role for FDA Center for Medical Devices. FCC, Washington, DC. July 2005.

Kessler LG. E&P Lab Progress: Tungus Tour, OSEL Laboratories, Rockville, MD, September 2005.

Kessler LG. Science prioritization process – how it works and what are some results? Science Board, Rockville, MD, September 2005.

Kessler LG. What is a device? Defense Advanced Research Projects Agency, October 2005.

Kyprianou IS, Gallas BD, Myers KJ. A model observer detectability which incorporates scatter and geometric unsharpness: evaluation with a 2AFC experiment. Annual Mid-Atlantic Chapter Meeting of the American Association of Physicists in Medicine, Flintstone, MD, June 3-4, 2005.

Kyprianou IS. Improved x-ray imaging in women for cardiovascular disease. National Institute for Biomedical Imaging and Bioengineering, Bethesda, MD, December 8, 2005.

Kyprianou IS. Improved x-ray imaging in women for cardiovascular disease. University of Buffalo, Buffalo, NY, December 13, 2005.

Kyprianou IS, Jennings RJ, Gagne RM, Petrick N, Gallas BD, Myers KJ. Designing and building a laboratory-based, high-resolution, high-frame-rate imaging system with extended dynamic range

for cone-beam computed tomography and dynamic imaging applications. 2005 FDA Science Forum, Washington, DC, April 27-28, 2005 (poster).

Landry RJ. Method for characterizing IOL glare. Interdisciplinary Club for Biomaterials and Regenerative Medicine in Ophthalmology 2005 Meeting, Rockville, MD, April 15, 2005.

Lucas A, Brown R. Release of the plasticizer di-2-ethylhexyl phthalate (DEHP) into normal saline stored in heated and nonheated PVC bags, 11th Annual FDA Science Forum, Washington, DC, April 27-28, 2005.

Luu HMD, Isayeva IS, Vorvolakos K, Patwardhan DV, Das SS. Materials issues in the post-market evaluation of bioresorbable iron cross-linked hyaluronic acid based adhesion prevention solution (Fe-HA). Abstract and poster presentation at the FDA Science Forum, Washington, DC, April 27-28, 2005.

Madden EF, Brown R, Goering PL. Utility of a subclinical renal injury model in rats for detection of increased sensitivity to site-specific nephrotoxic metals. Society of Toxicology, 44th Annual Meeting, Baltimore, MD, March 6-10, 2005.

Mahoney C, McDermott MK. Characterization of drug-eluting stent (DES) materials with cluster secondary ion mass spectrometry (SIMS). The 15th International Conference on Secondary Ion Mass Spectrometry (SIMS XV), Manchester, United Kingdom, September 12-16, 2005.

Malinauskas RA. Blood damage evaluation of medical devices: A biomedical engineering perspective of the Food and Drug Administration. State University of New York at Stony Brook, Department of Biomedical Engineering, September 14, 2005.

Matviyenko AV, Lewis M, Sergeev NV, Bockstahler KE, Rasooly A, Herold KE. Development of high speed nano-scale PCR for detection and identification of FDA relevant pathogens. 11th Annual FDA Science Forum, April 27-28, 2005, Washington, DC.

Matviyenko AV, Sergeev NV, Rasooly A. Development of miniature point-of-care microfluidic biosensor for simultaneous rapid detection of multiple microbial toxins. 11th Annual FDA Science Forum, April 27-28, 2005, Washington, DC.

Mendoza GG. Electromagnetic compatibility (EMC) of wireless personal digital assistants (PDAs) with active medical devices (MEDs). Catholic University of America, Washington, DC, November 29, 2004.

Midgette WH. Medical device risk management principles and practices. ASQ Biomedical Division Medical Device Risk Management Meeting, Boston, MA, December 4, 2004.

Midgette WH. Case studies in medical device risk management. ASQ Biomedical Division Risk Management Meeting, Ft. Lauderdale, FL, April 4, 2005.

Midgette WH. An FDA perspective on medical device risk management. AAMI Risk Management for Medical Device Manufacturers Course, Washington, DC, May 2-4, 2005.

Midgette WH. A perspective on medical device risk management. Heart Rhythm Society Policy Conference, Washington, DC, September 16, 2005.

Midgette WH. Medical device risk management and quality systems. AAMI Integration of Risk Management into the Quality System Course, San Francisco, CA, November 6-9, 2005.

Miller SA, Coelho SG, Zmudzka BZ, Bushar HF, Beer JZ. Recommended exposure schedules for indoor tanning: explorations to improve current FDA guidance. 11th Annual FDA Science Forum, Washington DC, April 2005.

Miller SA, Zmudzka BZ, Coelho S, Beer JZ. Comparison of different UV exposure regimens for cosmetic tanning. 66th Annual Meeting of the Society for Investigative Dermatology, St. Louis, MO, May 4-7, 2005.

Myers KJ. Image acquisition issues in quantitation tasks. Sixth Annual Forum on Biomedical Imaging in Oncology, Bethesda, MD, April 2005. *(Invited presentation)*

Myers KJ, Badano A, Gagne RM, Gallas BD, Kyprianou IS. Non-Fourier concepts in image quality. 47th Annual Meeting of the American Association of Physicists in Medicine, Seattle WA, July 27, 2005. *(Invited presentation)*

Myers KJ. Task-based assessment of imaging systems: background and current activities at the NIBIB/CDRH Laboratory for the Assessment of Medical Imaging Systems. Department of Radiology, Johns Hopkins Medical Institutions, Baltimore, MD, November 1, 2005. *(Invited presentation)*

Myers KJ. Unique issues in the assessment of medical imaging systems. Staff College Lecture Series on Statistics for Diagnostic Devices, Rockville, MD, November 21, 2005.

O'Hara MD. Science Prioritization Oversight Committee lecture: The relative biological effectiveness of low energy X-rays on MCF-7 breast cancer cells. Rockville, MD, March 21, 2005.

O'Hara MD. Lecture to the Radiation Oncology Residents at Thomas Jefferson University: Acute Radiation Syndromes, April 14, 2005.

O'Hara MD. Division of Biology Payday Seminar: A new review for an old radiobiology concept: relative biological effectiveness, May 31, 2005.

O'Hara MD. Science Prioritization Process lecture: Sensitization to thermoradiotherapy in human melanoma xenografts, Rockville, MD, October 25, 2005.

O'Hara MD, Desta AB, Cox AB. Science Prioritization Process lecture: The relative biological effectiveness of low energy x-rays for tumor treatment, October 25, 2005.

Petrick N, Wagner RF, Myers KJ. The FDA experience with LIDC: assessment of software tools in CT and image databases. Lung Cancer Workshop sponsored by the Cancer Research and Prevention Foundation, Annapolis, MD, April 28-29, 2005. *(Invited Presentation)*

Petrick N, Haider M, Summers RM, Iuliano E, Brown L, Pickhardt P. An observer performance study: computed tomographic colonography and computer-aided detection as a second reader. Annual Meeting of the Radiological Society of North America, Chicago IL, November 28-December 1, 2005.

Pritchard WF. FDA regulation of medical devices: bench to bedside to market. (Invited). Annual NIBIB Grantees Meeting/Workshop on Entrepreneurship, Washington, DC, August 8-9, 2005.

Quinn JB, Regnault WF, Antonucci JM, Skrtic D. Fractographic analysis of amorphous calcium phosphate/urethane composites. 83rd General Session of the International Association for Dental Research, Baltimore, MD, March 9-12, 2005.

Regnault WF, Antonucci JM, Skrtic D, Quinn JB. Environmental effects on the mechanical strength of amorphous calcium phosphate polymeric composites. 83rd General Session of the International Association for Dental Research, Baltimore, MD, USA, March 9-12, 2005.

Regnault WF. A workshop on evaluating AIMDS reliability: Measurement methods for evaluation of active implantable medical devices. Joint FDA/NIST Workshop, Gaithersburg, MD, October 3-4, 2005.

Rinaldi JE, Chen E, Berman MR. Pediatric circulatory support: An FDA perspective. The First International Conference on Pediatric Mechanical Circulatory Support Systems and Pediatric Cardiopulmonary Perfusion in Hershey, PA, May 21, 2005.

Robinson RA, Ilev IK. Fiber optic coupling methods for high peak-power laser delivery. 2005 SPIE Conference, San Jose, CA, January 2005.

Samuelson FW,Wagner RF. Comparison of parametric and nonparametric approaches to MRMC confidence intervals. MIPS XI, Medical Imaging Perception Society, Bowness on Windermere, United Kingdom, September 27-30, 2005.

Saylor DM. Materials science aspects of controlled drug delivery systems. FDA Science Forum, Washington, DC, April 27-28, 2005.

Saylor DM, Warren J, Wanner T. Pattern classification in controlled drug delivery systems. SIAM Conference on Applications of Dynamical Systems, Snowbird, UT, May 2005.

Saylor DM, Warren J, T. Wanner T. Structure evolution and release behavior in controlled drug delivery systems. Materials Science and Technology, Pittsburgh, PA, Sept. 2005.

Sergeev NV, Nandanie AD, Volokhov D, Jacobson A, Ranamukhaarachchi D. Oligonucleotide microarray based detection of bacterial pathogens relevant to food and reused medical devices. 11th Annual FDA Science Forum, April 27-28, 2005, Washington, DC.

Sergeev NV, Rasooly A. Comparison of whole genome amplification strategies for microarray-based analysis of bacterial pathogens. 11th Annual FDA Science Forum, April 27-28, 2005, Washington, DC, April 27-28, 2005.

Seidman S, Larrow J. Experimental wireless testing. 1073 Wireless EMC Task Group, FDA, Rockville, MD, March 22, 2005.

Shope TB. FDA activities to reduce risk from radiology. Annual Conference of the American College of Medical Physics, Orlando, FL, May 24, 2005.

Shope TB. Operator privileging for use of fluoroscopic equipment: FDA perspective. Melvin P. Judkins Cardiac Imaging Symposium, Society for Cardiovascular Angiography and Interventions, Pomte Vedra Beach, FL, May 4, 2005.

Shope TB. What's new at the FDA/CDRH. Annual Mid-Atlantic Chapter Meeting of the American Association of Physicist in Medicine, Flintstone, MD, June 3-4, 2005.

Shope TB. Refocusing of the Radiological Health Program at the FDA and the 2005 Amendments to the Performance Standard for Diagnostic X-ray Systems. Annual Meeting of the American Association of Physicists in Medicine, Seattle, WA, July 27, 2005.

Silberberg JL for Witters DM. Wireless technology in and around medical devices: addressing electromagnetic compatibility (EMC) and data integrity. AAMI 2005 Conference and Expo, Tampa, FL, May 14-17, 2005.

Spees WS, Jones PL. Adding flight data recording technology to medical device systems. 12th International Conference on Biomedical Engineering, Singapore, Malaysia, December 7-10, 2005.

Takahashi K, Yamaguchi Y, Hoashi, T, Zmudzka BZ, Miller SA, Beer JZ, Hearing VJ. Effects of ultraviolet radiation on signaling proteins of the melanogenic system. 19th International Pigment Cell Conference, Reston, VA, September 2005.

Tang X, Baeva L, Morris SL, Langone JJ, Bockstahler LE. A universal DNA microarray for detection of gene sequence changes. 2005 FDA Forum, 2005 CHI "Biomarker Meeting," Philadelphia,PA, 2005.

Tang X, Baeva L, Morris S, Langone J, Bockstahler L. A universal DNA microarray for detection of gene sequence changes - applications to the detection of mycobacterium tuberculosis (MTB) mutant genes associated with antibiotic drug-resistance and of pathogens contaminating medical devices. 2005 FDA Science Forum, Washington, DC, April 27-28, 2005 (poster (J-38)).

Taylor AR. Medical device risk management - common myths and misconceptions. Irvine, CA, May 2, 2005.

Taylor AR. Cybersecurity in healthcare networks. AdvaMed Software Conference, Washington, DC, November 3, 2005.

Taylor AR, Henderson JA. The operating room of the future plug-and-play program: exploring regulatory issues and approaches to medical device integration (poster). Regulatory Affairs Professionals Society 2005 Annual Conference, Baltimore, MD, October 19, 2005.

Tirat-Gefen, Pimentel YGCG, Vince F. Design verification of multi-million gate ASICs. Brazilian Symposium on Conception of Integrated Circuits, Florianopolis, Brazil, September 2005.

Tomazic-Jezic VJ, Umbreit TH, Stratmeyer ME. Methods for evaluation of the immunotoxicological responses to nanoparticles in mice. FDA Science Forum, Washington, DC, April 27-28, 2005.

Wagner RF. Some issues for the problem of missing truth: past, present, and future. The International Society for Optical Engineering (SPIE), San Diego, CA, February 2005. *(Invited presentation)*

Wagner RF. An introduction to assessment methods for diagnostic tests, diagnostic imaging, and computer-assist modalities. FDA/CDRH Staff College Lecture, Rockville, MD, June 2, 2005. (Webcast available on http://www.cdrh.fda.gov/Staffcol/webcasts.htm)

Wagner RF. Selected topics in ROC analysis of contemporary interest at CDRH: plus--statistical decision theory and the ROC curve in medical imaging. FDA/CDRH Staff College Lecture, Rockville, MD, June 9, 2005. (Webcast available on http://www.cdrh.fda.gov/Staffcol/webcasts.htm)

Wear KA. Ultrasound and the diagnosis of osteoporosis. National Institute for Biomedical Imaging and Bioengineering, Bethesda, MD, June 8, 2005.

Weininger S. System validation. AdvaMed software conference. Washington, DC, November 23, 2005.

Weininger S, Shang A. Using the raw plethysmogram for assessing performance of pulse oximeters (poster). Society for Technology in Anesthesia, Miami, FL, January 12, 2005.

Weininger S, Shang A, Goldman J. Using the raw plethysmogram for assessing performance of pulse oximeters (poster). World Conference on Anesthesia, Paris, FRANCE, January 20, 2005.

Weininger S. Pulse oximetry – theory and challenges. NIST technical presentation, Gaithersburg, MD, May 2005.

Weininger S. Developing a plug and play standard - system validation issues. Third Meeting of the ORF PnP Standardization Program, Boston, MA, June 5-6, 2005.

Weininger S. Assessing the performance of pulse oximeters under conditions of motion. Labview User's Group meeting, Rockville, MD, September 14, 2005.

Wray-Cahen D. Differential cardiovascular effects of stress or medical device residues in a large animal model. White Oak Reseach Seminar, Silver Spring, MD, October 13, 2005.

Wood SC, Bushar G, Tesfamariam B. Mechanistic insights into stent-mediated thrombosis and adverse events by stent-delivered drugs sirolimus and taxol. (Posters) 2005 FDA Science Forum, Washington, DC, April 27-28, 2005.

Wood SC, Brown RP, Chen J, Gordon EA, Harris GR, Hitchins VM, Maruvada S, Mtungwa AR, Stratmeyer ME. Bioeffects of ultrasound and ultrasound microcontrast agent on three mammalian cell lines. Seminar, Division of Biology/OSEL, White Oak, Silver Spring, MD, July 2005.

Woods TO. Fatigue testing of PMMA bone cement using ASTM F2118. ElectroForce Technology: Testing Biomedical Materials and Devices, Baltimore, MD, September 27, 2005.

Woods TO. Standards for MR safety: testing, terminology, and the FDA role. (Invited). ECRI Audio Conference on MRI Safety and Medical Devices, September 21, 2005.

Woods TO. ASTM standards for MRI: present and future," (Invited). ISMRM Workshop on MRI Safety: Update, Practical Information, Future Implications, McLean, VA, November 6, 2005.

Woods TO. Standards for MR safety: current status and future directions. (Invited) RSNA Refresher Course: Optimize Your Body MR Practice – From Safety to Protocol Design: MR Imaging Safety for Implants and Devices, RSNA 91st Scientific Assembly and Annual Meeting, Chicago, IL, November 27, 2005.

Wu D, Qiang R, Chen J, Kainz W, Seidman S. Safety evaluation of walk-through metal detectors. International Symposium on Electromagnetic Compatibility 2005, Chicago, IL, August 8-12, 2005.

Yamaguchi Y, Takahashi K, Zmudzka BZ, Kornhauser A, Miller SA, Tadokoro T, Berens W, Itamid S, Katayama I, Beer JZ, Hearing V. Pigment in the upper epidermis protects against DNA damage in the lower epidermis and facilitates apoptosis in response to low doses of UV. 66th Annual Meeting of the Society for Investigative Dermatology, St. Louis, MO, May 4-7, 2005.

Yamaguchi Y, Takashi K, Tadokoro T, Zmudzka BZ, KornhauserA, Miller SA, Berens W, Beer JZ, Hearing VJ. Human skin responses to UV radiation: pigment in the upper epidermis protects against dna damage in the lower epidermis and facilitates apoptosis. 19th International Pigment Cell Conference, Reston, VA, September 2005.

Yousef WA, Wagner RF, Loew MH. Performance assessment of classifiers or model observers trained and tested on finite samples: estimation of mean and variance of area and partial area under the ROC. MIPS XI, Medical Imaging Perception Society, Bowness on Windermere, United Kingdom, September 27-30, 2005.

Yousef WA, Wagner RF, Loew MH. Comparison of nonparametric methods for assessing classifier performance in terms of ROC parameters. Virginia Polytechnic Institute, Alexandria, VA, December 9, 2005.

Yousef WA, Wagner RF, Loew MH. Estimating the uncertainty in the estimated mean area under the ROC curve of a multi-feature classifier. 2005 FDA Science Forum, Washington, DC, April 27-28, 2005 (poster).

APPENDIX C – OSEL Academic Affiliations

January 1, 2005 – December 31, 2005

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 Department of Biological Resources Engineering Lecturer George Washington University Department of Electrical and Computer Engineering Adjunct Professor
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
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
Pollack, Steven, Ph.D.	University of Maryland, College Park College of Chemical and Life Sciences Department of Chemistry and Biochemistry Adjunct Professor
Avraham Rasooly, Ph. D.	Program Director, Cancer Diagnosis Program National Cancer Institute National Institutes of Health
Pfefer, T. Josh, Ph.D.	Rice University Department of Bioengineering Doctoral thesis committee
Valentine, Karen D.	Montgomery College Department of Continuing Education Instructor/lecturer
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

APPENDIX D – OSEL Patents

January 1, 2005 – September 30, 2005

Ilev IK, Robinson RA, Waynant R. All-hollow taper-waveguide high power laser delivery system for illumination for digital particle image velocimetry. Filing date: October 28, 2005.

Sliwa J, Robinson RA , Hariharan P, et al. Optical techniques for the non-invasive 3-d characterization of ultrasound beams. Filing date: December 21, 2005.

APPENDIX E – OSEL-Sponsored Seminars

January 1, 2005 – December 31, 2005

Duncan Maitland, Ph.D. Medical Technology Program Leader, Lawrence Livermore National Laboratory. Laser-activated shape memory polymer microsctuators for neurovascular intervention. FDA/CDRH, Rockville, MD, March 10, 2005.

CDRH Staff College. Accessing toxicological information. Rockville, MD, May 4, 2005 and October 17, 2005.

CDRH Staff College. Risk assessment for compounds released from medical devices. September-October 2005.

Bakic P. 3D anthropomorphic deformable software breast phantom: development and applications. University of Pennsylvania, June 23, 2005.

Bitter I. XP: eXtreme Programming. NIH Clinical Center, National Institutes of Health, March 17, 2005.

Dodge GR. Bioengineered Cartilage tissue equivalents and imaging methods to assess cartilage characteristics. A.I. duPont Hospital for Children, Wilmington, DE, March 3, 2005.

Hanson K. Improved predictive sampling using quasi-Monte Carlo with application to neutron-cross-section evaluation. Los Alamos National Laboratory, April 14, 2005.

He X. Three-class ROC Analysis. Division of Medical Physics, Johns Hopkins Medical Institutions, October 6, 2005.

Kinnard LM. Segmentation of dense breast masses on digitized mammograms. ISIS Center, Georgetown University, September 8, 2005.

Kundel HL (Professor Emeritus of Radiology). Substituting reliability for accuracy in image technology assessment. University of Pennsylvania, February 2, 2005.

Liang H. Studies of ferroelectric domain imaging using near-field optical microscopy and transient photoconductivity in conjugated polymers. University of Maryland College Park, April 21, 2005.

Liao G. Termotropic liquid crystalline properties of amphotropic branched glycolipids. Liquid Crystal Institute, Kent State University, April 26, 2005.

Mienko M. Tiled photoluminescent liquid crystal displays using LED illumination. Cambridge University, April 19, 2005.

Rajapakse C. Modeling of trabecular networks using digitized images. University of Houston, July 8, 2005.

Tsui BMW. Medical image assessment using simulation techniques. Division of Medical Physics Johns Hopkins University, August 4, 2005.

Wong KH. Evaluation of respiratory motion compensation methods for radiosurgery. ISIS Center, Georgetown University, October 20, 2005.

Zou J. Super fast fourier transform. Center for Scientific Computation and Mathematical Modeling, University of Maryland at College Park, September 15, 2005.

APPENDIX F – Interagency Agreements

FY 2005 Reimbursable IAG's

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

Defense Advanced Research Projects Agency (DARPA) (IAG #224-05-6016). Assistance in test bed development for deep bleeder acoustic coagulation program.

Defense Advanced Research Projects Agency (DARPA) (IAG #224-05-6009). Collaboration on innovative medical technology

U.S. Army Research Office (DOD) (IAG #224-05-6015). Joint funding of medical device software static and dynamic analysis tool development.

Environmental Protection Agency (EPA) (IAG #224-00-6062). Understanding and applying mode of action data for single and multiple agents in developmental toxicity risk assessments.

National Cancer Institute (NCI) (IAG #224-04-6058). Assessment of Computer-Aided Diagnostics.

National Institute for Biomedical Imaging and Bioengineering (NIBIB) (IAG #224-04-6055). Joint NIBIB/CDRH laboratory for the assessment of medical imaging system.

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

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

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

FY 2005 Service IAG's

Armed Forces Institute of Pathology (AFIP) IAG #224-82-5000). Collaborative Research and testing of medical implants

National Institutes of Health/National Cancer Institute (NIH/NCI) (IAG #224-04-6053). Roles and responsibilities for Avraham Rasooly, Ph.D.

National Institute of Standards and Technology (NIST) (IAG #224-05-6012). Measurements methods for evaluation of the reliability of active implantable medical devices

National Institute of Standards and Technology (NIST) (IAG #224-04-6062). Ionization Chamber Calibrations and Proficiency Testing

National Institute of Standards and Technology (NIST) (IAG #224-05-6006). Accreditation fees for the CDRH x-ray Calibration Laboratory (Code 105018-0)

Uniformed Services University of Health Sciences (USUHS) (IAG #224-98-6015). Maintenance of an animal model of the pathophysiology of diabetes for end organ host response studies

Uniformed Services University of Health Sciences (USUHS) (IAG #224-04-6064). Ethical and Psychiatric Aspects of Guidance Document for Manufacturers' Submission for Electroconvulsive Therapy Device Applications

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. (301.827.4876) or joyce.whang@fda.hhs.gov*
Experimental Pathology: *Steve Hilbert, MD (301.827.4756) or stephen.hilbert@fda.hhs.gov*

Division of Electrical and Software Engineering

Software: *Joseph Jorgens (301.443.5020 ext. 136) or joseph.jorgens@fda.hhs.gov*
Electrical Engineering: *TBD - contact Al Taylor, Director DESE (301.442.2536 ext. 147) or alford.taylor@fda.hhs.gov*
System Engineering: *TBD - contact Al Taylor, Director DESE (301.442.2536 ext. 147) or alford.taylor@fda.hhs.gov*

Division of Imaging and Applied Mathematics

Medical Imaging and Diagnostics: *Kyle Myers, Ph.D. (301.443.5020 ext. 150) or kyle.myers@fda.hhs.gov*

Ionizing Radiation Metrology: *Frank Cerra (301.443.2536 ext. 123) or frank.cerra@fda.hhs.gov*

Division of Physics

Electro-physiology and Electrical Stimulation: *Victor Krauthamer, Ph.D. (301.827.4956) or victor.krauthamer@fda.hhs.gov*
Electromagnetic and Wireless Technology: *Howard Bassen (301.827.4950) or howard.bassen@fda.hhs.gov*
Optical Diagnostics and Therapeutics: *Joshua Pfefer, Ph.D. (301.827.4679) or joshua.pfefer@fda.hhs.gov*
Optical Radiation Safety and Devices: *Sharon Miller (301.827.4692) or sharon.miller1@fda.hhs.gov*

Division of Solid and Fluid Mechanics

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Mechanics: *Stan Brown, PhD (301.827.4751) or stanley.brown@fda.hhs.gov*
Ultrasonics: *Gerald Harris, PhD (301.827.5616) or gerald.harris@fda.hhs.gov*

OFFICE OF SCIENCE AND ENGINEERING LABORATORIES

as of 2/1/06