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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 CDRH, contributes to the Center's mission by providing laboratory data and consults. 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 assessment.

From a science standpoint, OSEL conducts laboratory and field research in the areas of physical, life, and engineering sciences as related to the effects of medical devices on human health. 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.

OSEL long-term goals:

- 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.

OSEL completed the geographic consolidation of its six laboratory-based divisions (as part of the FDA campus consolidation) to Silver Spring, Maryland, in early 2007. Additionally, OSEL management concluded the Science Prioritization Process (SPP) in 2007. The SSP was created and designed to identify, evaluate, and prioritize existing and/or proposed research projects. The projects must directly address the high-priority review and regulatory needs of the Center and Agency.

The OSEL Annual Report provides current information about the Office's organization and intramural science activities; provides a summary of the Office's direct laboratory

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

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

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

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REGULATORY SUPPORT ACTIVITIES

Research conducted in the Office of Science and Engineering Laboratories supports the regulatory activities of the Agency, primarily as follows:

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

Both activities are coordinated within OSEL in an effective manner so as to best meet the Center's regulatory science needs. Laboratory research is the cornerstone upon which the Office provides the regulatory support function. (The research is described in subsequent sections.) It is largely based on investigations related to the mechanistic understanding of device performance or test procedures to enable the Center and device manufacturers to gain an improved understanding of issues related to safety and efficacy. In general, although the research is directed toward issues identified at the *pre-market* approval level, the reality is that the research has the largest 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 supporting 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. Consults provide information which contribute to sound regulatory decisions. They may be based on acknowledged scientific/engineering principles or on independent data generated in OSEL laboratories.

The following provides a consolidated picture of the breadth of OSEL consults in 2007:

Number of consults to pre-market issues:	**1494**
Number of consults to post-market issues:	**257**
Number of activities related to standards	**405**

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

- evaluate a pre-market submission (IDE, HDE, PMA, 510(k));
- support a compliance action (regulatory case support/development, Health Hazard Evaluation, Health Risk Assessments, etc.);

- assist a scientific collaboration;
- answer a consumer inquiry;
- provide opinions on guidance documents;
- provide revisions to one pagers for the new device approval page; and
- assist health hazard evaluation/health risk assessments or in device determinations/classifications.

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

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

Developing standards and measurements are also significant products of this office. OSEL continues to provide innovative solutions to public health problems by constructing generic techniques that lead to the creation of national and international standards that will enhance product safety and effectiveness. OSEL staff actively participate in developing standards at the national and international levels by performing research to establish standard procedures and by managing, developing, and supporting standards used for regulatory assessments.

Office of Science and Engineering Laboratories 2007 Highlights

Active Materials (Division of Chemistry and Materials Science)

Nanoparticles

Approximately 18 months ago, the Division of Chemistry and Materials Science began a study of the behavior of silver nanoparticles. This was driven both by the appearance of these materials in recently approved medical devices as well as the growing awareness of the need to better understand nanotechnology in general as it applies to medical devices. Scientists in the Division of Chemistry and Materials Science devised a two-pronged approach, using both experimental and computational approaches to access the ability of silver nanoparticles to act as a source of silver ions, a biocidal agent. To accomplish the experimental work, infrastructure was developed to prepare silver nanoparticles in-house so as to have full control of their surface chemistry. An analytical model was developed to account for the electrochemical processes responsible for the dissolution of the silver nanoparticles.

One of the early outcomes of this work has been the realization that the release rate of silver from the nanoparticles is strongly affected by the substrates they are deposited on. Initial theoretical work indicates that nanoparticles above a diameter of 20nm behave in a predictable manner, but below this size silver ions release at a much accelerated rate. Both findings have impact of efficacy and safety. In addition to impacting new devices employing silver nanotechnology, the National Toxicology Program will use initial data and study protocols developed by DCMS and the Division of Biology to define their research directions.

Biological Risk Assessment (Division of Biology)

The Department of Defense (DOD) awarded a grant to the Air Force Research Laboratories (AFRL) in partnership with the Food and Drug Administration (FDA) Centers for Devices and Radiological Health (CDRH) and Biologics Evaluation and Research (CBER); Center for Disease Control (CDC)- National Institute of Occupational Safety and Health (NIOSH); University of Florida (UF); North Carolina State University (NC State U) and University of Nebraska (NU). The specific aim of this project is to develop strategies for reusing single-use, disposable respirators in the event of a shortage.

The technical effort expended on this project provides a comprehensive approach to address the goal of developing and validating methods for decontaminating respirators. It is not certain that all of the decontamination technologies will be effective; but the strategy of trying many technologies attenuates the overall risk of failure, and the effort will validate some effective protocols. If many protocols are validated, first responders may select those protocols that best fit their needs. As a necessary condition to validating biological decontamination protocols, this effort will first develop and validate a standard biological aerosol test method (BATM). The BATM will both enable evaluation of the biological efficacy of decontamination technologies for this effort and provide a standard method to evaluate other antimicrobial/bio-decontamination methods. The BATM here focuses on viruses, but can readily be adapted to test with spores and vegetative bacteria. This work will result in the optimization and validation of some effective protocols and technical information that will be provided to the appropriate standards subcommittee for issuance as a new standard.

Electromagnetic and Wireless Technologies (Division of Physics)

Electromagnetic interference emitted by iPods

Recently, malfunctioning of a cardiac pacemaker electromagnetic, caused by electromagnetic interference (EMI) by fields emitted by personal portable music players (iPods) was highly publicized around the world. A clinical study of one patient was performed by a group not associated with the FDA. Two types of interference were observed when clinicians placed a pacemaker programming head and an iPod adjacent to the patient's implanted pacemaker. The authors concluded that "Warning labels may be needed to avoid close contact between pacemakers and iPods." EMI experts in OSEL's Electromagnetics And Wireless Laboratory were highly skeptical of this report. OSEL performed an *in-vitro* study to evaluate these claims of EMI and presented the findings of "no-effects" in a paper submitted and accepted for publication in a peer-reviewed journal.

OSEL performed *in-vitro* evaluations of the low frequency magnetic field emissions from various models of the Apple, Inc. iPod music player. OSEL measured magnetic field emissions with a three-coil sensor (diameter of 3.5 cm) placed within 1 cm of the surface of the player. Highly localized fields were observed (only existing in a one-square cm area). OSEL also measured the voltages induced inside an "instrumented-can" pacemaker with two standard unipolar leads. Each iPod was placed in the air, 2.7 cm above the pacemaker case. The pacemaker case and leads were placed in a saline-filled torso simulator per pacemaker electromagnetic compatibility standard ANSI/AAMI PC69:2000. Voltages inside the can were measured. Emissions were strongest ($\approx 0.2\ \mu T$ pp) near a few localized points on the cases of the two iPods with hard drives. Emissions consisted of 100 kHz sinusoidal signal with lower frequency (20 msec wide) pulsed amplitude modulation. Voltages induced in the iPods were below the noise level of

laboratory instruments (0.5 mV pp in the 0 – 1 kHz band or 2 mV pp in the 0 – 5 MHz bandwidth.

Laboratory measurements of the magnitude and the spatial distribution of low frequency magnetic flux density emissions by four different models of iPod portable music players. Levels of less than 0.2 μT exist very close (1 cm) from the case. The measured voltages induced inside an "instrumented-can" pacemaker were below the noise level of our instruments. Based on the observations of our *in-vitro* study we concluded that no interference effects can occur in pacemakers exposed to the iPod devices OSEL tested. A recent clinical study of a group of pacemaker patients was performed and confirmed that no effects on the proper performance of pacemakers could be induced by iPod music players.

Electrophysiology and Electrical Stimulation (Division of Physics)

Preclinical and clinical endpoints for cochlear implant safety
Safety testing of electrical stimulation from cochlear implants has been streamlined in order to get new stimulation paradigms implemented quickly. The streamlined safety criteria have both preclinical and clinical components. The preclinical electrical stimulation parameters are for electrode charge density (<100 micro-coulomb/square cm) and net DC (<1 micro-amp). When new stimulation paradigms are proposed in IDEs, the clinical testing endpoints are for stability in electrical threshold for auditory perception, maximum comfortable listening level, dynamic range, and electrode impedance. These streamlined clinical endpoints were validated with long-term, post-approval studies. One recent example of the application of the streamlined clinical testing was for the implementation of high frequency stimulation, which better matches the sound envelope. The stimulation parameters met the basic charge density and DC criteria, but little was known about the safety of high frequency. The streamlined clinical testing of these devices was consistent with safety. After approval on this basis, there have been no reports of stimulation-related safety problems in properly functioning cochlear implants. This success came about through collaborative efforts between OSEL's Division of Physics and ENT Branch of the Office of Device Evaluation.

Electromagnetic and Wireless Technologies (Division of Physics)

Electromagnetic compatibility (EMC) and radio frequency identification (RFID):
The OSEL Division of Physics has a long history of discovering electromagnetic (EM) sources that interfere with medical devices, and RFID is no exception. RFID is an automatic identification method that can read a tag from several meters away and does not require line of sight as barcodes do. To achieve this, an RFID reader transmits radio frequency (RF) energy to a tag. This tag then uses RF energy to respond with its unique

identifying information. FDA is promoting RFID technology to track and trace drugs through the supply chain to help mitigate counterfeit drugs.

A study was performed to test the effects RFID readers had on pacemakers and implantable cardiac defibrillators (ICDs). Collaborating with industry through AAMI standards, scientists in the Division of Physics adapted test methods to evaluate the EMC between pacemakers/ICDs and RFID readers. A total of 18 pacemakers and 19 ICDs from 5 of the leading pacemaker and ICD manufacturers were tested for immunity of RF emissions generated by 7 RFID readers. Reactions of the pacemakers and ICDs ranged from non-clinically significant events to the potentially harmful inappropriate tachyarrhythmia detection and delivery of therapy or complete inhibition of cardiac pacing. The research conducted is entirely proactive. There have been no incident reports of pacemakers or ICDs being adversely affected by RFID to this date.

The information collected in the aforementioned study has been documented and analyzed by FDA and industry and will be used to better current EMC standards for pacemakers and ICDs. These standards assist CDRH reviewers in pre-market determinations of devices. In addition, the information and experiences collected on RFID technology will assist CDRH in determining pre-market approval of RFID medical devices such as sponge counting systems and the human implanted VeriChip.

Fluid Dynamics (Division of Solid and Fluid Mechanics)

Evaluating the Use of In-Vitro Bench and Computational Techniques for Improving Cardiovascular Regulatory Decisions

This year OSEL scientists proposed a research project titled "Standardization of Computational Fluid Dynamic (CFD) Techniques used to Evaluate Performance and Blood Damage Safety in Medical Devices" that successfully competed for funding as a Critical Path Initiative project. This co-operative effort between FDA and several academic laboratories will refine the details of using computational techniques to model blood flow through medical devices to enable device manufacturers to optimize their designs to minimize damage to patients' blood exposed to such devices; this reduces the need for time consuming and expensive animal experiments. This multi-year project has two phases. The first phase compares independently derived results on an idealized model flow path. The second phase applies these techniques to a more realistic ventricular assist device flow path.

The core group of the FDA laboratory and three university laboratories has designed and built an initial physical device model, have implemented first pass computer simulations, and have measured flow patterns through the model. A web site for enrolling perhaps a few dozen additional university participants and for sharing data among the collaborators should go live in early 2008. The primary goal of the project is to develop information

necessary for a guidance document on proper validation of computational flow modeling of medical devices, which will include mesh design and refinement, model verification, and parameter sensitivity testing.

Imaging Analysis (Division of Imaging and Applied Mathematics)

Full Field Digital Mammography Guidance Development
Digital mammography came to the Center's attention in the early 1990s. At that time the clinical impact of the new technology was unknown. Attempts to clear this device through the pre-market notification path, known as a 510(k), failed due to significant variability in reader performance. Since then about five systems have been approved for marketing through the PMA process. During the intervening years many papers have been published on digital mammography, and our knowledge of these devices has improved to the point where PMAs are no longer necessary to assure safety and effectiveness. This view was ratified by a May 2006 Radiological Devices panel meeting, and a project to reclassify digital mammography devices to class 2 was initiated at that time. To accomplish this, a working group drawn from the Center's Office of Device Evaluation, Office of Communication, Education, and Radiation Programs, and Office of Science and Engineering Laboratories was formed. The group moved swiftly to draft a special control guidance for Digital Mammography devices, a 510(k) guidance for Digital Mammography Accessories, a notice of availability, and a proposed rulemaking document.

OSEL research played a unique role in the path to this reclassification action. Research performed in the Division of Imaging and Applied Mathematics has contributed significantly to the professional consensus in the imaging community regarding the appropriate physical measurements necessary to characterize the technical efficacy of digital x-ray detectors. The expertise accumulated over years of investigation on full-field digital detectors and x-ray imaging physics enabled OSEL scientists to take the lead in developing clear technical requirements and measurement methods to assure the safety and efficacy of new digital mammographic systems.

Imaging Diagnostics (Division of Imaging and Applied Mathematics)

Bone sonomety reclassification
OSEL has played a lead role in efforts to reclassify bone sonometry, which is an ultrasound-based technology for screening for osteoporosis. Reclassification from class 3 to class 2 will greatly decrease the regulatory burden for manufacturers. The reclassification will be accompanied by the publication of a special controls guidance document, which will provide manufacturers with explicit recommended protocols for establishing safety and efficacy of bone sonometers. The development of this guidance

has been facilitated by years of laboratory bench work and clinical trials conducted within OSEL, which have enabled OSEL scientists to test basic measurement procedures before recommending them to manufacturers. We expect this reclassification to result in 1) new devices getting to market more quickly and 2) an increase of access to new diagnostic devices for those at risk for osteoporosis.

Software Forensics (Division of Electrical and Software Engineering)

Explaining software forensics

Forensic is an adjective, relating to or dealing with the application of scientific knowledge to legal problems. A *forensic laboratory* is one devoted to the application of science in the investigation of crimes or other legal matters. The focus is on understanding the root cause of software failures in medical devices with an eye toward public health protection. It is remotely possible that our findings might lead to a criminal prosecution; it is far more likely, however, that our efforts will lead to a voluntary recall or other regulatory remedy. In some cases, our investigations have eliminated the software as the "culprit" in an adverse event.

All CDRH research laboratories, including the software laboratory, have conducted these kinds of forensic investigations for many years. In the past, when a software defect was suspected in an adverse event, and the manufacturer would not or could not confirm the root cause of the failure, CDRH engineers would audit the software design by hand--a laborious and difficult process. But this was not the main focus of the laboratory. Our principal interest was --- and remains --- developing analytical methods and tools for assuring the safety and security of software. In other words, the ultimate objective of the research is to enable software developers to “get it right” the first time. As we have worked with academic researchers toward this goal, we gradually realized that some of the software development tools we were studying could be applied in forensic investigations to speed up the analysis of suspect software and detect latent design errors. Our first attempts to use these software design tools in a forensic investigation were highly successful. This early success led to a structured effort to develop a software forensic capability.

Limitations in assessing software problems

Computers keep growing exponentially in terms of processing power and memory capacity per unit cost. As a consequence, medical device software is becoming more complex with each passing year. For many medical devices, software now determines much of the product's functionality and performance. We routinely see medical devices containing more than 100,000 lines of code. In addition, there are devices exchanging data over computer networks and being controlled by software running on another computer. The management of complexity is a huge challenge for medical device designers and regulators alike.

With many early software-controlled medical devices, it was reasonable to rely on a clinician to intervene before a software error caused harm. As computers have become more powerful, many health care protocols have been automated to the point that competent medical intervention is no longer viable as a control measure. The combination of increased complexity and decreased user oversight can be deadly.

Collaborations and partnerships

We have on-going research collaborations with several software experts and agencies. As it happens, our software laboratory is at the forefront when it comes to investigating the performance of embedded software. The FBI, for example, devotes a lot of effort to detecting accounting fraud, pornography, cybersecurity threats, and online terrorism activities; but embedded software is simply not high on their list of "bad guys." NASA and the Department of Defense (DoD), by contrast, have a great deal of interest in embedded software and, like FDA, are focusing primarily on defect prevention. We are participating in an interagency committee, led by the National Science Foundation, devoted to coordinating Federal research efforts in this area.

Continued growth of the software forensics laboratory and relevance to post-market issues

Our forensic capability is still in the early stages of development. We are evaluating a number of commercially available tools and some that are still the subject of academic research. Each tool has different strengths and weaknesses with respect to finding various kinds of design defects. We expect to publish some of our findings when we have gained a little more experience.

Given the current state of the art, the tools are still very expensive and require highly skilled analysts to use them successfully. Most of them produce a fairly lengthy list of questionable situations, which then need to be reviewed manually. In one recent case, analysis of 100,000 lines of code identified about 180 questionable constructs. Only two of those turned out to be real design issues. Nevertheless, those 180 areas of interest represented only a tiny fraction of the total body of code, so you can see how effective the tools were in zeroing in on the problems. Additionally, many of the 180 red flags were examples of poor coding practice, so the manufacturer gained a great deal of insight into ways to increase their defensive posture by utilizing more robust coding practices in the future.

We do not expect to reach the point where we would use these tools routinely in either pre-marketor post-marketsituations. Only cases that present an imminent public health threat warrant the level of effort required to do the analysis. Over the long term, we believe that these tools will progress to the point that they will routinely be used by software developers.

"High-profile" cases

The Software Forensics Laboratory has exposed several software design errors that were linked to adverse events, and at least one latent error that had the potential to cause an injury. Each of these cases resulted in appropriate corrective actions. In two other cases, the software received a clean bill of health.

Manufacturer implementation

Some of these tools are being employed in other industry sectors, notably in mission-critical applications like automotive control systems and aeronautics. We are aware of a few medical device companies that have begun to apply the tools and analytical methods. In an ideal world, some of these early adopters might "report out" their experience in the medical device trade press. Unfortunately, we believe that those who have traversed the learning curve may view this as a competitive advantage and thus be reluctant to share their experience.

Solid Mechanics (Division of Solid and Fluid Mechanics)

Fatigue Testing of PMMA Bone Cement

PMMA (polymethyl methacrylate) bone cement continues to be an essential material in joint replacement surgery to fix metal and plastic prosthetic devices to living bone. In recent years, surgeons have begun using PMMA bone cement (also referred to as acrylic bone cement) to treat pathological fracture including osteoporotic vertebral body compression fractures (VBCFs) in two new applications (vertebroplasty, and kyphoplasty). Although fatigue failure has been identified as a clinical failure mode, no standard fatigue test method existed until very recently. The lack of a reliable standard test method makes comparison of fatigue results from different regulatory submissions and in the published literature difficult or impossible and keeps open the possibility that an inappropriate formulation could be used clinically.

Standards groups have been working for many years to develop standard fatigue test methods for acrylic bone cement. ASTM International recently published a standard test method for fatigue testing of acrylic bone cement, F2118, and the Material Test Methods subcommittee conducted round robin testing to establish precision and bias data for this method. OSEL engineers participated in the round robin testing. The first round of testing showed large variations between laboratories and within some laboratories. The participants identified some areas in which the test method could be improved. In particular, we determined that the sample preparation procedure needs to be investigated and specified more precisely in the standard. We have begun a study to systematically investigate the effects of specimen fabrication techniques on the mechanical properties and fatigue life of acrylic bone cement. The data on the effects of specimen fabrication techniques will allow us to define an optimal method of sample preparation that can be included in a revision to F2118.

Ultrasonics (Division of Solid and Fluid Mechanics)

Development and Characterization of a Blood Mimicking Fluid for High Intensity Focused Ultrasound

A blood-mimicking fluid (BMF) has been developed for the acoustic and thermal characterization of high intensity focused ultrasound (HIFU) ablation devices. This fluid, when combined with the tissue-mimicking material previously developed here, can be incorporated into instrumented test phantoms to allow meaningful evaluations of new HIFU devices and indications involving or affected by flowing blood. The BMF is based on a degassed and de-ionized water solution dispersed with low-density polyethylene micro-spheres, nylon particles, gellan gum and glycerol. A broad range of physical parameters, including attenuation coefficient, speed of sound, acoustical impedance, viscosity and thermal conductivity and diffusivity were characterized as a function of temperature (20 ºC to 70 ºC). The nonlinear parameter B/A and backscatter coefficient were also measured at room temperature. Importantly, the attenuation coefficient is linearly proportional to the frequency (2 MHz – 8 MHz) with a slope of about 0.2 dB/cm-MHz in the 20 ºC to 70 ºC range as in the case of human blood. Furthermore, sound speed and blood-like backscattering also indicate the usefulness of the BMF for ultrasound flow imaging and ultrasound-guided HIFU applications. Most of the other temperature-dependent physical parameters are also close to the reported values in human blood. These properties, along with the ability to withstand temperature increases above 70 ºC without significant damage, make it a unique HIFU research tool. This reusable, nontoxic BMF is appropriate for developing standardized exposimetry techniques, validating numerical models, and determining the safety and efficacy of HIFU ablation devices.

DIVISION DESCRIPTIONS

DIVISION OF BIOLOGY (DB)

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

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

Laboratories

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

DIVISION OF CHEMISTRY AND MATERIALS SCIENCES (DCMS)

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

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

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

Laboratories

- Active Materials
- Materials Performance

DIVISION OF ELECTRICAL AND SOFTWARE ENGINEERING (DESE)

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

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

Laboratories

- Electrical Engineering

- Software
- Systems Engineering

DIVISION OF IMAGING AND APPLIED MATHEMATICS (DIAM)

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

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

Laboratories

- Image Analysis
- Imaging 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 Therapeutic Devices
- Optical Therapeutics and Medical Nanophotonics

DIVISION OF SOLID AND FLUID MECHANICS (DSFM)

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

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

Laboratories

- Fluid Dynamics
- 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.

The MSS team collaborates with the Center and Agency Information Management offices in implementing major information technology 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.

Office of Science and Engineering Laboratories

Active Materials (Division of Chemistry and Materials Sciences)

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

Biological Risk Assessment (Division of Biology)

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

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

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

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

Biomolecular Mechanisms (Division of Biology)

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. Additionally, the Cell Biology Laboratory is investigating immunotoxicity related to particular patient susceptibility, in regards to biomaterials and devices that contact patient blood.

Biotechnology (Division of Biology)

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

Cardiovascular and Interventional Therapeutics (Division of Biology)

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, such as 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 identifying and assessing 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.

Electrical Engineering (Division of Electrical and Software Engineering)

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

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

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

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

Electromagnetic and Wireless Technologies (Division of Physics)

Research is focused on several concerns associated with medical devices that utilize or are affected by electromagnetic (EM) fields. The primary concern is to address the rapid deployment of wireless technology around and into medical devices, and to address the

safety and effectiveness issues associated with electromagnetic interference (EMI) disruption of medical devices and the deposition of the electromagnetic energy in the human body. Another concern is to develop methods to evaluate medical devices used for ablation of body tissues and the measurement and evaluation of EM heating and the evaluation of devices used intentionally to hear body tissues. A principle goal of this effort is to develop standard techniques for the measurement and evaluation of RF heating for both high and low frequency electromagnetic devices. A third area involves the safety of patients undergoing magnetic resonance imaging procedures. Patients with implanted devices, and electrodes or other devices attached to the body, are being imaged by MRI, and some are being injured or even killed due to heating from the intense EM fields produced by the radiofrequency (RF) coils during clinical imaging procedures. Medical device manufacturers are submitting requests for approval of their devices as MRI compatible, e.g., allowed to be in or attached to the patient during MR imaging procedures

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

Electrophysiology and Electrical Stimulation (Division of Physics)

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

devices. The scientific discipline of electrophysiology forms a unified basis for the scientific evaluation of all of these devices. The scientific issues involve the basic electrophysiology of a number of body systems and the biomedical engineering of the devices.

The work ranges from research directly applied to a single device type (the retinal stimulator), to broader work that is relevant to a class of devices (cardiac stimulators for treating arrhythmias and heart failure), to far-reaching work on the development of optical stimulation of excitable tissue (supported extramurally). In addition to these areas of research, this laboratory is heavily involved in direct regulatory activities with staff performing as lead reviewers, expert consultants, subject matter experts to FDA Advisory Panels, authors of guidance documents and the revision of international medical device standards.

Fluid Dynamics (Division of Solid and Fluid Mechanics)

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.

Image Analysis (Division of Imaging and Applied Mathematics)

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

computer-aided diagnosis, and gene expression. This program is located within the Division of Imaging and Applied Mathematics (DIAM).

Imaging Diagnostics ((Division of Imaging and Applied Mathematics)

A wide variety of new advanced imaging systems with solid state detectors and digital display devices are under development by academia and industry, with a broad range of performance characteristics. To support the Center's need for assistance evaluating such devices, OSEL scientists are developing evaluation methodologies for diagnostic medical imaging systems such as mammography and fluoroscopy, computed tomography, nuclear medicine, diagnostic ultrasound, and magnetic resonance imaging, as well as for novel soft-copy display devices for viewing medical images. This program is located within the Division of Imaging and Applied Mathematics (DIAM).

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

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.

Materials Performance (Division of Chemistry and Materials Sciences)

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

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

Optical Diagnostics (Division of Physics)

The rapid proliferation of medical devices employing minimally invasive optical technology is revolutionizing modern health care. However, these devices also represent a significant new challenge to FDA. For many of these devices, guidance documents and reliable test methods are currently not available. Basic mechanism data is needed to facilitate the development of relevant evaluation criteria early in the regulatory process, thus enabling thorough and swift reviews of this cutting edge technology. The Optical Diagnostics laboratory 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).

Optical Therapeutic and Medical Nanophotonics (Division of Physics)

Biophotonics is an emerging biomedical technology that is increasingly being applied in the extensive areas of life sciences and medicine. Minimally invasive biophotonics techniques have been recently developed as potential alternatives to conventional medical methods for diagnostics, monitoring and treatment of a variety of diseases, drug discovery, proteomics, and environmental detection of biological agents. These techniques offer a non-contact, effective, fast and painless way for sensing and

monitoring of various biomedical quantities. Medical devices utilizing minimally invasive biophotonics technology are rapidly finding their way into the mainstream for early disease diagnosis and improved patient acceptance and comfort.

The Optical Therapeutics and Medical Nanophotonics Laboratory (OTMNLab) was established as part of OSEL's Division of Physics in September 2006. OTMNLab is responsible for maintaining state-of-the-art knowledge of biomedical optics and laser field to assist the Center and Agency in the following:

- Evaluating new medical therapeutics devices that employ the latest minimally invasive medical laser technology.
- Evaluating critical fundamental parameters of key laser and fiber-optic components employed in recently developed optical therapeutics devices.

Radiation Biology (Division of Biology)

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

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 initiative to focus on the most pressing radiological problems and to anticipate the evolution of new medical radiation systems, we continue to concentrate 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.

Software (Division of Electrical and Software Engineering)

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.

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.

An 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.

Systems Engineering (Division of Electrical and Software Engineering)

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

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. 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.

Toxicology ((Division of Biology)

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

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

Ultrasonics (Division of Solid and Fluid Mechanics)

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.

CDRH Standards Management Program

The Standards Management Staff (SMS) is responsible for facilitating the recognition of national and international medical device consensus standards. CDRH is invested in the development of medical device standards and participates significantly in the development process. SMS manages the Standards Program, a regulatory support activity consisting of cross-office teams within CDRH and FDA. 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. SMS also participates in the coordination of GHTF activities. The GHTF was formed in 1992 in an effort to achieve greater uniformity between national medical device regulatory systems.

SMS continually updates currently recognized standards and coordinates the recognition of new voluntary consensus standards for medical devices and radiation-emitting electronic products. SMS ensures appropriate medical device standards are published in the Federal Register at least twice annually and maintains an electronic database for easy access. 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.

Accomplishments

Recognized Standards for 2007

- 73 new standards
- 120 standards that were withdrawn and new versions were recognized
- 241 changes to the existing recognized standards
- 35 standards were withdrawn

Radiology. The recognition of two radiology standards: NEMA XR 22-2006, "Quality Control Manual" Template for Manufacturers of Displays and Workstations Labeled for Final Interpretation in Full-field Digital Mammography and NEMA XR 23-2006, "Quality Control Manual" Template for Manufacturers of Hardcopy Output Devices Labeled for Final Interpretation in Full-field Digital Mammography is important for 2007. Mammography remains the best method of early breast cancer detection. However, traditional film-screen mammography is limited in its ability to detect some cancers, especially those occurring in women with radiographically "dense" breasts." For this reason, extensive research efforts to improve mammography have occurred. Digital mammography offers theoretical advantages compared to film-screen mammography for cancer detection. These standards define the minimum set of quality control tests which manufacturers should include as part of the quality assurance plan for the Full Field Digital Mammography System.

Ophthalmics Instruments. The recognition of - ISO 15004-2:2007 *Ophthalmic Instruments - Fundamental requirements and test methods Part 2: Light hazard protection* - is an important ophthalmic standard recognition for 2007. An example of one medical device in this area would be the ophthalmoscope, which is a device containing illumination and viewing optics to examine the cornea, aqueous, lens, vitreous, and the retina of the eye. This standard specifies fundamental requirements for optical radiation safety for ophthalmic instruments such as the ophthalmoscope and is applicable to all ophthalmic instruments that direct optical radiation into or at the eye and for which there is a specific light hazards requirement section within their respective International Standards. It is also applicable to all new and emerging ophthalmic instruments that direct optical radiation into or at the eye.

Steam sterilization in health care facilities. The recognition of ANSI/AAMI ST79:2006 *Comprehensive guide to steam sterilization and sterility assurance in health care facilities* combined five standards into one comprehensive standard. This standard is intended to promote sterility assurance and to guide health care personnel in the proper use of processing equipment. Included within the scope of the recommended practice are functional and physical design criteria for sterilization processing areas (decontamination, preparation, sterilization, and sterile storage areas); staff qualifications, education, and other personnel considerations; processing procedures; installation, care, and maintenance of steam sterilizers; quality control; and quality process improvement.

Lasers and laser-related equipment. The recognition of ISO 11810-2:2007--*Lasers and laser-related equipment: Test method and classification for the laser-resistance of surgical drapes and/or patient-protective covers -- Part 2: Secondary ignition.* This standard is an important recognition for 2007. The use of surgical lasers offers the medical community distinct advantages in the operating room. Although laser surgery affords the public improved health care, the use of lasers present new hazards in the operating room environment. Despite efforts to confine laser beams to the intended

operative site, lasers can and inadvertently do sometime become focused on unintended locations, either as the direct laser beam or as stray light from the beam. This has resulted in burns, permanent eye damage, fires and, in some instances, death. All materials reflect portions of the beam, and it is necessary for the user to decide whether specular reflection may be a hazard. The purpose of ISO 11810-2:2007 is to provide a standardized method for testing and classifying surgical drapes and/or patient protective covers with respect to laser-induced hazards. ISO 11810-2:2007 is applicable to disposable and re-usable, as well as woven and non-woven materials, used as surgical drapes and/or patient protective covers which claim to be laser-resistant.

Software/Informatics. Due to the increasing emphasis in informatics and the relationship between informatics and software, the name for the Software STG was changed to the Software/Informatics STG. This change was vital to keep our program current with changes in medical devices.

17th Annual AAMI/FDA International Conference on Medical Device Standards and Regulation. The conference is sponsored jointly by the Association for the Advancement of Medical Instrumentation and the U.S. Food and Drug Administration. It provided detailed information about the latest standards and regulatory initiatives that affect manufacturers of medical devices — both in the U.S. and overseas. As an annual co-sponsor of this significant conference, Carol Herman, Director of the Standards Management Staff, helped develop the agenda and identify appropriate speakers. There were eight speakers from FDA/CDRH, with topics covering risk management, global harmonization, the CDRH ombudsman and other important areas. Nearly 200 participants attended the conference representing the medical device industry and FDA staff.

The Standards Study. The studies goal was to review the utilization of standards in the pre-market review program, to determine if there was added value, and to show the value of the standards program beyond reduced review times. The sample for the study was comprised of approximately 20% of ODE (Office of Device Evaluation) and OIVD (Office of In Vitro and Diagnostic Device Evaluation and Safety) pre-market review staff. The survey consisted of 16 questions designed to capture the opinions of each reviewer on the value of standards. The results indicated that 100% of those surveyed were either *satisfied* or *very satisfied* with the program. A majority of those surveyed felt there was a need for greater training. Over all there was satisfaction with the program in helping with the pre-market review process.

Guidances: OSEL issued four guidances in 2007. Mr. Donald Witters, Jr. , Division of Physics, led a team that drafted *Draft Guidance for Industry and FDA Staff - Radio-Frequency Wireless Technology in Medical Devices*. Ms. Herman led a team that revised three standards guidances: (1) *Guidance for Industry and FDA Staff - Recognition and Use of Consensus Standard*s, (2) *Guidance for Industry and FDA Staff - CDRH Standard Operating Procedures for the Identification and Evaluation of Candidate Consensus*

Standards for Recognition, and (3) *Guidance for Industry and FDA Staff - Frequently Asked Questions on Recognition of Consensus Standards*.

Global Harmonization Task Force (GHTF). 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.

The Chairmanship of GHTF rotated to FDA after being held by the European Union for 3 years. FDA assumed the Chair of GHTF in late December 2006 and will hold the Chair for 18 months, until June 2008. FDA appointed Dr. Larry Kessler, Director of the CDRH Office of Science and Engineering Laboratories, to be the Chair and Ms. Jean Olson, Standards Management Staff, to the Secretariat.

In May 2007, Dr. Kessler chaired a 3-day steering committee meeting held in FDA's District Office in Irvine, California. A joint GHTF study group meeting was also held concurrently with the steering committee meeting, both on that site. Approximately 35 people attended the steering committee meeting, and approximately 90 people attended either the steering committee or joint study group meetings.

In October 2007, Dr. Kessler chaired a second steering committee meeting held in Washington, D.C. (for 3 days) in conjunction with the (2-day) GHTF Conference. Approximately 300 persons attended the Conference which included workshops on nanotechnology (Emergence of Nanotechnology and Its Impact on Device Regulatory Harmonization) led by OSEL Deputy Director Dr. Subhas Malghan (two sessions) and on software (Regulatory Considerations of Medical Device Software) led by Mr. Brian Fitzgerald. The conference was followed by 2 days of training on GHTF documents. Ms. Olson worked with a team from FDA and AdvaMed to coordinate the logistics of the steering committee meeting and the conference.

Dr. Kessler and Mr. Fitzgerald worked on the ad hoc software group. As a result, the Software ad hoc group was formed, headed by Mr. Fitzgerald, and the group forwarded work items to the GHTF Steering Committee for approval in November 2006. The software ad hoc group continues its work under Mr. Fitzgerald's leadership. Dr. Kessler also leads the ad hoc group working on GHTF Training and the ad hoc group exploring

developing GHTF's relationship with the World Health Organization (WHO). FDA/CDRH continues to manage the GHTF website.

OSEL 2007 Laboratory Accomplishments

Biological Risk Assessment (Division of Biology)

Optimize the technical assay conditions for the renal toxicity chip

Research indicates some initial success in developing a custom chip that can detect changes in gene expression in cells shed into urine following acute kidney injury. We hope to optimize the technical assay conditions in FY 08. This new scientific tool is likely to result in a product that will directly benefit patients.

Develop a guidance document on the use of renal biomarkers for preclinical evaluation of medical devices

One of the markers we evaluated last year with our collaborators at Harvard University, kidney injury molecule-1 (KIM-1), is found to have high prognostic value based on the statistical evaluation performed by the Preclinical Safety Testing Consortium (PSTC). This qualification effort is expected to play an important role in determining regulatory acceptance of this renal biomarker and others for use in preclinical studies evaluated by CDRH and CDER. Our goal in FY 08 is to expand this analysis to evaluate the ability of renal biomarkers other than Kim-1 to serve as indicators of acute renal injury in preclinical studies and to prepare a guidance document with colleagues in CDRH/ODE on how to use these data in preclinical biocompatibility assessment.

Biomolecular Mechanisms (Division of Biology)

There has been substantial progress in determining the effect of hyaluronic acid (HA) samples of different molecular weights on RAW 264.7 inflammatory nitric oxide response to specific amounts of endotoxin +/- gamma-interferon. Several samples of HA were assayed for their endotoxin levels using the kinetic chromogenic limulus lysate assay. No direct effect of HA on the macrophage cell line has been observed; however, the endotoxin response of RAW 264.7 is under some circumstances increased---and more so if interferon gamma is present. These early data in the project agree with preliminary pilot experiments that HA may be *enhancing* ongoing inflammatory responses but may not be directly *causing* inflammation.

Electromagnetic and Wireless Technologies (Division of Physics)

The Electromagnetic and Wireless Laboratory initiated new work on laboratory measurements and computer modeling of the currents induced in medical implants by the intense pulsed magnetic fields from gradient coils of MRI systems. The implants of interest are electrically conductive leads for implanted pacemaker/defibrillators and spinal or brain stimulators. The leads are in the bodies of patients who would be prescribed MRI imaging studies. This work is highly relevant since implanted device manufacturers are now developing MRI-compatible versions of their products and will seek pre-marketapproval from FDA. A literature search revealed that this work is unique and has not been studied or published by other organizations. It is completely different from the well-known MRI heating effect on implanted leads that is induced by RF fields of MRI systems.

- Developed new or improved several techniques for assessing MR safety--specifically the RF-induced voltages at the tips of leads of implanted medal devices by the intense low frequency MRI gradient fields. This work included measurement techniques and computational modeling.

- ***MRI RF induced heating.*** The findings of the FDA-directed international intercomparison demonstrated that ASTM and other standard test methods for MRI heating of medical implants are highly flawed. Heating depends on the *specific* MRI clinical system, the patient-simulating phantom, and the lead location.

- Measured the magnetic field produced by iPod music players and attempted to detect any voltages these fields might produce within the protective "can" of a pacemaker placed inside a simulated human torso. Results of our tests concluded that no interference effects can occur in pacemakers exposed to the iPods. These results were published in the online journal *Biomedical Engineering Online*.

Electrophysiology and Electrical Stimulation (Division of Physics)

- Established an *in-vitro* system for applying mechanical stretch at different phases of the cardiac excitation cycle. This system is being used to examine timing of cardiac electric pulses in relation to the mechanical cycle, and how arrhythmias are generated by these phase relationships.

- Adopted porcine model of heart failure for gender-related studies. This is the initial part of our research for the Office of Women's Health that is developing female-specific animal models for heart failure. We measure calcium signaling in this model and are in the process of establishing a transmural wedge preparation to examine arrhythmogenesis in this model.

- Designed and tested, in collaboration with the Italian National Institute of Health, an arbitrary waveform defibrillator. This is being used to determine the maximum safe duration of biphasic shocks used in Automatic External Defibrillators (AEDs). It is to meet a specially requested objective to determine the safe limit of shock duration, which is in-preparation for device submissions for a new generation of defibrillators.

- Published a journal paper that delineates the types of interactions that occur between cardiac stimulation devices and cardiac medications (Krauthamer, 2007). This paper points to important factors to consider during clinical trials during which all possible drug-device interactions cannot be tested.

- Developed biomarkers for safe retinal stimulation and included anatomical markers (propidium iodide exclusion) and functional markers (ganglion cell firing). Also published reviews on methods for prosthetic stimulation of the human visual system.

Fluid Dynamics (Division of Solid and Fluid Mechanics)

- Formed a collaboration with three universities to help design and fabricate the necessary flow models; performed preliminary computational simulations and flow visualization on the models; developed an FDA website to publicize the project; and worked with scientific organizations (e.g., the American Society for Artificial Internal Organs and the American Society of Mechanical Engineers Biofluid's Group) to recruit participants for the round-robin evaluation.

- Received approval from FDA's Human Use Committee and NIH's Blood Research Donor Program to begin blood damage testing using human blood. A single-pass orifice system was used to investigate the fragility of human blood for comparison to that of bovine blood. This is important since most *in vitro* testing is

performed on animal blood and the relationship to human blood is not established.The geometry of the single-pass orifice system was reproduced in a computational fluid dynamic simulation program to meet the program objective of correlating shear force exposure to actual blood cell damage (hemolysis and platelet activation).

- Established experimental protocols for assessing platelet activation with flow cytometry, whole blood aggregometry, platelet counting, and ELISA analysis.

- A CRADA (#128-07) was completed and signed by Epicor St. Jude Medical and FDA in April 2007.

- Epicor heart ablation transducer (HAT SN GGDY) was characterized for velocity profiles at 10, 15, 20, 30, and 40 V rms and for several transducer locations of midline, rear line, and frontline. The new differentiation numerical algorithm will be used on this data to predict the 3D acoustic intensity distribution.

Image Analysis (Division of Imaging and Applied Mathematics)

- IHC sub-project: IHC sub-project: Finished the first stage of the HER2 CAD algorithm development. This study has been submitted for publication, and the work will be presented at ISBI 2008.

- IHC sub-project: Defined protocol for reader study experiment to assess both intra- and inter-reader variability

- Investigated the impact of patient-based and location-based assessment methods on the impact of reading mode on clinical utility. This study showed that selecting different assessment methodologies can lead to conflicting study conclusions. This work was presented at SPIE 2008.

- Completed data collection for all of the attached spherical nodules of densities -800 HU, -630HU and +100HU and are receiving requests for use of the data by outside groups.

- Completed initial assessment of a single software tool for measuring nodule volume and presented at SPIE 2008.

Imaging Diagnostics ((Division of Imaging and Applied Mathematics)

- Extended computer simulation activity 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.

- 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.

- Developed method and graphical interface software to run viewing angle observer studies using Tcl/Tk.

- Conducted experimental and computational observer studies of viewing angle effects.

- Developed a feature extraction method for a linear imaging system for use in efficient computation of ideal-observer performance.

- Developed efficient computation tools for ideal-observer based performance metrics in detection tasks involving non-Gaussian, randomly varying backgrounds.

- Developed the first set of physical breast phantoms that consist of PMMA balls with different sizes and different densities for use in validation of simulation tools and evaluation of 3D breast imaging systems.

Optical Diagnostics (Division of Physics)

- Validated a novel multi-wavelength optical property measurement system.

- Performed extensive measurements in porcine mucosal and liver tissues with fiberoptic probe.

- Analyzed results to identify the site quantifying the level of natural variations in optical properties and identify significant light absorption components as a function of wavelength.

- Modification of the OCT system to perform measurements on nanoshell-based phantoms is underway, with measurements to begin in the next few months.

- Performed initial round of artificial human skin and mucosal tissue. Initial results have not shown significant consistency or expected damage levels.

- Revised methodology for irradiation, biopsy, and fixation. Results from second round of sample measurements are currently being processed.

Optical Therapeutic and Medical Nanophotonics (Division of Physics)

- Developed a standard test method for evaluating glare from IOLs to determine which methods can be used to characterize and pinpoint the source of extraneous glare images from intraocular lens implants from point light sources [Landry, RJ, Ilev, IK, Pfefer, TJ, Wolffe, M, and Alpar, JJ, Eye, 21, 1083-1086, 2007, *Nature Publishing Group*]. The haptic insertion in the optic of three-piece IOL's has been identified as a source of line glare images. These test methods will be considered for manufacturer and reviewer guidance and for incorporation into national and international IOL standards. This project will also provide laboratory testing to evaluate IOLs and new IOL designs as needed by ODE.

- Determined in cell culture work the importance of hydrogen peroxide produced inside the cells by the mitochondria. This production of hydrogen peroxide is able to escape the cell producing it and enter other cells thus acting deeper into tissue than just those cells penetrated by light. Understanding biological response to non-ionizing radiation for various light therapeutic devices is important to CDRH. There is growing evidence in the literature showing that "low-level light" exposures can produce positive therapeutic responses to many illnesses, diseases, and injuries. Further investigations have confirmed that catalase, an enzyme reducing hydrogen peroxide to water and oxygen, can scavenger hydrogen peroxide outside the cell and reduce its interaction with other cells. Additionally,

we have measurements that show that cell proliferation or inhibition is directly related to the dose of light given.

Software (Division of Electrical and Software Engineering)

Collected usage model state data with the help of a sole-source contractor, in consultation with domain experts. The usage model state transition probabilities were defined and corroborated. The model was implemented with the help of MATLAB Simulink/Stateflow suite, and exhaustively verified for anomalies and inconsistencies. Test scripts were derived for the generic pump model, to be used as a basis for manufacturer software validation.

Toxicology ((Division of Biology)

- Characterized TiO2 particles by dynamic light scattering spectrometry prior to experimental use, and by electron microscopy and energy dispersive X-ray scattering to visualize particles (or aggregates) in tissues after exposure.

- *In vivo* studies – Determined the tissue distribution of aggregates, histopathology, the time course of distribution, blood cell changes, and production of inflammatory cytokines. Specific results: 1) route of administration (intravenous vs. subcutaneous) affects tissue distribution; 2) observed a re-distribution but no clearance of clumps of nanoparticles up to 6 months post-exposure; and 3) observed minimal toxic responses to titanium nanoparticles after 6 months exposure.

- *In vitro* studies - Increased production of reactive oxygen species and loss of cell membrane integrity was observed at higher TiO2 doses and longer exposure times in cultured J774 macrophage cells. Cytokines released from cells included TNF-a, IL-1b, IL-6, and GM-CSF with increasing dose and exposure time to TiO2. These data suggest macrophage accumulation of TiO2 aggregates may result in cytokine release and potential cytotoxicity in cells and tissues responsible for TiO2 clearance from circulation.

- Established working collaborations with the University of Florida (tissue silver analysis via ICP-MS) and The George Washington University. Initiated studies of placental transport of silver nanoparticles into mouse embryos after exposure of pregnant dams have been initiated. We have detected silver from treated mice in embryonic tissues and adult tissues.

- Established working collaborations with University of Maryland and NIST to produce well characterized, sterile, endotoxin-free silicon nanoparticles. Observed apparent intracellular uptake of fluorescent silicon (4-nm) particles by murine macrophage cells, a cell line relevant to measure potential inflammatory responses to particles. Studied effect of particle size on biological effects. Measured tumor necrosis factor-α, interleukin-6, and nitric oxide production by macrophages in the presence of silicon nano- and micro-sized particles.

Ultrasonics (Division of Solid and Fluid Mechanics)

- Continued collaboration with NIST to provide calibrated transducers and customized radiation force balance (RFB) targets with which we can further calibrate and characterize the RFB system.

- The Epicor-St. Jude Medical/FDA CRADA (# 128-07) was signed and executed on May 1, 2007. Additionally, a final non-provisional patent was submitted to U.S. Patent office on March 12, 2007, by Epicor-St. Jude Medical. The acoustic streaming characteristics of an experimental heart ablation HIFU transducer (Epicor-St. Jude Medical) were measured in support of the CRADA.

- Developed measurement protocol for characterizing acoustic intensity distribution from HIFU transducers at high intensities, using acoustic streaming and numerical differentiation methods. Unlike the previous streaming technique, these "direct" methods do not involve iterative numerical algorithms, and are much faster. The direct methods have been validated using the iterative streaming technique as well as hydrophone scanning.

- Designed, implemented, tested, and documented a general axisymmetric HIFU simulation package for in-house and possibly external use. The package is easy to use and runs in Matlab. It computes pressure, intensity, heating rate, temperature rise, and thermal dose for a broad range of HIFU systems. This is a frequency-domain code suitable for continuous beams and complements the existing short pulse, time-domain "Texas code."

- Initiated efforts to develop analytical models that will characterize the heat source resulting from propagation of acoustic waves in visco-elastic solids. These models will be used in conjunction with acoustic field data from the validated linear wave propagation code (WavePro) and from a nonlinear wave propagation code (KZK) to compute the heat source terms that will be used in the future heat-transfer simulations of HIFU sonications in bone-tissue models.

APPENDIX A – OSEL Publications

January 1, 2007 – December 31, 2007

Journal Articles

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Abstracts, Book Reviews, etc.

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Choi J, Zhang Q, Hitchins VM, Stratmeyer M, Goering P, Reipa V, Wang NS. Toxicity of silicon nanoparticles and microparticles. American Society of Toxicology, September 2007.

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Espandiari P, Zhang J, Rosenzweig B, Zhou Y, Vaidya VS, Herman EH, Miller TJ, Knapton A, Honchel R, Weaver J, Noory L, Adeyemo O, Benedick M, Goering PL, Brown RP, Bonventre JV, Thompson K, Sadrieh N and Hanig J. Age-related differences in susceptibility to cisplatin-induced renal toxicity. International Congress of Toxicology, Montreal, Canada, July 15-19, 2007.

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Frentz S, Summers RM, Yao J, Brown L, Louie A, Petrick N. The importance of polyp conspicuity for CT colonography computer-aided detection, *RSNA*, Chicago IL, 2007.

Goering PL , Zhou Y, Brown RP, Ferguson MA, Zhang J, Miller TJ, Bonventre JV, Vaidya VS. Kidney injury molecule-1 (Kim-1) expression during acute kidney injury induced by gentamicin, mercury, or chromium. *Toxicologist* **96(1):**96-97, 2007 - Society of Toxicology, 46th Annual Meeting, Charlotte, NC, March 25-29, 2007.

Guerraty M, Grant G, Pritchard WF, Karanian JW, Davies PF. Aortic valve endothelial phenotype sensitivity to brief hypercholesterolemia in swine is side-specific. Experimental Biology 2007, Washington, DC, 2007.

Harris, Liu, Maruvada, Gammell. Finite amplitude method for measurement of nonlinearity parameter B/A using plane-wave tone bursts. IEEE Ultrasonics Symposium, New York, NY, October 2007.

Hsu ER, Gallas BD, Jeronimo J. Colposcopic reader agreement using images of the cervix. Biomedical Engineering Society 2007 Annual Fall Meeting, Los Angeles, CA, September 26-29, 2007.

Ilev I, Faaland R, Calogero D. A novel confocal fiber-optic laser method for exact intraocular lens power measurement. International Conference on Lasers and Electro-Optics (CLEO-2007), Paper JTuA48, Baltimore, MD, May 6-11, 2007.

Ilev I. Advanced confocal bioimaging and sensing approaches: From ultrahigh-resolution nanobiophotonics to clinical measurements. FDA/CDRH Staff College "Modern Topics in Biomedical Optics", May 1, 2007.

Ilev I. Laser-based techniques for innovative biosensing", SPIE Photonics West–LASE 2007 International Conference, Invited Paper 6458B-06, San Jose, CA, January 20-25, 2007.

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Jones PL. The application of (software safety) assurance cases in regulatory processes. NEMA, Philadelphia, PA, November 7, 2007.

Kang JU, Do-Hyun Kim. Temperature independent birefringence in polarization maintaining photonic crystal fiber. Invited OSA Conference on Lasers and Elec. Opt Pacific-Rim (CLEO PR 2007), Seoul, Korea, August 2007.

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Paquerault S, Petrick N, Myers KJ, Samuelson FW. Impact of a computer-aided detection (CAD) system on reader performance: Assessment based on a Truthing Panel compared to the True Gold Standard. *RSNA*, 2007.

Petrick N, Gallas BD, Samuelson FW, Paquerault S. Assessing computer-aided diagnosis algorithms: algorithm architecture, statistical tools and study designs. The International Biometric Society/Eastern North American Region (ENAR) Program, ENAR (invited presentation), Atlanta, GA, March 2007.

Pritchard WF, Peregoy JA, Murray TL, Chiesa OA, Karanian JW. Computed tomography and uniquely labeled therapeutic agents allow detailed evaluation of pharmacokinetics in local drug delivery. 2nd Annual Imaging in Pre-clinical & Clinical Drug Development, Cambridge, MA, March 15-16, 2007.

Rodriguez, A, Kim D-H, Kang JU. Endoscopic fiber confocal microscopy using a GRIN lens. OSA Conf Lasers and Elec. Opt (CLEO2007), Baltimore, MD, May 2007.

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Vassilev B, Gorman E, Kim D, Ilev I. Nanoscale fiber-optic biosensor probes: characterizing fundamental laser delivery properties", 2007 FDA/CDRH Summer Student Forum, Silver Spring, MD, July 23, 2007.

Weaver JL, Umbreit TH, Miller TJ, Zhang Z, Stratmeyer ME, Tomazic-Jezic VJ. Toxicology of titanium dioxide (TiO2) nanoparticles: 2. Immunological effects in subcutaneously and intravenously injected mice. *Toxicologist* **96(1)**, 2007.

Weaver JL, TJ Miller TJ, TH Umbreit TH, VJ Tomazic-Jezic VJ, N Sadrieh N. Responses to titanium dioxide nanoparticles following *in vivo* administration. Gordon Conference, 2007.

Weaver JL, Umbreit TH, Miller TJ, Zhang J, Stratmeyer ME, Tomazic-Jezic VJ. Toxicology of Titanium Dioxide (TiO2) nanoparticles: immunological effects in subcutaneously and intravenously injected mice. FDA Science Forum 2007: Nanotechnology: No Small Matter at the FDA, p. 20, abstract N22, 2007.

Yamaguchi Y, Coelho SG, Beer JZ, Miller SA, V.J. Hearing VJ. Photoprotection of human skin against repeated UV exposures. Materials of the Meeting of the European Society for Pigment Cell Research, Bari, Italy. Pigment Cell Research, **20:**449, 2007.

Zhou Y, Vaidya VS, Shaw M, Keenan J, Ferguson MA, Zhang J, Brown RP, Bonventre JV, Goering PL. Comparison of urinary biomarkers to detect metal-induced nephrotoxic effects in gentamicin-pretreated rats. Toxicologist 91(1): 97, 2007 -Society of Toxicology, 46th Annual Meeting, Charlotte, NC, March 25-29, 2007.

Posters

Choi J, Zhang Q, Hitchins V, Reipa V, Wang NS. Probing biological responses of silicon nanoparticles in RAW 264.7 murine macrophage cells. Poster presentation. FDA Science Symposium, Silver Spring, MD, October 23, 2007.

Karakas B, Weaver J, Park BH, Elespuru RK. Detection of mutant-tumor cancer biomarkers by BEAMing. Environmental Mutagen Society Meeting on Mutational and Epigenetic Mechanisms of Susceptibility and Risks for Genetic Diseases, Atlanta, GA, October 23, 2007.

Letters to the Editor

Miller SA, Coelho SG, Zmudzka BZ, Beer JZ. Criticism of FDA pilot study unfounded (response to R.M. Sayre and J.C. Dowdy). *Photodermatology. Photoimmunology. Photomedicine* **23:**59-60, 2007.

Internet Posts

Spees W. Medical device plug and play prototype SW interface. August 1, 2007.

APPENDIX B – OSEL Presentations

January 1, 2007 – December 31, 2007

Agrawal A, Pfefer J. Characterization of gold nanoshells for optical imaging and laser therapy. FDA Science Symposium on Nanotechnology, 2007.

Agrawal A, Parker C, Qazi T, Agrawal KM, Pfefer TJ. Sensitivity and robustness of methods for analyzing time-resolved fluorescence measurements of layered biological tissue. SPIE BiOS, Jan 2007.

Bandos A, Rockette HE, Gallas BD, Gur G. Multi-Reader ROC methods: Explicit formulations and relationships between DBM, multi-WMW, BWC and Gallas's methods. International Biometric Society, Eastern North-American Region Conference (ENAR), Atlanta Georgia, 2007.

Bassen H, Seidman S, Rogul J, Desta A, Wolfgang S. An exposure system for evaluating possible effects of RFID on various formulations of drug products. IEEE International Conference on RFID, Gaylord Texan Resort, Grapevine, TX, USA, March 26-28, 2007.

Chan DD, Krauthamer V. Effects of high-rate stimulation in modeled axons and role of calculation time step interval on simulations, Biomedical Engineering: Recent Developments, 2007.

Chiesa OA, Li H, Karanian JW, Pritchard WF, Smith M, von Bredow J. Gasless (isobaric) laparoscopic serial kidney and liver biopsies in standing sedated steers. 4th Veterinary Endoscopy Society Meeting. Hawk's Cay, FL, March 26-28, 2007.

Coelho SG, Yamaguchi Y, Miller SA, Zmudzka BZ, Takahashi K, Beer JZ, Hearing VJ. Skin pigmentation induced by repeated uv exposures and the role of melanin in photoprotection. 14th Annual Meeting of the PanAmerican Society for Pigment Cell Research, Chicago, IL, September 13-16, 2007.

Elespuru RK. FDA use of genotoxicity data. Toxic Embedded Fragments meeting, Veteran's Administration, Baltimore, MD, November 6, 2007.

Harris GR, Diagnostic ultrasound regulatory guidance and output display indices (invited presentation), Short Course on Regulatory and Safety Issues in Biomedical Ultrasound 2007. IEEE International Ultrasonics Symposium, New York City, NY, October 2007.

HitchinsVM, Petricoin EF, Calvert V, Kaplan DS, Au R, Grzanna R, Wood SC, Frondoza CG. Phenotype shift of human chondrocyte monolayer cultures maintained on polystyrene surfaces is associated with AKT/GSK/Forkhead pro-survival signaling. Gordon conference, Holderness School, Holderness, NH, July 22-27, 2007.

Hsu ER, Gallas BD, Jeronimo J. Colposcopic reader agreement using images of the cervix. *Biomedical Engineering Society 2007 Annual Fall Meeting*, Los Angeles, CA, September 26-29, 2007.

Karanian JW, Chiesa OA & Pritchard WF, Modeling Drug Delivery: Tools for Assessment of Arterial Intramural Kinetics. 14th International Local Drug Delivery Meeting. Geneva, Switzerland, February 1-3, 2007.

Karanian JW. Future perspectives and challenges for the validation of devices to treat cardiovascular disease. Vulnerable Plaque Summit 2007, Houston, TX, September 15, 2007.

Karanian JW. Preclinical animal studies: DES: TCT 2007, Washington, DC, October 20, 2007.

Liang H, Park S, Gallas BD, Badano A, Myers KJ. Assessment of temporal blur reduction methods using a computational observer that predicts human performance. SID (Society for Information Display) international symposium, Long Beach, CA, May 19-25, 2007 (oral presentation).

Liang L A. Xu, Gallas BD, Park S, Myers KJ, Badano A, Detectability decreases when browsing large image sets in slow display devices. RSNA 2007, Chicago, IL, 2007 (oral presentation).

Li J, Huang A, Yao J, Petrick N, Choi JR, Pickhardt PJ, Summers RM. Improved performance of computer-aided detection for medium-sized polyps on CT colonography. *European Congress of Radiology Program, ECR*, March 2007.

Midgette WH. ISO 14971 and the 3rd edition. 2007 AAMI International Standards Conference, March 21, 2007.

Midgette WH. Risk management and the 3rd edition. 2007 AAMI International Standards Conference, Marech 21, 2007.

Myers KJ, Barrett HH, Gallas BD, Gagne RM, Petrick N, Wagner RF. Unique issues in the assessment of biomarkers from imaging. RSNA Imaging as a Biomarker for Planning and Monitoring Therapy Workshop, Bethesda, MD, May 3-4, 2007.

O'Hara MD. Seminar series at the FDA's White Oak Campus Department of Radiation Oncology, University of Maryland, College Park, MD, September 10, 2007.

Paquerault S, Petrick N, Myers KJ, Samuelson FW. Impact of a computer-aided detection (CAD) system on reader performance: assessment based on a truthing panel compared to the true gold standard. Radiological Society of North America (RSNA 2007).

Petrick N, Gallas BD, Samuelson FW, Paquerault S. Assessing computer-aided diagnosis algorithms: Algorithm architecture, statistical tools and study designs. Eastern North American Region International Biometric Society Annual Meeting, Atlanta, GA, March 2007.

Pfefer TJ. Introduction to Biomedical Optics," presentation for FDA Staff College Course on Modern Topics in Biomedical Optics, 2007.

Pritchard WF, Peregoy JA, Murray TL, Chiesa OA, Karanian JW. Computed tomography and uniquely labeled therapeutic agents allow detailed evaluation of pharmacokinetics in local drug delivery. 2nd Imaging in Pre-clinical & Clinical Drug Development. Boston, MA, March 10-14, 2007.

Rasooly AR. Microarrays for analysis and detection of microbial pathogens and their toxins (invited presentation). Annual Meeting of the International Association for Food Protection, Orlando FL, July 11 2007.

Seidman S, Ruggera P, Lewis B., Brockman R, Shein M., "*Electromagnetic Compatibility of Pacemakers and Implantable Cardiac Defibrillators Exposed to Radio Frequency Identification Readers,"* Academic Convocation at RFID Journal Live April 30-May 2, Orlando FL, 2007.

Spees W. Medical device plug and play prototype SW interface. Center for the Integration of Medicine & Innovative Technology (CIMIT), Cambridge, MA, June 25, 2007.

Stratmeyer M. Safety and regulatory considerations in the non-clinical use of medical ultrasound devices (invited presentation). WFUMB/ISUOG Workshop on Safety of Non-Clinical Use of Ultrasound, 17th World Congress on Ultrasound in Obstetrics and Gynecology, Florence, Italy, October 7-11, 2007.

Tata D, Waynant RW. Applications of Novel sources in the Suppression of Human Brain Cancer Metabolic activity: An In-vitro study. To be published in the proceedings of Light-Activated Tissue Regeneration and Therapy II, Tomar, Portugal.

Tata D, Waynant RW. Near-IR picosecond pulsed laser induced suppression of metabolic activity in malignant human brain cancer: An in-vitro study. To be published in the proceedings of Light-Activated Tissue Regeneration and Therapy II, Tomar, Portugal.

Taylor A. Compliance alliance. Medical Device Validation Seminar, NEMA, San Francisco, CA, March 13-15, 2007.

Taylor A. Overview of design controls and Cybersecurity for medical devices. Safety Risk Management and Design Control, Compliance Alliance, MITA, McLean, VA, September 11-13, 2007.

Wallace G, Chiesa OA. Penicillin tissue-fluid correlations in swine using video-assisted serial sampling. Food and Drug Administration, Center for Veterinary Medicine, Office of Research, Laurel, MD, August 24, 2007.

Wang Q, Agrawal A, Pfefer J, Wang NS. Measurement of internal tissue optical properties in ultraviolet and visible spectral regions: development and implementation of a multi-wavelength system. University of Maryland Bioscience Research & Tech Review Day, 2007.

Wang Q, Agrawal A, Matchette S, Wang NS, Pfefer J. Evaluation of a multi-wavelength reflectance system for determination of tissue optical properties in the UVA-VIS. Conference on Lasers and Electro-Optics, 2007.

Weininger S. Plan for Quality. The Future of Manufacturing is Innovation conference, CT Center for Advanced Technology, East Hartford, CT, June 21, 2007.

Witters D. Wireless Technology in Healthcare: an FDA Perspective, ECRI Institute's web conference on Managing a Hospital Wireless infrastructure, November 14, 2007.

Witters D. Addressing RF Wireless Technology and Electromagnetic compatibility (EMC) for Medical Devices: an FDA Perspective, GLORE Global Coordination of Research on Electromagnetic Fields, EMF-NET Coordination Action Funded by the European Union's Sixth Framework Programme of Research, Nov 26-27, 2007, Brussels, Belgium.

Wilson O, Agrawal A. Inorganic Liquid Crystals for Biomedical Imaging. Materials Science and Technology Conference, September 2007.

Yamaguchi Y, Coelho SG, Beer JZ, Miller SA, Hearing VJ. Photoprotection of human skin against repeated UV exposures. Meeting of the European Society for Pigment Cell Research, Bari, Italy, October 14-16 2007 (Invited Lecture).

APPENDIX C – OSEL Academic Affiliations

January 1, 2007 – December 31, 2007

Agrawal, Anant, Ph.D.	Virginia State University Department of Mathematics and Computer Science Member, Master's thesis committee
Badano, Aldo, Ph.D.	University of Michigan College of Engineering and Computer Science Visiting research scientist
Bassen, Howard I.	University of Maryland College of Engineering Lecturer
Chang, Isaac A, Ph.D.	Catholic University of America Department of Biomedical Engineering Assistant professor George Washington University Department of Electrical and Computer Engineering Research advisor, Master's student University of Florida Department of Mechanical and Aerospace Engineering Research advisor, Master's student
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

Kainz, Wolfgang, Ph.D.	University of Houston Department of Electrical and Computer Engineering Member, Doctoral thesis committee
Karanian, John W., Ph.D.	Georgetown University School of Medicine Department of Physiology Adjunct Professor
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
Kyprianou, Iacovos, Ph.D.	University of Maryland at College Park, Dept. of Bioengineering Adjunct assistant professor
Myers, Kyle J., Ph.D.	University of Arizona Optical Sciences Center Adjunct professor
Myklebust, Joel, Ph.D.	George Washington University Department of Electrical and Computer Engineering Adjunct assistant professor
O'Hara, Michael D., Ph.D.	Thomas Jefferson University Department of Radiation Oncology Adjunct Assistant Professor
Patwardhan, Dinesh V, Ph.D.	Pennsylvania State University

	Department of Chemical Engineering Adjunct professor
Petrick, Nicholas, Ph.D.	University of Michigan Department of Radiology Adjunct assistant professor
Pfefer, T. Josh, Ph.D.	University of Maryland Department of Chemical and Biomolecular Engineering Doctoral thesis committee
Pollack, Steven, Ph.D.	University of Maryland, College Park College of Chemical and Life Sciences Department of Chemistry and Biochemistry Adjunct professor
Rasooly, Avraham, Ph.D.	Program Director, Cancer Diagnosis Program National Cancer Institute National Institutes of Health
Spees, William, Ph.D.	University of Phoenix Adjunct practitioner faculty member
Waynant, Ronald W., Ph.D.	Catholic University of America Electrical Engineering Department Adjunct associate professor Uniformed Services University of the Health Sciences Adjunct professor
Wear, Keith A., Ph.D.	Georgetown University Department of Radiology Adjunct Professor Henry M. Jackson Foundation for the Advancement of Military Medicine Guest scientist

Weininger, Sandy, Ph.D. Drexel University
School of Biomedical Engineering
Visiting lecturer

APPENDIX D – OSEL–Sponsored Seminars

January 1, 2007 – December 31, 2007

Carton, Ann-Katherine. Department of Radiology, University of Pennsylvania**.** Optimization of a dual-energy contrast-enhanced technique for a photon counting digital breast tomosynthesis system. Silver Spring, MD, November 29, 2007.

Chen, Weijie. University of Chicago. Computerized image analysis in dynamic contrast-enhanced magnetic resonance imaging of the breast. FDA/CDRH, Rockville, MD, January 18, 2007.

Coakley, Kevin J. National Institutes of Standards and Technology, Boulder, CO. Statistical learning methods for neutron transmission tomography of fuel cells. Silver, Spring, MD, June 14, 2007.

Feldman, Raimund L. The Fraunhofer Center, Maryland. Overview of FC-MD initiatives in the medical bio IT domain. Silver Spring, MD, November 14, 2007.

Masmoudi H. Automated quantitative assessment of her 2 expression in breast cancer tissue using immunohistochemistry. Silver Spring, MD, August 9, 2007.

Miller, James G. NSF-FDA Scholar-in-Residence, Washington University. Tissue characterization with ultrasound: heart and bone., Silver Spring, MD, August 16, 2007.

Morrissey, Joseph. Motorola Laboratories. The growing impact of wireless technology on health and medical devices. Silver Spring, MD, October 23, 2007.

Patri, Anil K. Nanotechnology Characterization Laboratory Advanced Technology Program, National Cancer Institute (Frederick, MD). Dendrimers in Nanomedicine. Silver Spring, MD, October 2, 2007.

Sayre, Robert M. Rapid Precision Testing Laboratories. Darkness at noon: sunscreen and vitamin D3. FDA/CDRH, Silver Spring, MD, January 31, 2007.

Sempau, Joseph. Developments involving PENELOPE and Monte Carlo radiation dose calculations. Universitat Politecnica de Catalunya, Barcelona, Spain. FDA/CDRH, Rockville, MD, March 1, 2007.

Small, John A. Microanalysis Research Group,National Institute of Standards and Technology. Measurement methods and standards for engineered nanomaterials. Silver Spring, MD, September 18, 2007.

Tan, Sovira. National Institutes of Health (visiting fellow). Computer-aided evaluation of ankylosing spondylitis using high-resolution CT. FDA/CDRH, Rockville, MD, January 11, 2007.

Zeng,Rongping. Ph.D. candidate, University of Michigan. Estimating respiratory motion in radiation oncology via deformable models and priors. Silver Spring, MD, April 16, 2007.

APPENDIX E – Interagency Agreements and CRADAs

FY 2007 Reimbursable IAG's

Defense Advanced Research Projects Agency (DARPA). Assistance in test bed development for deep bleeder acoustic coagulation program.

Office of Public Health Emergency Medical Countermeasures (OPHEMC). Development of a rapid point of care test for filoviruses and a portable lab-on-chip to assess potency and neutralization of botulinum neurotoxins.

National Institute on Disability and Rehabilitation Research (NIDRR). Joint laboratory focused on the facilitation of innovative and underdeveloped technologies for medical device applications in rehabilitation medicine and engineering.

National Institutes of Health (NIH). Image-guided interventional therapeutics.

National Institute for Biomedical Imaging and Bioengineering (NIBIB). Continuation of LAMIS for objective assessment and systematic optimization of high-resolution, high-dimensional medical imaging systems.

National Cancer Institute (NCI). Assessment of computer-aided diagnostics.

FY 2007 Service IAG's

National Institutes of Health/National Cancer Center (NIH/NCI). Roles and responsibilities for Avraham Rasooly, Ph.D.

Armed Forces Institute of Pathology (AFIP). Collaborative research and testing of medical implants.

National Voluntary Laboratory Accreditation Program/National Institute of Standards and Technology (NVLAP-NIST). Accreditation fees and onsite assessment of the CDRH X-Ray Calibration Laboratory.

Cooperative Research & Development Agreements (CRADAs)

Mobile Manufacturers (MMF). Medical device electromagnetic interference (EMI) from wireless data devices and inter-laboratory comparison of radio frequency (RF), dosimetry data from hand-held transmitters.

Cellular Telecommunications and Internet Association (CTIA).

University of Pennsylvania (U-Penn).

The Foundation for Research on Information Technologies in Society (IT'IS). Numerical models and tools for the virtual family.

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

FIMI/Philips (Italy) (FIMI). High-dynamic-range display of medical images.

OSEL Laboratory Leaders

DIVISION OF BIOLOGY

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

Biomolecular Mechanisms (molecular biology, immunology, allergy, cell biology, genomics/genetics): *Avi Rasooly* 301.496.8639 ar338b@NIH.gov

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

Cardiovascular and Interventional Therapeutics: *John Karanian* 301.210.4247 john.karanian@fda.hhs.gov

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

Radiation Biology (photosciences - retired): *Howard Cyr*

DIVISION OF CHEMISTRY AND MATERIALS SCIENCE

Active Materials: *Dinesh Patwardhan* 301.796.2622 dinesh.patwardhan@fda.hhs.gov

Materials Performance: *Benita Dair* 301.796.2614 joyce.whang@fda.hhs.gov

DIVISION OF ELECTRONICS AND SOFTWARE ENGINEERING

Electrical Engineering: *Al Taylor* 301.796.2583 alford.taylor@fda.hhs.gov

Software: *Brian Fitzgerald* 301.796.2579 brian.fitzgerald@fda.hhs.gov

Systems Engineering: *Al Taylor* 301.796.2583 alford.taylor@fda.hhs.gov

DIVISION OF IMAGING AND APPLIED MATHEMATICS

Image Analysis: *Nicholas Petrick* 301.796.2563 nicholas.petrick@fda.hhs.gov

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Ionizing Radiation Measurements: *Mary Walker* 301.796.2558
mary.walker@fda.hhs.gov

DIVISIONOF PHYSICS

Electrophysiology and Electrical Stimulation: *Victor Krauthamer* 301.796.2474
victor.krauthamer@fda.hhs.gov

Electromagnetic and Wireless Technologies: *Howard Bassen* 301.796.2472
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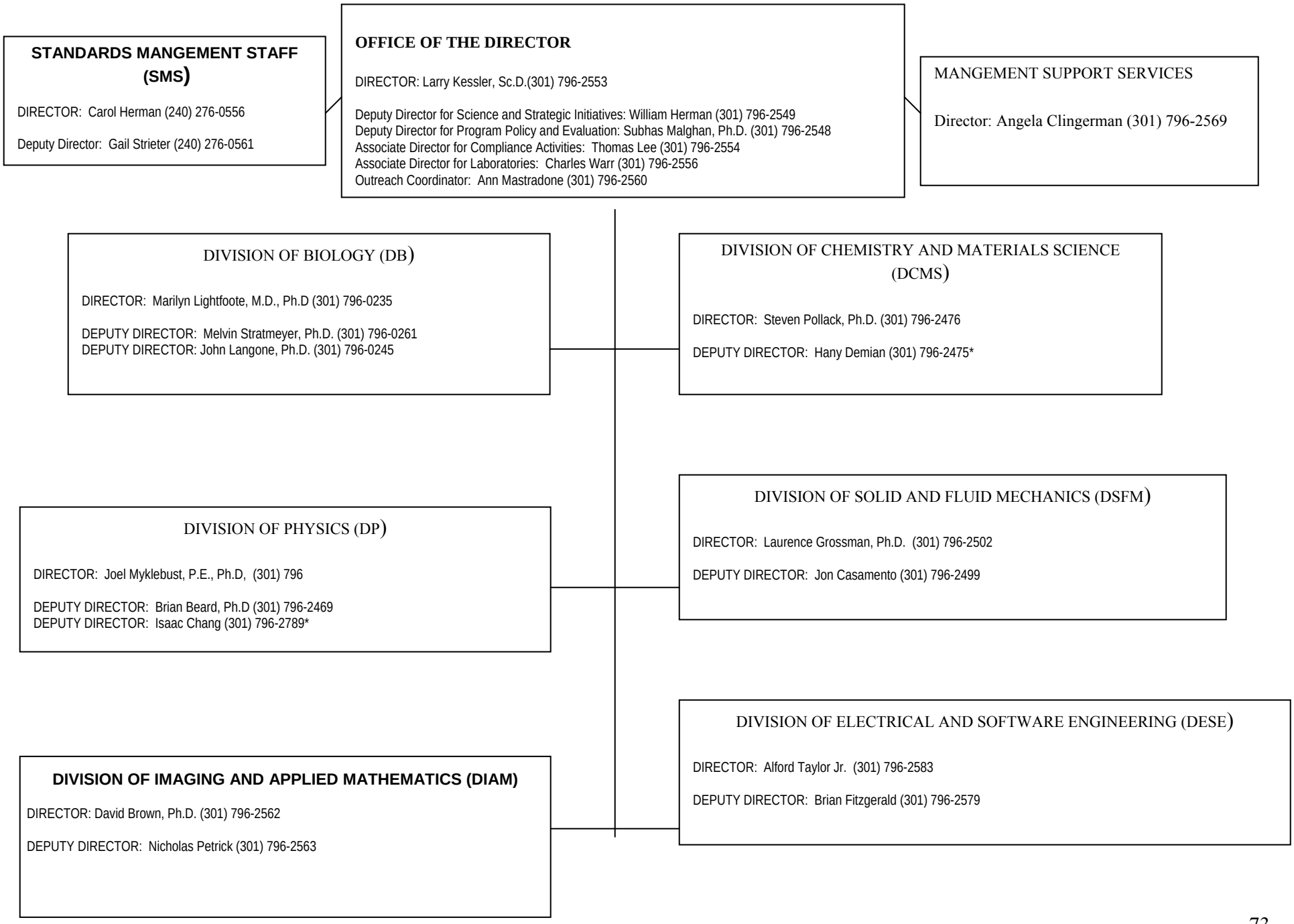
OFFICE OF SCIENCE AND ENGINEERING LABORATORIES

as of November 2007



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