OFFICE OF SCIENCE AND ENGINEERING LABORATORIES (OSEL)

(Formerly Office of Science and Technology (OST))

Annual Report

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U.S. Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Devices and Radiological Health

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), formerly the Office of Science and Technology (OST), is one of seven Offices within the Center for Devices and Radiological Health (CDRH). The seven CDRH Offices are comprised of six program offices (of which OSEL is one) and one administrative and technological support office. OSEL serves as the laboratory science nucleus for the Center. Specifically, OST/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, OST/OSEL researchers are involved in mission-oriented science activities including test methods development, risk assessments, forensic investigations, product evaluations, and technology forecasting.

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

Since mid-2003, the Office has undergone at least three major changes which have helped shape the new organization, the Office of Science and Engineering Laboratories (OSEL). The first was the move of the newly reorganized Division of Biology to the newly constructed FDA Life Science Laboratories in White Oak, Maryland. This move was the beginning of a planned consolidation of FDA facilities. The remaining OSEL divisions are expected to move to the White Oak facilities in 2006. The second change concerns the science prioritization process. In the beginning of 2004, the Office conducted a review of all 14 programs in an ongoing process. The third and final major change is the reorganization itself. OST was formally reorganized in early 2004 to improve the overall operating efficiency of the Office and to better integrate it into the mission and functions of CDRH. This reorganization is expected to clarify the ongoing research within the Office for both FDA and outside scientists. The reorganization has created a new structure in which six new divisions have replaced the four former divisions in OST and has removed all designated branches. The new office is named the Office of Science and Engineering Laboratories (OSEL).

This reorganization has taken place at a crucial time. Over the past few years, with MDUFMA (Medical Device User Fee and Modernization Act of 2002) legislation and

accompanying resources, the Office has had an opportunity to broaden and improve its scientific program. This gives the management an excellent incentive to increase the collaboration with other components of CDRH. Finally, with the recent move of the life sciences staff to White Oak and the impending construction of the engineering and physics building, the prospects for OSEL are promising.

OSEL long-term goals focus on the following:

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

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

The OSEL Annual Report provides current information about the Office's organization and intramural science activities; provides a summary of the Office's direct laboratory support for pre-market review and compliance cases; and provides a bibliography of scientific publications, presentations, and research seminars for the fiscal year. OSEL management welcomes comments on the programs described in this report. We hope you find this report useful and informative, and your comments are welcome.

For additional information, please contact us at 301.827.4777.

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OFFICE OF SCIENCE AND ENGINEERING LABORATORY DIVISIONS

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.

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.

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.

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.

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.

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.

STANDARDS MANAGEMENT STAFF (SMS)

The SMS is responsible for developing, managing, and supporting standards used for regulatory assessments. SMS manages the participation of CDRH and other FDA staff in standards development. 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.

SMS supports participation in medical device standards committees. The staff accomplishes these tasks with the help of Standards Task Groups (STGs). Additionally, the SMS assists in setting teams in the development of guidance documents that help CDRH stakeholders in improving the quality of submissions as well as in faster approval of device applications.

MANAGEMENT SUPPORT STAFF (MSS)

MSS provides leadership and support to the Office of the Director, Division Directors, and laboratory professionals on all administrative, general management, and knowledge management issues. MSS is responsible for planning, developing, and implementing Center and OSEL programmatic matters concerning financial management, personnel, procurement, contracts, inter-agency agreements, employee training, and facilities.

MSS is tasked with the managing and administering OSEL resources designed to support ongoing programs. The staff ensures the proper distribution of operating and payroll dollars, facility plans, procurement and property, travel requests and ADP needs. MSS advises the Office of the Director on potential issues that may affect resources, staffing, and management issues to comply with policies and avoid potential conflicts. In addition, MSS directs and conducts special assignments or projects for the Center as well as the Office Director.

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

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

OSEL PROGRAM AREAS

Genomic and Genetic Devices

Scope

The revolution in human genetics and the sequencing of the human genome have created new opportunities for advances in public health and new challenges for FDA. Opportunities include the integration of genetic information into routine medical practice, e.g., for use in optimizing individual therapies. The new technologies can also be used to address the issues of safety and effectiveness of products undergoing pre-market review and to address post-marketing issues such as adverse responses. The challenges arise for CDRH as the Center responsible for approving new genetic and genomic diagnostic devices. A major challenge is establishing approaches for review and approval of novel diagnostic devices that provide hundreds or thousands of data sets generated simultaneously on microarrays. A microarray is a small piece of glass, plastic, silicon, or other material on which thousands of samples of DNA (e.g., oligonucleotide probes) or other receptor material (e.g., antibodies, tissues) have been attached in tiny pinpoint samples in a two- or three-dimensional format.) Microarrays are used to screen a biological sample for the presence of thousands of genetic sequences, proteins, or other targets at once, for example, to study gene expression. The need for genetic diagnostic tests that rapidly identify agents of bioterrorism and genomic human responses to these agents will add a level of urgency to the pre-market review responsibility faced by the center.

Background

Projects under this program are designed to provide hands-on knowledge and experience using the new technologies. A major effort is being devoted to the evaluation of microarray technology and device performance, in order to contribute substantively to standards development for genetic and genomic diagnostic devices. Although the technologies are new in some respects, they can still be validated against known surrogates. Projects are chosen that are informative for a particular device issue, such as factors related to microarray performance, a new approach to safety or effectiveness evaluation, or data that contribute to understanding and preventing adverse events. Projects are also designed to provide a basis for keeping up with the technologies as they evolve.

There are two basically different types of devices representing the new technology coming to CDRH for review: genetic and genomic testing devices.

A genetic test determines the presence or absence of a particular, targeted DNA sequence already known (or suspected) to be related to a health outcome. Examples are mutations in the cystic fibrosis gene (human genetic disease), in a drug metabolizing gene (efficacy of a given class of drug), in the p53 gene of a tumor (prognosis and therapeutic stratification), or in genes related to susceptibility to cardiovascular disease or cancer. One expectation is that pharmaceutical companies will submit applications for approval of combination products, e.g., a genetic diagnostic test *along with* a drug, in order to stratify a clinical trial population, or to include or exclude a certain segment of the population. Another use of genetic tests is to rapidly identify pathogens that may be used in terrorist attacks. Genetic testing is an established technology. It involves a query for a mutant sequence, usually within one gene. Microarrays can be used for parallel queries of many potential mutations or sequence identities.

The genomic type of diagnostic test involves gene expression, usually measured by mRNA or a surrogate, often in comparison to a reference set of expressed genes. Genomic technology involves analysis of many hundreds or thousands of genes that are up-regulated or down-regulated either constitutively or in response to a stimulus. The result is a pattern of gene expression that is designed to be diagnostic or characteristic of a condition. Examples would be patterns related to toxic responses, characteristic of a disease subset or representative of a human response to a pathogen. Diagnostic devices can also be used to analyze expression profiles of proteins, the end-products of gene expression (i.e., Proteomics). Microarrays can be used to generate, and bioinformatics used to analyze, the complex patterns generated by genomic/proteomic and genetic devices. Whole genome analysis is relatively new and experimental, and methods and analytical approaches are still being developed.

Program Description

Because genetic and genomic devices are based on different technologies, projects are underway in each area. Issues are described below.

- ***Genomic Diagnostic Devices*** (*RNA and DNA technologies, complex microarrays, bioinformatics*). Project: Diagnostic gene expression microarray for Type I latex allergy

Project: Beta testing of new genomic technologies (*keep pace with new developments)*

- ***Genetic Diagnostic Devices*** (DNA *technologies; high-throughput genetic analysis*)

Project: Microarray detection of drug-resistant strains of *M. tuberculosis;*

These projects provide a base for genomic and genetic device performance evaluation, and for continuously updating our capability in new technologies as they evolve. The knowledge and experience gained including methods design and development, as well as device performance evaluation, will enable OSEL scientists to do the following: 1) make

informed regulatory decisions by critically evaluating data obtained with diagnostic devices based on genomic and genetic technology, and 2) contribute to writing standards and guidance documents. The projects will also demonstrate some of the ways in which new genetic and genomic approaches can enhance public health. Mastery of genomic and genetic technologies involved in these projects will prepare us for possible future projects involving the rapid detection of microorganisms and human host responses associated with biodefense. The projects in this program support the CDRH Strategic Plan, especially the Total Product Life Cycle and Magnet for Excellence. Additionally, collaborations within FDA, with other government organizations, academia, and industry have provided ample opportunity for significant leveraging of resources and expertise.

Relevance to FDA and CDRH Mission, Program, and the Public Health impact

Scientists in this program area are developing and performing laboratory projects that give them hands-on experience with emerging microarray-based and related molecular technologies. The knowledge and experience gained, including methods design and development, as well as device performance evaluation, will enable OSEL scientists to 1) participate effectively in the CDRH regulatory review of pre-market device applications, 2) make informed regulatory decisions by critically evaluating data obtained with diagnostic devices based on genomic and genetic technology, 3) contribute to writing standards and guidance documents. The projects will also demonstrate some of the ways in which new genetic and genomic approaches can enhance public health. Mastery of genomic and genetic technologies involved in these endeavors will prepare us for possible future projects involving the rapid detection of microorganisms and human host responses associated with biodefense. In addition, collaborations within FDA, with other government organizations, and with academia and industry have provided ample opportunity for significant leveraging of resources and expertise.

Five-Year Objectives

- Gather additional data to anchor new genomic and genetic technologies:
    - Rapidly detect drug-resistant strains of *M. tuberculosis*: validation with clinical samples
    - Understand gender differences in genomic responses to latex
    - Understand genomic responses to latex: latex specific or a marker for Type I allergy?
    - Research microarray-based genotyping of p53 mutations in human tumors

- Utilize genomic and genetic technologies to address device issues
    - Test new device/implant materials for host responses
    - Stratify patients to the most appropriate device therapy
- Protein microarray technology (Proteomics)
    - Proteomic analysis of restenosis following stent placement

- Diagnostic test validation for counter-terrorism (if so directed)
    - Microarray screening of mutant microorganisms of significance to biodefense research
    - Diagnostic genomic tests for CDC-listed biological threat agents
    - Evaluation of genetic tests for detection of chemical toxicants that pose a terrorism threat

Host Response: Tissue-Materials Interactions and Tissue-Device Interactions

Scope

This is an interconnected program of laboratory research, risk assessment, and standards development activities designed to provide a scientific basis for regulatory decision making in CDRH. The data on potential adverse effects of medical device materials and chemicals gathered from pre-clinical experimental approaches in this program are used to reduce uncertainties in assessing risks to patients exposed to physical and chemical insults, and protect their health.

Background

In 1983, the Bureau of Radiological Health and the Bureau of Medical Devices were merged into the Center for Devices and Radiological Health. This merger presented the new Center with a disparity between the research programs devoted to radiation issues and those devoted to medical device issues. Additionally, a discontinuity existed between classical chemical toxicology and the potential adverse health effects posed by exposure to medical devices. To address this need, OSEL expanded the existing radiation research program to include medical device toxicology. More recently, the program has evolved to address the development of toxicological and microbiological approaches to risk assessment and investigation of biological issues relating to infection control and tissue-engineered medical products (TEMPs). Program Description:

The "Host Responses: Tissue-Materials Interactions, Tissue-Device Interactions" research program encompasses two major areas: 1) Biological Effects of Chemicals and Medical Device Materials, and 2) Infection Control.

1) Biological Effects of Chemicals and Medical Device Materials

OSEL is conducting a wide range of projects designed to examine the biological effects of chemicals released, intentionally or unintentionally, from medical device materials or the tissue-device interactions themselves. The general goals of these studies are to evaluate the

safety of these chemicals and materials and to develop or refine test methods that improve preclinical testing of device materials. Studies in this area fall into several subcategories:

Immunological/Inflammatory/Proliferative effects. OSEL scientists are conducting research to examine the immunological, inflammatory, and proliferative effects of materials and chemicals released from materials, including examination of the stimulation of chronic inflammation by particles using both *in vitro* and *in vivo* models, and the induction of allergic responses by material constituents, such as natural rubber latex proteins and metals. In addition, scientists are conducting research on the ability of compounds incorporated into a device (e.g., drug-eluting coronary stents) that are intentionally released in order to mitigate inflammatory or cell proliferative responses induced by the device.

Toxicity of compounds released from medical device materials. OSEL is involved in investigating the adverse effects of compounds (e.g., metals, DEHP, ethylene oxide, bisphenol A, endocrine disruptors) released from medical device materials using small and large animal models, developing toxicity tests specific for medical device materials (e.g., polymers that cure *in situ*), and developing biomarkers to detect early cell and tissue damage caused by compounds released from devices.

Biological effects of nanotechnology products and tissue engineered medical products (TEMPs). The development of TEMPs and nanoparticles in health care delivery is at the cutting edge of medical device technology. OSEL is developing test methods to examine the potential tissue interactions of these materials and medical devices, such as TEMPs scaffold materials and nanoparticles, in patients receiving the device and on the cells and tissues that are components of the device.

2) Infection Control

Infection at the site of an implanted device represents a potentially devastating event, often requiring surgical intervention to remove the device. Prevention of infection is the key to infection control and a wide range of CDRH-regulated devices are required to ensure sterility in surgical procedures. OSEL scientists have addressed the issues of infection control through the development of cleaning procedures for new and reusable devices; examination of disinfection and sterilization equipment and procedures; assessment of chemical sterilant residuals on devices; development of test methods to ensure that barriers such as surgical drapes, gowns and gloves are tested for effectiveness in preventing transmission of microorganisms; and evaluation of the impact of bacterial adherence to materials (biofilms and endotoxins) on infection risks.

Relevance to FDA and Public Health Impact

The experimental studies in this laboratory research program generate independent data for assessing toxicological risks and for developing standards and guidance documents. OSEL

remains at the forefront in medical device toxicology and for developing methods for risk assessment. Specifically, OSEL serves as an independent source of data on medical device toxicology and risk assessment for risk managers in CDRH Offices. These data and risk assessments provide a scientific basis for developing important pre-clinical and post-market activities, such as developing ASTM standards for testing biological responses to particles both *in vivo* (F1904-98) and *in vitro* (F1903-98), ISO standards (e.g., ISO 10993-17) for establishing tolerable intake values, Federal rule-making (e.g., for natural rubber latex protein content in gloves and condoms), and for risk management decision-making in the Center (e.g., FDA Public Health Notification for DEHP in medical plastics).

Five-Year Objectives

Long-term objectives include 1) develop and establish test methods and models for evaluation of potential adverse effects of medical device materials, and medical devices, including elucidation of new, clinically relevant, and sensitive biomarkers to predict adverse effects in the preclinical stages of product development, and 2) characterize the potential adverse effects using pre-clinical laboratory models and utilizing the data to predict the likelihood of adverse effects in humans.

Biological Risk Assessment

Scope

Risk assessment is the process of determining the extent of human health hazard relative to exposure conditions. Staff in the OSEL biological risk assessment program conduct research to address CDRH's regulatory need for improved methods of detecting and quantifying risks associated with 1) chemical compounds released from medical device materials, 2) microorganisms associated with medical devices, and 3) exposure to radiation. Research in the program is designed to reduce uncertainties in the risk assessment process and to support risk management decision-making in the Center. The program is closely linked with the Tissue-Material Interaction Program and includes staff with expertise in toxicological, microbial, and radiation risk assessment.

Background

OSEL staff has long been responsible for conducting risk assessments of compounds released from medical device materials. These risk assessments have been directly used to support regulatory decision making in the Center (e.g., microbial risk assessment to support Sterility Assurance Levels, DEHP Safety Assessment to support the issuance of a Public Health Notification and draft labeling guidance). More recently, staff have been involved with the development of the ISO 10993-17 standard, *Method for the Establishment of Allowable Limits for Residues Using Health Based Risk Assessment.*

Toxicity studies used for the risk assessment of compounds released from medical devices are almost always conducted using healthy animals; however, patients exposed to these compounds may be critically ill or injured.

A number of studies have demonstrated that the potency of some compounds is potentiated by conditions such as renal failure, liver failure, and sepsis. Therefore, a tolerable intake (TI) value derived for a compound in a study that uses healthy animals may not be adequately protective for a critically injured patient. In the ISO/DIS 10993-17 standard, the approach for deriving a TI involves application of a default Uncertainty Factor (UF) of 10 to account for inter-individual variability in the human population, in the absence of more specific data to identify sensitive subpopulations. However, it is not clear whether this default UF is adequate to protect critically ill or injured patients from the toxic effects of compounds released from medical devices. To address this broad issue, animal models of compromised health will be developed in our laboratory and used to examine whether the potency of compounds is increased in experimental animals with compromised health compared to healthy animals. These models will also be used to assess the impact of ultrasound contrast agents on the vascular endothelium and to develop new devices that can be used to assess tissue damage and functional changes in diabetic patients.

Program Description

FDA's Center for Devices and Radiological Health (CDRH) is responsible for ensuring the safety and effectiveness of medical devices and eliminating unnecessary human exposure to man-made radiation from medical, occupational and consumer products. This broad mandate requires chemical, microbial, and radiation risk assessments to be performed to support regulatory decision making in these areas. Chemical risk assessment activities in CDRH focus on three areas: 1) the development and validation of new risk assessment methodologies, 2) bench-top research to provide information for the hazard identification and dose-response assessment stages of the risk assessment process, and 3) the application of risk assessment approaches to assist with regulatory decision making. Risk assessments have been used by CDRH to assist in reaching decisions on various issues that have received considerable attention in the media, including the safety of phthalate esters released from PVC devices, dioxin released from tampons, and 2,4-toluenediamine released from polyurethane-foam covered breast implants. The research component of the program is key in addressing uncertainties regarding the response of sensitive subpopulations to the effects of chemical compounds. Radiation risk assessment activities in CDRH focus on three areas: 1) assessing the risk of skin cancer, particularly malignant melanoma, from exposure to tanning lamps, 2) evaluating published results that state that there are possible health risks from exposure to radiofrequency radiation from cellular telephones, and 3) assessing any potential increases in risk from unnecessary ionizing or non-ionizing radiation from regulated medical devices and radiological products.

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

Efficient, science-based risk management is a component of the FDA Commissioner's five-part strategic action plan to protect and advance the health of Americans (http://www.fda.gov/oc/mcclellan/strategic.html). Risk assessment is the first step in the risk management process. The OSEL program in risk assessment involves laboratory-based efforts to address risk assessment uncertainties, development and validation of new risk assessment methodologies, and use of risk assessment to support regulatory decision-making. A key laboratory-based effort is directed towards examining whether critically ill or injured patients represent a sensitive subpopulation and can be more susceptible to adverse effects of chemicals. Research is also being conducted to address data gaps identified in risk assessments performed by the research staff (e.g., studies on the pulmonary effects of DEHP). Risk assessment methods are being developed as part of the process to create consensus standards for the biological evaluation of medical devices under the auspices of ISO.

Five-Year Program Objectives

- Develop and validate rodent models of renal failure, liver failure, and sepsis.
- Develop a rat model of atherosclerosis and investigate the ability of ultrasound to accelerate the progression of atherosclerotic lesions.
- Develop and validate a pig model of sepsis.
- Evaluate the feasibility of using the models for biocompatibility assessment.
- Use the compromised health animal models to address risk assessment questions regarding the relative sensitivity of sick vs. healthy animals to chemical compounds.
- Use the models to address mechanistic questions about the potential role of compounds released from devices in the etiology of adverse effects seen in critically ill patients.
- Determine the feasibility of using imaging techniques (i.e., MRI) to detect subtle physiological changes associated with renal failure, liver failure, and sepsis.
- Use the sand rat model to develop a non-invasive diagnostic device for the early assessment of diabetic ocular and retinal damage, a *de novo* biosensor device for glucose sensing and a level laser therapy device for wound healing.
- Determine the tanning characteristics of different skin types in an attempt to reduce the dosage of ultraviolet radiation needed to produce and maintain a tan.
- Attempt to reproduce studies that showed an increase in micronuclei following exposure to radiofrequency radiation similar to that from cellular phones.
- Determine potential risks from UV-emitting lamps used to disinfect air in public areas such as nursing homes, TB wards, homeless shelters, and prisons.

Biotechnology and Biomolecular Studies

Scope

The laboratory studies of this program aim to ensure that there are consistent testing requirements and that the Center is aware of and understands cutting-edge biological technologies in developing new devices or device materials.

Program Description

Studies are proposed to address safety concerns about current and impending submissions of combination products, including the importance of possible immunotoxic reactions to incorporated biomaterials. The goal of these studies is to develop critical issues in the emerging field of combination product (i.e., biological matrices used in wound healing); issues in cardiovascular surgery; and issues addressing cell encapsulation. These studies will also address the potential of combination products to cause chronic inflammation.

Laboratory investigations will address intravascular catheters which are coated or impregnated with antimicrobial or antiseptic agents. It is important to assess microbial contamination of catheters and other medical devices and to compare and evaluate the efficacy of antimicrobial treatments. These studies use biosensors which are tools for effective real-time biological analysis. Bioluminescence is explored as the technology for such analyses.

Other studies explore the detailed mechanism of action of taxol or sirolimus in drug elutes stents. Mechanisms of action of platelets and delayed endothelial healing leading to thrombosis will be investigated. Laboratory *in vivo* and *in vitro* exploration of neointimal hyperplasia leading to in-stent re-stenosis, as well as clarifying the factors that contribute to fatalities, are planned in these studies. Techniques using differential display will be developed for these analyses.

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

Using new technology in developing medical devices for pre-market approval is anticipated as the trend of products generated by creative research and biotechnological progress. Much of the laboratory work at CDRH evaluates production of leachables released from devices. Questions about whether a finished device, device material, or extract of the device produce adverse biological effects can be addressed using new technology. Output from this work would appear in guidance documents, in review consults, and via scientific exchange. Reviewers can use these resources for rapid access to cutting-edge information.

Five-Year Program Objectives

1) Scientific interactions through professional societies and meetings will be maintained to serve as knowledge managers of emerging technologies anticipated for new devices.
2) Collaborating with review groups in the Office of Device Evaluation to keep pace with scientific queries of special interest to reviewers so that needed technology information will be readily available from OSEL scientists.
3) Planned workshops and access to NIH and other government and academic centers will be maintained and developed for awareness of current cutting-edge emerging technology.
4) Review annually the status of the research targets and accomplishments.

Materials Characterization and Polymer Degradation

Scope

In the pre-market phase, the synthesis, processing, and fabrication of materials are evaluated. These processes affect the molecular structure, phase, and ultimately the physical, chemical, mechanical properties, and biocompatibility of medical devices. Studies include residue and contamination analysis, purity, chemical structure and formulations, thermal stability, phase stability and transformation, transport and thermodynamic properties, viscoelastic, wet surface and adhesive properties. Computational methods are also used to predict physical and chemical properties when appropriate.

Background

The performance of a medical device in its intended function is ultimately related to the performance of the materials used under the particular service conditions to which the device is subjected. Thus, investigating the failure mechanism of medically relevant materials under a variety of service conditions becomes critical to CDRH's mission of assuring that medical devices are safe and effective. In order to achieve this goal, this program focuses on developing predictive, laboratory-based methods for determining the long-term stability of materials in contact with a variety of service environments. Included in this determination is identifying critical parameters, either in the device fabrication history, storage, or in the service environment, which can lead to failure through material related causes. These service environments vary by site of implantation, application

conditions (oxygen rich atmospheres for example), or storage conditions of devices and components that could affect shelf life.

Program Description

The program is designed to contribute to evaluating medical device materials safety and effectiveness in the *total product life cycle*. The program laboratories are capable of testing the performance of chemical processes of importance to medical devices, such as mass transfer through membranes used in dialysis and manufacturing processes used to fabricate materials. The laboratories also contribute to testing, developing and assessing consistent and suitable characterization methods for the chemical, physical, and biological properties and characteristics of materials and devices. This program provides the Center with independent data as well as intramural knowledge and experience concerning the use of preclinical/post-market studies for the evaluation of medical device materials safety and performance. Additionally, the program evaluates the degradation of materials in storage or use *in vivo* or *ex vivo*, and identifies potential materials related failure modes. It contributes to the development of regulatory guidance and test methods to ensure the safety and effectiveness of medical devices and their material components.

The materials degradation program evaluates the chemical, thermal, and environmental degradation of materials and the affect of degradation on medical device performance and safety. This effort includes many post-market evaluations of device failures and forensic investigations. Post-market forensic investigations of materials failures are very useful in advancing knowledge to ensure future problems are avoided. Factors such as the release of toxic degradation products, and diminished chemical or physical properties are evaluated.

In addition to identifying the degree and mechanism of materials degradation, several models of materials degradation both *in vivo* and *in vitro* have been developed to predict the effect of the human body on materials in terms of degradation routes and ultimate outcome of degradation products. Some on-going and recent activities include unidentified particles in PVC blood bags, defective IV set fabrication, Intergel Adhesion Barrier and counterfeit polypropylene hernia repair mesh.

The program's experimental pathology laboratory is equipped to evaluate the explant pathology of medical devices utilizing gross pathology, histopathology, immunohistochemical staining and molecular pathology studies. Additionally, physical and morphological materials characterization studies can be conducted focusing on x-ray, infrared and dynamic mechanical techniques to determine structure, chemical and morphologic changes resulting from the exposure of materials to the implant environment. The research program has provided independent data identifying heart valve failure modes associated with emerging polymeric and tissue-derived materials as well as the identification of a mechanism for the loss of cuspal cells in viable allograft heart valves following implantation. The knowledge and experience gained through these investigations

have supported the regulatory decisions and recommendations made concerning four generations of replacement valves.

The research in this program area is directed toward the development and establishment of *in vitro* and *in vivo* studies and models suitable for the evaluation of materials-tissue interactions, failure modes and effects analysis, and the assessment of medical device-related pathology. Peer-reviewed publications in the medical, materials science, and engineering literature serve as the scientific basis for regulatory guidance recommendations and standards development.

Five-Year Program Objectives

- Develop test methods to ensure the safety and effectiveness of new device technologies;
- Increase peer-reviewed publications, presentations, and test methods developed in support of guidance and standards;
- Provide independent laboratory data on materials failures to improve the pre-market evaluation and post-market issues;
- Contribute to the missions and functions of CDRH and other FDA centers by solving interdisciplinary problems involving materials;
- Enhance active participation with external partners including governmental partners, academia, and industry; and
- Provide independent data based on *in vivo* preclinical studies evaluating the next generation of replacement materials in devices such as stents, heart valve, and cardiovascular device materials.

Medical Imaging and Diagnostics

Scope

A wide variety of new digital imaging and display devices are under development by academia and industry, with a broad range of performance characteristics. The Center thus requires new/improved guidance for the evaluation of such devices. To this end, OSEL scientists are developing evaluation methodologies for diagnostic medical imaging systems such as mammography and fluoroscopy, computed tomography, nuclear medicine, diagnostic ultrasound, and magnetic resonance imaging, as well as novel soft-copy display devices for viewing medical images. This program is located within the Division of Imaging and Applied Mathematics (DIAM).

Background

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

Program Description

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

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

The expertise developed through this program is being applied to the review of PMAs for ultrasound bone sonometers and new digital radiographic imaging systems, the development of amendments to the diagnostic x-ray performance standard, the development of an advisory pertaining to pediatric CT exposures, and the joint planning of a consensus development conference on CT with NIH. The x-ray spectral measurements program provides a source of otherwise unavailable data to the entire mammography research community. Finally, investigating computer-assisted diagnosis devices provide the Center with the scientific basis to effectively regulate this fast growing field.

Five-Year Objectives

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

The Medical Imaging and Diagnostics program has made fundamental contributions to the field of statistical analysis of diagnostic imaging and systems for computer-aided diagnosis. We would like to exploit this work and validate its range of utility through extensive computer simulations. In the process, we would be seeking the most efficient or statistically powerful approaches to the evaluation of medical imaging and computer-assist decision modalities. An ultimate goal is the development of a multiple-reader (e.g., multiple radiologists, multiple pathologists) multiple-case (MRMC) version of our current software for ROC analysis in the absence of ground truth (i.e., without a gold standard). Development of such a system would address one of the most difficult yet most common assessment problems in the field of diagnostic medicine. Many statistical problems in the new field of bioinformatics remain unsolved. We would like to extend our contemporary successful research into new realms of bioinformatics that are opening up due to the accumulation of data from multiple testing and patient demographics. This will require continual upgrading of our computational facilities.

Fluid Dynamics and Ultrasonics

Scope

The rapid development of medical devices employing minimally invasive technologies has revolutionized modern health care. Diseases that once required invasive surgery for diagnosis and treatment are now routinely addressed on an outpatient basis. The goal has been a reduction in health care costs and an increase in patient safety. In addition, many diseases can now be diagnosed much earlier, resulting in more effective treatment.

Background

The continuing dearth of natural donor organs, the inherent shortcomings of existing prosthetics, and significant advances in the understanding of the fundamental requirements of artificial organs all fuel significant research, development, and regulatory activity that drive the fluid dynamics research projects. The medical products in this area are among the most complex that the Center evaluates, and their public health significance is often profound. Similarly, the rapid growth of diagnostic techniques and minimally invasive therapies drives our current work in ultrasonics. Specifically, in the area of ultrasound tissue ablation, significant advances in image guidance, transducer design and non-invasive in-situ temperature determinations are lending great impetus to the development of viable clinical therapies.

The maintenance of blood transport is a major focus of the fluid dynamics program, as heart failure is the prime cause of death in this country. Prosthetic heart valves, ventricular assists, total heart replacements, grafts, stents, bypass pumps, hemodialysis systems, and oxygenators all must avoid placing unusual hydrodynamic loads on the body; they must avoid damaging the cellular components of blood, and they must minimize the activation of platelets that initiates the clotting cascade. The requirements imposed by the above constraints are primary concerns of the fluid dynamics research effort.

In ultrasonics, the variable of ultimate interest is that of tissue temperature, as temperature profiles largely determine cell viability. Thermal injury is highly desirable for therapies intended to shrink or ablate tumors. However, injury is usually highly undesirable in the case of diagnostic imaging. Either way, the ability to predict the temperature-time response requires accurate knowledge of the ultrasound fields, and how they are absorbed. This becomes particularly important in the relatively new technology of high intensity-focused ultrasound ablation where energy levels are high and the targets may be deep within the body.

Program Description

A variety of approaches are employed depending upon the specifics of the issue and the devices in question.

High-intensity focused ultrasound (HIFU) holds the potential for radically advanced surgical techniques, including ablation of both malignant and benign lesions and cessation of internal bleeding in injured vessels and organs. Although some clinical success has been achieved, the lack of standardized methods to assess the acoustic and thermal characteristics of the focused beam is one factor that has hampered general understanding and acceptance and has slowed the regulatory review process, especially in the preclinical

phase. The objective of OSEL current research is first to develop methods for assessing the acoustic beam characteristics of HIFU devices. Then, temperature profiles will be calculated using computer models. Finally, the results of these two tasks will be validated by measuring the temperature distributions of HIFU beams under various exposure conditions using thermal test objects and other tissue-equivalent materials.

For prosthetic heart valves, the effective orifice area and regurgitation are macroscopic quantities that provide key descriptions of the valve operation. Researchers have worked with industry and academia via standards development to define useful characterization tests for prosthetic heart valves. Current work in this area centers on the need to remove the dependence of test results on the specific pulse duplicator hardware employed. Other recent work involving prosthetic heart valves examined the physical stresses inherent in the fluid-solid interaction. These stresses are an important predictor of valve life. For mechanical valves, they are determinants of potential crack propagation and of cavitation. Either effect can lead to valve failure.

Thrombosis is a major concern for any device with direct blood contact. The clotting cascade is an extremely complex process; however, flow stagnation is often involved in triggering platelet activation and initiating the cascade. Tiny regions that allow flow stagnation in or around medical devices can act as seeds for the development of thrombus. OSEL is developing and employing advanced flow visualization techniques to allow evaluation of the potential for thrombus formation. Current work involves evaluating the clot trapping and flow characteristics of vena cava filters. These techniques are also needed for evaluating regions of high shear stress, where mechanical damage to red blood cells and platelet activation may occur. Scientists are also performing systematic testing to identify and control the primary variables that determine the mechanical fragility of blood. Researchers anticipate that these tests of mechanical hemolysis and flow visualization would be incorporated into the preclinical screening of any device for which such testing would be beneficial.

Five-Year Objectives

Long-term planning guides decisions about major equipment, infrastructure, and personnel investments. OSEL anticipates that the use of mechanical organ replacement and assists will continue to grow over the time period in question. Advances in genetics and tissue engineering that would render mechanical assists or artificial organs obsolete are not yet on the horizon. These alternate approaches are not likely to reduce the regulatory workload for mechanical organ assists and replacements in the coming decade. Advances in electronics, computer technology, and materials will allow for devices of increased capability, complexity, and yet smaller size. However, a fundamental shift away from technologies currently employed is unlikely. OSEL will continue to maintain a heavy investment in life-extending/saving technologies, principally those in the cardiovascular area. The

interactions of blood with the body form the primary limitations for these devices and, thus, this is where the most improvement is likely to come.

This program will continue to examine new ultrasonics devices and technologies for safety and effectiveness. New policies, regulations, standards and guidance will be needed to enable individuals to safely operate and maintain these devices. This information will be obtained from independent laboratory studies, and in-house research that is conducted to anticipate new directions of this technology and will be disseminated in the form of peer-reviewed publications, consultative reviews, and guidance documents.

Radiation Bioeffects

Scope

Numerous medical devices and consumer products regulated by CDRH emit radiation: ionizing (x-rays) or non-ionizing (ultraviolet radiation [UV], radio frequency, or acoustic radiation). In order for the public to enjoy the benefits of these products and technologies, it is necessary to establish safe limits for the exposures to these emissions (whether intentional or incidental) or provide scientific basis for reducing the exposures. The goal of the radiation bioeffects program is to develop scientifically based criteria for evaluating radiation-emitting medical devices and consumer products and for developing relevant CDRH/FDA guidelines and standards.

Background

Currently over 100 million Americans use wireless phones. Data relating to the safety of radiation from wireless phones are inadequate, however they suggest that exposures to radio frequency radiation at levels relevant to wireless phone use may cause biological effects. In this area, the OSEL bioeffects project serves as the coordinator of independent research conducted in several laboratories. These laboratories have been selected by CDRH, and OSEL is extensively involved in these investigations. The new findings together with other published data are being evaluated by OSEL for inclusion in appropriate FDA guidelines and standards.

Program Description

OSEL currently has a number of active programs to investigate (1) the safety of cell phones, (2) the biological effects of radiation emitted by radiation therapy devices for treating cancer or dermatological conditions, and (3) radiation emitted by or transmitted through consumer products such as tanning equipment or cosmetics (in collaboration with

CFSAN, NCTR, and NCI). OSEL evaluates the bioeffects of acoustic (ultrasound) radiation to ensure safety of the diagnostic and therapeutic use of this modality. The bioeffects program also collaborates with other agencies, such as the National Toxicology Program, to initiate and coordinate broader programs such as a national study of the possible carcinogenicity of radio frequency radiation (nominated for study by members of the OSEL bioeffects program). In past years, the radiation bioeffects program has been involved in extensive collaborative research efforts with other national agencies in the areas of electromagnetic fields involved in the transmission and use of commercial electric power. In the future, the bioeffects program expects to become increasingly involved in the support of homeland defense and counter-terrorism that may involve radiological incidents. Currently the program is developing collaboration with the Department of Defense to study methods for identifying and testing new drugs to protect people from the effects of radiation such as might be released in a terrorist act. In another counter-terrorism area, our involvement will be needed for evaluating the radiation-emitting equipment proposed for security control at the entrances to sensitive areas (e.g., metal detectors at airport terminals).

Five-Year Objectives

The radiation bioeffects program is currently undergoing a shift in emphasis away from electromagnetic fields research, which was successfully completed with external funding from the National Electromagnetic Fields research program funded by Congress and administered by NIEHS. The currently strong program of UV research will continue to pursue new problems relating to UV radiation/tissue interactions and tanning equipment and is partnering with CFSAN and NCTR to investigate problems related to the interaction of UV with cosmetics. The program is expected to begin collaborating with CDER in the area of sunscreen testing, especially regarding UVA protection. The ionizing radiation program is expected to strengthen with the recent relocation to the White Oak campus where facilities will become available for the installation of upgraded ionizing radiation sources. Operating these new radiation sources is critical to the strengthening of the radiation bioeffects program. The program is thus becoming less involved with the risk assessment of electromagnetic fields (which formed the backbone of the program in the 1990's) and more oriented toward the radiation-emitting medical devices and consumer products, as well as the radiation-related issues in the area of counterterrorism.

Electrophysiology and Electrical Stimulation

Scope

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

Background

There is large and increasing interest in the scientific and medical communities in the use of electrophysiology and electrical stimulation in diagnosis and treatment of diseases and disorders. Between 1998 and 2002 electrophysiological devices comprised 22% of all PMAs and 31% of all IDEs for CDRH. The need for specialized skills from OSEL related to electrical stimulation has increased. As a result, three recent temporary shared positions between staff from OSEL and ODE have been appointed. One such position is for a cardiac electrophysiologist, the second is for a retinal electrophysiologist, and the third is for a computational neuroscientist. The requirement within ODE for scientific skills in these areas is substantial. The American College of Cardiology recently advised that the patient population to be implanted with automatic defibrillators be expanded, and there are a host of new electrical stimulation device applications being submitted for approval. Retinal stimulators have become devices of major public interest because of their potential to treat the blindness afflicting millions of Americans. Electrical stimulation devices are being submitted for urological conditions and even for the diagnosis of breast cancer. There are a host of brain and nerve stimulators along with the long-standing need for a guidance document for electroconvulsive therapy device submissions.

The diversity of devices and the large number of regulatory applications has focused OSEL's laboratory work broadly on the basic mechanisms by which these devices exert their effects. Understanding basic mechanism, especially regarding safety, is a unique primary concern for CDRH. These studies permit expert consultations for preclinical device reviews in every area of CDRH activity; they provide the basis for guiding clinical

trials and guidance documents; they prove useful as part of the approach that assists firms with the least burdensome route to approval; and they generate publications that draw the attention of the scientific community to issues of safety. Current staff performs in-house laboratory studies encompassing cellular neurophysiology, cardiac electrophysiology, and visual science.

Program Description

OSEL's investigations of electrophysiology and electrical stimulation center on clarifying the mechanisms of interaction of the technology with the body. The work is specifically aimed at forming the scientific basis for regulatory decisions, developing guidance documents that speed device approvals, and establishing industry safety standards for electrical stimulation. Specific areas of investigation are the cellular basis of electrical stimulation safety in nerve and heart, cardiac electrophysiology and defibrillation, and retinal electrophysiology and stimulation. These areas map onto the anticipated regulatory needs of the Center in this broad area of medical devices. Current areas of investigation and accomplishments are listed below:

- *Cellular Studies of the Safety of Electrical Stimulation* – Many neurological and cardiac devices employ electrical stimulation to affect or replace neural function. Initial studies defined the possible dangers of electrical stimulation and the related stimulus parameters. OSEL researchers systematically studied the effects of different electrical stimulation parameters and safety in both cultured human neural tissue and animals. The results showed a hierarchy of effects depending upon the electrical parameters. For example, high energy deposits cause tissue heating, large voltages cause cell membrane damage, repetitive stimulation can lead to excitotoxicity, and weak electric fields can interfere with normal nerve impulse propagation. OSEL studies showed that for most stimulation devices the primary safety concern is that electrical stimulation can cause metabolic fatigue in nerve cells, which leads to subsequent functional as well as histopathic changes.

- *Neurological devices (including cochlear implants and deep-brain stimulators)* – Present studies are focusing on the effects of high-frequency stimulation. These studies are being performed with computational modeling of action potential propagation, with confirmatory studies in animal central nervous system. The results demonstrate that high-frequency stimulation is likely to fatigue nerve and produce conduction block (even for subthreshold stimulation). This work is serving as a basis for requesting post-market studies of certain devices to include human neuropathological studies.

- *Cardiac electrical stimulation* –OSEL scientists are technically unique in their combination of intracellular electrical recording and high-time-resolution optical recording. The work is examining the safety basis for effective cardiac

defibrillation and pacing to improve cardiac function. We have been investigating how the defibrillation shock interacts with cardiac tissue, to the improvement of safety and patient outcome. Our initial studies showed the relationship between shock strength, waveform, and duration on the arrest time and intracellular calcium dynamics in tissue-cultured heart cells. This work demonstrated deleterious cellular effects from certain combinations of shock parameters. Extramural studies have pointed to similar effects in animals and in the clinic, and they have contributed to the development of safer and more effective defibrillator waveforms.

Five-Year Objectives

The use of electrical stimulation and electrophysiology in medical devices will continue to grow for the foreseeable future. Our focus will be on developing research that will have general applicability to the regulatory process including providing the scientific expertise for reviews, guidance document development, and contributions to industry standards. This program will continue to examine new devices and technologies for safety and effectiveness. The information will be obtained from independent laboratory studies and from in-house research conducted to anticipate new directions of this technology and will be disseminated in the form of peer-reviewed publications, consultative reviews, and guidance documents. It will assist in speeding the rapid movement to market of safe and effective medical devices benefitting the U.S. public.

The specific plan includes developing test methods and guidance documents (with the necessary supportive research and extramural interactions) for devices that stimulate the nervous system and heart with electrical current.

- **Computational Human Model to Test Cardiac Electrophysiology Devices**: OSEL scientists will also use advanced computer models of heart as a means of establishing realistic human models for device testing that will supplement present animal and *in vitro* models.
- **Safety and Efficacy Limits of Retinal Prosthetics:** The research that determines physiological limits of stimulation will be written into a guidance document to assist device sponsors and used for developing industry standards.
- **Electroconvulsive Therapy Submission Criteria:** This guidance document is of immediate need and has been requested by ODE/DGRND. Its purpose is to provide the information necessary to assure the safety and effectiveness of electroconvulsive therapy devices.
- **Definitions and Effectiveness Testing of CAM Devices:** This guidance document has been of long-term interest because of the inordinate amount of review time taken by devices in the category of complimentary and alternative medicine (CAM). It will first define these devices for which no known mechanism of action exists; it will next establish the levels of proof necessary for approval.

Electrical, Electronics, and Software Engineering

Scope

This program, based in the Division of Electrical and Software Engineering, provides highly specialized technical support for Center and Agency regulatory activities in the areas of electrical/electronics engineering, software engineering, and systems engineering. While the bulk of our work in recent years has been in the medical device arena, the Division of Electrical and Software Engineering traces its roots to the Bureau of Radiological Health and continues to devote a portion of its efforts in support of the "rad health" mission of the Center.

Background

The program focuses on *product realization*, a term used by engineers to describe the process of converting a design concept into a viable product. Product realization encompasses 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. We examine the adequacy of the manufacturer's documented processes, the extent to which the documented processes are being followed in practice and, in particular, the decisions arising from the application of those processes. We assure that the processes are grounded in established quality management and risk management principles, and that design decisions affecting safety and effectiveness of the product are consistent with established scientific and engineering principles. Our goal is to ensure that products consistently perform as intended, fulfilling the requirements of customers and other stakeholders.

As a result, our program emphasizes analysis, laboratory testing, and educational activities over basic and applied research. Another important reason for this emphasis is that most regulatory issues involving electronics and/or software have historically arisen from misapplication of these technologies, rather than any inherent limitations.

The research program currently focuses on two specific needs: objective methods to assess the performance of intelligent medical devices (specifically, those that provide clinical interpretation of physiological waveforms) and formal methods of software verification.

The Division also routinely provides engineering support services to customers in CDRH, in other FDA Centers, and even external to FDA. These services include developing custom electronic instrumentation, designing and fabricating mechanical components and assemblies, procuring specialized electrical and electronic components, and maintaining and calibrating test equipment.

Program Description

Regulatory Support. While many groups within the Center have the need for electronics or software expertise, very few have sufficient need to justify a full-time engineering staff. By building a relatively small team of engineers who are highly qualified and making this critical mass of expertise available throughout the Center, OSEL is able to direct as much effort as needed to particular problems on an ad-hoc basis, thereby freeing the Center of the need to place engineering specialists in every Office of the Center. Centralizing the engineers in this fashion also facilitates communication and collaboration, ensuring that analyses and opinions rendered by the group have the benefit of extensive peer interaction and review. Furthermore, centralizing this function makes it possible to provide effective logistic support (laboratory facilities, supplies, test equipment, specialized software, and support personnel) to the team.

Historically, many device problems arise at the confluence of hardware and software, the user, the manufacturing process, and the use environment. We apply a broad range of analytical tools to develop an understanding of these problems and engage the manufacturer in voluntarily seeking a solution. When the manufacturer is not responsive, we may test the device in question in our laboratory to develop evidence justifying unilateral action by FDA to remedy the problem.

Education. Given the sheer numbers of medical devices that incorporate electronics and/or software, there is no practical way to ensure their safety and effectiveness through a program of retrospective reviews and inspections. Safety and effectiveness must be designed in by the manufacturer. Established manufacturers generally do a good job of this; but some manufacturers lack the requisite technical expertise and fail miserably.

Over the long term, we believe that the principles and practices of product realization need to be better integrated into the core engineering curriculum at both the undergraduate and graduate levels. We have had some promising conversations with a number of educators and this is an initiative that bears further investment.

Standards Development. Consensus standards represent another excellent tool for leveraging industry to improve the quality of medical devices, as well as streamlining the review process.

Engineering Support Services. Originally, developing custom electronic instrumentation and test methods in support of FDA research and compliance activities was the principal mission of our staff. We have earned a number of patents for our innovative designs. Today, support services form a smaller, but still important, component of the mission.

Research. The research program is aimed not at developing new technologies but at improving our capabilities in measurement and analysis. For example, our research

involving test methods is aimed at improving FDA's ability to objectively compare the performance of diagnostic medical devices, even though those devices may use different modalities to sense the clinical conditions of interest. This is an avenue that medical device manufacturers are understandably reticent to pursue, even though it is clearly in the public interest to do so. Our research into formal methods of software verification, by contrast, is enthusiastically embraced by manufacturers because it will lead to tools that they can use for software development, help them to establish the safety and effectiveness of their devices, and streamline the regulatory approval process.

Five-Year Objectives

Expertise in the areas of software engineering and risk management is to be expanded since they are becoming of critical importance to the increasingly sophisticated medical devices for which the Center bears regulatory responsibility. Of particular importance is developing educational initiatives. OSEL believes that every CDRH and ORA employee should be familiar with the principles of quality management and risk management. Because of our systems engineering orientation, we have been at the forefront of efforts to increase staff awareness of these topics. Educational outreach to industry and academia is also being explored.

In the risk management arena, investigations into methods for establishing acceptability criteria for evaluating risk, performing risk-benefit evaluations, using post-production information, and evaluating drug/device combinations must be initiated. Work is under way within CDRH to establish a uniform risk-based approach to device regulation. Guidance must be developed for performing risk management and reporting risk management results in pre-market submissions, establishing risk management as a component of a quality system, integrating risk management with design controls for both device design and design of manufacturing processes, and reconciling post-production information with prior risk management results.

Optical Physics – Diagnostics and Therapeutics

Scope

The rapid development of medical devices employing minimally invasive optical technologies is revolutionizing modern health care. Diseases that once required invasive surgery for diagnosis and treatment are now routinely addressed on an outpatient basis. The goal is a reduction in health care costs and an increase in patient safety and comfort. In addition, many diseases can now be diagnosed much earlier, resulting in more effective treatment. For many of these devices, reliable test methods and guidance documents are

not available. The Optical Physics laboratory program is directed at early identification of (1) key scientific questions, (2) safety and effectiveness issues, and (3) the mechanisms of interaction for new optical diagnostic and therapeutic technologies. This information should facilitate the development of relevant evaluation criteria early in the review process.

Background

There is increased interest in the scientific and medical communities in the use of optical technologies for the diagnosis and treatment of disease. Minimally-invasive optical devices are rapidly becoming commonplace in clinical settings. For example, techniques which use light to measure bilirubin levels in neonatal skin, monitor oxygen saturation in blood and detect precancers in the colon and lungs have already been approved by the FDA. Furthermore, novel diagnostic approaches based on optical phenomena such as coherence and fluorescence are being studied in laboratories and hospitals throughout the world, and are likely to have a significant impact on modern medicine. As a consequence, CDRH is receiving an ever increasing number of submissions in these areas. OSEL is investigating a number of high-priority, optical technologies in order to assist Center reviewers in the timely assessment of manufacturer's submissions. Much of this research focuses on development of reliable standardized test methods that examine specific device attributes. There is a lack of basic scientific knowledge on the mechanisms of interaction of optical devices with tissues. Understanding the mechanisms of interaction, especially regarding safety, is critical to CDRH's ability to make science-based regulatory decisions for this growing class of products.

In a separate, but related area, CDRH has the responsibility for evaluating and approving implanted devices designed to improve human vision. OSEL maintains laboratory instrumentation to evaluate the quality of intraocular lens implants (IOLs). In the past, this activity has aided in the establishment of standard test methods and guidance for product reviews. Currently, new types of IOLs are being developed for which present test methods are not appropriate. Further, new test methods need to be developed to evaluate the safety of new IOL materials and designs.

Program Description

The mission of the Optical Physics Laboratory is to perform forward-looking research on FDA-specific topics relevant to medical devices that CDRH will be called on to evaluate for safety and effectiveness now, and in coming years. In order to achieve a solid understanding of these technologies, we are analyzing the physical mechanisms of these approaches as well as evaluating device performance and the factors that influence them. Results of these activities have been used, and will continue to be used, in guidance and standards for device performance.

OSEL's investigations center on clarifying the mechanisms of interaction of optical physics technology with the body and on developing meaningful performance assessment procedures. In the area of optical diagnosis, our scientists are developing analytic techniques to identify optical tissue properties by using diffuse reflectance data, evaluating fiber optic probes used in optical diagnosis, and developing mathematical models to assist in quantifying the distribution of optical energy within tissues. OSEL is also studying laser therapy devices in order to elucidate the mechanisms of interaction in order to maximize treatment effectiveness. Examples of other products currently being investigated include optical coherence tomography (OCT) for high-resolution imaging, dual-modality fluorescence spectroscopy and spectral reflectance spectroscopy for early diagnosis of disease, ablative lasers used for ophthalmic, cardiovascular, and dermatologic tissues, and optical biosensors for detection of glucose, oxygen, and pharmaceuticals.

OSEL already maintains laboratory instrumentation to evaluate the quality of intraocular lens implants (aphakic IOLs). However, new phakic intraocular lenses (IOLs) are being developed for the correction of myopia and hyperopia; these new IOLs require development of new test methods for product evaluation. Additionally, many patients have reported both temporary and permanent glare resulting from implanted IOLs, in some cases requiring IOL explantation and replacement; again, reliable test methods are needed.

There is a lack of standardization of terminology and parameters, and standardized test methods for evaluating many optical medical devices. In some cases there is even a lack of basic scientific knowledge on the mechanisms of interaction of optical energy with tissue. This program addresses the current gap in scientific knowledge by continuing laboratory studies of optical medical devices, developing test methods, and using our data as input to guidance and standards for streamlining the review of these products in CDRH.

Five-Year Objectives

The use of optical medical devices will continue to grow for the foreseeable future since they can be used with far less discomfort, pain, and inconvenience than the more conventional methods used to detect and treat disease. Also, the use of optical devices will involve individuals more directly in their own health care. For example, there is an emergent need for more frequent and convenient monitoring of chronic disease conditions, giving individuals warnings of problems early, so that medical intervention or prevention measures can be initiated. This program will continue to examine new devices and technologies for safety and effectiveness. New policies, regulations, standards and guidance will be needed to enable individuals to safely operate and maintain devices. This information will be obtained from independent laboratory studies and in-house research that is conducted to anticipate new directions of this technology and will be disseminated in the form of peer-reviewed publications, consultative reviews, and guidance documents.

Electromagnetics and Wireless Technologies

Scope

This program focuses on the various issues associated with medical devices that utilize or are affected by electromagnetic (EM) fields. One issue is to address the rapid deployment of wireless technology around and into medical devices, and the safety and effectiveness concerns associated with electromagnetic interference (EMI) disruption of medical devices and the deposition of the electromagnetic energy in the human body.

Another issue 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 (heat?) body tissues. A principle goal of this effort is to develop standard techniques for measuring and evaluating RF heating for both high- and low-frequency electromagnetic devices.

Additionally, CDRH has the responsibility in the federal government to study and assess the risks of exposure to humans from electromagnetic non-ionizing radiation from radio frequency and microwave emitting electronic products. This is a complex and challenging field. OSEL scientists work vigilantly to stay abreast of the many hundreds of papers produced annually on this subject. The Division of Physics within OSEL performs measurements and dosimetry to evaluate the most common emitters of em fields, e.g., cellular phones and MRI devices.

Background

Responding to numerous adverse event and other reports, OSEL evaluated many types of medical devices for their susceptibility to interference from electromagnetic-field emitting sources such as wireless (cellular) telephones and magnetic-field emitting security devices. OSEL has already found the causes of several specific EMI problems and published results in peer reviewed literature. Additionally, OSEL was assigned by CDRH to lead the Center's Electromagnetic Compatibility (EMC) group that develops Center-wide EMC solutions for medical device EMI problems.

In a separate but related area, CDRH has been involved in responding to a number of concerns expressed by numerous groups about the safety of human exposure to electromagnetic radiation emitted by hand-held wireless (cellular) telephones and other wireless devices. OSEL began addressing this issue by chairing or actively contributing to several international standards-setting groups. The groups are developing wireless phone measurement standards. A well-defined measurement standard is necessary if both the manufacturers of wireless devices and the regulatory agencies that protect public health are

to agree on compliance with existing FDA and FCC radiation emission standards or set new standards for wireless devices. Further, research into the potential biological effects of non-ionizing RF radiation is highly dependent on the amount (dose) of absorbed RF radiation. Accurate and repeatable measurement of the RF radiation dose (dosimetry) is critical for laboratory and epidemiological studies. The thermal injury that results from tissue heating for electromagnetic devices needs to be tested. Given the wide variety of device designs and tissues in which the devices are used make it difficult to generalize the dosimetric and thermal heating patterns of medical devices.

Finally, this program area develops standard techniques for measuring and evaluating RF heating for both high-and low-frequency electromagnetic devices.

Program Description

OSEL has an active ongoing program of testing high-risk medical devices for susceptibility to electromagnetic interference (EMI) emitted by a wide variety of common sources of electromagnetic fields. Examples of sources of EMI include wireless personal communications devices (e.g., cellular phones) and radio or TV broadcast towers. In addition to laboratory work, OSEL researchers routinely perform regulatory reviews of pre-market submissions awaiting approval by FDA as well as post-market assessments of EMI on medical devices.

This program covers a wide range of medical device areas that include essentially all electrically powered devices, as well as the human exposures and energy deposition from a wide range of commonly used radio frequency emitters (e.g., cell phones, wireless computer links, security systems).

The objective of the program is to develop independent data, measurement and computational techniques, and test methods that will serve as solid scientific foundations for regulatory guidance, proposals for national and international standards, and peer-reviewed technical publications. All of the work is driven to promote the public health by developing and coordinating vital information that is unavailable elsewhere. The program utilizes the unique OSEL expertise and facilities built-up over several years of successfully performing research and taking active leadership in addressing the hazards from medical device EMI and human exposure to electromagnetic non-ionizing energy.

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) and other medical devices such as shortwave diathermy and magnetic resonance imaging (MRI). OSEL 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, the public and news media continually express concerns about the possible harmful effects of exposure to radio frequency (RF) electromagnetic fields (also known as non-ionizing RF radiation) from hand-held wireless (cellular) telephones and other wireless personal communications devices.

Five-Year Program Objectives

OSEL will study the general issue of safety, data integrity, and risks to patients in the clinical or home being monitored by wireless medical device technology. Researchers will evaluate potential EMI/EMC problems associated with various wireless technology products (e.g., cellular phones, two-way radio transmitters) and wireless-connected palm/pocket computers that are increasingly being deployed in hospitals. It will also evaluate medical devices with wireless interfaces (Bluetooth, IEEE 802.11b) as sources and victims of EMI.

OSEL scientists will also evaluate the measurement and computer modeling of human exposure to radio frequency non-ionizing radiation emitted by wireless electronic products worn on the body and others. In each of these areas, scientists will perform independent laboratory experiments and make measurements in the clinical environment to develop independent data on each subject area. This information will be disseminated in the form of peer-reviewed publications, input to national and international standards efforts, consultative regulatory reviews, and guidance documents.

Radiological Health and Safety

Scope:
The scope of this program is to provide laboratory and technical support to the Center's Radiological Health mission. FDA serves as a reference laboratory in the national measurement system for safety from radiation-emitting electronic products. OSEL maintains measurement and calibration facilities for x-ray, laser, non-coherent optical sources, and microwave measurements. These calibration labs provide traceability for standards enforcement measurements, facilitate uniformity of measurements, and provide metrology expertise for pre- and post-market issues.

Background

The program began in the early seventies with the implementation of mandatory performance standards for electronic product radiation. With nationwide compliance

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

In the nineties, with the implementation of the Mammography Quality Standards Act (MQSA), the laboratory workload increased as FDA began annual inspections of mammography facilities. The laboratory was instrumental in developing the national calibration standard for mammography x-ray beams maintained by NIST. The CDRH X-ray Calibration Laboratory contributed to many of the standards for calibrations of ionizing radiation measuring instruments. In 1992 the laboratory was the first to receive accreditation from NIST's National Voluntary Laboratory Accreditation Program for this type of calibration. Through the years, the laboratory has provided FDA and agreement-state agencies with reliable ionizing radiation calibrations and metrology support.

Program Description

Radiation safety continues to be a significant concern for the Center. To help address this topic, OSEL maintains measurement and calibration facilities for x-ray, laser, non-coherent optical sources, and microwave measurements.

Each year FDA is responsible for the inspections of over 11,000 mammography facilities under the MQSA. Additionally, about 1600 installations of general radiographic equipment are inspected against the mandatory performance standards mandated by the Radiation Control for Health and Safety Act (RCHSA). FDA also tests a number of industrial x-ray facilities each year. These inspection and testing programs involve measurements of ionizing radiation. OSEL supplies OC, OHIP, ORA, and Agreement States (states that have a contract or agreement to perform FDA inspections) with calibrated x-ray instruments and supplies for the various compliance inspection programs; support for special measurements as needed, such as measuring the ionizing radiation output from personnel security scanners, night vision devices, radioactive contamination of medical or consumer products, and CT beam profiles; and technical consultation. Traceability of measurements is achieved through the operation of a standard laboratory accredited by the National Voluntary Laboratory Accreditation Program (NVLAP).

In addition to ionizing radiation instrument calibrations, OSEL provides laboratory measurements and calibrations of light meters, laser measurement instrumentation, and microwave oven instruments for field enforcement of FDA performance standards. Staff

also provides pre- and post-market evaluations of selected products for compliance with FDA radiation standards.

Five-Year Objectives

In addition to the present level of support, the x-ray program expects increased activity in support of the field programs during the next 5 years. The increases are necessitated mainly by two new requirements: 1) new metrology support and calibration needs due to proliferation of x-ray security screening systems; 2) need to replace the main field instrument for testing medical diagnostic x-ray equipment and adaptation to states as partnership customers. Calibration support for the MQSA and Diagnostic X-ray field inspection programs is expected to continue at or near the present level.

Necessary new activities in support of OC and ORA for screening system safety include working with instrument manufacturers to produce field instruments capable of making appropriate radiation measurements, developing new calibration techniques and procedures for these instruments, working with OC in developing field testing procedures, increased number of routine calibrations of survey instruments in low intensity x-ray fields, and involvement in developing new performance standards for non-medical x-ray equipment.

The main instrument that is used in the field compliance procedure for medical diagnostic and mammography x-ray equipment, the Radcal 1015, is based on old technology that is no longer cost-effective. A replacement instrument needs to be incorporated into the Diagnostic and MQSA field testing programs. Providing the calibration service to the states as a successful leveraging tool requires an increase in the types of instruments accepted for calibration. It also presents new bookkeeping and logistics challenges. New program activities will involve testing instruments, writing specifications, developing and implementing new calibration facilities and writing new procedures.

The x-ray program also expects to complete the upgrade of all its facilities to modern computer equipment and to install new x-ray equipment for non-invasive kV meter calibrations.

For the laser program, instrumentation has not been upgraded to keep pace with innovation in the industry, both in laser products available in the consumer market and in the medical device market. In order to address this need, a multi-year program to modernize and upgrade the laser measurement and calibration capabilities is needed. State-of-the-art measurement equipment is needed to provide support to the Office of Compliance and the Office of Device Evaluation when testing is needed to verify product classification or to obtain data for risk assessment of new laser devices. Amendments to the FDA laser standard will implement new requirements which will necessitate changes in measurement techniques.

Mechanics of Materials and Structures

Scope

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

Background

The Mechanics of Materials and Structures program is structured to help CDRH understand materials issues of concern in both pre-market evaluations and post-market reported adverse events. The materials of interest include synthetics like metals and polymers, materials of biological origin, and those used in tissue engineered medical products (TEMPs). OSEL has the capabilities to measure mechanical properties ranging from the tensile strength of sutures and medical glove materials to the fatigue strength of total joint prostheses. Besides purely mechanical characterizations, our measurement capabilities for TEMPs constructs and scaffolds include quantification of phenotypic stability and the histomorphology of TEMPs relevant cell types. The combined output of this effort includes improved critical review of manufacturers' claims and data, test method development, material and methods standards development, and publications related to the public health impact of medical device materials design, fabrication, or failure.

Program Description

Activities in this program may be triggered within any phase of the product life cycle. In general, the activities of this group are directed not only towards resolving the specific issue that provided the trigger, but also in finding ways to apply the knowledge gained to future device problems. Since the inception of the FDA Medical Device program, this program has been heavily involved with voluntary device standards organizations, such as ASTM International. Participation in these standards activities has leveraged Agency resources with industry and academia, creating lasting consensus solutions to these

regulatory issues once the laboratory studies have been completed. A few examples of these activities are provided in the following paragraphs.

Compatibility issues involving magnetic resonance imaging (MRI) systems and implants or support equipment have existed since this imaging technology was introduced. CDRH has received reports of adverse events through both its post-market monitoring system and the scientific literature describing deaths, burns, and other injuries from dislodged aneurysm clips, failed pacemakers, hurtling oxygen bottles, and brain stimulators. In addition, pre-market clearance of devices likely to be exposed to MRI has been a continuing problem. Some implants can be used near the magnet but not in the magnet. Other implants cease to function temporarily in the magnet but restart when the device is removed. Still, other devices fail completely in MRI. Some devices interfere with imaging but are immune from damage. And, in some cases, the device can produce RF heating when placed within the MRI system, resulting in serious burns. In response, OSEL scientists performed a number of experiments supporting their lead in the development of four ASTM International standards on MRI compatibility that are now utilized in pre-market reviews.

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

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

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

Five-Year Objectives

Materials issues will continue to play a major role in the overall safety and effectiveness of medical devices. History will repeat itself: things will continue to degrade, wear, and break. Additionally, we must be able to anticipate new areas of development and areas where problems may arise. New materials and new technologies, such as nanophase composites, hydrogels, biointeractive surfaces and TEMPs will see future applications in the universe of new medical devices. Also, challenges presented by custom-designed components and the development of ever smaller-scale minimally invasive and nanodevices will create a need for more sensitive and miniaturized methods. The features that limit the usefulness of these materials in these applications need to be identified to prevent injuries and also insure that post-market problems are handled correctly.

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

APPENDIX A – OSEL Publications

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Karanian JW, Wray-Cahen D, Hilbert SL, Ashby A, Abii P, Pritchard WF. Development of a predictive animal model to evaluate safety and effectiveness of interventional cardiovascular device therapeutics. FDA Science Forum, Washington, DC, Abstract O-05, p. 153, April 2003.

Karanian JW, Kipshidze N, Wray-Cahen D, Hilbert SL, Ashby A, Pritchard WF. Systemic and local drug delivery inhibit vascular stenosis following angioplasty and grafting: safety and effectiveness and routes of administration. FDA Science Forum, Washington, DC, Abstract O-07, p. 154, April 2003.

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Lucas AD, Merritt K, Hitchins VM. How much EO residue to expect if the device you mail gets EO sterilized? FDA Science Forum, Washington, DC, Abstract I-08, p. 111, April 2003.

Lucas AD. How NRL proteins, powders, and extracts affect NRL accelerants. FDA Science Forum, Washington, DC, Abstract A-PO-2, p. 52, April 2003.

McDermott MK. Mechanical properties of polyurethane film exposed to solutions of nonoxynol-9 surfactant and polyethylene glycol. Doctoral thesis dissertation, University of Maryland, College Park, MD, December 2002.

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Pfefer TJ, Matchette LS, Ross AM, Ediger MN. Influence of fiberoptic probe geometry on the origin of detected fluorescence: experimental validation of computational results. Proceedings of the SPIE **4957**:142-148, 2003.

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Tomazic-Jezic VJ, Lucas AD. Factors affecting binding of natural rubber latex (NRL) proteins to glove dusting powder. *The Toxicologist* **72:**229, 2003.

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Woods TO, Brown SA, McNamee SG. The effect of cyclic loading on the strength of new and resterilized synthetic absorbable suture. Transactions of the 29th Annual Meeting of the Society for Biomaterials, Reno, NV, April 30–May 3, 2003, p. 593.

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Zmudzka BZ, Beer JZ, Bushar HF, Coelho SG, Hearing VJ, Miller SA, Tadokoro T, Yamaguchi Y. Constitutive melanin, MED, and UV-induced DNA damage in different racial/ethnic groups. Materials of the 31st Annual Meeting of the American Society for Photobiology, Baltimore, MD, p. 58, 2003.

APPENDIX B – OSEL Presentations

October 1, 2002 – September 30, 2003

Alderson N, Ali SF, Bond S, Coles B, Debrabant A, Faustino PJ, Grant M, Khan A, Kulka A, Lucas A, Momcilovic D, Patterson T, Rosebaugh C, Spence M, Stern A, Ward J, Wood G. Committee for the advancement of FDA science (CAFDAS): the FDA scientist's liaison to the Commissioner's office. FDA Science Forum, Washington, DC, April 2003.

Alderson N, Ali SF, Bond S, Coles B, Debrabant A, Faustino PJ, Grant M, Khan A, Kulka A, Lucas A, Momcilovic D, Patterson T, Rosebaugh C, Spence M, Stern A, Ward J, Wood G. Committee for the advancement of FDA Science (CAFDAS): a series on leveraging techniques. FDA Science Forum, Washington, DC, April 2003.

Badano A., Gallas BG, Myers KJ, Burgess AE. Translating viewing angle measurements into signal detectability maps. MIPSX: Medial Image Perception Conference, Durham, NC, September 2003.

Beer JZ. Sunlamps and tanning: our research and our positions. Tanning Symposium: American Academy of Dermatology Association, American Society for Photobiology and the U.S. Food and Drug Administration. Washington, DC, June 28, 2003.

Beer JZ, Hearing VJ, Miller SA, TadokoroT, Yamaguchi Y, Zmudzka BZ. DNA damage and the dynamics of its removal in different racial/ethnic groups. 31st Annual Meeting of the American Society for Photobiology, Baltimore, MD, July 5-9, 2003.

Beer JZ, Hearing VJ, Miller SA, Tadokoro T, Yamaguchi Y, Zmudzka BZ. UV-induced erythema and DNA damage in different U.S. racial/ethnic groups. Invited lecture, 10th Congress of the European Society of Photobiology, Vienna, Austria, September 6-11, 2003.

Beer JZ, Hearing VJ, Miller SA, Tadokoro T, Yamaguchi Y, Zmudzka BZ. UV responses in human skin of different racial/ethnic origin. Invited lecture: 1st Annual Skin of Color Summit, organized by Johnson & Johnson/Neutrogena, Philadelphia, PA, 2003.

Bowley SM, Malinauskas RA. Evaluation of parameters affecting bovine blood hemolysis testing. American Society of Mechanical Engineers: 2003 Summer Bioengineering Conference, Key Biscayne, FL, June 2003 (extended abstract).

Brown RP, Stratmeyer ME, Alonge LA, Phillips PJ. Use of safety assessment to support regulatory decision making and risk communication efforts in CDRH: DEHP in PVC medical devices. FDA Science Forum, Washington, DC, April 2003.

Brown RP, Stratmeyer ME. Conversion factors for deriving interim parenteral tolerable intake (TI) values from oral toxicity data. FDA Science Forum, Washington, DC, April 2003.

Brown SA, Merritt K. Studies on the effects of nitric acid and citric acid on neutralization of endotoxin. Presented to ASTM F04.12, May 2003.

Brown SA, Asher D. CDRH-CBER TSE instrument decontamination project. Presented to the TSE Advisory Committee, July 17, 2003.

Brown SA. Issues in SUDs reuse. MDUFMA ReSUDs course. Presentation, July 28, 2003.

Brown SA, Asher D. CDRH-CBER TSE instrument decontamination project. Progress report and presentation to FDA Office of Science and Health Coordination, September 4, 2003.

Brown SA , Merritt K. Biocompatibility, metal ions, and corrosion products. Abstract and presentation for the ASMInternational, Materials and Processes for Medical Devices Conference, Anaheim, CA, September 8-10, 2003.

Brown SA. Let's not repeat history: good examples of bad ideas. Abstract and keynote address for the ASM International. Materials and Processes for Medical Devices Conference, Anaheim, CA, September 8-10, 2003.

Coelho S, Miller SA, Beer JZ. The use of digital photography to document & quantify erythema & pigmentation induced in human skin exposed to tanning lamps. 31st Annual Meeting of the American Society for Photobiology, Baltimore, MD, July 5-9, 2003.

Coleman JA, Wood B, Phillips JL, Lee C, Pritchard WF, Wray-Cahen D, Walther M, Linehan WM. Circumferential radiofrequency coagulation for partial nephrectomy and partial adrenalectomy. American Urological Association, Chicago, IL, April 2003.

Coleman JA, Wood B, Phillips JL, Lee C, Pritchard WF, Wray-Cahen D, Walther M, Linehan W. Characterization of renal lesions created during circumferential RF assisted partial nephrectomy. World Congress of Endourology, Montreal, September 2003.

Elespuru RK Genetics vs. genomics: a paradigm for microarray issues. FDA Science Forum, Washington, DC, April 24-25, 2003.

Elespuru RK, Garrett-Young R. Analysis of p53 mutations in human tumors: integration of new technology in pre-clinical cancer risk assessment. FDA Science Forum, Washington, DC, April 24-25, 2003.

Elespuru RK. Analysis of p53 mutations in colon adenocarcinomas: molecular epidemiology approach using the IARC TP 53 database, at the Environmental Mutagen Society satellite meeting on colon cancer, Miami, FL, May 2003.

Elespuru RK. Analysis of p53 mutations in human esophageal cancer: a molecular epidemiology approach, Environmental Mutagen Society annual meeting, Miami, FL, May 2003.

Gagne RM. Relationship of DQE to visual signal detection. Invited talk at Annual Meeting of American Association of Physicist in Medicine, San Diego, August 2003.

Gagne RM. Measures of image quality in digital mammography invited talk at Johns Hopkins University Breast Imaging Physics Symposium, Baltimore, MD, September 2003.

Gummalla S, Krause PR, Merritt K, Hitchins VM, Kopecko DJ, Mtungwa AR, Wekell MM, Bhiladvala R, Craighead HG, Hall RH. Nanotechnology biosensor to identify microbial contamination of foods, biologics and medical devices. FDA Science Forum, Washington, DC, April 2003.

He Z, Grimm S, Wagner RF, Wear KA, Jannicky E, Garra BS. Dependence of tissue characterization features on region of interest size: studies on phantoms and *in vitro* tissues. Proceedings of the 28th International Symposium on Ultrasonic Imaging and Tissue Characterization, Arlington, VA, May 28 - 30, 2003.

He Z, Grimm S, Trainer TD, Kalof A, Souchon R, Ophir J, Wear KA, Wagner RF, Huston D, Weiss LJ, Garra BS. Integrating elastography with ultrasound (US) backscatter and image texture features for prostate cancer detection: pathology - US data registration method and results. Tenth Congress of the World Federation for Ultrasound in Medicine and Biology, Montreal, Canada, June 1-4, 2003

Hilbert SL . Preclinical evaluation of flexible leaflet replacement heart valves: assessment of the potential for calcification. Biomineralization in Biomaterials Workshop sponsored by the Surfaces in Biomaterials Foundation, Scottsdale, AZ, 2002.

Hilbert SL. Preclinical *in vivo* studies: FDA perspective. Bioengineering and Materials Applications, National Academy of Sciences, Washington, DC, 2002.

Hilbert SL. Replacement heart valve-related pathology: preclinical *in vivo* studies. 9th Annual Science Forum, Washington, DC, April 24-25, 2003.

Hitchins VM, Mtungwa AR, Merritt K. Induction of TNF-alpha, IL-6 and nitric oxide by titanium nitride, titanium silicide and titanium telluride particles and LPS in RAW 264.7 murine macrophage cells. FDA Science Forum, Washington, DC, April 2003.

Hitchins VM, Mtungwa AR, Merritt K. Induction of TNF-alpha, IL-6 and nitric oxide by titanium nitride, titanium silicide and titanium telluride particles and LPS in RAW 265.7 murine macrophage cells. Society for Biomaterials Meeting, Reno, NV, April 30-May 3, 2003.

Hitchins VM, Merritt K. Production of IL-6, IL-1 beta, TNF-alpha, and nitric oxide by murine macrophages, murine bone cells and human bone cells exposed to alginates of different MG ratios and different purities. Gordon Research Conference on Biomaterials/Biocompatibility/Tissue Engineering, July 21-25, 2003.

Howard PC, Molefe DF, Koddel RF, Wamer WG, Beer JZ, Mellick PW. Photocarcinogenesis: histological classification of skin lesions induced in mice by simulated solar light. 31st Annual Meeting of the American Society for Photobiology, Baltimore, MD, July 5-9, 2003.

Ilev I, Waynant R, Romanczyk T, Gorman E, Luedtke R, Pollard H, Anders J. On-the-spot brain tissue ablation using smart infrared fiber probes. LEOS 2002 – Annual Meeting of the IEEE Lasers and Electro-Optics Society, Glasgow, UK, November 10-14 2002.

Ilev I, Waynant R. Photonic biosensing using smart optical fiber structures. First World Congress on Biomimetics and Artificial Muscles, Albuquerque, NM, December 9-11, 2002.

Ilev I. Modern minimally invasive biophotonics delivery, sensor and imaging systems. National Institutes of Health/NICHHD, Bethesda, MD, January 16, 2003.

Ilev I, Waynant R, Gorman E, Luedtke R, Byrnes K, Anders J. Combined fiber-optic confocal microscopy for noninvasive optical sensing. Photonics West–BiOS 2003 International Conference, San Jose, CA, January 25-31, 2003.

Ilev I, Waynant R. Optical techniques for breath analysis. First FDA/Virginia Tech/AFOSR Workshop on Optical Techniques for Breath Analysis, Falls Church, VA, March 13, 2003.

Ilev I, Waynant R, Byrnes K, Gorman E, Anders J. *In vivo* spectral transmission measurements through single and multiple tissue layers and blood. International Conference on Lasers and Electro-Optics (CLEO-2003), Baltimore, MD, June 1-6, 2003.

Ilev I, Waynant R, Gorman E. A noncontact laser refractometer and caliper based on a simple dual-confocal fiber-optic sensor technique. International Conference on Lasers and Electro-Optics (CLEO-2003), Baltimore, MD, June 1-6, 2003.

Ilev I, Waynant R, Romanczyk T, Gorman E, Moore C, Anders J. *In-vivo* precise brain tissue ablation using smart infrared optical fiber. LEOS 2003 – Annual Meeting of the IEEE Lasers and Electro-Optics Society, Tucson, AZ, October 26-30, 2003.

Ilev I, Waynant R. Noninvasive optical monitoring of smoking-induced effects on exhaled nitric oxide. 2003 National Conference on Tobacco or Health, Boston, MA, December 10-12, 2003.

Kaplan DS. Development of standards for the characterization of natural materials used in TEMPs. ASTM Symposium on Tissue Engineered Medical Products (TEMPs), Miami, Florida, November 4-5, 2002.

Kaplan D, Malinauskas R, Vegella T, Schaefer D, Mars S. A mechanism for evaluating cell adhesion on natural materials. Gordon Research Conference on Biomaterials: Biocompatibility/ Tissue Engineering, Plymouth, NH, July 2003.

Karanian JW. Preclinical animal trials and cardiovascular interventional devices: academic and regulatory perspectives. Second International Interdisciplinary Conference on Cardiovascular Medicine, Surgery, Science, and Mechanics, Bethesda, MD, 2003.

Karanian JW. Thrombosis and restenosis: preclinical interventional device failure modes. International ICB Thrombosis Conference, Bethesda, MD 2003.

Karanian JW. Interventional device implant performance in preclinical animal models of cardiovascular disease. Holland Research Laboratory, ARC, Rockville, MD, 2003.

Kornhauser K, Wei RR, Beer JZ, Coelho SG, Miller SA, Zmudzka BZ, Hearing VJ. Effects of topically applied alpha- and beta-hydroxy acids on the sensitivity of human skin to UV-induced damage. FDA Science Forum, Washington, DC, April 24-25, 2003.

Krauthamer V. The safety of electrical stimulation in the heart and nervous system. University of the District of Columbia, Department of Chemistry Seminar Series, Washington, DC, February 27, 2003.

Krauthamer V. The safety of electrical stimulation. CDRH Staff College "Meet the Experts" seminar, Rockville, MD, July 2, 2003.

Lucas AD, Merritt K, Hitchins VM. How much EO residue to expect if the device you mail gets EO sterilized? Society for Biomaterials Meeting, April 30-May 3, 2003.

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Luu HMD. Use of biological modeling in risk assessment. FDA Science Forum, Washington DC, April 24-25, 2003.

Luu HMD.: Bioavailability of Bisphenol A: prediction of estrogen disruption in humans. SOT Annual Meeting, Salt Lake City, Utah, March 2003.

Malinauskas RA. Hemocompatibility testing of medical devices based on damage to red blood cells. Second International Conference on Cardiovascular Medicine and Science, Bethesda, MD, July 2003. Abstract published in *International Journal of Cardiovascular Medicine and Science*, Vol. 6, No.2, 2003.

Merritt K, Hitchins VM, Lucas AD. Effect of gamma, electron beam and ethylene oxide gas (ETO) sterilization on various medical and personal use items. FDA Science Forum, Washington, DC, April 2003.

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Miller SA, Beer JZ, Coelho SG, Sliney DH. UV tanning – the good, the bad, the beautiful and the ugly. 5th International Lighting Research Symposium on Light and Human Health, Orlando, FL, November, 2002.

Miller SA, Coelho SG, Howard P, Kornhauser K, Wei RR, Beer JZ. UV tanning – the good, the bad, the beautiful, and the ugly. FDA Science Forum, Washington, DC, April 24-25, 2003.

Miller SA, Beer JZ. UV optimization study: research and standards. The Joint Meeting of the American Academy of Dermatology, the American Society for Photobiology and the Food and Drug Administration, Washington, DC, June 28, 2003.

Miller SA, Zmudzka BZ, Coelho S, Beer JZ. How much UV is really needed to produce a tan? 31st Annual Meeting of the American Society for Photobiology, Baltimore, MD, July 5-9, 2003.

Myers KJ. Objective assessment of image quality. NIBIB/UMMC Workshop on Defining the State-of-the-Art in Biomedical Imaging: Research Needs for the Future, Jackson, MS, March 2003.

Myers KJ. Quantitative system evaluation and optimization. Biomedical Imaging Research Opportunities Workshop I, Bethesda, MD, January 2003.

Petrick N, Hadjiiski, LM, Chan H-P, Helvie M.A, Sahiner B, Myers KJ. Assessment of a mammographic mass detection scheme with prior cases. MIPSX: Medical Image Perception Conference, Durham, NC, September 2003.

Petrick N, Badano AG, Chan HP, Sahiner B, Helvie. Digital flat-panel x-ray detectors: improving light collection with microlenses. FDA Science Forum, Washington, DC, April 23-24, 2003.

Pfefer TJ, Matchette LS, Bennett CL, Gall JA, Wilke JN, Durkin AJ, Ediger MN. Reflectance-based determination of optical properties in highly attenuating tissue. FDA Science Forum, Washington, DC, 2003. (Poster presentation)

Ranamukhaarachchi D, Bright R, Chan M, Farr S, Langone J, Neft R, O'Neill JP, Slater J, Wood S, Elespuru R. Development of a diagnostic microarray for type 1 latex allergy, FDA Science Forum, Washington, DC, April 24-25, 2003.

Papaconstantinou AD, Goering PL, Umbreit TH, Brown KM. Regulation of uterine hsp90α, hsp72 and HSF-1 expression in B6C3F1 mice by β-estradiol and Bisphenol A: involvement of the estrogen receptor and protein kinase C. Annual Meeting of the Society of Toxicology, Salt Lake City, Utah, March 2003.

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Pritchard WF, Karanian JW. Regulation of medical devices: FDA perspectives for university researchers. Institute for Medicine and Engineering, University of Pennsylvania, Philadelphia, PA, 2003.

Ranamukhaarachchi D, Langone J, Elespuru R. Assessment of target cell and mRNA detection limits in disease diagnosis using real-time PCR, FDA Science Forum, Washington, DC, April 24-25, 2003.

Stratmeyer ME. Regulatory approaches to natural latex allergy. Meeting of the Additives and Ingredients Subcommittee, Food Advisory Committee of the US FDA's Center for Food Safety and Applied Nutrition, Washington, DC, August 2003.

Tomazic-Jezic VJ, Sanchez BA.. Allergenic natural rubber latex (NRL) proteins binding to glove powder. FDA Science Forum, Washington, DC, April 2003.

Tomazic-Jezic VJ. Comparative evaluation of non-ammoniated latex (NAL) protein extracts for the D6499 revision studies. Semi-annual ASTM D11.40 meeting, Denver, CO, June 2003.

Tomazic-Jezic VJ. Progress in the Management of NRL Allergy: impact on Food Safety. Meeting of the Additives and Ingredients Subcommittee, Food Advisory Committee of the US FDA's Center for Food Safety and Applied Nutrition, Washington, DC, August 2003.

Tomazic-Jezic VJ. Validation of NAL reagent for the revision of the D6499 standard; round robin data report. Semi-annual ASTM D11.40 meeting, Tampa, FL, December 2003.

Waynant R, Ilev I. Delivery of coherent radiation from terahertz to x-rays. LEOS 2002 – Annual Meeting of the IEEE Lasers and Electro-Optics Society, Glasgow, UK, November 10-14 2002.

Waynant RW, Mitra K, Ilev IK. A concept for early cancer detection and therapy. Photonics West, BIOS 2003 International Conference, San Jose, CA, January 25-31, 2003. Published in Lasers in Surgery: Advanced Characterization, Therapeutics and System XII 4(1):425-432, 2003.

Waynant RW. Comparison between lasers and other treatments. Laser Florence 2003, Florence, Italy, November 6-8, 2003.

Wear KA, A Laib. The dependence of ultrasonic backscatter on trabecular thickness in human calcaneus: theory and experiment. Proceedings of the 28th International Symposium on Ultrasonic Imaging and Tissue Characterization, Arlington, VA, May 28-30, 2003.

Wear KA. The dependence of ultrasonic backscatter on trabecular thickness in human trabecular bone: theory and experiment. Proceedings of the Tenth Congress of the World Federation for Ultrasound in Medicine and Biology, Montreal, Canada, June 1-4, 2003, *Ultrasound in Medicine and Biology*, **29,** 5S, p. S20, 2003.

Wear KA. Relationship between ultrasonic backscatter and trabecular thickness in human calcaneus: theory and experiment. SPIE Medical Imaging Conference, San Diego, CA, February 19, 2003.

Wear KA , Garra BS , Pinet MC , Felker S , Mai J. Measurements of ultrasonic backscattered spectral centroid shift from spine *in vivo* – methodology & preliminary results. SPIE Medical Imaging Conference, San Diego, CA, February 19, 2003.

Weber R., Waynant R, Ilev I, Key T, Norman P. Earth oxide: aluminum oxide for mid-range infrared devices. Photonics West–BiOS 2003 International Conference, San Jose, CA, January 25-31, 2003.

Weininger S. Design for quality. Drexel University, Department of Biomedical Engineering, Philadelphia, PA, February 24, 2003.

Weininger S. Integrating the product development process with regulatory requirements and 2. simulator requirements for pulse oximeters. The Fitzpatrick Center, The Pratt School of Engineering, Duke University, Durham, NC, February 25, 2003.

Weininger S. Systems engineering and software development for the NIH fetal saturation (FOX) trial. IEEE 29th Annual Northeast Bioengineering Conference proceedings, March 22, 2003.

Weininger S. Overview of FDA requirements and points to consider during prototype development. Drexel University, Department of Biomedical Engineering, Philadelphia, PA, May 9, 2003.

Woods T, Brown S, McNamee S, Merritt K, Lucas A, Hitchins V. The effects of loading and repeated ethylene oxide sterilization on the mechanical strength of opened but not used (OBNU) synthetic absorbable sutures. FDA Science Forum, Washington, DC, April 2003.

Wray-Cahen D, Pritchard WF, Hilbert SL, Ashby AE, Elsasser T, Vossoughi J, Abii PO, Karanian JW. The coronary artery histopathologic response to angioplasty balloon injury in a swine model is gender- and hormone-dependent. Endocrine Society Meeting, Philadelphia, PA, June 2003.

Yamaguchi Y, Tadokoro T, Beer JZ, Zmudzka BZ, Miller SA, Hearing VJ. Effects of UV on melanocytes in human skin of various phototypes. 31st Annual Meeting of the American Society for Photobiology, Baltimore, MD, July 5-9, 2003.

Zmudzka BZ, Beer JZ, Bushar HF, Coelho SG, Hearing VJ, Miller SA, Tadokoro T, Yamaguchi,Y. Constitutive melanin, MED, and UV-induced DNA damage in different racial/ethnic groups. 31st Annual Meeting of the American Society for Photobiology, Baltimore MD, July 5-9, 2003.

APPENDIX C – OSEL Academic Affiliations

October 1, 2002 – September 30, 2003

Badano, Aldo, Ph.D.	University of Michigan College of Engineering Department of Electrical Engineering and Computer Science Visiting Research Scientist
Bassen, Howard I.	University of Maryland Department of Biological Resources Engineering Lecturer George Washington University Department of Electrical and Computer Engineering Adjunct Professor
Brown, Stanley A.	University of Maryland Baltimore County (UMBC) Mechanical Engineering Adjunct Professor
Chenault, V. Michelle, Ph.D.	Uniformed Services University of the Health Sciences Adjunct Assistant Professor
Das, Srilekha S., Ph.D.	Henry M. Jackson Foundation for the Advancement of Military Medicine Guest Scientist
Goering, Peter L., Ph.D.	University of Maryland School of Medicine Graduate Program in Toxicology Adjunct Professor George Washington University Department of Biological Sciences Adjunct Associate Professor

Harris, Gerald R., Ph.D.	Drexel University Department of Electrical and Computer Engineering Member, Doctoral Dissertation Committee
Hilbert, Stephen L., M.D., Ph.D.	Brown University School of Medicine Department of Surgery Division of Cardiothoracic Surgery Adjunct Professor of Surgery (Research)
Karanian, John W., Ph.D.	Georgetown University Medical Center 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
Myers, Kyle J., Ph.D.	Georgetown University Medical Center Department of Radiology Adjunct Associate Professor University of Arizona Optical Sciences Center Adjunct Associate Professor
Petrick, Nicholas, Ph.D.	University of Michigan Department of Radiology Assistant Research Scientist
Valentine, Karen D.	Montgomery College Department of Continuing Education Instructor/lecturer

Waynant, Ronald W., Ph.D.	Catholic University of America Electrical Engineering Department Adjunct Associate Professor Uniformed Services University of the Health Sciences Adjunct Professor
Wear, Keith A., Ph. D.	Georgetown University Department of Radiology Adjunct Professor Henry M. Jackson Foundation for the Advancement of Military Medicine Guest Scientist

APPENDIX D – OSEL Patents

October 1, 2002 – September 30, 2003

Chen ET. Ameprometric biomimitic enzyme sensor based on modified cyclodextrin as electrocatalysts. **U.S. Patent** 6,582,583, June 24, 2003.

Anders J, Byrnes K, Ilev I, Waynant R. Light promotes regeneration and functional recovery after spinal cord injury. 60/460.42 patent granted **April 7, 2003**

APPENDIX E – OSEL-Sponsored Seminars

October 1, 2002 – September 30, 2003

Adali T. (University of Maryland Baltimore County) Independent component analysis in fMRI analysis. June 26, 2003.

Agrawal A. Detecting cervical precancer *in vivo* with UV-VIS optical spectroscopy. OST/OSEL presentation, May 12, 2003.

Aguel F. (Johns Hopkins University). Fibrillation and defibrillation in a computer model of the rabbit heart, May 8, 2003.

Apollonov VV. Latest results in laser diode pumped solid state lasers in the UV and VUV and applications in medicine: new results in tuberculosis treatment, June 11, 2003.

Barrett HH. (University of Arizona) Some new approaches in speckle statistics. May 8, 2003.

Burgess AE. (Brigham and Women's Hospital) Evaluation and modeling of detection, location, and discrimination of lesions in mammograms. April 10, 2003.

Cohen ED. (Harvard University) Synaptic mechanisms underlying receptive field properties of ganglion cells in mammalian retina, June 6, 2003.

Derakhshani R. (West Virginia University) Biomedical pattern recognition: perspiration-based vitality assessment. August 14, 2003.

Gannot I. Medical informatics – an emerging field. Tel Aviv University, Tel Aviv, Israel, August 21, 2001.

Glick S. (University of Massachusetts) Feasibility of CT mammography using flat- panel detectors. March 27, 2003.

Grundfest WS. New Technology & the Revascularization of Hibernating Myocardium, June 6, 2003.

Hoppin J. (University of Arizona) Comparing estimation techniques in medical imaging without a gold standard. January 24, 2003.

Lehovich A. (University of Arizona) List-mode SPECT reconstruction using empirical likelihood. July 10, 2003.

Miller SA. Bioeffects of optical radiation, Staff College Radiological Health Course, Gaithersburg, MD, February 2003.

Oliver W. (Armed Forces Institute of Pathology) Image processing and forensic pathology. May 27, 2003.

Samuelson FW. (Los Alamos National Labs) Very high-energy astrophysics. October 2, 2003.

Wang Y. The Catholic University of America, Virginia Polytechnic Institute and State University, "Overview on Methods for Blind Source Separation," June 26, 2003.

Wang J, Liu R. (University of Maryland at College Park) Maximum likelihood system identification in DCE-MRI analysis. June 26, 2003.

Wear K. CDRH/OST/DECS/MICAB Ultrasound Laboratory and tour of Medical Imaging Ultrasound Laboratory to Center Director, April 17, 2003.

Wear K. CDRH/OST/DECS/MICAB Ultrasound Laboratory of Medical Imaging Ultrasound Laboratory to CDRH Staff College, video tour, May 15, 2003.

Xuan J. (The Catholic University of America) Computed simultaneous imaging of multiple biomarkers in functional/molecular imaging. May 22, 2003.

Xuan J. (The Catholic University of America, Virginia Polytechnic Institute, and State University) Multivariate clustering and partially-independent component analysis in DCE-MRI analysis. June 26, 2003.

Yousef WA. (George Washington University) Some general principles of multivariate statistical pattern recognition. July 23, 2003.

APPENDIX F – OSEL Laboratory Tours

October 1, 2002 – September 20, 2003

OSEL began conducting tours of their research laboratories for CDRH managers in the spring of 2003. The tours have provided a major opportunity for OSEL to share its research activities and accomplishments with its colleagues throughout CDRH.

April 2003
The Division of Imaging and Applied Mathematics (formerly the Division of Electronics and Computer Science) sponsored a tour of its Medical Imaging and Computer Applications Branch Ultrasound Laboratory. The tour centered on ultrasound bone densitometry and how this technology fits into the CDRH/FDA regulatory mission.

May 2003
The Division of Chemistry and Materials Science (formerly the Division of Mechanics and Materials Science) sponsored a tour of their laboratories comprising three areas: compliance investigation, medical hydrogels, and estrogen disruption.

June 2003
The Electro-Optics Branch within the Division of Physics (formerly the Division of Physical Sciences) maintains a laboratory capability for evaluating the optical performance of intraocular Lenses (IOLs). IOLs are an evolving technology and new designs are continually being submitted to CDRH for pre-market approval. This tour offered a demonstration of ray trace analysis of an IOL in a model eye and air bench testing for the determination of power and resolution of IOL. Ray trace analysis can be used for a theoretical evaluation of the optical performance of IOL designs. The results of this analysis may be used to establish benchmarks for acceptance criteria.

July 2003
The Division of Biology (formerly the Division of Life Sciences) presented a discussion of the Interventional Device and Applied Cardiovascular Research Program. The performance of angioplasty balloons and stents are being evaluated in healthy and atherosclerotic vessels of swine. The research has demonstrated that gender, hormones, age and parameters such as device over-sizing and implant time play a significant role in the overall performance of these devices. Additionally, the safety and effectiveness of systemic versus local drug delivery on long-term performance is being determined. These studies analyze the safety and effectiveness of routes of administration (e.g., luminal vs abluminal) and the pharmacodynamics and pharmacokinetics of various drug therapeutics (e.g., estrogen, paclitaxel and rapamycin) to mitigate stenosis, restenosis and lesion development. The discussion took place during a preclinical study evaluating percutaneous coronary interventions in an atherosclerotic swine.

August 2003
The Medical Electronics Branch of the Division of Electronics and Software Engineering (formerly the Division of Electronics and Computer Science) conducted a laboratory tour to focus on recent

and ongoing activities involving product realization. Product realization is the term used to embrace the engineering processes by which scientific advances are transformed into successful products that consistently perform as intended and satisfy user needs. This tour demonstrated how OSEL research, regulatory support, and outreach activities involving product realization contribute to CDRH's public health mission.

September 2003
There were no laboratory tours conducted this month.

APPENDIX G - FDA FY 2004 Award Grants for Collaborative Science Projects

Proposal #	Title/Investigators	Funds Awarded
6	Detection, Identification and Evaluation of the Virulence Potential of FDA Relevant Pathogens Using: 1) Combined Real-time PCR plus Microarray Approaches, and 2) a Novel High Speed Nano-scale PCR Procedure **Larry E. Bockstahler, Ph.D., CDRH/OST-OSEL** **Daya Ranamukhaarachchi, Ph.D., CDRH/OST-OSEL**	**150,000.00**
17	Semiconductor Nanocrystal Field Deployable Biosensor for Simultaneous Detection of Biological Warfare Agents including *Clostridium botulinum* Neurotoxins A, B, E, and F **Kun-Ho Seo, Ph.D., CFSAN**	**50,000.00**
23	Decontamination of surgical and other instruments exposed to the infectious agents of transmissible spongiform encephalopathies (TSE agents or proions) **David M. Asher, M.D., CBER**	**92,535.00**
29	Prioritizing sources of variability in genomic profiling data for standards and guidance development **Rosalie Elespuru, Ph.D., CDRH/OST-OSEL**	**114,465.00**
33	Mass Spectrometric Screening for Protein Biomarkers to Indicate Food Animal Origin of Bacterial Pathogens **Tracie L. Williams, CFSAN**	**93,000.00**
	TOTAL	**$500,000.00**

APPENDIX H - Abbreviations and Acronyms

AAMI	-	American Association for Medical Instrumentation
AAPM	-	American Association of Physicists in Medicine
ACCA	-	Associate Commissioner for Consumer Affairs, OC, FDA, DHHS
ACF	-	Administration for Children and Families, DHHS
ACCME	-	Accreditation Council for Continuing Medical Education
ACHA	-	Associate Commissioner for Health Affairs, OC, FDA, DHHS
ACLA	-	Associate Commissioner for Legislative Affairs, OC, FDA, DHHS
ACMP	-	American College of Medical Physicists
ACOM	-	Associate Commissioner for Office of Management, OC, FDA
ACPA	-	Associate Commissioner for Public Affairs, OC, FDA, DHHS (Press)
ACPE	-	Associate Commissioner for Planning and Evaluation, OC, FDA, DHHS
ACPE	-	American Council on Pharmaceutical Education
ACR	-	American College of Radiology
ACRA	-	Associate Commissioner for Regulatory Affairs, OC, FDA, DHHS
ADA	-	American Dental Association
ADAMHA	-	Alcohol, Drug Abuse, and Mental Health Administration, PHS, DHHS
AFGE	-	American Federation of Government Employees (Union)
AFIP	-	Armed Forces Institute of Pathology (located at WRAMC), DOD
AHA	-	American Hospital Association
AHCPR	-	Agency for Health Care Policy and Research, PHS, DHHS
AIMBE-	-	American Institute of Medical and Biological Engineering
AMA	-	American Medical Association
ANSI	-	American National Standards Institute
ARCRT	-	American Registry of Clinical Radiography Technologists (MQSA)
ARPA	-	Advanced Research Projects Agency
ARRT	-	American Registry of Radiologic Technologists (MQSA)
ASH	-	Assistant Secretary for Health, DHHS
ASPE	-	Assistant Secretary for Planning and Evaluation, DHHS
ASPER	-	Assistant Secretary for Personnel Administration, DHHS
ASTM	-	American Society for Testing and Materials
BRMD	-	Bureau of Radiation and Medical Devices, CANADA
CBER	-	Center for Biologics Evaluation and Research, FDA, DHHS
CC	-	Clinical Center (Warren Magnuson Clinical Center), NIH, DHHS
CEU	-	Continuing Education Unit
CDC/CDCP	-	Centers for Disease Control/Centers for Disease Control and Prevention
CENELEC	-	European Committee for Electrotechnical Standardization (French term, English translation)
CDER	-	Center for Drug Evaluation and Research, FDA, DHHS
CDRH	-	Center for Devices and Radiological Health, FDA, DHHS
CFSAN	-	Center for Food Safety and Applied Nutrition, FDA, DHHS
CIA	-	U.S. Central Intelligence Agency (Headquarters: Arlington, VA)
CIRMS	-	Council on Ionizing Radiation Measurements and Standards, NIST
CLIA	-	Clinical Laboratory Improvement Amendments of 1988
CME	-	Continuing Medical Education
CRADA	-	Cooperative Research and Development Agreement
CRCPD	-	Conference of Radiation Control Program Directors
CTIA	-	Cellular Telephone Industry Association

CVM	-	Center for Veterinary Medicine, FDA, DHHS
DASH	-	Deputy Assistant Secretary for Health, OASH, DHHS
DCP	-	Division of Commissioned Personnel, OASH, OSG (Parklawn Building)
DHHS	-	U.S. Department of Health and Human Services
DHSS	-	Department of Health and Social Security, ENGLAND
DOC	-	U.S. Department of Commerce
DOD	-	U.S. Department of Defense
DOL	-	U.S. Department of Labor
DOE	-	U.S. Department of Energy
DOT	-	U.S. Department of Transportation
ECRI	-	Emergency Care Research Institute (no longer uses name—initials only)
EEO	-	Equal Employment Opportunity Act
EMBS	-	Engineering in Medicine and Biology Society, IEEE
ERIM	-	Environmental Research Institute of Michigan
FAA	-	Federal Aeronautics Administration
FBI	-	Federal Bureau of Investigation, Department of Justice
FCC	-	Federal Communications Commission
FCCSET	-	Federal Coordinating Council for Science, Engineering and Technology,
FIC	-	Fogarty International Center, NIH, DHHS
FDA	-	U.S. Food and Drug Administration, PHS, DHHS
FDAMA	-	Food and Drug Administration Modernization Act of 1997
FDLI	-	Food and Drug Law Institute
FOIA	-	Freedom of Information Act
FTC	-	U.S. Federal Trade Commission
GAO	-	General Accounting Office
GC	-	General Counsel, FDA (now Office of Chief Counsel, FDA)
GPRA	-	Government Performance and Results Act
GPRE	-	Government Program Review and Evaluation
GSA	-	General Services Administration
HCFA	-	Health Care Financing Administration
HIMA	-	Health Industry Manufacturers Association
HRG	-	Health Research Group (Public Citizen: Ralph Nader-Dr. Sidney Wolfe) (Consumers Health Political Action Committee - PAC)
HRSA	-	Health Resources and Services Administration, PHS, DHHS
ICRP	-	International Commission on Radiological Protection
ICRU	-	International Commission on Radiation Units and Measurements
IEC	-	International Electrotechnical Commission
IEEE	-	Institute of Electrical and Electronic Engineers, Inc.
IFIP	-	International Federation for Information Processing
IG	-	Inspector General, OIG, DHHS
IHS	-	Indian Health Service, DHHS
INNS	-	International Neural Networks Society
INS	-	U.S. Immigration and Naturalization Service
IOM	-	Institute of Medicine, NAS
IRB	-	Institutional Review Board
IRS	-	U.S. Internal Revenue Service
ISO	-	International Standards Organization

JCAHCA - Joint Commission on Accreditation of Health Care Organizations
MDUFMA - Medical Device User Fee and Modernization Act of 2002
NAAP - National Association of Apnea Professionals
NAS - National Academy of Sciences
NBS - National Bureau of Standards, DOC (No longer exists: See NIST),
NCCLS - National Committee for Clinical Laboratory Science
NCHS - National Center for Health Statistics, CDCP, DHHS
NCHGR - National Center for Human Genome Research, NIH, DHHS
NCI - National Cancer Institute, NIH, DHHS
NCNR - National Center for Nursing Research, NIH, DHHS
NCRP - National Council on Radiation Protection
NCTR - National Center for Toxicological Research, FDA, DHHS
NEI - National Eye Institute, NIH, DHHS
NEMA - National Electrical Manufacturers Association
NHLBI - National Heart, Lung, and Blood Institute, NIH, DHHS
NIA - National Institute on Aging, NIH, DHHS
NIAAA - National Institute on Alcohol Abuse and Alcoholism, NIH, DHHS
NIAID - National Institute of Allergy and Infectious Diseases, NIH, DHHS
NIAMSK - National Institute of Arthritis and Musculoskeletal and Skin Diseases, NIH, DHHS
NICHHD - National Institute of Child Health and Human Development, NIH,
NIDCD - National Institute on Deafness and Other Communication Disorders, NIH, DHHS NIDA
NIDA - National Institute on Drug Abuse, NIH, DHHS
NIDDKD - National Institute of Diabetes and Digestive and Kidney Diseases, NIH NIDR
- National Institute of Dental Research, NIH, DHHS
NIEHS - National Institute of Environmental Health Sciences, NIH, DHHS
NIGMS - National Institute of General Medical Sciences, NIH, DHHS
NIMH - National Institute of Mental Health, NIH, DHHS
NINDS - National Institute of Neurological Disorders and Stroke, NIH, DHHS
NIH - National Institutes of Health
NIOSH - National Institute for Occupational Safety and Health, CDCP, DHHS
NIST - National Institute of Standards and Technology, DOC (formerly NBS)
NLM - National Library of Medicine, NIH, DHHS
NMQAAC - National Mammography Quality Assurance Advisory Committee, FDA
NRC - National Research Council
NRC - U.S. Nuclear Regulatory Commission
NSA - U.S. National Security Agency (Headquarters: Fort Meade, MD)
NSF - National Science Foundation
NOAA - National Oceanographic and Atmospheric Administration
NVLAP - National Association of Voluntary Laboratory Accreditation Practices
OC - Office of the Commissioner, FDA
OCA - U.S. Office of Consumer Affairs
OCC - Office of the Chief Counsel, FDA (formerly OGC)
OCR - Office for Civil Rights, DHHS
OHA - Office of Health Affairs, FDA, DHHS
OIG - Office of the Inspector General
OLA - Office of Legislative Affairs, OC, FDA, DHHS
OMB - Office of Management and Budget
OPA - Office of Public Affairs, OC, FDA, DHHS (Press Office/Relations)
OPE - Office of Planning and Evaluation, FDA, DHHS

ORA - Office of Regulatory Affairs, FDA, DHHS
OPM - Office of Personnel Management
OS - Office of the Secretary, DHHS
OSG - Office of the Surgeon General, PHS, DHHS (Commissioned Corps)
OSHA - Occupational Safety and Health Administration
PAC - Political Action Committee
PAHO - Pan-American Health Organization, WHO, UN
PHS - U.S. Public Health Service
RESNA - Rehabilitation Engineering Society of North America, ANSI
RSNA - Radiological Society of North America
SAMHSA - Substance Abuse and Mental Health Services Administration, DHHS
SCVIR - Society for Cardiovascular and Interventional Radiology
SMDA - Safe Medical Devices Act of 1990
SNL - Sandia National Laboratories
SPIE - Society of Photo-Optical Instrumentation Engineers
SSA - Social Security Administration (formerly part of DHHS)
SSRCR - Suggested State Regulations for Control of Radiation
UL - Underwriters Laboratories
UN - United Nations
USDA - U.S. Department of Agriculture
WCNN - World Congress of Neural Networks
WEAC - Winchester Engineering and Analytical Center, FDA, DHHS
WHO - World Health Organization, UN
WRAIR - Walter Reed Army Institute of Research, WRAMC, U.S. Army
WRAMC - Walter Reed Army Medical Center, U.S. Army

CDRH ABBREVIATIONS AND ACRONYMS

DB - Division of Biology
DCLD - Division of Clinical Laboratory Devices, ODE
DCMS - Division of Chemistry and Materials Sciences
DCRND - Division of Cardiovascular, Respiratory and Neurological Devices, ODE
DDL - Devices and Diagnostics Letter (also known as The Orange Sheet) (Weekly Trade Magazine)
DECS - Division of Electronics and Computer Science, OST
DESE - Division of Electronics and Software Engineering
DGRD - Division of General and Restorative Devices, ODE
DIAM - Division of Imaging and Applied Mathematics
DLS - Division of Life Sciences, OST
DMISS - Division of Management, Information and Support Services, OST
DMMS - Division of Mechanics and Materials Science, OST
DMQRP - Division of Mammography Quality and Radiation Programs, OHIP
DOD - Division of Ophthalmic Devices, ODE
DP - Division of Physics
DPS - Division of Physical Sciences, OST
DRAERD - Division of Reproductive, Abdominal, ENT, & Radiological Devices, ODE
EIR - Establishment Inspection Report
DSFM - Division of Solid and Fluid Mechanics
EMC - Electromagnetic Capability
EMI - Electromagnetic Interference

ERC	- NSF Engineering Research Center, Duke University (National Science Foundation)
510(k)	- Five-Ten K: Pre-market Notification of New Medical Device (Clearance Based on a Similar, Previously Cleared Device)
HL	- High Level or High-Level Control
IDE	- Investigational Device Exemption
IND	- Investigational New Device (or Drug) (application for transitional devices)
IAG	- Interagency Agreement
kVp	- Measurement of Meters (as in kVp Meters)
MDDI	- Medical Devices, Diagnostics & Instrumentation (also known as The Gray Sheet) (Weekly Trade Magazine))
MDH	- X-ray radiation instrument used by FDA in its inspections (originally marketed by a company called MDH)
MDR	- Mandatory Device Reporting Program
MON	- Memorandum (Memoranda) of Need
MQC	- Mammography Quality Control (as in MQC Manual)
MQSA	- Mammography Quality Standards Act of 1992
MRI	- Magnetic Resonance Imaging (formerly nuclear magnetic resonance)
MRS	- Magnetic Resonance Spectroscopy
NEXT	- Nationwide Evaluation X-ray Trends (Data Bank)
NSWL	- Naval Surface Warfare Laboratory (in White Oak, Silver Spring)
NVLAP	- National Voluntary Laboratory Accredited Program, (NIST, DOC) (MQSA)
OC	- Office of Compliance, CDRH, FDA
OCD	- Office of the Center Director, CDRH, FDA, DHHS
ODE	- Office of Device Evaluation, CDRH, FDA
OHIP	- Office of Health and Industry Programs, CDRH, FDA
OSM	- Office of Systems and Management, CDRH, FDA
OPA	- Office of Public Affairs, FDA, DHHS (Press Office)
ORA	- Office of Regulatory Affairs, FDA, DHHS (field offices)
OSB	- Office of Surveillance and Biometrics, CDRH, FDA
OST	- Office of Science and Technology, CDRH, FDA
PDP	- Product Development Protocol
PMA/PMAA	- Pre-Market Approval Application
PMS	- Post-Market Surveillance
QA	- Quality Assurance
QC	- Quality Control
RIHSC	- Research Involving Human Subjects Committee, FDA
ROC	- Receiver Operating Characteristic Curve
RRHR	- Regional Radiological Health Representative, FDA
SCLIR	- Secondary Calibration Laboratories for Ionizing Radiation
SIDS	- Sudden Infant Death Syndrome
TEPRSSC	- Technical Electronic Product Radiation Safety Standards Committee, CDRH, FDA, DHHS
TMJ	- Temporomandibular Joint
TQM	- Total Quality Management